CDER overview of Non-Human Primate (NHP) use in drug development and pathways for the qualification of New Alternative Methods (NAM)

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Outline

- Overview of FDA's legal and regulatory framework for submitting data to support the safety of investigational drugs.
- Overview of recent NHP studies submitted to CDER
- Overview of the Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program

FDA's legal and regulatory framework for investigational drugs

- The Federal Food, Drug, and Cosmetic Act (FD&C Act) provides a limited exemption to the prohibition on the distribution of unapproved new drugs which is initiated by the submission of an investigational new drug application (IND) by the sponsor of a drug or biological product.

- The law requires that the sponsor submit "[a]dequate information about pharmacological and toxicological studies of the drug involving laboratory animals **or in vitro**, on the basis of which the sponsor has concluded it is reasonably safe to conduct the proposed clinical investigations."

- An IND submission must include a description of the pharmacological effects of a drug, drug disposition, and a summary of the toxicological effects of a drug, including "the results of acute, subacute, and chronic toxicity tests; tests of the drug's effects on reproduction and the developing fetus; any special toxicity test related to the drug's particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); **and any in vitro studies intended to evaluate drug toxicity**."

FDA's legal and regulatory framework for investigational drugs

- FDA's legal and regulatory framework does not dictate the type or design of studies used (whether animal, in vitro, or other tests) to support that a drug considered for clinical investigation is reasonably likely to be safe in humans.

- The areas where non-animal methods, would not be acceptable to support the safety of a drug are not imposed by statute or regulations, but instead by those areas where there are no scientifically valid non-animal methods in existence able to produce the data needed.

- Any non-animal method needs to be backed by science; if a new non-animal method replaces a previously used animal-based method, it should provide information at least as useful as the animal method it replaces.

The following are examples where FDA has worked to accept non-animal methods:

- ICH S10 Photosafety Evaluation of Pharmaceuticals
  - This guidance recommends a stepwise assessment of phototoxicity that can include photochemical reactivity and in vitro assays and no animal studies. This guidance refers to OECD Guideline 432 In Vitro 3T3 NRU Phototoxicity Test, which FDA's Center for Drug Evaluation and Research (CDER) routinely accepts.

- ICH S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals
  - This guidance includes an annex devoted to alternative assays for the evaluation of malformations or embryo-fetal lethality. Specific alternative assays are not described, but the principles for determining when an assay is appropriately qualified to support the risk assessment of a drug product are explained.

- ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk
  - This guidance describes the use of computational methods (Quantitative Structure Activity Relationships) for the assessment of mutagenic potential of drug impurities.

The following are examples where FDA has worked to accept non-animal methods:

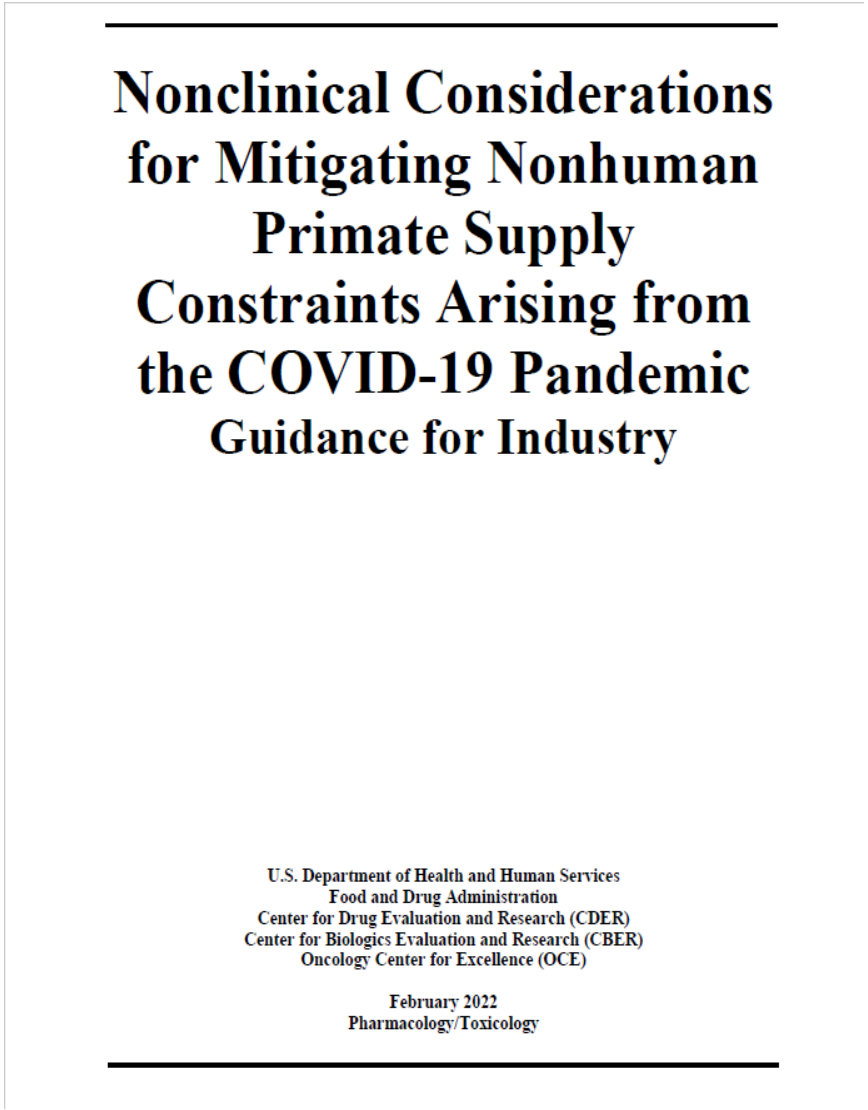
- OECD Test Guideline 437 Bovine Corneal Opacity and Permeability Test Method
  - This method is routinely accepted by CDER for the assessment of ocular irritation potential of drugs that may be accidentally introduced to the eye and is accepted in place of studies for eye irritation in animals.

- OECD Test Guideline 439 In Vitro Skin Irritation
  - This method is routinely accepted by CDER for the assessment of skin irritation potential and is accepted in place of dedicated skin irritation studies in animals.

- Non-animal-based methods are routinely accepted for potency assays, and FDA strongly encourages sponsors using animal-based potency assays to develop non-animal-based potency assays whenever possible.

- FDA accepts new alternative non-animal methods that are scientifically supported for assessing the safety of biological products derived from cell lines of human or animal origin from adventitious agents such as viruses.

Covid-19 Pandemic NHP study guidance



Nonclinical Considerations for Mitigating Nonhuman Primate Supply Constraints Arising from the COVID-19 Pandemic

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)
Oncology Center for Excellence (OCE)

February 2022
Pharmacology/Toxicology

NHP guidance content

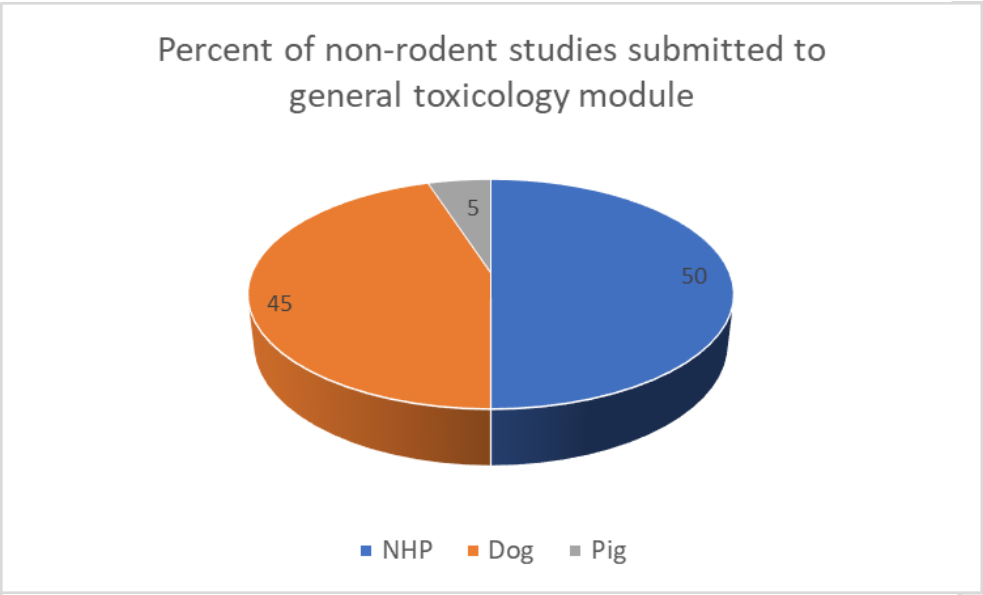
- Much of what appears in the COVID-19 NHP guidance is a restatement of flexibility that is already reflected in existing guidance documents, including:

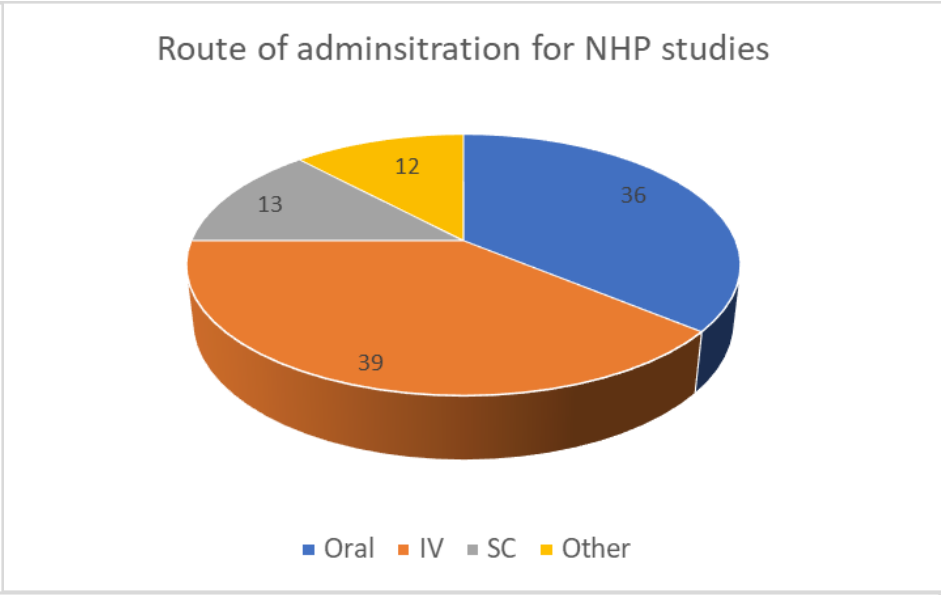
  - Using other nonrodent species.
  - Conducting warranted general toxicity studies only in the rodent.
  - Using a weight of evidence approach for DART studies.
  - Using fewer test article groups, provided the exposure achieved in the treated group provides saturation of target binding, maximal pharmacologic effect, and/or an adequate margin to clinical exposure.

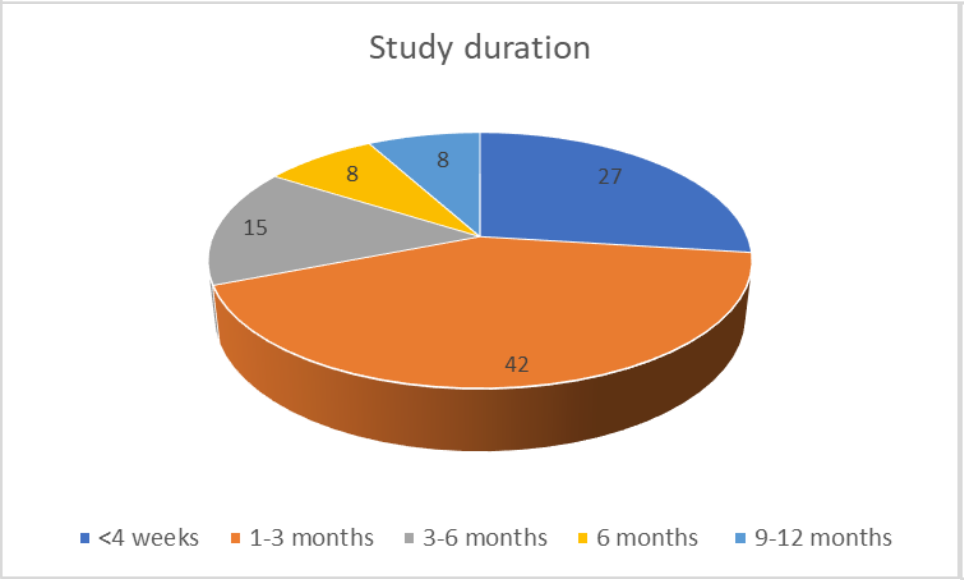
Non-Human Primates in drug testing

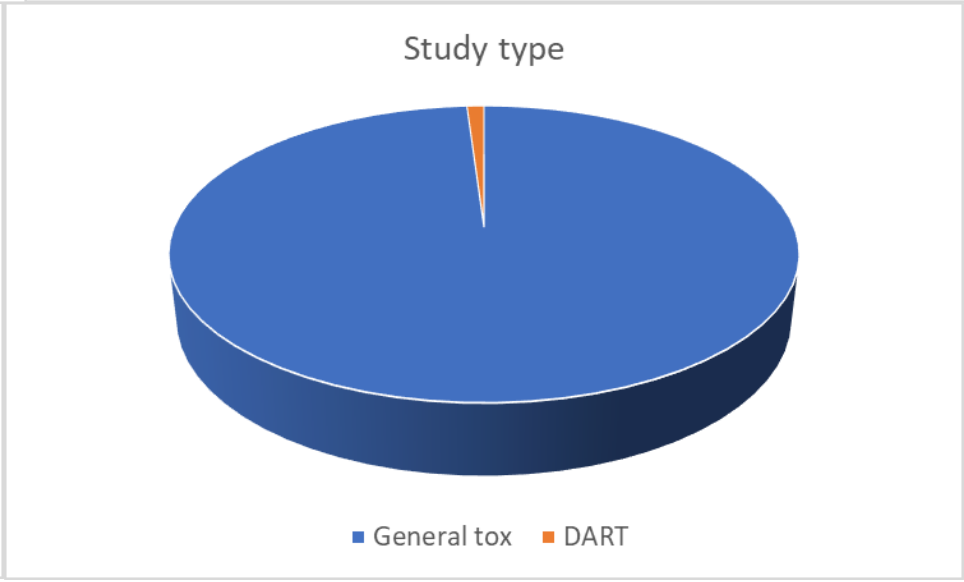
1. Been extensively studied as models of human disease and pharmacology.
2. Helped characterize the nonclinical safety profile of both small and large molecule drug candidates.
3. Been recognized as often being the only pharmacologically relevant species for biopharmaceuticals for toxicity testing of the protein that is intended to be used in humans (ICH S6).
   - Many biologics are proteins designed to engage human targets with high specificity and they typically only manifest their intended pharmacological activity in other primates.
4. Often been used as the only pharmacologically relevant species for safety assessment, when a single-species approach was used.
5. Been discouraged in existing FDA guidance documents unless they are necessary.

Limited data mining of CDER submissions received January 1, 2020 to September 1, 2021









Typical NHP general toxicology study endpoints

- **In life observations:**
- 1. Clinical observations
- 2. Body weight measurements
- 3. Food consumption
- 4. Ophthalmology
- 5. Electrocardiography
- 6. Respiratory rate
- 7. Echocardiography
- 8. Cardiovascular analysis (heart rate, blood pressure, body temperature, activity data)
- 9. Clinical laboratory measurements (hematology, coagulation, clinical chemistry, urinalysis)
- 10. Toxicokinetics
- 11. Antidrug antibody measurements

- **Post-mortem observations:**
- 1. Collection of about 50-60 unique tissues
- 2. Organ weight measurements
- 3. Macroscopic tissue evaluation
- 4. Microscopic tissue evaluation of 50-60 tissues

- Studies typically include 4 males and 4 females treated with 3 doses and one vehicle control.

Summary of preliminary FDA analysis of studies reviewed over a 20-month period

- NHP are the most common non-rodent for general toxicology studies
- Bulk of NHP use is for general tox, not DART
- Equal if not greater use of NHPs for small molecule programs vs. biologics
- A single NHP study can result in the simultaneous measurement of thousands of endpoints of toxicity.

Looking forward

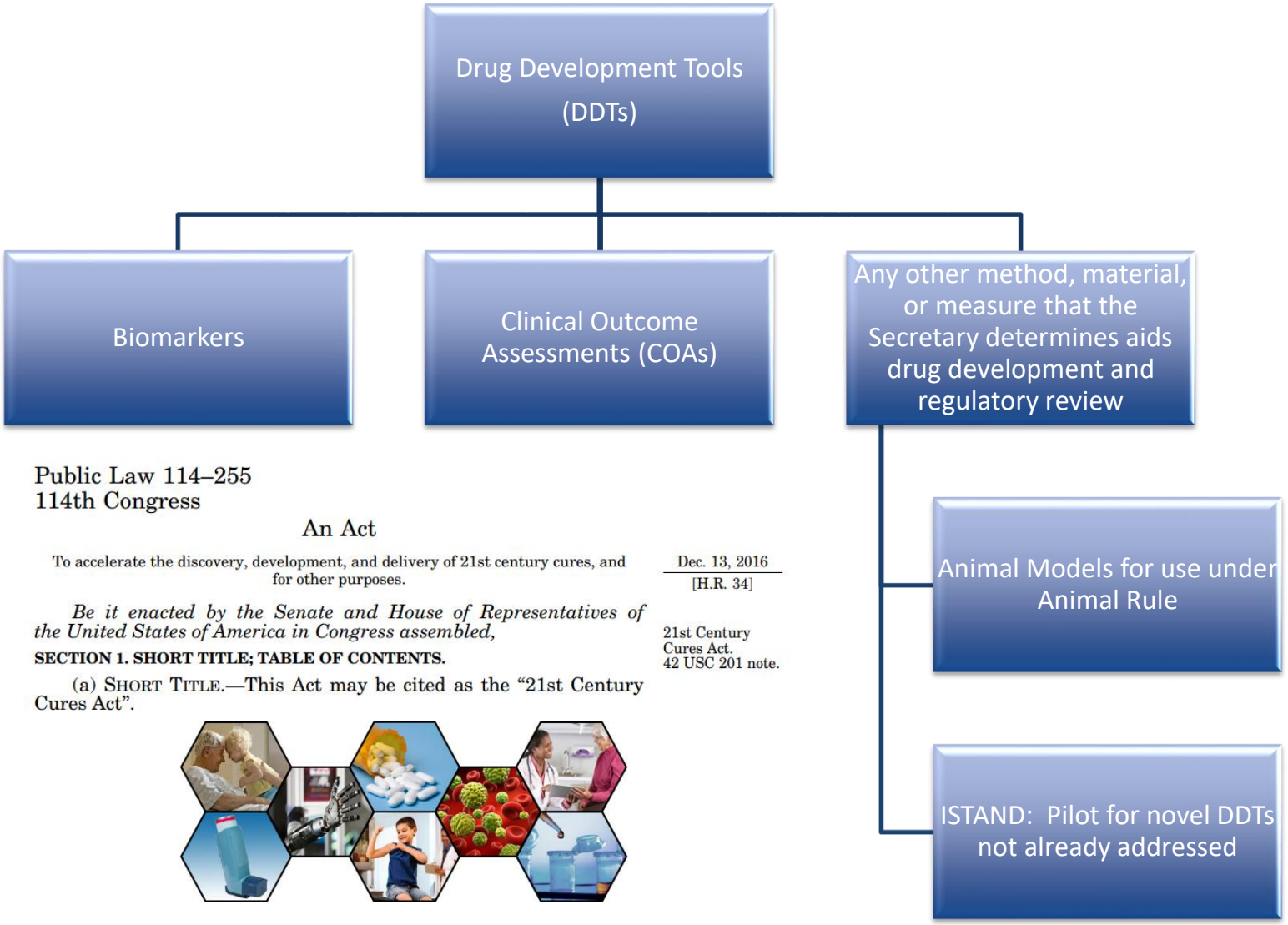
- The recent shortage of NHP has provided opportunities to rethink nonclinical development strategies including the development and use of alternative methods such as advanced cellular systems and in silico analysis to reduce dependency on in vivo NHP models and enhance the translational relevance of nonclinical risk assessments.

ISTAND Website Now Live

Accepted ISTAND submissions will be posted here soon with other DDTs: https://fda.force.com/ddt/s/

For inquiries: ISTAND@fda.hhs.gov

21st Century Cures: Drug Development Tool Qualification



https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tool-ddt-qualification-programs

Definitions

- **Qualification** is a conclusion that within the stated context of use, the DDT can be relied upon to have a specific interpretation and application in drug development and regulatory review. Once qualified, DDTs will be publicly available to be used in any drug development program for the qualified context of use without needing FDA to reconsider and reconfirm its suitability.
  - Biomarkers qualification means providing evidence that biomarker is linked with a certain biological process and clinical endpoint.

- **Context of Use (COU)**: In order to be qualified, a NAM must have a COU, which is a statement that fully and clearly describes the way the drug development tool will be used and the drug development-related purpose of the use.

- **Validation** is the process by which the reliability and relevance of a test method are evaluated for the purpose of supporting a specific use.
  - Biomarker validation refers to the assessment of performance characteristics, such as, precision, accuracy, detection limit and robustness.

ISTAND Pilot – Value Statement

- **The ISTAND Pilot Program was created to deliver value to applicants and to FDA Staff:**

- Provide a path for development and eventual acceptance of novel technologies
- Provide an appropriate level of regulatory certainty
- Enhance communication and information sharing
- Establish a predictable yet flexible process
- Provide uniformity of advice to requestors within and between Centers
- Enhance knowledge about emerging technologies
- Reduce SME workload and simplify communications
- Speed the decision-making process

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