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.

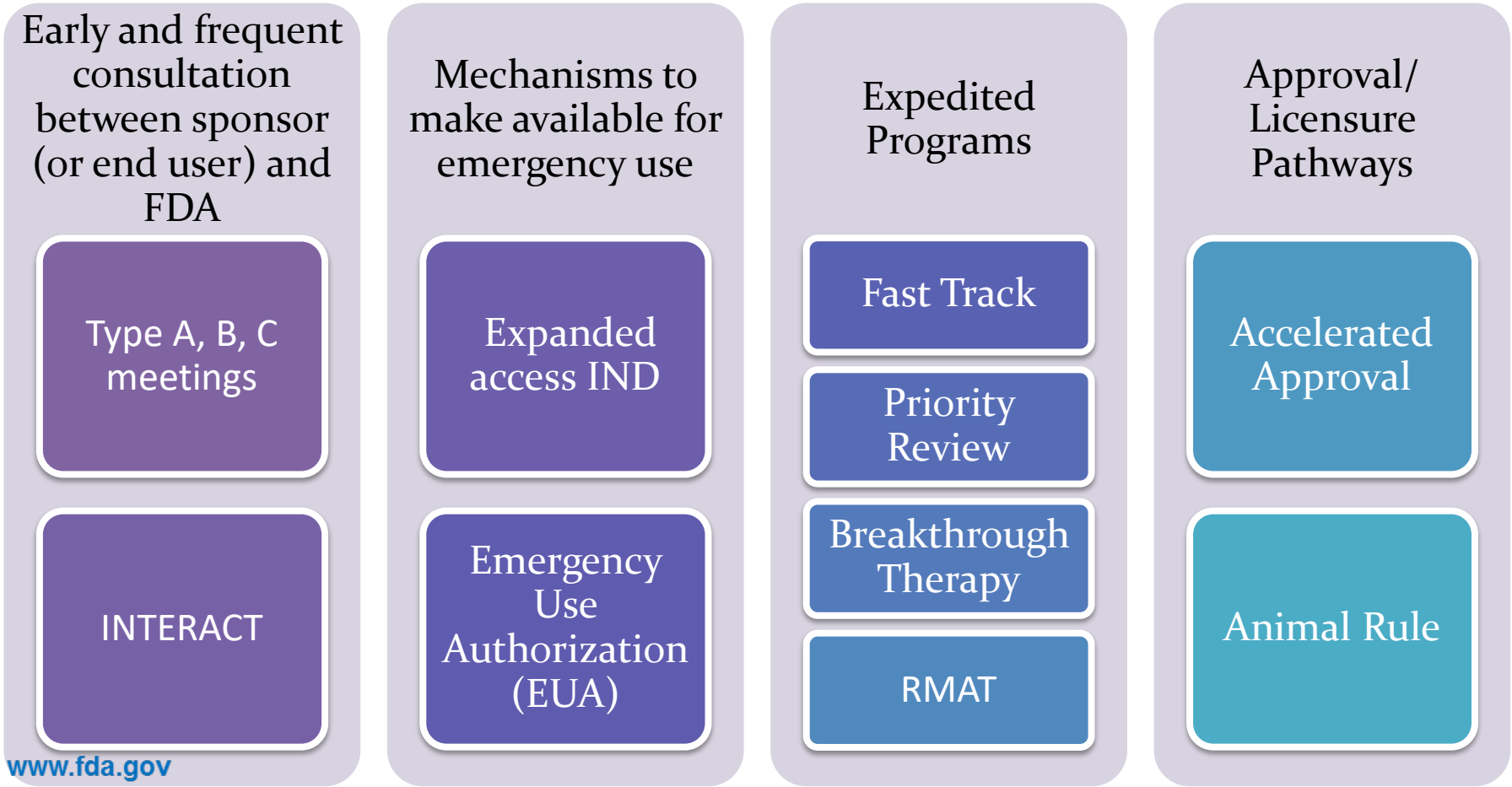
Many more meetings with sponsors to encourage/speed development of new products.

- 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



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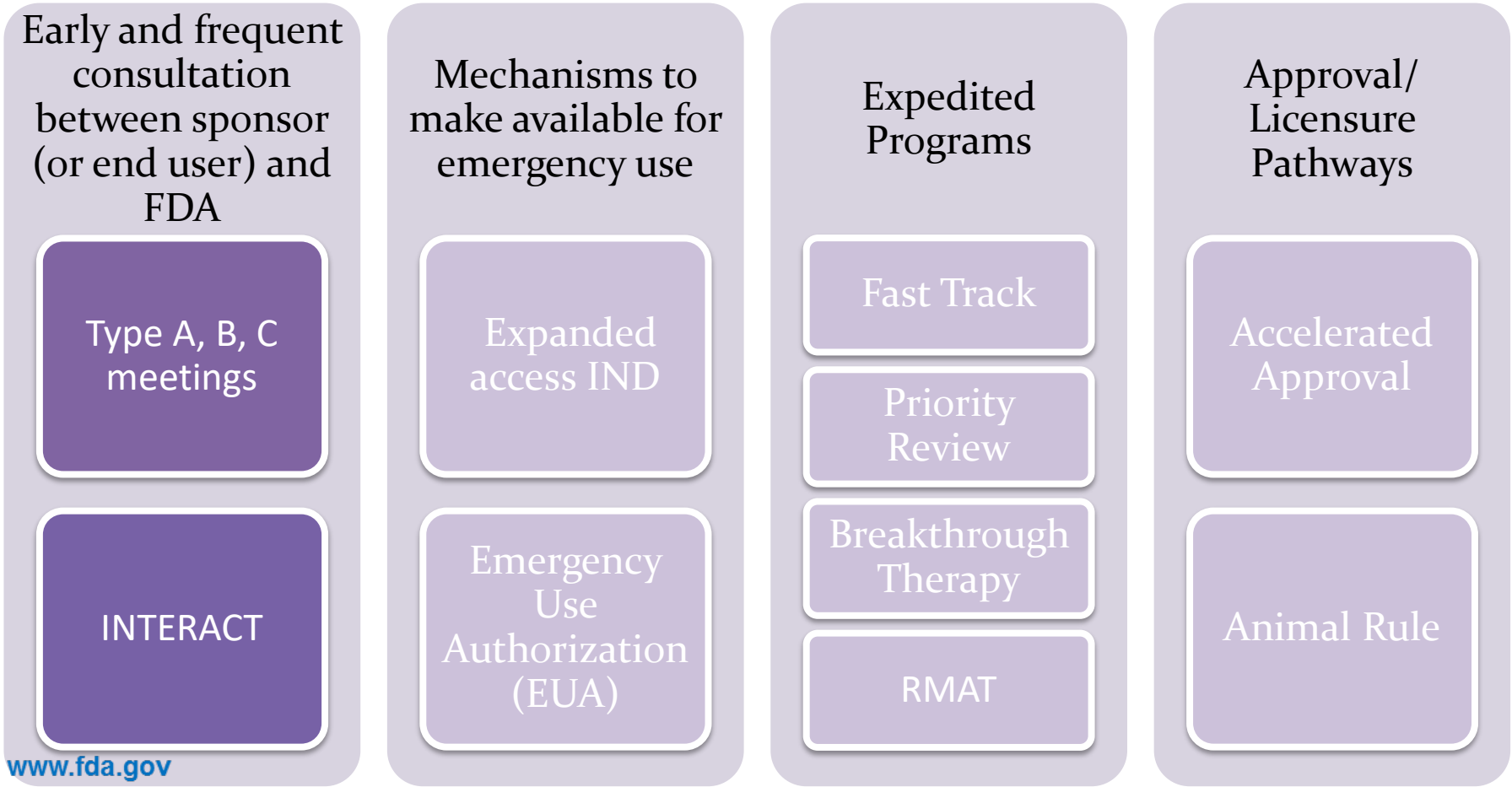

Meetings with FDA

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

- **IN**itial **T**argeted **E**ngagement for **R**egulatory **A**dvice on **C**BER produc**T**s
- 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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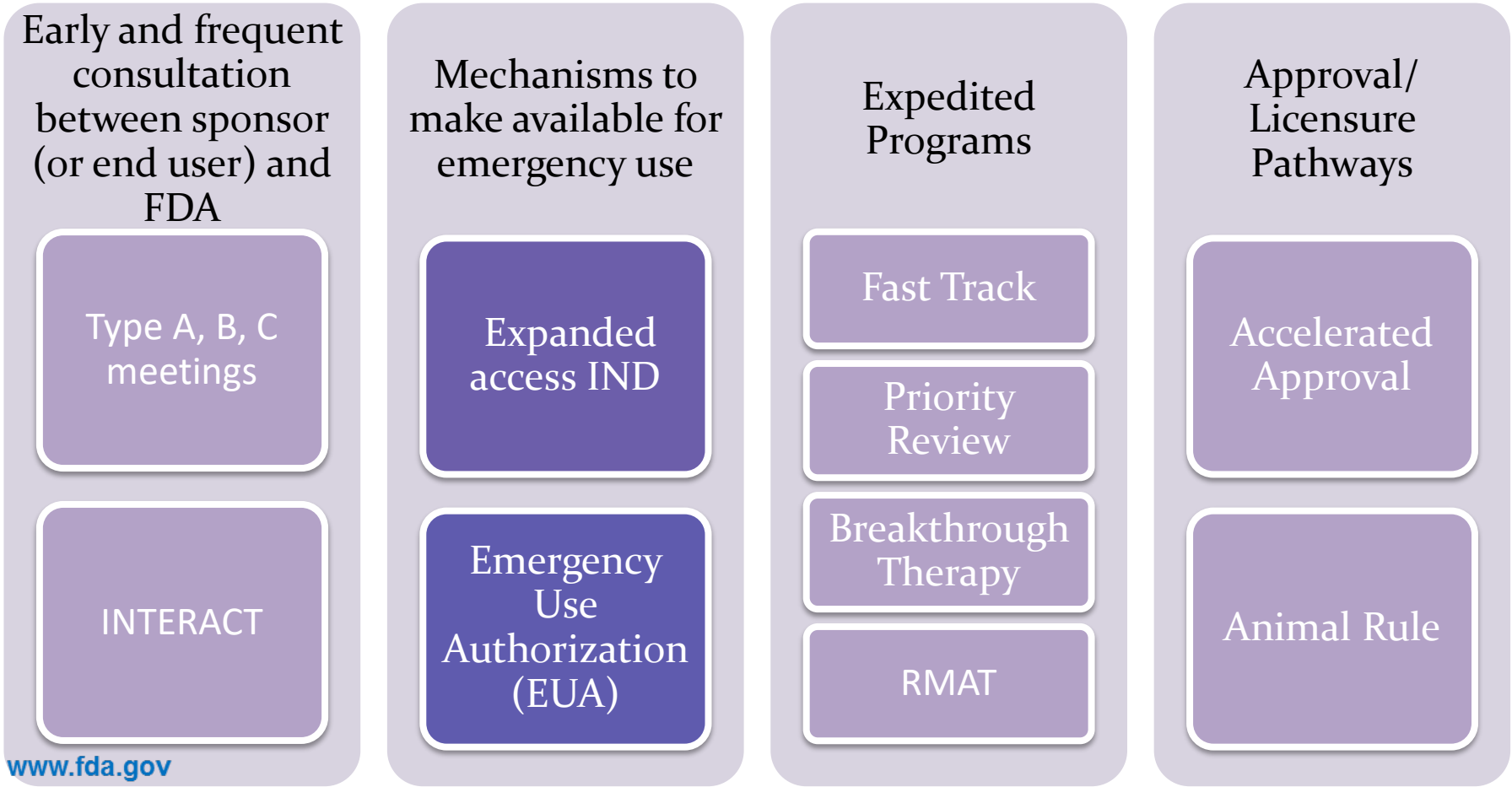


Expanded Access IND

Individual patient – use under an emergency IND (eIND)	Intermediate size Populations	Treatment IND
• 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	• 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	• 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 events

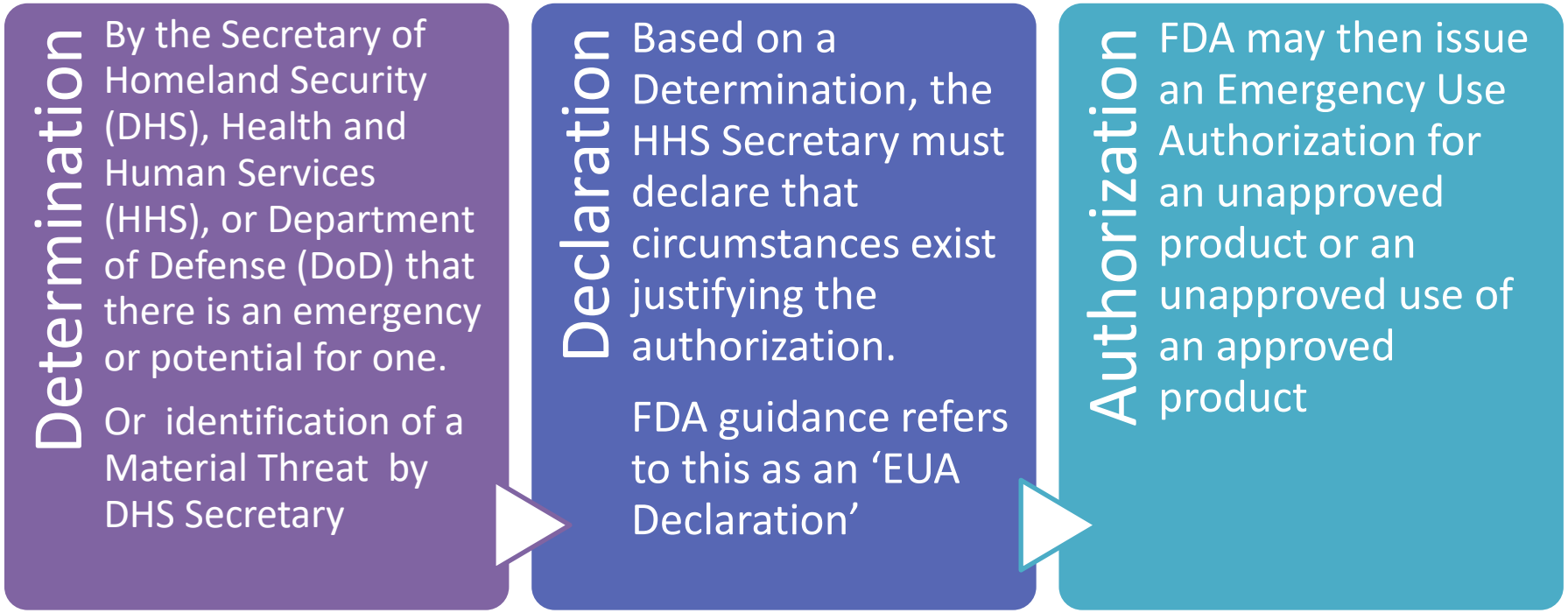
Cures Act (2016)

- Authorize emergency use of unapproved animal drugs or unapproved uses of approved animal drugs

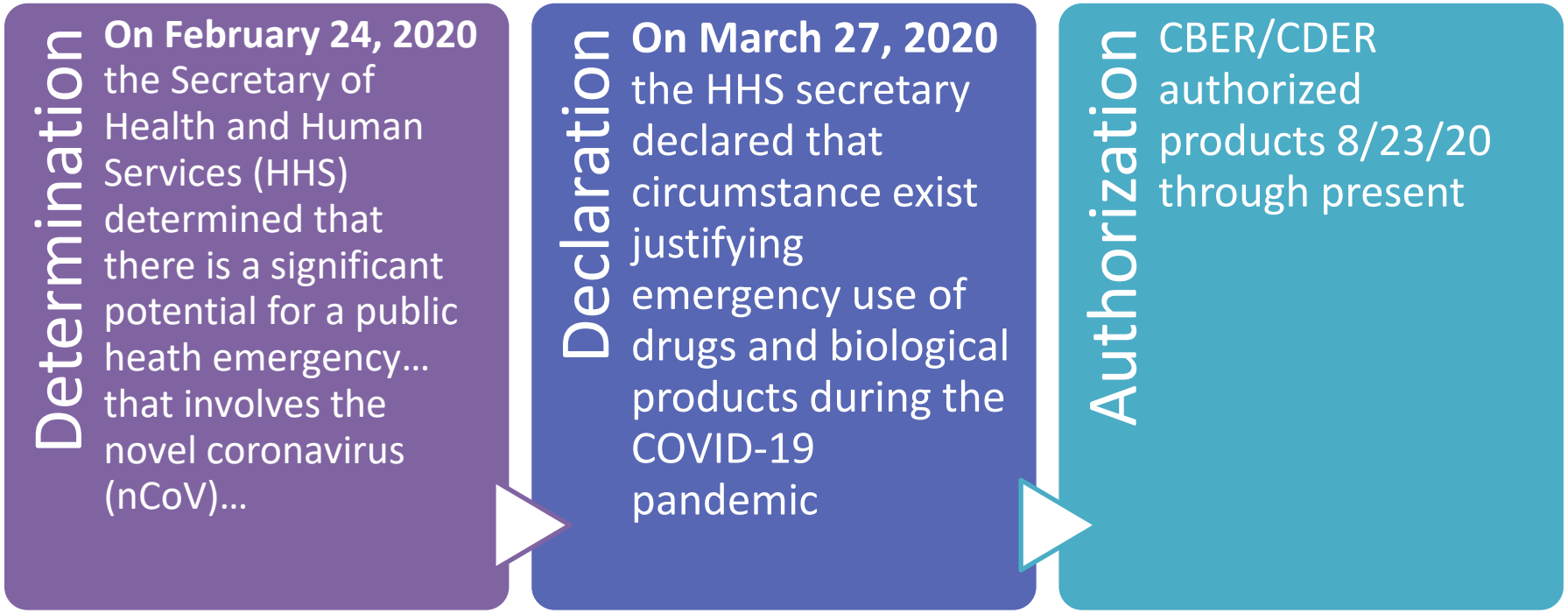
Public Law 115-92 (12/2017)

- Added any agent(s) that might cause life-threatening injuries to US military personnel

EUA Authorization Process



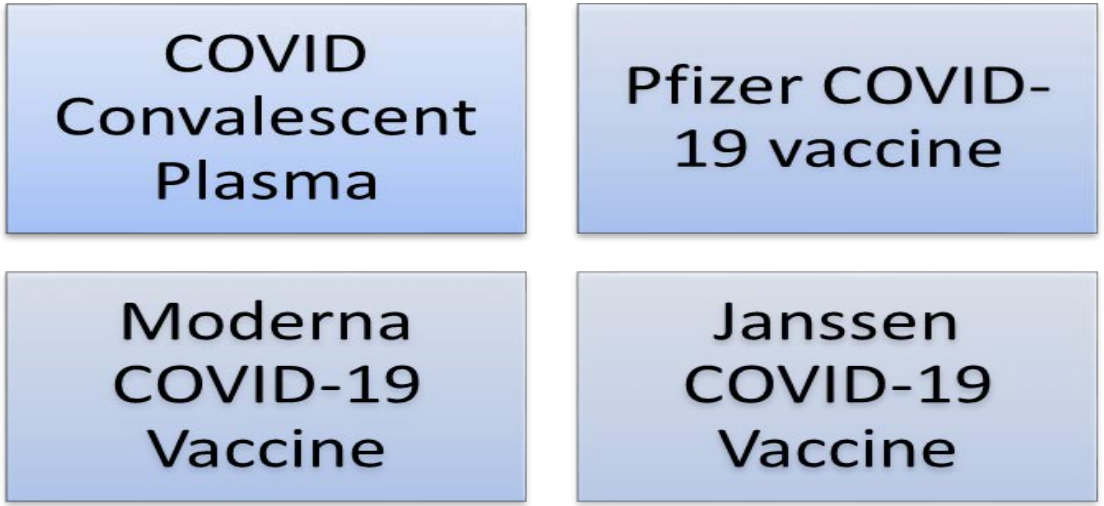
EUA Authorization Process for COVID-19 pandemic



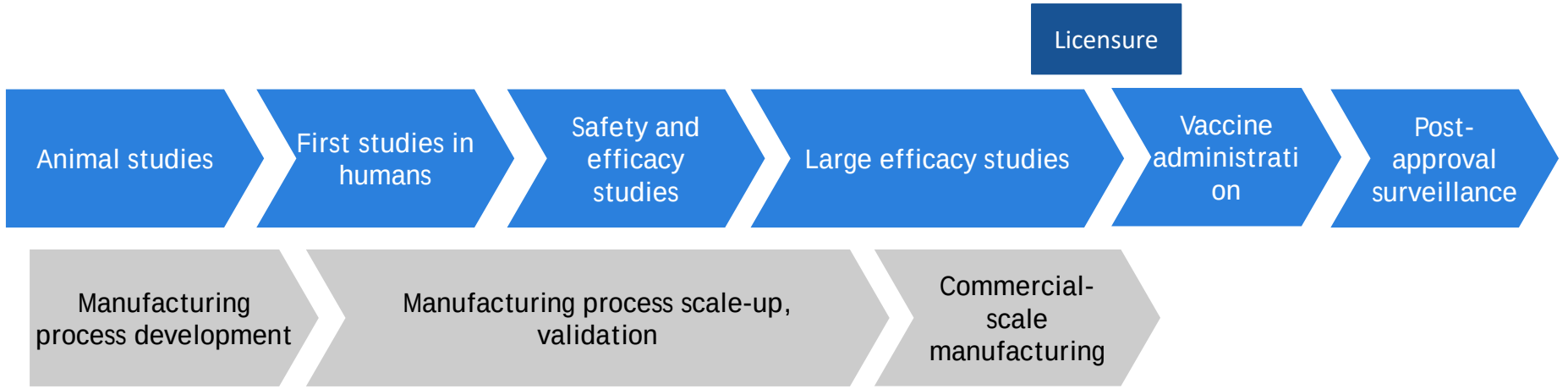
Emergency Use Authorization (EUA)

- 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.

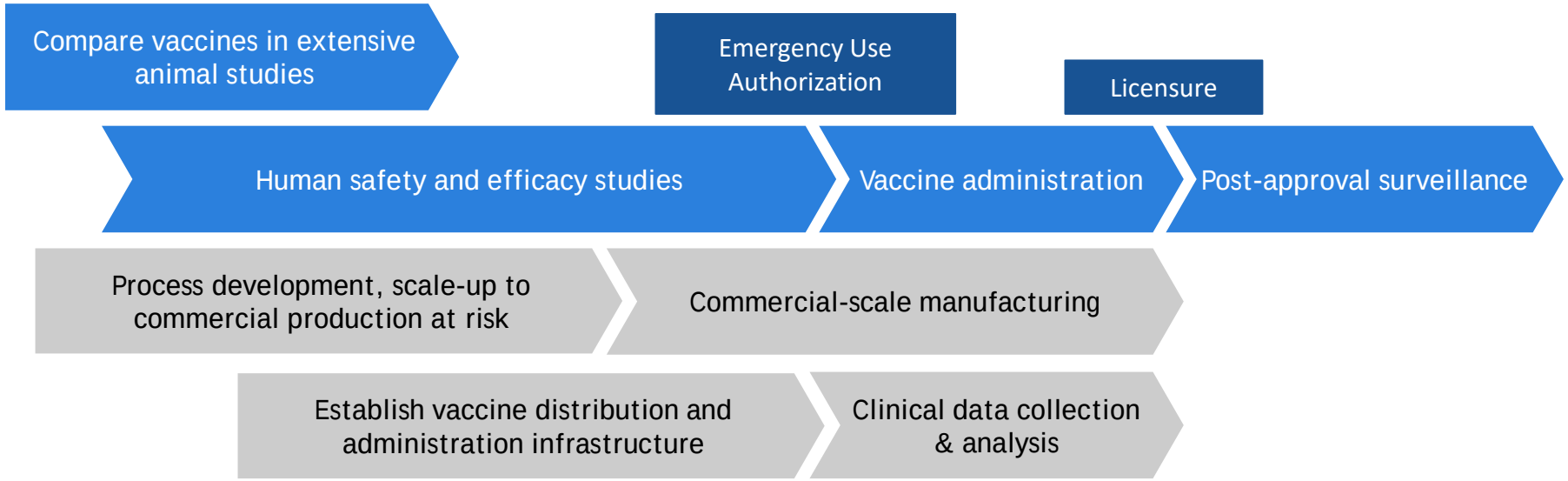
COVID EUAs Authorized by CBER



Traditional Vaccine Development



Accelerated Vaccine Development



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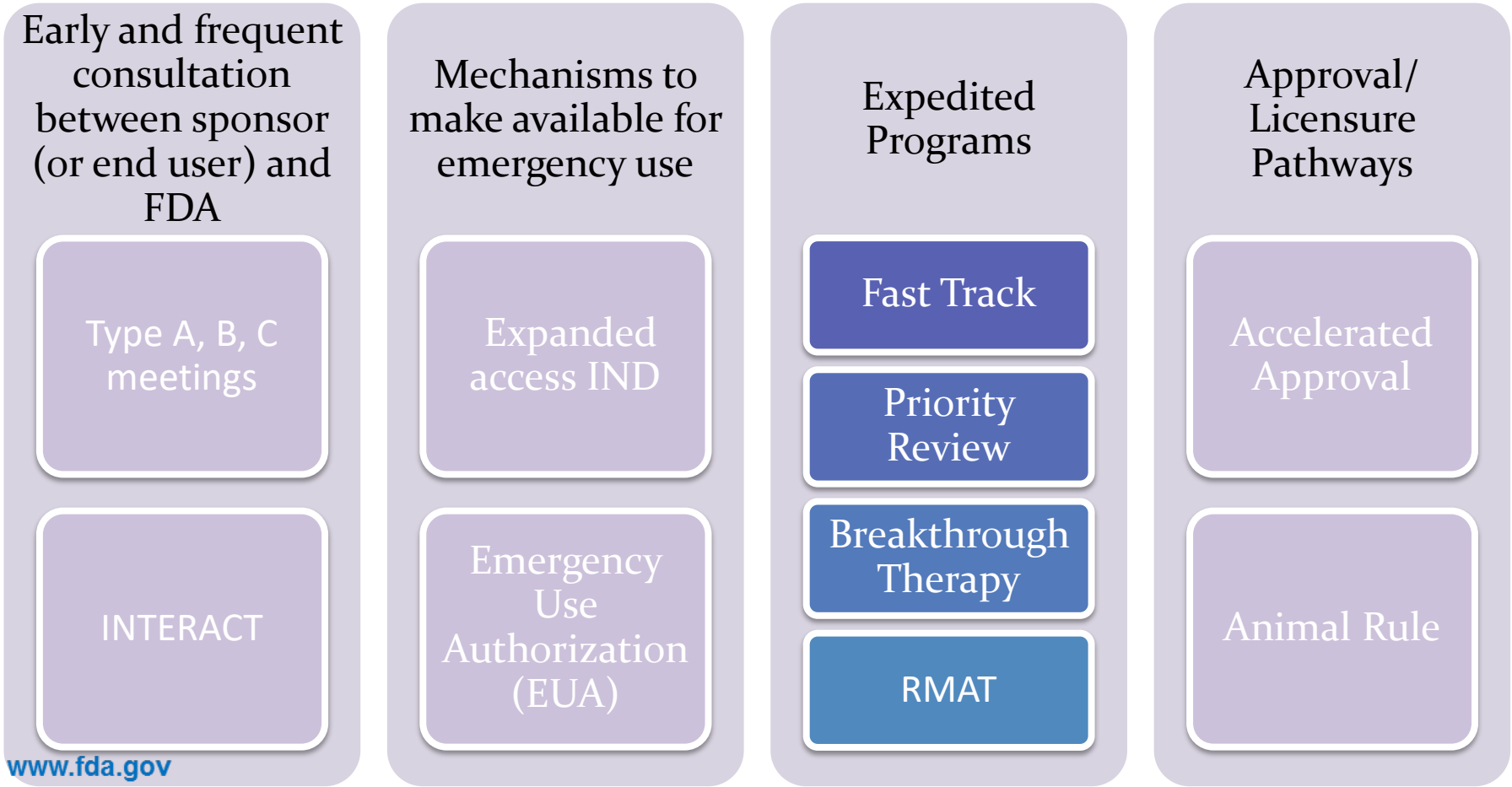

Expedited Programs available during product development

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

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

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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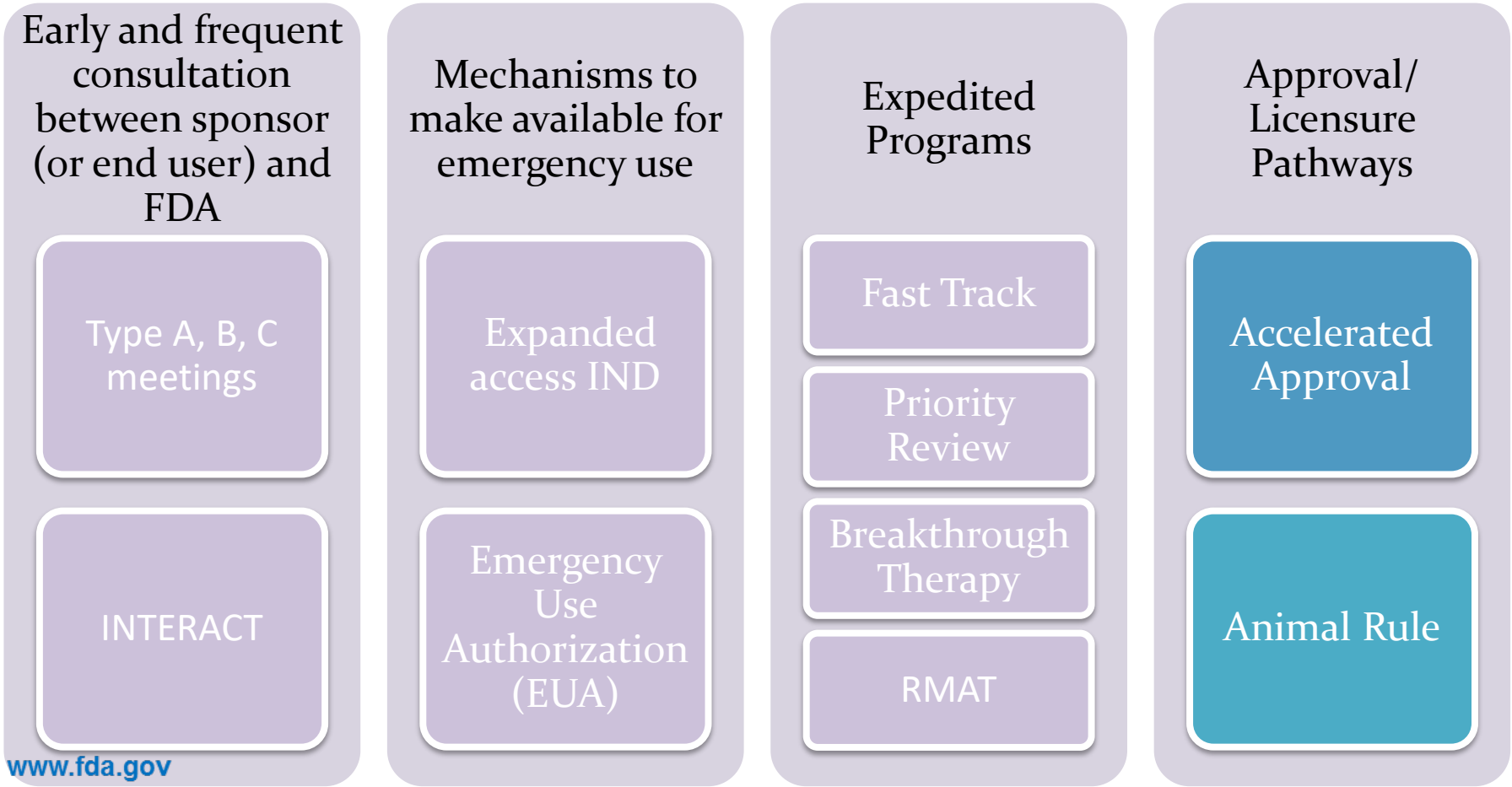

Accelerated Approval

- 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

U.S. FOOD & DRUG ADMINISTRATION

Resources

FDA Websites

- **INTERACT meetings** https://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/ucm611501.htm
- **Emergency Use Authorization**

  https://www.fda.gov/emergencypreparedness/counterterrorism/medicalcountermeasures/mcmlegalregulatoryandpolicyframework/ucm182568.htm
- **Expanded Access INDs**

  https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm
- **RMAT designation**

  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

NDA	New Drug Application	OTC	Over the Counter
BLA	Biologics License Application	CTAP	Coronavirus Treatment Acceleration Program
EUA	Emergency Use Application	PDUFA	Prescription Drug User Fee Act
IVD	In vitro Diagnostics	COVID	**CO**rona **VI**rus **D**isease
IND	Investigation New Drug	AE	Adverse Event
GLP	Good Laboratory Practice	CBRN	Chemical Biological Radiological Nuclear
RMAT	Regenerative Medicine Advanced Therapy	PAHPRA	Pandemic and All-Hazards Preparedness Reauthorization Act
MCM	Medical Countermeasure	INTERACT	**IN**itial **T**argeted **E**ngagement for **R**egulatory **A**dvice on **C**BER produc**T**s
CBER	Center for Biologics Evaluation and Research	CDER	Center for Drugs Evaluation and Research
FDA	Food and Drug Administration	DHS	Department of Homeland Security
USG	United States Government	HHS	Health and human Services
CDC	Centers for Disease Control and Prevention	DoD	Department of Defense
EOP	End of Phase		