FDA Regulation of Drugs and Biologics during COVID-19

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FDLI

Agenda

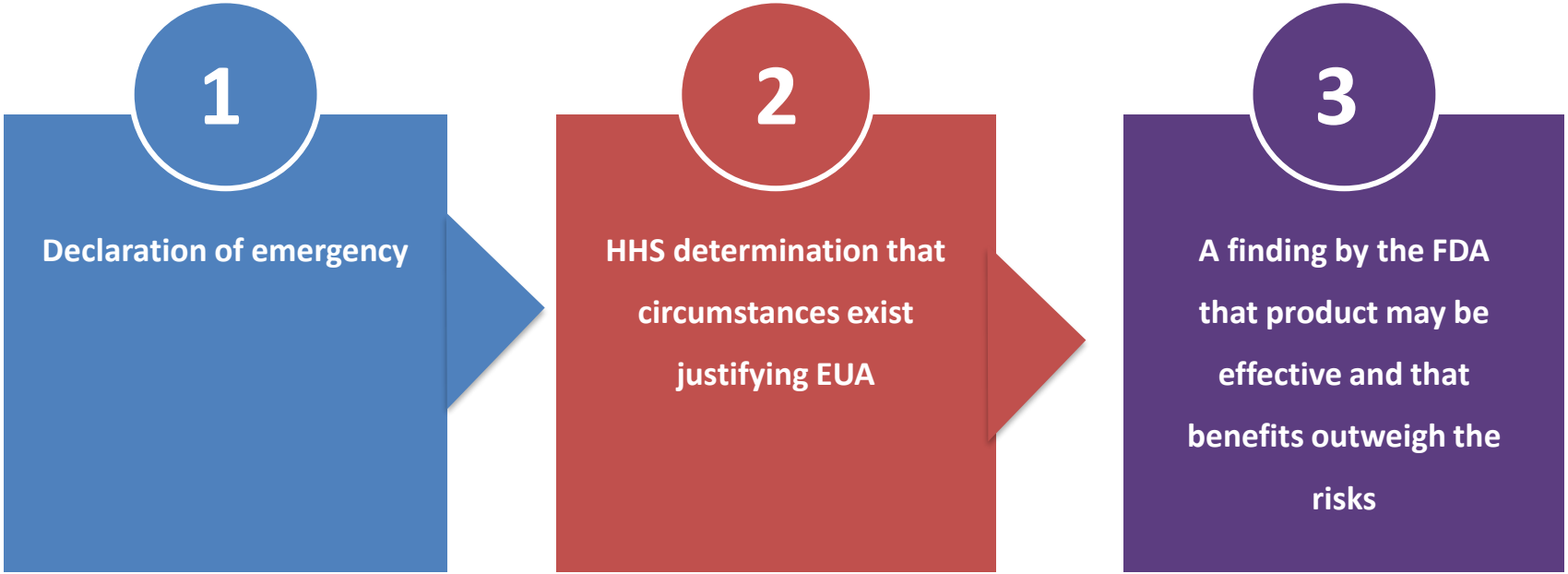
- **Development/Use of Products for COVID-19**
  - Emergency Use Authorizations
  - Enforcement Discretion
  - Expanded Access/Right to Try
  - Vaccine Development
- **Impact of COVID-19 on non-COVID Products**
  - Clinical Trials
  - Post market Requirements (Safety Reporting, Supply Chain Security, Shortage Reporting, GMPs, REMS)
  - Inspections & Enforcement

Development/Use of Products for COVID-19

Available Investigational / Marketing Pathways

Pathway	Drugs/Biologics
Public Health Emergencies	• Emergency Use Authorization • Enforcement Discretion
Treatment Use of Investigational Products	• Expanded Access Programs (including single patient emergency use) • Right to Try
Traditional Investigational Applications	Investigational New Drug Applications (INDs)
Traditional Premarket Pathway Options	• New Drug Applications (NDAs) • Abbreviated New Drug Applications (ANDAs) • Biologic License Applications (BLAs)

EUA Under FD&C Act § 564



EUA Criteria

LIFE THREATENING

The CBRN agent specified in the declaration of emergency can cause a serious or life-threatening disease or condition

EFFECTIVE

It is reasonable that the product may be effective in diagnosing, treating, or preventing the disease or condition

BENEFITS OUTWEIGH RISKS

The known and potential benefits outweigh the known and potential risks

NO ALTERNATIVE

There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition

Conditions on Authorization

INFORMATION TO PROVIDERS

Disseminate information to healthcare providers/dispensers regarding the EUA, potential risks and benefits, alternative therapies

INFORMATION TO PATIENTS

Disseminate information to patients regarding the EUA, potential risks and benefits, alternative therapies, the option to accept or refuse the EUA product

MONITORING

Monitoring and reporting adverse events

OTHER

Restricted advertising, distribution, and administration; data collection and analysis; recordkeeping and FDA records access; compliance with cGMP

Potential Waivers: cGMPs; Prescription Requirements; REMS

Duration and Termination

- The EUA is in effect for as long as the HHS secretary's § 564 emergency declaration is in effect
- Continued marketing after the emergency is over requires FDA clearance, approval, or authorization
- The EUA can be amended and may be revoked earlier if the criteria for issuance are no longer met or revocation is appropriate to protect public health or safety

Current EUAs

- Vaccines (currently 3)
- Therapeutics (currently 10)
- In Vitro Diagnostic Devices
- Personal Protective Equipment
- Ventilators
- Decontamination Systems, Respiratory Assist, Blood Purification, and Other Medical Devices

Other Emergency Measures for Marketed Products

- Eligible Products
  - FDA approved/cleared
  - Intended for their approved/cleared use for a disease/condition involving a CBRN agent or serious/life-threatening disease/condition caused by a product used for a CBRN agent
  - Determination of an emergency/significant potential for an emergency by DOH, DOD, or HHS, OR material threat by DOH
- Potential Actions
  - Expiration date extensions
  - Emergency dispensing

Enforcement Discretion for Drugs (noncomprehensive)

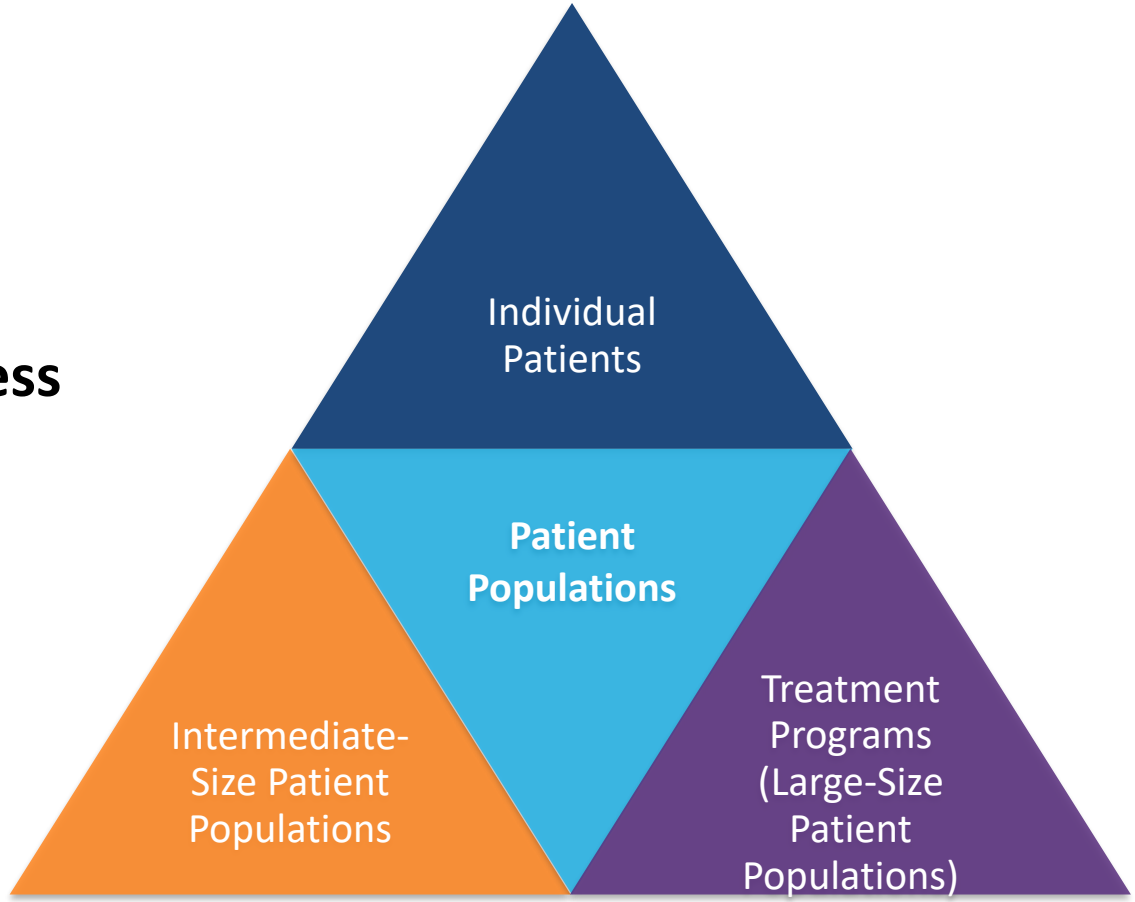
Guidance Title	Date Issued	Status
Temporary Policy for **Manufacture of Alcohol for Incorporation into Alcohol Based Hand Sanitizer Products** During the Public Health Emergency (COVID -19)	02/11/2021	Final
Temporary Policy for **Preparation of Certain Alcohol-Based Hand Sanitizer Products** During COVID-19 Public Health Emergency	02/10/2021	Final
Policy for **Temporary Compounding of Certain Alcohol-Based Hand Sanitizer Products** During the Public Health Emergency	02/10/2021	Final
Temporary Policy for **Compounding of Certain Drugs for Hospitalized Patients by Outsourcing Facilities** During COVID-19 Public Health Emergency	05/21/2020	Final
Temporary Policy for **Compounding of Certain Drugs for Hospitalized Patients by Pharmacy Compounders not Registered as Outsourcing Facilities** During COVID-19 Public Health Emergency (Revised)	05/21/2020	Final
Temporary Policy for **Compounding of Repackaging or Combining Propofol Drug Products** During COVID-19 Public Health Emergency	04/22/2020	Final

What Does Expanded Access Mean?

Expanded Access programs allow treatment use of an investigational drug/biologic when necessary conditions are met

- Serious or immediately life-threatening disease or condition
- No comparable or satisfactory alternative therapy
- Potential benefits justifies potential risks, and risks are not unreasonable
- Access will not impede development of investigational drugs
- Compliant with FDA requirements in IND regulations

Types of Expanded Access Uses



The Right to Try Act

- Signed into law as the Right to Try Act, or the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act, on May 30, 2018.
- The main difference between “Right to Try” and “Expanded Access” is that under the Right to Try Act, patients may pursue unapproved treatments *without FDA oversight*, which has made it controversial
  - Reporting requirements are also less robust

The Right to Try Act - Criteria

Patient Prerequisites

1) Life-threatening disease or condition
2) Exhausted all approved treatment options
3) Unable to participate in a clinical trial
4) Must provide informed consent

Investigational Drug Prerequisites

1) Complete phase 1 clinical trial
2) Cannot be FDA-approved for any use
3) FDA marketing application must be submitted or the drug must be under investigation in a clinical trial intended to form the primary basis of an efficacy claim and subject to an active IND
4) An active drug development or production program must be ongoing

COVID-19 Drug/Biologic Development

Therapeutic Development

- Covers Phase 2/3 clinical development
  - Preference for randomized, placebo-controlled, double blind, superiority design

- Trial design depends on intended use
  - Population
  - Treatment v. Prevention
  - Regional differences

- Requires maintenance of standard of care
  - May mean use of products off-label
  - May require study amendments as standard of care changes

- Need to characterize drug resistance pathways and potential for cross-resistance
- Encourages minimization of in-person data collection
- Encourages use of data monitoring committees and futility stopping criteria

Therapeutic Development

- Provides for potential for innovative study designs (e.g., decentralized/platform studies, adaptive studies, etc.)
- Real World Data may supplement safety monitoring

- Amount of initial evidence determines trial progression
  - Compelling initial evidence may permit direct progression to phase 3
  - If there is limited evidence, recommends initial benefit assessments

- Potentially important clinical outcomes
  - Mortality
  - Respiratory failure
  - Need for invasive mechanical ventilation
  - Need for hospitalization/ICU care
  - Sustained improvement/recovery
  - Confirmed infection

Vaccine Development

- Goal of full Biologic License Application approval
  - EUA may be appropriate following phase 3 studies or through interim data

- Preclinical Development
  - Address Enhanced Respiratory Disease and immunogenicity
  - If information is available from a similar platform, may be able to initiate clinical trials without preclinical safety data

- Clinical Development
  - Scientifically sound & direct evidence of safety/efficacy
    - Potential accelerated approval based on immune response once more information is known
    - May use innovative trial designs (adaptive/seamless)
    - Diverse study population
  - Randomized, controlled, double blind study
  - Median follow up of at least 2 months in over 3,000 subjects, with post-market follow-up
  - 50% efficacy with hypothesis testing based on disease severity

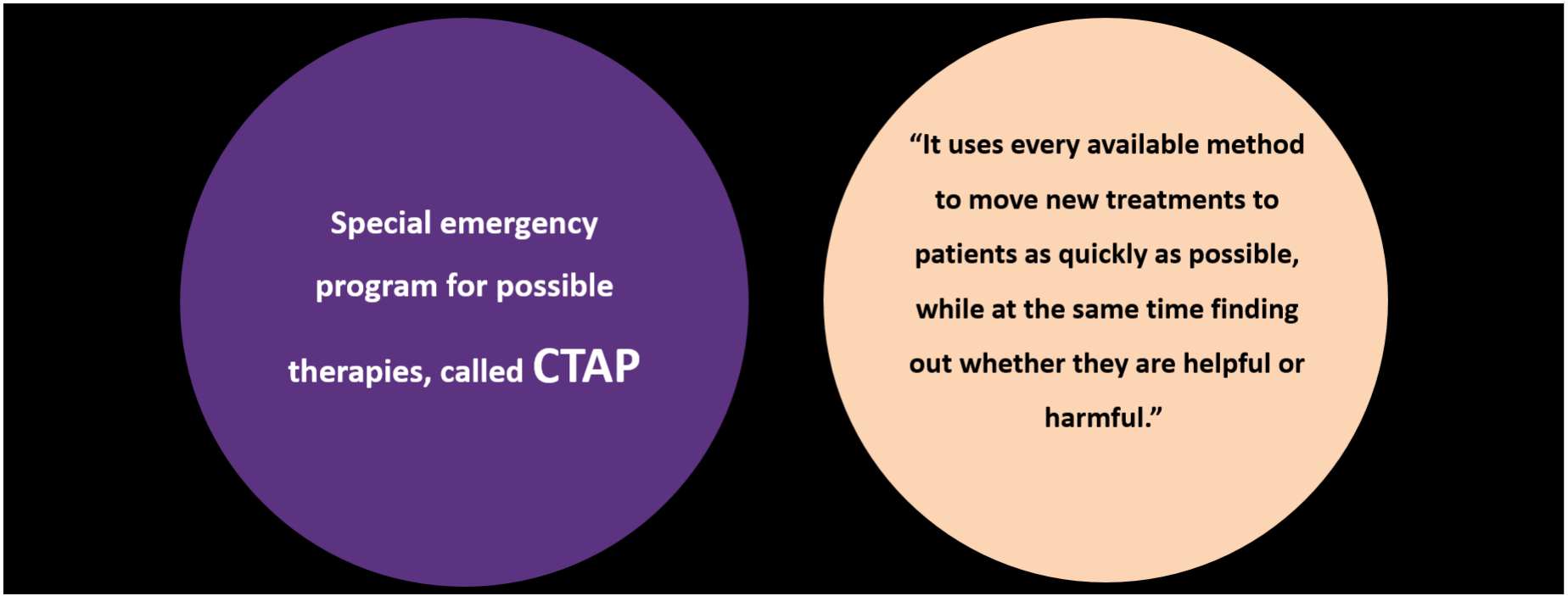
Vaccine Development

- Chemistry, Manufacturing & Controls
  - May accelerate initial development based on use of the same platform for similar products
  - Otherwise, will require traditional manufacturing information
  - Outstanding question of on-site inspections

- Post-Approval
  - Pharmacovigilance planning for rapid vaccination
  - Post market studies and expectation of continued collection of placebo-controlled data
  - Issuance of EUA must not interfere with ability of an ongoing phase 3 study to support full licensure

- Availability of vaccines has design implications for future trials
  - FDA encourages sponsors to contact the agency early in the planning process
- Special FDA procedures for supplements to address viral variants (e.g., variant efficacy may be demonstrated through clinical immunogenicity studies comparing immune responses)

CTAP - Overview



600+

Drug development programs in planning stages[1]

440+

Trials reviewed by FDA[2]

10

COVID-19 treatments currently authorized for Emergency Use[3]

1

Treatments currently approved by FDA for use in COVID-19

www.fda.gov

[1]Active Pre-INDs. Excludes vaccines.
[2]Safe to proceed INDs. Excludes vaccines.
[3]Please see the Emergency Use Authorization webpage for more details. This number includes 1 EUA authorizing both medical devices and a drug for emergency use.

Other Agency Programs

Accelerating COVID-19 Therapeutic Interventions and Vaccines Partnership

- Collaboration among government and industry
- Prioritize vaccine and therapeutic candidates
- Streamline clinical trials
- Rapidly expand clinical research resources
- Provides subject matter expertise and/or funding

Operation Warp Speed

- Aims to delivery 300 million doses of a safe and effective vaccine by January 2021
- Multiagency and industry partnership
- Protocol alignment
- Grant funding/government investment
- Simultaneous development steps (e.g., industrial scale manufacturing during clinical trials)
- Distribution infrastructure planning

COVID-19 & FDA Regulation

Clinical Trials

- **Clinical subject safety is the priority**
- New considerations when deciding whether to initiate, continue, or discontinue trials
  - Availability of sites and clinical trial staff
  - Availability of clinical trial supplies and investigational products
  - Feasibility of enrollment given public health measures
  - Clinical subject response to date and availability of alternative treatments
  - Data monitoring committees can assist with decisions on continuation
- Potential for increased AE reporting due to COVID-19 (hinges on causation)

Clinical Trials

- Clinical Trial Modifications
  - Use of virtual site visits and alternative sites
  - Alternative investigational product delivery methods
  - Remote monitoring
  - Added COVID-19 screening procedures
  - Study modifications must be done in consultation with IRB
    - FDA consultation also recommended
  - Modifications to immediately assure patient safety can be immediately implemented
- Alternative methods of informed consent
- Increased reliance on electronic records and signatures
- Detailed data recording is critical, including relationship of deviations/missing information to COVID-19
- Specific considerations for ANDA applicants/BE studies

Good Manufacturing Practices

- Vigilant employee monitoring
- Exclusion of employees with COVID-19 from drug manufacturing area until CDC recommendations completed
- Increased importance of good sanitation and health practices
  - Manufacturers should assess internal controls and conduct risk assessments regarding ability of systems and processes to prevent COVID-19 contamination
  - Any changes must be conducted in accordance with change controls (e.g., quality unit approval)

Good Manufacturing Practices

- Contingency planning for manufacturers of medically necessary drugs
  - e.g. Remote record review
- Specific recommendations for cell/gene therapies
- Resumption of normal activities
  - Assess impact of COVID-19 (including on activities outside of immediate control)
  - Identify remediation
  - Quarantine batches as necessary
  - Prioritize activities based on a risk management approach
  - Establish a resumption plan

Safety Reporting and Post-Market Requirements

- Safety Reporting
  - FDA is exercising enforcement discretion for certain categories of safety reports
    - Limited to firms experiencing circumstances that prevent meeting standard reporting timeframes
  - Stored reports must be reported within 6 months of restoration of reporting processes
- Drug Supply Chain Security Act
  - Exemption from DSCSA tracing and product identification requirements for products subject to an EUA, approved for COVID-19, and products directly impacted by COVID-19 and that meet emergency medical needs
  - BUT, manufactures must continue to be alert to fraudulent products
- Risk Evaluation and Mitigation Strategies
  - FDA is exercising enforcement discretion for laboratory testing and imaging prerequisites when prescribing and dispensing products subject to REMS

Safety Reporting and Post-Market Requirements (cont.)

- Shortage Reporting
  - Drug sponsors must notify FDA of permanent discontinuance of product manufacturing or interruptions likely to lead to meaningful supply disruption
    - Applicable to products that are life supporting, life sustaining, intended for use in prevention or treatment of debilitating diseases, or critical to public health, as well as active ingredients that could lead to meaningful supply chain disruptions
  - FDA requests notice if product demand cannot be met (not a legal requirement)
  - FDA is exercising flexibility and providing priority review for supplemental applications needed to address supply chain disruptions/product shortages

Enforcement & Inspections

Inspections

- Foreign and domestic inspections were suspended in March 2020
- Domestic inspections resumed July 10, based on risk assessment ratings
- Under some circumstances, FDA could conduct inspections via a desk review or other remote alternative methods (April 2021 Guidance)
- However, inspection difficulties may result in approval/supplement delays

FDA and FTC actively monitoring product promotion related to COVID-19

- Numerous warning letters sent to manufacturers and providers related to false and misleading COVID-19 prevention/treatment claims
- FTC took action to sue a marketer of a COVID-19 “Treatment” Plan, after the company failed to heed a warning letter
- April 2021, FTC sought monetary penalties regarding deceptive marketing of COVID-19 treatment

Lessons Learned

- FDA communication
- FDA guidance strategies
- Clinical trial design and conduct
- Implications for new pathways/PDUFA

Questions