

AACT & ATA Webinar

Overview of Non-Clinical Safety Assessment for Antiviral Drugs and Vaccines Development

May 26, 2021

Moderators:

Weimin Chen, PhD;
Yongbin Zhang, PhD

Speakers:

Hanan Ghantous, PhD
Nabil Al-Humadi, PhD



Agenda

- ❖ Introductions
- ❖ Overview of Nonclinical Safety Assessment for Antiviral Drugs
- ❖ Toxicology Investigation During Vaccine Development
- ❖ Q & A section

Introduction of Invited Speaker



Hanan Ghantous Ph.D., DABT

Dr. Ghantous is the Division Director of Pharmacology/Toxicology for Infectious Diseases. She joined the US FDA as a reviewer in 2001 and was the supervisor at the Division of Antiviral Products, CDER, since 2007. Dr. Ghantous has served on several US FDA committees, has been involved in writing Guidance documents, and has represented the Agency at various public forums. She received a PhD in toxicology from the University of Uppsala, Sweden, and a postdoctoral training at the University of Arizona. Dr. Ghantous has over 30 years of combined experience in general and regulatory toxicology. She has been a member of SOT since 1989, served on many committees and specialty sections, and was the president of the ABT board for 2013–2014. She has been a member of ACT since 2000, served on many committees and Council over the years, and was the President of ACT in 2016.



OVERVIEW OF NONCLINICAL SAFETY ASSESSMENT FOR ANTIVIRAL DRUGS

Hanan Ghantous, PhD, DABT
FDA/CDER/OND/DPT-ID

Presentation Overview

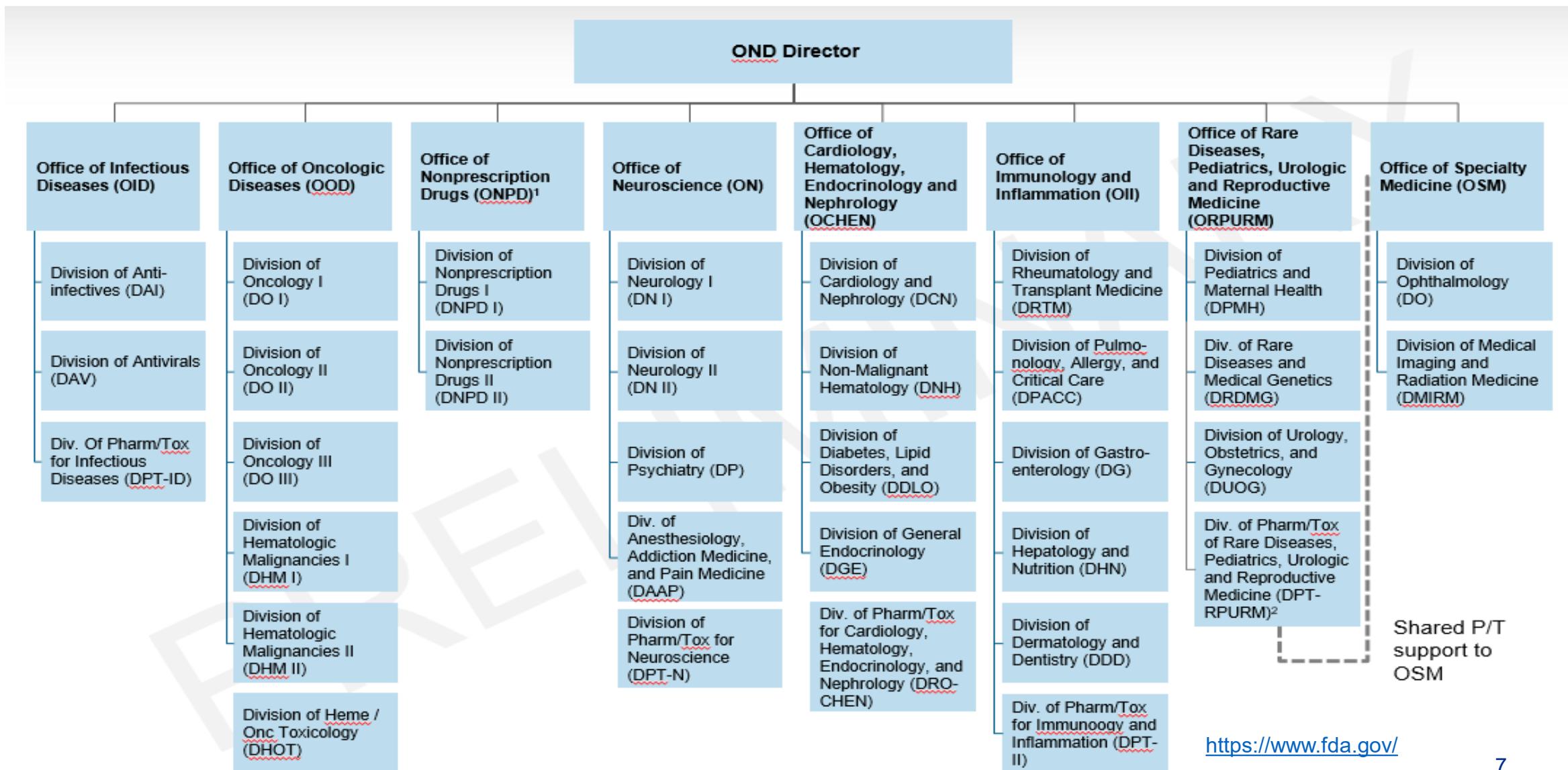
Reorganization of Pharmacology/Toxicology Structure in OND
Overview of Drug Development
Nonclinical Regulations and Guidance Documents
Coronavirus Disease 2019 (COVID-19) Public Health Emergency
FDA/CDER Response

CDER Mission Statement

Promote and protect public health by assuring that safe and efficacious drugs and biologics are available to Americans

CDER accomplishes this mission by reviewing data that sponsors submit to support the safe and efficacious use of new drugs in humans

Reorganization of Clinical and Pharm/Tox Structure in OND



Sources of US FDA Regulatory Authority

Laws passed by Congress

- Federal Food, Drug, and Cosmetic Act of 1938 (sulfanilamide and diethylene glycol)
- Kefauver Harris Amendment of 1962 (“Drug Efficacy Act”) (Thalidomide and birth defects)
- Prescription Drug User Fee Act of 1992 (PDUFA; renewed 1997, 2002, 2007, 2012, and 2017)
- Food and Drug Administration Modernization Act of 1997 (FDAMA) (6 M pediatric exclusivity and Fast Track)
- Food and Drug Administration Amendments Act of 2007 (FDAAA) (REMS)
- Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) (Biosimilars)

Code of Federal Regulations (CFR)

- 21 CFR 58—Good Laboratory Practice for Nonclinical Laboratory Studies
- 21 CFR 312—Investigational New Drug Application
- 21 CFR 314—Applications for FDA Approval to Market a New Drug

Manual of Policies and Procedures (MaPPs)

Guidance for Industry (US FDA, ICH)

Types of New Products Regulated by US FDA/CDER

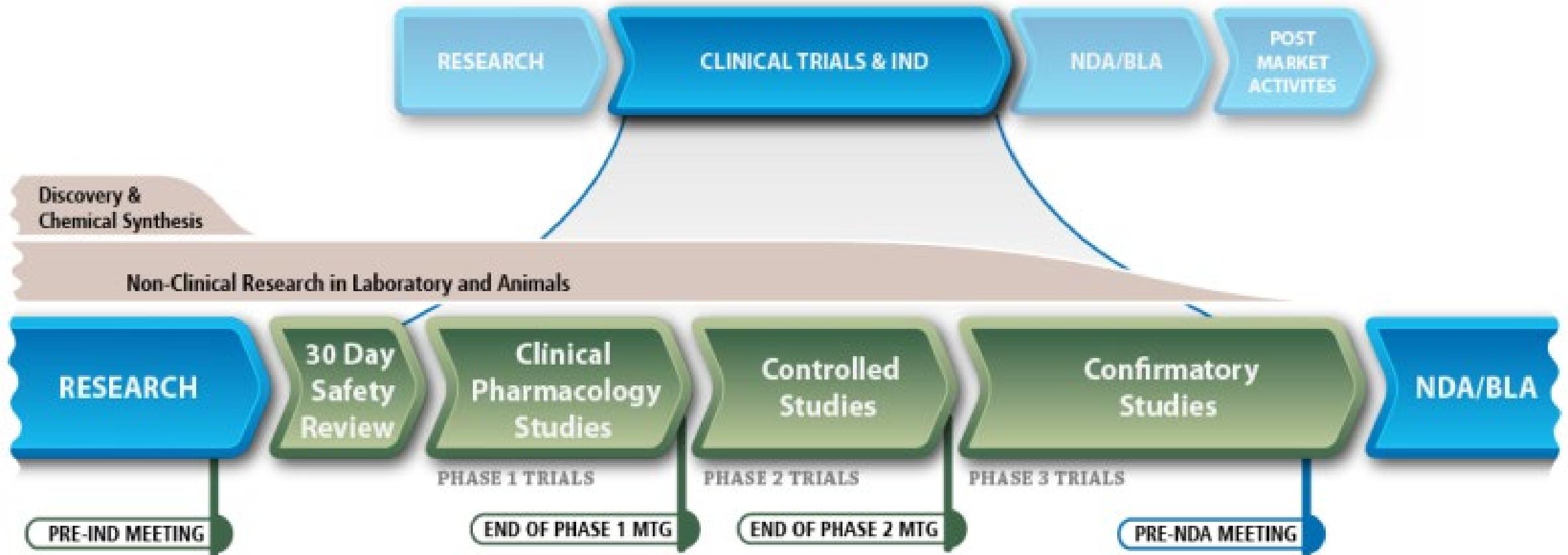
New entities

- Small molecule, biologic, other
- Not previously tested in humans

New formulations (reformulations) for previously tested/approved drugs

Combinations of previously approved drugs

The Drug Development/Review Process



Stages of Drug Development

- Pre-IND
- IND
 - Phase 1 clinical trials
 - Phase 2 clinical trials
 - Phase 3 clinical trials
- NDA/BLA
- Post-marketing

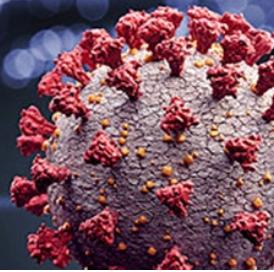
Testing of New Drugs for Safety and Efficacy

US FDA/CDER does not test new drugs

- Sponsors and/or their contractors conduct studies (e.g., nonclinical, clinical, CMC) needed to support drug development
- Sponsors submit study reports to US FDA/CDER for review

Sponsors

- Pharmaceutical, biopharmaceutical companies, academic, government institutions, and others



Coronavirus (COVID-19) Pandemic

- December 31, 2019: WHO learns there is a cluster of 'viral pneumonia' cases in Wuhan, People's Republic of China.
- January 9, 2020: CHINA CDC report a novel coronavirus as the causative agent (SARS-CoV-2)
 - Rapid transmission
 - Severe Respiratory Symptoms
 - Lethal
- US FDA has on-going working relationship with WHO and other federal health partners academia and industry
 - Meet regularly
 - On- going medical countermeasure projects (Ebola, MERS, SARS, etc.)
 - Open communication alerted FDA of concern

COVID-19 Public Health Emergency

FDA/CDER's key priorities during this public health emergency include:

- Supporting the development of novel drugs
- Repurposing of existing therapies
- Monitoring the nation's supply of medicines
- Taking action to mitigate or prevent drug shortages
- Working to help ensure the health of all patients

[cders-work-protect-public-health-during-covid-19-public-health-emergency](#)

Coronavirus (COVID-19) Pandemic



- **Early Division of Antivirals response**
 - Survey current portfolio of coronavirus antivirals
 - Identify investigational drugs that may have activity
 - Request any outstanding toxicity data needed to open an IND immediately
 - Reach out to Sponsor of potentially useful drugs
 - Discuss plans to rapidly test in humans
 - Coordinate with CDC and NIH
 - FDA launched a new program:

Coronavirus Treatment Acceleration Program (CTAP)

Coronavirus Treatment Acceleration Program

Goal: Move potential treatments into patients as quickly as possible

- Engage in public-private partnerships
 - On-going relationships with drug manufacturers and clinical trial research sites
 - Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Partnership
- Provided guidance to innovators and researchers
 - Recommendations for submitting applications
 - Enhanced communication and coordination with Review Division
 - Provide transparency for Emergency Use

Development of Potential COVID-19 Therapeutics

<https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap>



610+

Drug development programs in planning stages¹



9

COVID-19 treatments currently authorized for Emergency Use³



450+

Trials reviewed by FDA²



1

Treatments currently approved by FDA for use in COVID-19

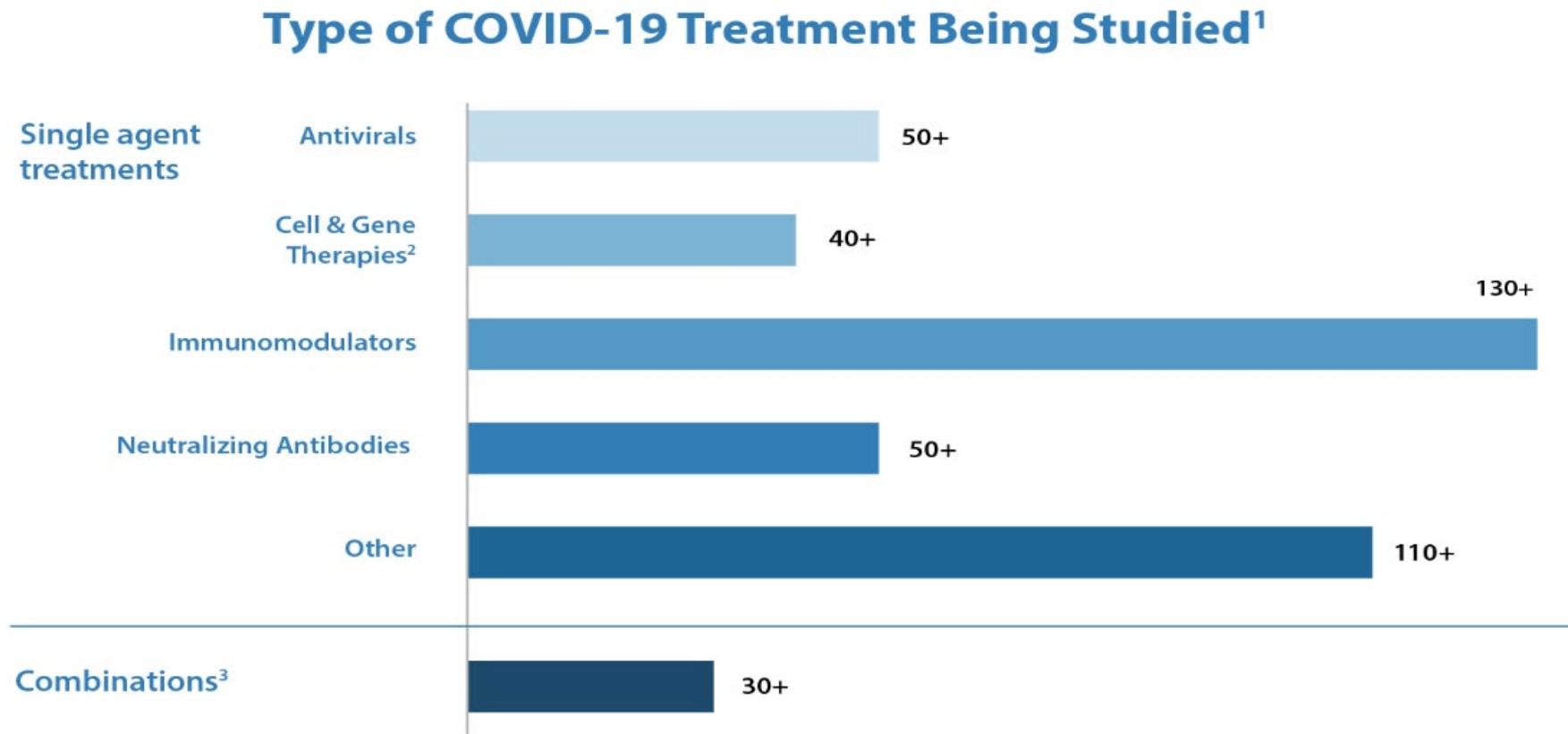
¹ Active Pre-INDs. Excludes vaccines.

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.

Development of Potential COVID-19 Therapeutics

<https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap>

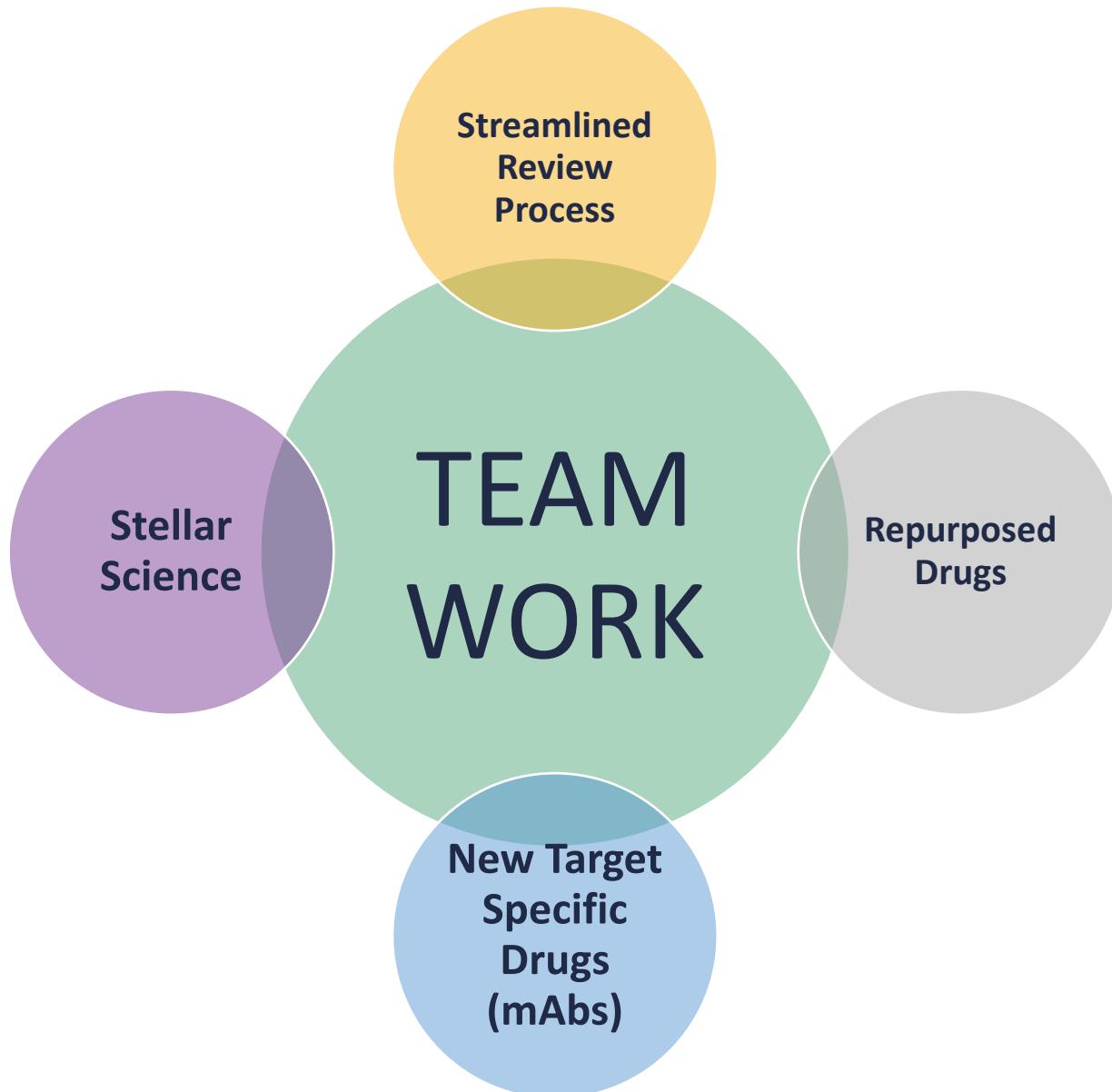


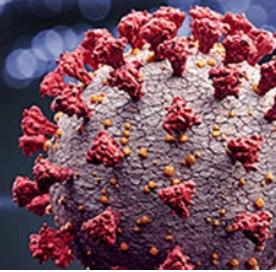
¹ Corresponds to number of safe to proceed INDs. Excludes INDs related to vaccines

² For additional information, please see [Cellular & Gene Therapy Products](#)

³ Includes INDs with more than one product

How was this accomplished?





Streamlined Review Process

- Pre-Investigational New Drug (pre-IND) Consultation
 - Identify issues that may hinder development
 - Communication between Sponsor and Agency allowing more efficient IND review
- Investigational New Drug (IND) Application
 - Determine the most essential toxicity data needed to support a safe trial
 - Encouraged IND to be opened in a life-threatening patient population (Phase 2) rather than healthy volunteers (Phase 1)
- Emergency Use Authorization (EUA)
 - Establish minimum criteria to demonstrate a clinical benefit
 - Determine outstanding nonclinical toxicity data needed
 - Develop labeling for use
- New Drug Application (NDA) or Biologic License Application (BLA)
 - Priority Review
 - Rolling Review



CDER/OND Nonclinical Perspective

- **General Nonclinical Considerations for pre-IND for COVID**

- Pre-IND consultation is recommended prior to submission of an IND
- Summary of the available nonclinical pharmacology and toxicology data
 - Standard toxicology with toxicokinetic endpoints
 - Evaluation of the potential for reversibility of safety findings
 - Any relevant activity data
- Proposed duration of the clinical trial
- Intended route of administration
- All drug substance and formulation data, including any differences in clinical and toxicology lots

Nonclinical Assessment of Safety

- **To Open an IND for Small Molecule Drugs**

A battery of nonclinical studies to support a first-in-human (FIH) trial should include:

- **STANDARD SAFETY PHARMACOLOGY STUDIES** (e.g., cardiovascular, respiratory, and central nervous system assessments) but can be incorporated into general toxicology studies
- **GENERAL TOXICOLOGY STUDIES** in two species (at least one nonrodent)
- **GENETIC TOXICOLOGY**, including an Ames reverse mutation assay and a second in vitro assessment
- The drug substance used in the toxicology studies should be identical to that proposed for clinical investigation.”



Nonclinical Assessment of Safety

- **To Open an IND for Biological Products**

A battery of nonclinical studies to support a FIH trial should include:

- **SAFETY PHARMACOLOGY STUDIES** (e.g., cardiovascular, respiratory, and central nervous system assessments) but can be incorporated into the general toxicology study
- **GENERAL TOXICOLOGY STUDY** in a relevant species
- **TISSUE CROSS-REACTIVITY ASSAY** in human tissue
- Sponsors should consider studies that assess enhanced potential for toxicity in an animal model of infection
- The drug product that is used in the definitive pharmacology and toxicology studies should be comparable to the product proposed for the initial clinical studies



Antiviral Drugs

- **Additional Recommendations for Demonstrating Activity of Antiviral Drugs**
 - Cell culture antiviral activity data (i.e., half maximal effective concentration (EC_{50}) value and therapeutic index)
 - Findings in any animal model of disease [Note: these activity data may not reliably predict benefit in human patients]
 - The sponsor will need to establish the antiviral effectiveness of the drug
 - Studies should include viral indices
 - Assessment/characterization of the virus
 - Viral resistance profiles



Drugs with Uncommon ROA

- **Additional Recommendations for Inhalational Drugs**

- A pre-IND meeting request for a drug for inhalation (e.g., metered dose inhaler, nebulization) should include data to support use of the proposed drug for this route of administration in humans
 - Details of the proposed formulation (including drug product excipients)
 - A description of the device for administration (including current use)
 - GLP toxicology studies with the intended route of administration (inhalation)
- The GLP toxicology studies should support the proposed dose and duration
 - Reference: For general information, see Tepper, J. S., et al., 2016, Symposium Summary: “Breathe In, Breathe Out, It’s Easy: What You Need to Know About Developing Inhaled Drugs,” *Int J Toxicol*, 35(4): 376–392

Additional Clinical Guidance for COVID-19

- Assist sponsors in the clinical development of drugs for the treatment or prevention of COVID-19. (Preventative vaccines and convalescent plasma are not within the scope of this guidance.)
- Focuses on the development of drugs with direct antiviral activity or immunomodulatory activity. However, the recommendations in this guidance may be applicable to development plans for drugs for COVID-19 with other mechanisms of action
- Clinical Considerations:
 - Patient population
 - Trial design
 - Efficacy endpoints
 - Safety considerations
 - Statistical considerations

COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry

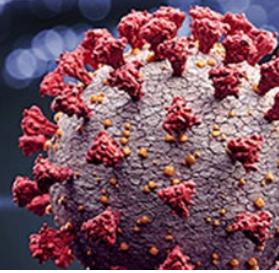
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2020
Clinical/Medical

Created a Streamlined Pre-IND and IND Review Process

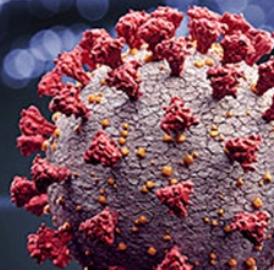


Though the timeline was shortened, the Agency's high safety standards were maintained



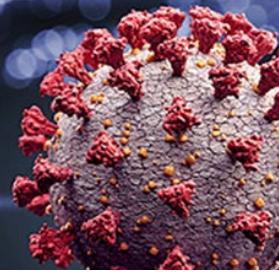
Repurposed Drugs

- Many of the proposed drugs for COVID 19 were previously approved for other indications or under investigation for another indication
- Nonclinical and clinical safety data was already available to aid in the risk/benefit determination
- Remdesivir is an example of an investigational product repurposed for COVID 19



Remdesivir

- Pre-IND open in Feb 2015 for treatment of Ebola virus disease
 - A nucleoside inhibitor for the Ebola Virus
 - A complete Nonclinical package
- IND was received July 2015 for Ebola
 - Allowed to proceed August 2015
 - Based on early results of the Ebola Trial, it was decided that it will no longer be used for first line Ebola treatment
 - However, it was the Agency's first consideration for Covid because of the MOA



Remdesivir for COVID?

- Generic MOA
 - Should work for all RNA viruses
 - Data demonstrating activity for SARS and MERS
- Status of Nonclinical Program
 - All toxicology studies to support approval were submitted and reviewed by 2019
- No additional data were necessary to support IND for COVID
- IND was submitted for COVID in February

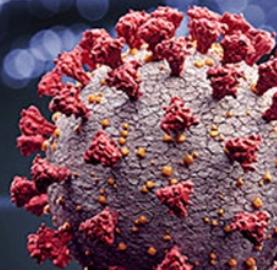
Remdesivir Receives Fast Track Designation

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
May 2014
Version 1
OMB Control No. 0918-0762
Expiration Date: 04/30/2021 (Note: Expiration date updated 06/21/2020)
See additional PRA statement in section X of this guidance

- Expedited Development/Review
 - More frequent interactions with the review team and sponsor
- EUA Determination
 - March 27, 2020: HHS Secretary declaration
 - Scientific evidence that benefits outweigh risks
- Conditions of Authorization
 - Fact Sheet for Health Care Providers
 - Information for any Recipients
 - Monitoring/Reporting Adverse Events
- NDA Submission (Rolling Review), April 2020
 - Consider reviewing portions of marketing application before the sponsor submits the complete application (CMC/Tox) (Virology/Clinical)

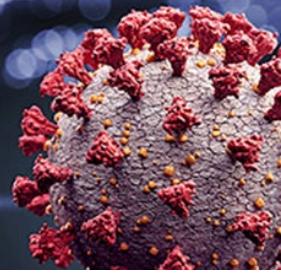
NDA for RDV approved in 10 weeks





New Target Specific Monoclonal Antibodies

- Many newly developed therapies are biologics directed against SARS-CoV-2
- Studies needed to support the use of a mAb with a nonendogenous target:
 - Tissue cross reactivity studies to determine the most appropriate species
 - Short-term safety studies in a single species with a recovery period
 - Duration should cover the human exposure period therefore, the frequency of administration in animals may be increased compared to the proposed schedule for the human clinical studies in order to compensate for faster clearance rates
 - Safety pharmacology parameters can be included
 - Recovery period should allow for clearance of the mAb (~5 half-lives)



Can You Go into Clinical Trials?

Small Molecule

Biologic

Drug 1



Approved for use



Drug 2



In development for another disease



Under IND



Drug 3

New entity

Some animal/in vitro data



MOA?

Preliminary Tox Data?



Species Relevance?

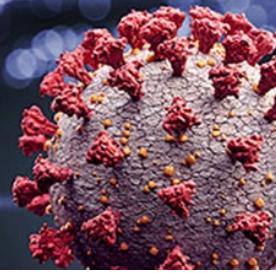
Drug 4

New entity

No data



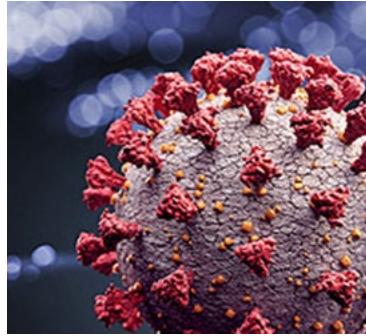
Off Target Potential?



Teamwork

- Externally
 - Across Federal Government Agencies
 - With Innovators and Scientist
- Internally
 - Division of Antivirals (DAV) and Division of Pulmonology, Allergy, and Critical Care (DPACC)
 - Reviewers (clinicians, pharmacologists, toxicologist, chemists, statisticians) from all CDER divisions assisted with reviews





Summary – How We Got It Done

- Coronavirus Treatment Acceleration Program (CTAP) issued guidance
- Instituted a streamlined review process without compromising our high safety standards
- Determined the most essential nonclinical toxicology assessments needed to support COVID-19 therapies
- Repurposed drugs that were approved or under investigation for other indications
- Use of new biologics that specifically target the virus
- Teamwork within the agency and with outside stakeholders

Acknowledgments

- Arianne Motter, PhD, DABT
- John Dubinion PhD
- Ilona Bebenek, PhD, DABT
- DPT-ID DAV Reviewers



COVID-19 and CTAP Resources

- <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders>
- https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap?utm_campaign=FDA%20posts%20an%20updated%20CTAP%20webpage&utm_medium=email&utm_source=Eloqua#activities
- <https://www.fda.gov/drugs/emergency-preparedness-drugs/coronavirus-covid-19-drugs>

Guidances and other information for industry on developing COVID-19-related treatments

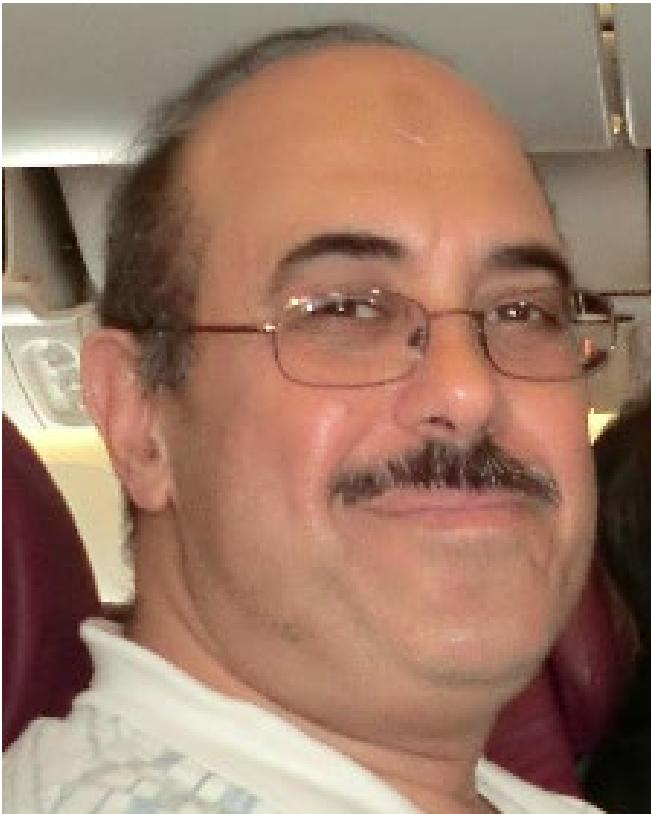
- Information and guidance on how to efficiently engage with FDA and expedite clinical trial initiation may be found at: [Drug Development Inquiries for Drugs to Address the COVID-19 Public Health Emergency](#)
- General advice concerning the development of COVID-19 treatments may be found at: [COVID-19: Developing Drugs and Biological Products for Treatment or Prevention](#)
- The availability of COVID-19 treatments under an Emergency Use Authorization may be found at: [FDA's Emergency Use Authorization \(EUA\)](#)
- General advice concerning pre-IND meeting request content for COVID-19 treatments is provided at: [COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products](#)
- Guidance on development of monoclonal antibody products targeting SARS-CoV-2 may be found at: [Development of Monoclonal Antibody Products Targeting SARS-CoV-2, Including Addressing the Impact of Emerging Variants](#)
- Guidance on development of COVID-19 treatment and prevention products : [COVID-19: Developing Drugs and Biological Products for Treatment or Prevention](#)

Contact information for Sponsors

- Sponsors of **CDER** regulated therapeutics should send COVID product development inquiries to COVID19-productdevelopment@fda.hhs.gov
- Sponsors of **CBER** regulated therapeutics should send COVID product development inquiries to CBERProductJurisdiction@fda.hhs.gov. Additional information about CBER-Regulated Therapeutics and CTAP can be found at [Coronavirus \(COVID-19\) | CBER-Regulated Biologics](#)
- Sponsors who are unsure of whether their drug is CDER- or CBER-regulated should make initial contact for COVID-19 drug development by contacting FDA at COVID19-productdevelopment@fda.hhs.gov
- Medical devices do not fall within the CTAP program. Device sponsors should contact CDRH directly at CDRH-EUA-Templates@fda.hhs.gov for in vitro diagnostics (IVDs) and CDRH-NonDiagnosticEUA-Templates@fda.hhs.gov for non-IVD medical devices



Introduction of Invited Speaker



Nabil Al-Humadi Ph.D.

Dr. Al-Humadi is a pharmacologist/toxicologist at the Center of Biologics in the US Food and Drug Administration, where he reviews applications for biological licenses. He received his master's degree and doctorate in pharmaceutical sciences from West Virginia University in 1992 and 2002, respectively. He has more than 30 years combined government and industry experience in toxicology. Dr. Al-Humadi has served on the Neurotoxicity assessment subcommittee [Member since 2014], Pharmacology/Toxicology working group [Co-Chair, 2013-present], and CBER Committee for Promotion of Researchers-Reviewers (2017-present). He presented more than 50 posters in scientific meetings and published more than 12 papers in peer reviewed journals. Dr. Al-Humadi's recent publication is a review paper in Vaccine journal titled "Pre-Clinical Toxicology Considerations for Vaccine Development". Also, Dr. Al-Humadi's current publication is a chapter "pre-clinical toxicology of vaccines" in "comprehensive guide to toxicology in preclinical drug development" book. Currently, Dr. Al-Humadi is writing a second chapter in a book titled "Animal Models for Infectious Diseases". He has been a full member of the SOT since 1992.



Toxicology Investigation During Vaccine Development

**Nabil Al-Humadi, PhD
OVRR/CBER**

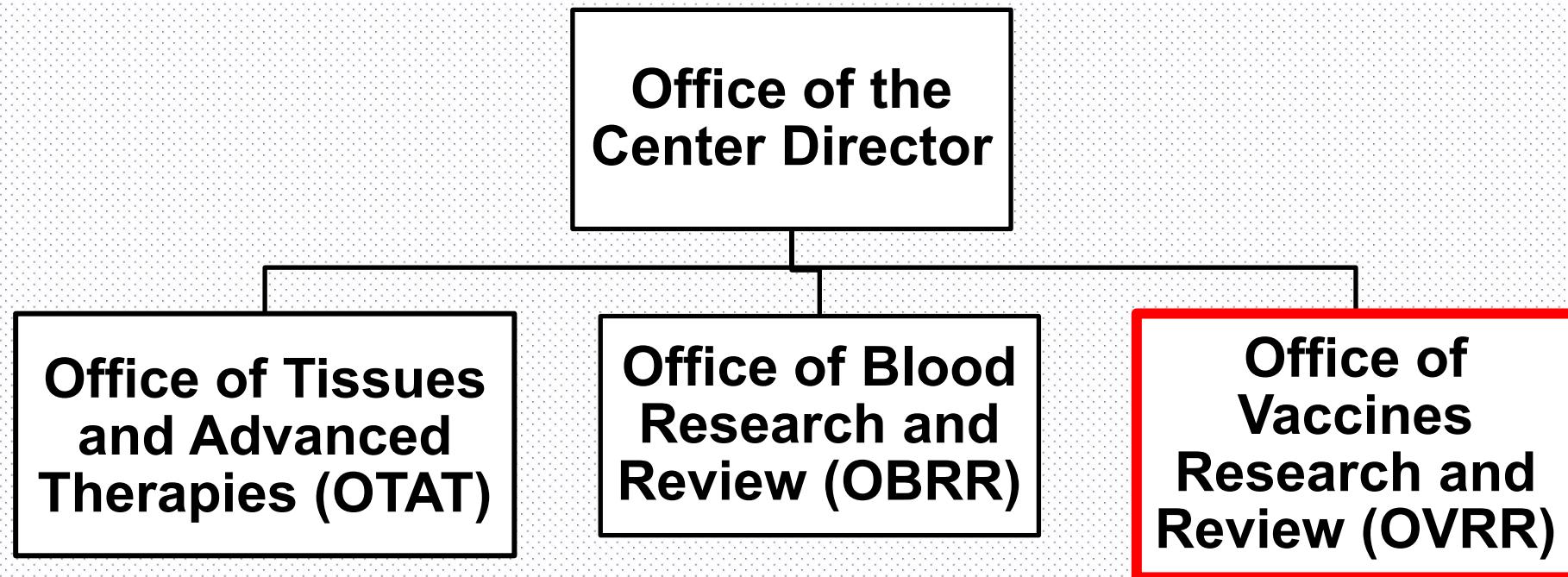
***Disclaimer: This presentation reflects the views of
the author and should not be construed to
represent FDA's views or policies.***

The Process of Vaccine Development

Includes:

- 1- Pre-Clinical Investigation for Safety
- 2- Phases 1, 2, and 3 Clinical Trials
- 3- Biological License Application (BLA) Submission
- 4- Phase 4 (Post-Marketing)

CBER Product offices



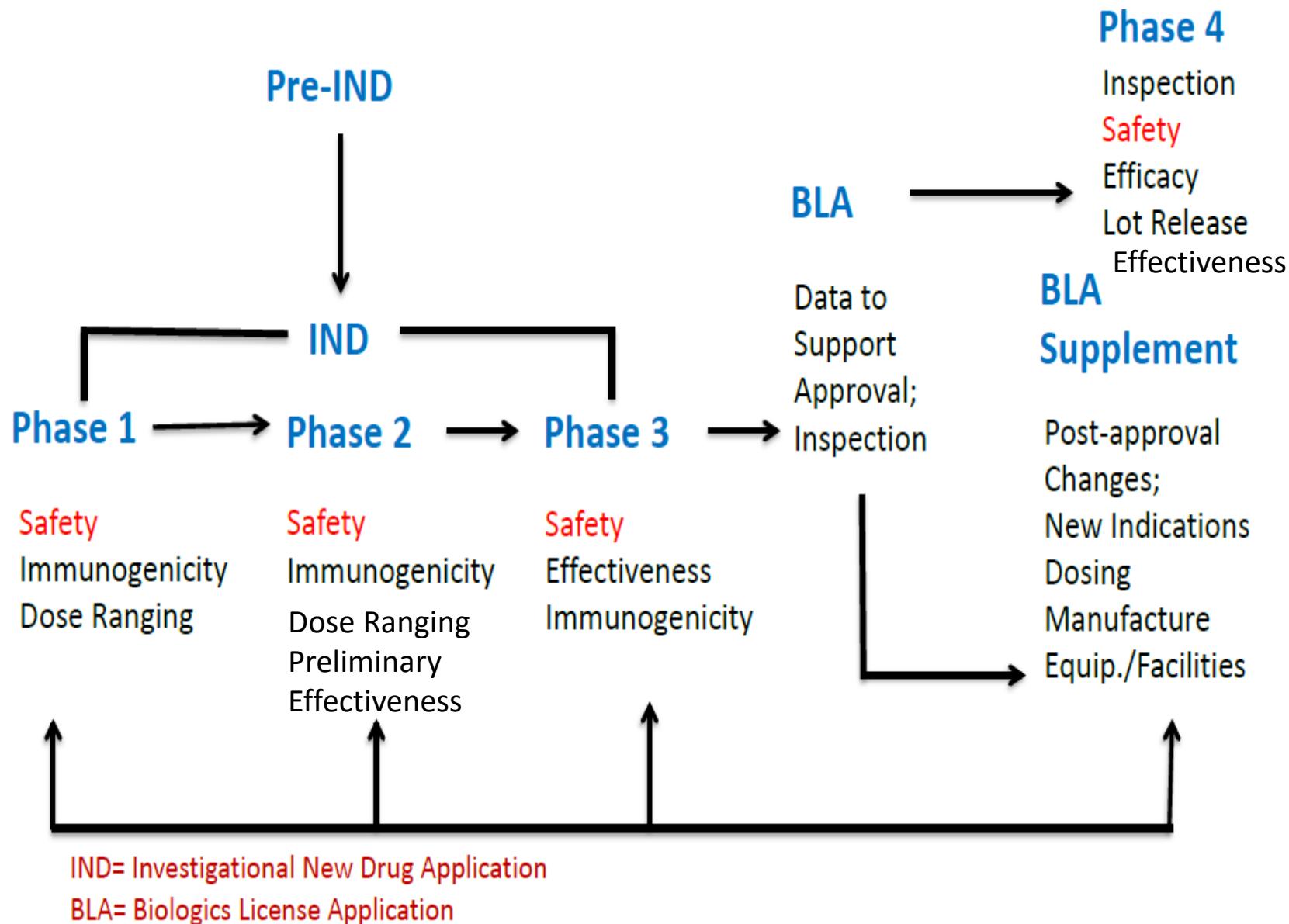
OVRR Regulates the Following:

- **Vaccines for Infectious Diseases**
- **Allergenics**
- **Live Biotherapeutic Products**
- **Bacteriophage Therapeutic Products**
- **Skin Test Antigens**

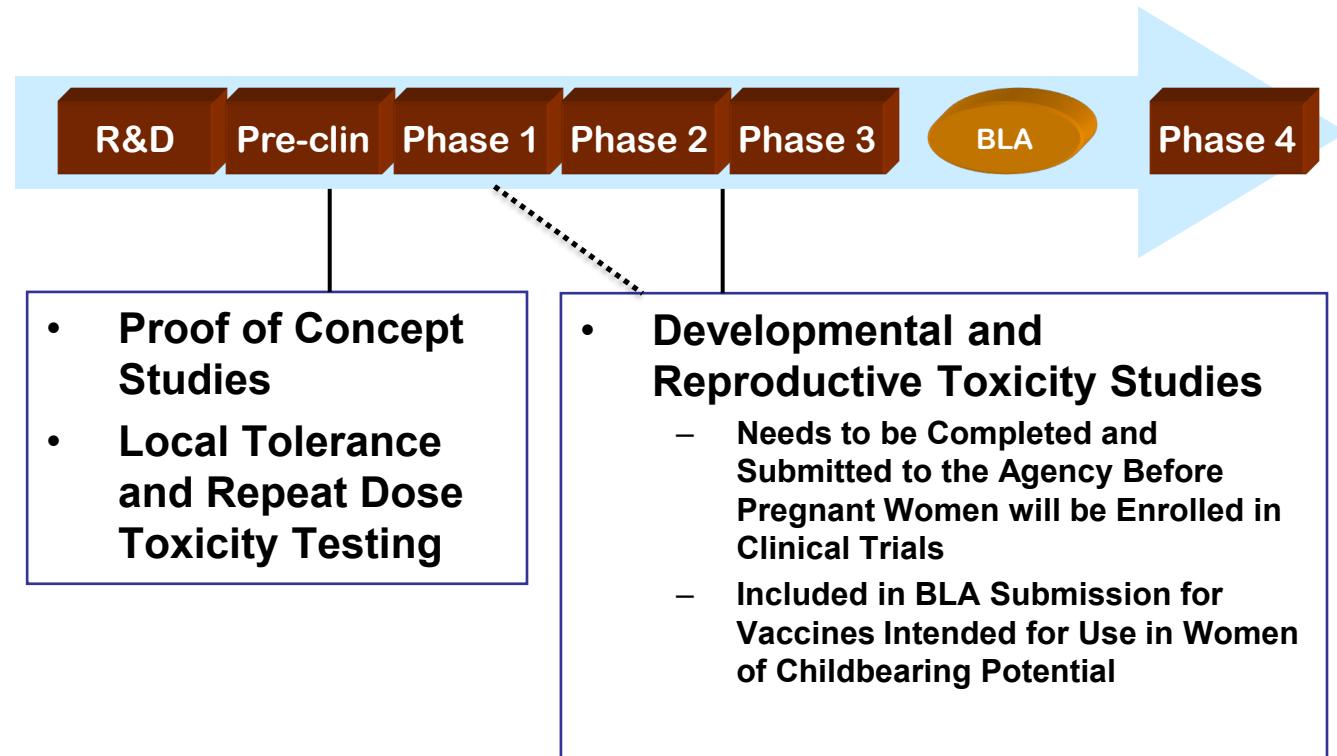
Vaccine Types

- **Live Attenuated**
- **Inactivated**
- **Toxoid**
- **Polysaccharide/Conjugated**
- **Peptide**
- **Virus Like Particles (VLPs)**
- **Proteins**
- **DNA and mRNA**
- **Replicating/Non-Replicating Vectors**

Vaccine Development



Vaccine Development: Timing of Toxicity Studies



From IND Regulations [21 CFR 312.22 (a)]

FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety. Therefore, although FDA's review of Phase 1 submissions will focus on assessing the safety of Phase 1 investigations, FDA's review of Phases 2 and 3 submissions will also include an assessment of the scientific quality of the clinical investigations and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval.

Product Development Process

- Inspiration
- Bench/Proof of Concept Studies
- Toxicology/Animal Testing
- Clinical Testing (Pilot/Pivotal)
- Pre-Market Review & Product Approval
- Commercial Use (Post-Market Studies)
- Refinement (e.g., New Indications, New Populations, CMC Changes)

Inducing an Immune Response

- B Cells and Antibodies
- CD8⁺ T Cells
- CD4⁺ T Cells

Humoral and Cellular Responses

Vaccines Prevent Infections or Interfere with the Pathogenesis of Infectious Diseases by:

- Neutralizing Viral Replication, e.g., Preventing Viral Binding and Entry into Cells
- Enhancing Clearance through Macrophages and Neutrophils
- Activating the Complement Cascade and Antibody-Dependent Cellular Cytotoxicity
- Binding to the Enzymatic Active Sites of Toxins or Preventing their Diffusion

Memory B Cell Responses

- Only Generated During T Cell-Dependent Responses
- Undergo Affinity Maturation During Several Months
- Resting Memory B Cells do not Produce Antibodies
- Rapidly (Days) Differentiate into Antibody Secreting Plasma Cells upon Re-Exposure to Antigen

Vaccine Induced CD4⁺ T Cells

- Production of **IFN- γ , TNF- α /- β , IL-2 and IL-3**;
Participate in Elimination of Intracellular Pathogens Directly (Cytokines) and Indirectly (Activation of CD8⁺T Cells and Macrophages) (Th1 Response)
- Production of **IL-4, IL-5, IL-13, IL-6 and IL-10** for
Elimination of Extracellular Pathogens (Th2 Response)
- **Th1 and Th2 Cells Support B Cell Activation and Differentiation**

Vaccine Induced CD8⁺ T Cells

Reduce, Control, and Clear Intracellular Pathogens by:

- **Directly Killing Infected Cells**
- **Indirectly Killing of Infected Cells Through Antimicrobial Cytokine Release (Macrophage Activation)**

Challenges in Toxicity Assessments of Vaccines

- **Potential Inherent Toxicity of the Active and Inactive Ingredients**
- **Potential Toxicity Linked to the Immune Response to the Vaccine**

Goals in Non-clinical Safety Evaluation

- To Establish a Safe & Immunogenic Dose
- To Identify Potential Toxicities & Target Organs
- To Identify Safety Parameters for Clinical Monitoring
- To Support Entry into Clinical Trials

Potential Safety Concerns Evaluated in Non-Clinical Studies

- General Systemic Toxicity
- Induction of Local Toxicity
- Pyrogenicity
- Autoimmunity or Sensitization
- Paradoxical Disease Enhancement
- Teratogenicity

Types of Non-Clinical Studies for Vaccines

- **Repeated Dose Toxicity Studies**
- **Local Tolerance Studies**
- **Developmental and Reproductive Toxicity Studies**
- **Immunogenicity Studies**
- **Genotoxicity Studies**

Repeat Dose Toxicity Studies for Vaccines

- **Use Same Route of Administration as Planned in Clinical Trial**
- **Use Vaccine from a Lot Manufactured with the Same or Comparable Lot as the One Intended for Clinical Testing**
- **Full Human Dose should be Administered, However, mg/kg is Allowed in Some Instances**
- **One Additional Vaccination (N+1) Relative to the Maximum Number of Doses Planned for the Clinical Trial is Recommended**

Specific Endpoints in Repeated Dose Toxicity Studies



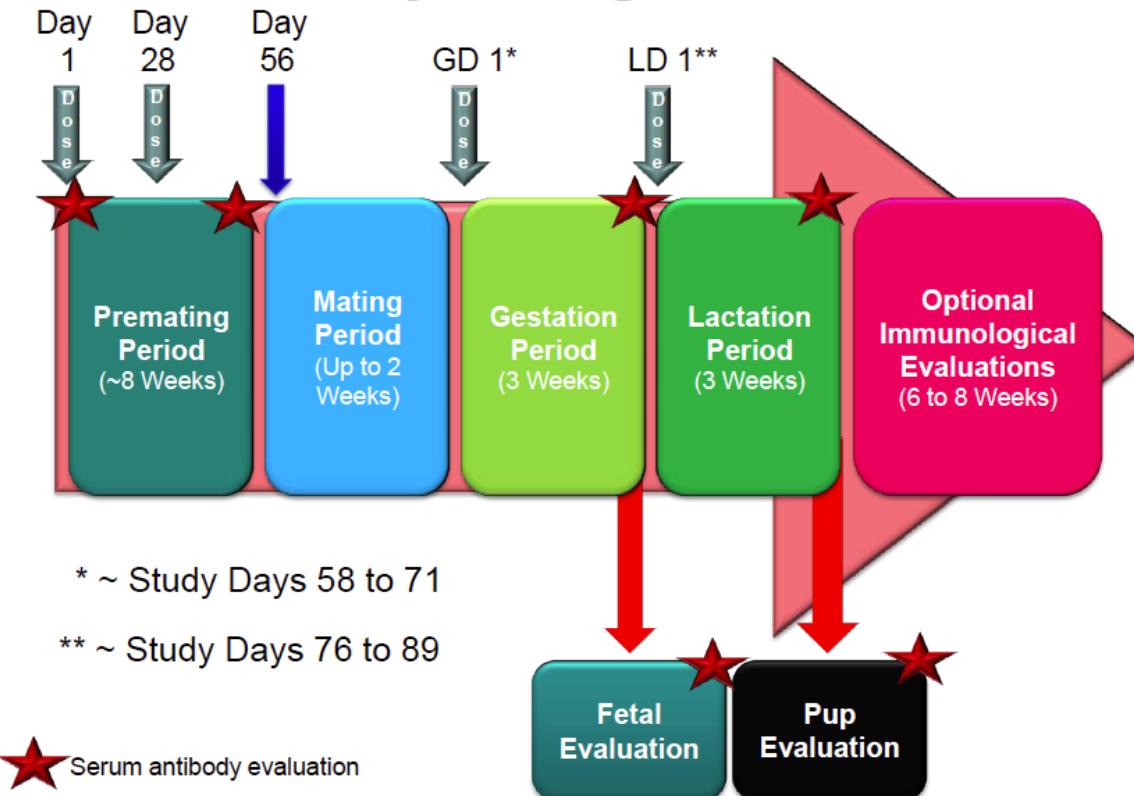
- **Body Temperature: 6 Hours and 24 Hours after Vaccine Administration**
- **Daily Measurement of Food Consumption and Body Weight: 24 to 48 Hours after Dosing**
- **Ophthalmologic Examination**
- **Evaluation of Local Reactogenicity (Draize Scoring)**
- **Evaluation of Vaccine-Specific Immune Response (Humoral and/or Cellular)**
- **Clinical Pathology; Hematology & Clinical Chemistry (Acute Phase Reactants [CRP in Rabbits, A2M in Rats; 24-48 Hours after Dosing] is Recommended)**
- **Macroscopic and Microscopic Examinations**

Considerations for Choosing an Animal Model

- **In General, One Species is Adequate**
- **Adequate Historical Control Data**
- **Animal Model Preferred to be Sensitive to the Targeted Pathogen**
- **Include Sufficient Number of Animals per Sex per Group**
- **Include Rational for Choice of Species**

Developmental and Reproductive Toxicology (DART) Study Design for Vaccines

Case study design



DART Study Design

Pilot Studies to Evaluate Response to Vaccine Study Design:

- **Route of Administration (Mimic Clinical Route)**
- **Maximal Dose Response (Peak Antibody During Period of Organogenesis)**
- **Pre-Mating Treatment, Treatment During Gestation, Postnatal Follow-up**
- **Perform in Compliance with GLP**

DART Study Design (Continued)

Number of Doses:

Depends on Response Onset and Duration

- **Episodic Dosing**
- **Sometimes Dosing of Subgroups at Different Times During Organogenesis**

Difficult to Adjust Vaccine Administrations to Developmental Timelines

DART Study Design (Continued)

Endpoints:

Developmental Toxicity Endpoints Including Evaluation of F1 Generation through Weaning

- **Viability, Resorptions, Abortions, Fetal Body Weight, Morphology, Pup Weight Gain, Nursing Activity, Maternal Effects**
- **ICH S5 (R3) Guideline: Detection of Toxicity to Reproduction for Human Pharmaceuticals**

Divide Study Groups into Subgroups

- **Caesarean**
- **Weaning**

Timing for Toxicology Studies for Vaccines

- **Recommend Formal Pre-IND Meeting Prior to Initiating Preclinical Safety Studies**
- **Study Reports of Proof-of-Concept Studies, Immunogenicity, and Preclinical Toxicology Studies should be Provided Prior to Phase 1 Initiation**
- **Study Report of Reproductive Developmental Toxicology Study should be Submitted Before or with BLA Submission (the Latest) for Vaccines Intended for Use in Women of Childbearing Potential**
- **Additional Toxicology Studies may be Necessary as Product/Clinical Development Continues**

Acknowledgment

Martin David Green, Ph.D.
Claudia Wrzesinski DVM, Ph.D.

Selected Documents Relevant to Nonclinical Evaluation of Vaccines

- **WHO Guidelines on Nonclinical Evaluation of Vaccines (2003)**
- **WHO Guidelines on Nonclinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines (2013)**
- **Guidance for Industry: “Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications” (2006)**
- **Guidance for Industry: “Considerations for Plasmid DNA Vaccines for Infectious Disease Indications” (2007)**

Selected Helpful References:

- **Pre-clinical toxicology considerations for vaccine development**
- <https://pubmed.ncbi.nlm.nih.gov/28916246/>
- **Preclinical Toxicology of Vaccine (Chapter in a Book)**
- [A Comprehensive Guide to Toxicology in Nonclinical Drug Development.](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7054702/) 2017 : 709–735. Published online 2016 Nov 11. doi: [10.1016/B978-0-12-803620-4.00027-X](https://doi.org/10.1016/B978-0-12-803620-4.00027-X)
- **Types of acute phase reactants and their importance in vaccination**
- <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7054702/>



**THANK YOU
QUESTIONS?**

