

Considerations Regarding Nonhuman Primate Use in Pharmaceutical Development

Ron Wange
OND/CDER/FDA



Disclaimer

The content of this presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies

High-level Overview

- Presentation will be in two parts
 1. FDA's response to the COVID-19-related disruption in the supply of NHPs
 - “Nonclinical Considerations for Mitigating Nonhuman Primate Supply Constraints Arising from the COVID-19 Pandemic”
 2. Alternatives to the use of the NHP for assessing the embryofetal and postnatal development risks of biotherapeutic proteins
 - Use of weight-of-evidence to assess and communicate risk
 - Source of information used to communicate risk in section 8.1 of US product labels for BLAs

Overview for Part One

- Challenges in conducting studies in NHPs
 - Underlying (baseline) issues
 - COVID-19-related
- FDA efforts to limit NHP use generally
- FDA response to the COVID-19-related disruption in the NHP supply
 - Guidance issued under our public health emergency authority



General Issues with NHP Use & FDA Efforts to Limit Use

Challenges with NHP as a Test Species



- NHPs (*cynomolgus macaques*) have always been a limited resource
 - Highly variable timing of onset of puberty and progression to sexual maturity
 - Advanced age at sexual maturity (compared to other models)
 - 3 years for females, 5 years for males
 - Low fecundity: Less than 1 infant per female per year
 - high frequency of pregnancy loss, stillborn and postnatal mortality
- Ethical and political concerns associated with testing in primates

Discouragement of NHP Use (1)



- Multiple guidances have provisions that are intended to limit NHP use to scenarios where they are the only scientifically relevant model
- ICH S6(R1) - Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
 - Use of single species (rodent preferred) in longer term general tox studies
 - For EFD toxicity assessment:
 - Use of NHP for EFD studies only if it is the only relevant species
 - Supports use of GM rodent models and surrogates (but not “preferred”)
 - For MoA with established EFD risk, NHP studies not warranted

Discouragement of NHP Use (2)



- ICH M3(R2) - Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
 - Silent on species selection for general tox studies
 - Some specialized scenarios discourage NHP use
 - Nonclinical support for exploratory trials
 - Juvenile animal studies: Single relevant species, preferably rodent
 - Nonclinical abuse liability studies: Discourages use of NHPs

Discouragement of NHP Use (3)



- **ICH S5(R3)** - Detection of developmental and reproductive toxicity for human pharmaceuticals
 - NHPs should be considered a nonroutine test species for small molecule drugs
 - There can be adequate information, based on a weight-of-evidence assessment to communicate risk w/o conducting EFD studies

IMPACT OF COVID-19 ON NHP SUPPLY

Brief Recap—Origin of the Problem

- In February 2020 China implemented a ban on the trade in live animals, including NHPs, on the premise that the wild animal trade could be contributing to the spread of SARS-CoV2
 - Disruption in supply—60% of NHPs used in research in US in 2019 were sourced from China
 - Other countries increased exports, but...
 - There remains a shortfall in the number of available animals
 - Available animals are much younger than those previously exported
- NHP Demand Increased due to COVID-19 pharmaceutical and vaccine development programs, and increase in number of biologics in development generally



FDA RESPONSE TO CURRENT COVID-19-RELATED SUPPLY CONSTRAINTS

Approaches to Reduce Demand

- Avoid unnecessary use of NHPs, generally
 - Discourage use for small molecule drug programs, except when only reasonable model
- Avoid unnecessary use of sexually mature (SM) NHPs in DART studies
 - Encourage broader use of WOE and non-NHP animal models
- Allow ePPND studies to be conducted under a PMR (when appropriate)
 - Saves SM-NHPs if clinical development terminated before filing BLA
 - For approved biologics, pushes out need for SM-NHP to time when supply may have normalized
- Adjust the number of pregnant females used in each DART study

**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

**Co-issued by CDER, CBER and OCE
Posted 2/4/2022 as final guidance**

NHP COVID GUIDANCE

Overview 1



- Primary focus on conserving sexually mature NHPs
 - In most acute shortage
 - Maintain availability of SM NHPs for programs for which there are no reasonable alternative methods to gather DART endpoints
 - Maintain availability of SM NHPs for breeding programs
- Secondary focus on conserving NHPs, regardless of maturation status

NHP COVID GUIDANCE

Overview 2



- Most provisions of the guidance merely emphasize the flexibility that is already supported under existing guidance
- Some provisions reflect new guidance
 - Don't directly conflict with existing guidance, but neither are they supported
- One provision reflects a change in guidance
 - Potentially conflicts with existing guidance

What's Inside?

Introduction Section



- Over a page of standard language required for COVID-19 guidances
- Purpose
 - “...to help sponsors mitigate the challenges related to the constrained supply of nonhuman primates (NHPs) available for conducting nonclinical toxicity assessments, which has arisen as a consequence of the current COVID-19 pandemic.”
- Duration
 - Throughout COVID-19 public health emergency (PHE)
 - Will be revised and replaced “[to reflect] any appropriate changes based on comments received on this guidance and the Agency’s experience with implementation”

What's Inside?

Background Section

- Brief overview of the problem and why the guidance is needed
 - Reduction in supply due to COVID-19 pandemic
 - Increased demand related to development of pharmaceuticals and vaccines to treat or prevent COVID-19
 - Scarcity of NHPs has the “potential to significantly delay the development of new medications for the treatment of diseases currently without effective treatment options.”
 - Sexually mature NHPs are particularly scarce

NHP COVID GUIDANCE

General Tox – Small Molecules



- “We discourage the use of NHPs for the general toxicology assessment of small molecule drugs, unless the sponsor can provide a scientifically compelling reason why NHPs must be used.”
- “Sponsors should not use sexually mature NHPs in toxicity studies designed specifically to assess fertility by histopathological examination when fertility parameters can be assessed in rodents.”

NHP COVID GUIDANCE

General Tox – Biologics



- If the biological product is active in other nonrodent species, the sponsor should conduct any warranted general toxicity studies in a nonrodent species other than the NHP, whenever scientifically justified.
- On a case-by-case basis, if the biological product is active in a rodent and acts on a well-characterized target (e.g., vascular endothelial growth factor, or its receptor), it may be scientifically appropriate for sponsors to conduct warranted general toxicity studies only in the rodent.

NHP COVID GUIDANCE

DevTox – Small Molecules



- Consistent with current FDA guidance on the assessment of developmental and reproductive toxicity (DART), FDA considers NHPs to be a nonroutine test species for the DART assessment of small molecule drugs. FDA strongly discourages sponsors from using NHPs for assessing DART endpoints for their small molecule drug development programs.

NHP COVID GUIDANCE

DevTox – Biologics (1)



- Consistent with current FDA guidance, sponsors should only use NHPs for the DART assessment of biological products if they are the only relevant species.

NHP COVID GUIDANCE

DevTox – Biologics (2)



- For the duration of the COVID-19-related disruption in the supply of NHPs, consider:
 - ...we strongly encourage the use of appropriate alternative models for assessing DART endpoints (e.g., species-specific surrogates in rodents, genetically modified rodents) when scientifically justified.
 - On a case-by-case basis, a sponsor can consider conducting a DART assessment solely using a weight-of-evidence approach. Typically, FDA would consider this approach to be scientifically justified only in instances where strong scientific evidence indicates risk or where the mode of action clearly indicates negligible risk (e.g., viral or bacterial target, with no cross-reactivity with human tissues).

NHP COVID GUIDANCE

DevTox – Biologics (3)



- For the duration of the COVID-19-related disruption in the supply of NHPs, consider:
 - ...an adequately designed enhanced pre- and post-natal development (ePPND) study in the NHP with fewer test article groups (e.g., one control group and one treated group) may be adequate to assess risk, provided the exposure achieved in the treated group provides saturation of target binding, maximal pharmacologic effect, and/or an adequate margin to clinical exposure.
 - For indications where use of the product in women of childbearing potential is unlikely, it may be acceptable to collect embryo-fetal developmental and pre- and post-natal development data in the postmarketing setting.
 - We recommend that sponsors discuss their proposed approaches to assessing DART endpoints, and their timing, with the appropriate review divisions before initiating any of the alternative DART assessments described in this guidance.

NHP COVID GUIDANCE

What's Next?



- Can the provisions of this guidance be made permanent?
 - Most provisions in the guidance are a restatement of flexibility that already exists in current guidance
 - A few provisions could be perceived as providing new guidance or of conflicting with internationally harmonized guidance
 - Making these provisions permanent might require revision of those guidances

NHP COVID GUIDANCE

Potential Deviation from Existing Guidance



FDA NHP COVID-19 Guidance Small Molecule	Nonsupporting/ Conflicting Language from Existing Guidance
“We discourage the use of NHPs for the general toxicology assessment of small molecule drugs, unless the sponsor can provide a scientifically compelling reason why NHPs must be used.”	Neither supports nor contradicts. ICH M3 does not contain language regarding nonrodent species selection for general toxicity studies.

NHP COVID GUIDANCE

Potential Deviation from Existing Guidance



FDA NHP COVID-19 Guidance Biologic	Nonsupporting/ Conflicting Language from Existing Guidance
“If the biological product is active in other nonrodent species, the sponsor should conduct any warranted general toxicity studies in a nonrodent species other than the NHP, whenever scientifically justified.”	Neither supports nor contradicts. S6(R1) does not contain language regarding selection of nonrodent species for general toxicity studies.

NHP COVID GUIDANCE

Potential Deviation from Existing Guidance



FDA NHP COVID-19 Guidance Biologic	Nonsupporting/Conflicting Language from Existing Guidance
“...we strongly encourage the use of appropriate alternative models for assessing DART endpoints (e.g., species-specific surrogates in rodents, genetically modified rodents) when scientifically justified.”	“When the clinical candidate is pharmacologically active only in NHPs, there is still a preference to test the clinical candidate. However, an alternative model can be used in place of NHPs if appropriate scientific justification is provided.”

PART 2

ALTERNATIVES TO THE NHP IN DART ASSESSMENT FOR BIOLOGICS

Overview for Part Two

- Current “regular” regulatory framework (CDER)
 - ICH S6(R1)
 - ICH S5(R3)
 - Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations
- How have we been doing in using WOE?
 - Source of information for 8.1 labeling (2015–2021)
 - Product characteristics driving data source in labels

CURRENT “REGULAR” REGULATORY FRAMEWORK

ICH S6 (1997)

- The need for DART studies is dependent upon the product, clinical indication and intended patient population
- Note two (paraphrased): If there are extensive public data available to indicate a clear DART risk for a particular class of compounds, and the NHP is the only relevant species, mechanistic studies for a new member of the class may be sufficient to assess the risk, with scientific justification

ICH S6 (R1 Addendum) (2012)

- “Developmental toxicity studies should only be conducted in nonhuman primates (NHPs) when they are the only relevant species.”
 - Assessment of clinical candidate “preferred” (even if it means using the NHP)
 - An alternative model can be used in place of NHPs if appropriate scientific justification is provided

ICH S6 (R1 Addendum) (2012)

- If no relevant species exists
 - transgenic mice expressing the human target
 - homologous protein in a species expressing an ortholog of the human target
- No DART assessment expected for products targeting exogenous target, which don't cross-react with any endogenous molecules
 - e.g., viral or bacterial
- WOE can provide information to communicate risk to reproduction in some instances
 - e.g., when mechanism of action, phenotypic data from genetically modified animals and/or class effects suggest that there will be an adverse effect on fertility or pregnancy outcome

ICH S5(R3) (2021)

- NHPs are non-routine DART test species for small molecule drugs
- Biologics were explicitly brought into the scope of ICH S5
- “To the extent that it does not diminish the overall risk assessment, the experimental strategy should minimize the use of animals.”

ICH S5(R3) (2021)

- **Strategies To Address Embryo-Fetal Development (EFD) (4.2)**

“...there can be adequate information to communicate risk without conducting EFD studies. Evidence suggesting an adverse effect of the intended pharmacological mechanism on EFD (e.g., mechanism of action, phenotypic data from genetically modified animals) can be sufficient to communicate risk.”

ICH S5(R3) (2021)



- **GENERAL CONSIDERATIONS ON REPRODUCTIVE TOXICITY ASSESSMENT (3.0)**

Key factors to consider when developing an overall integrated testing strategy to evaluate effects on reproduction and development include:

- The targeted patient population and conditions of use (especially in relation to reproductive potential and severity of disease)
- The formulation of the pharmaceutical and route(s) of administration intended for humans
- Relevant data on toxicity (which can also include data from in vitro, ex vivo and nonmammalian studies, and structure-activity relationships), pharmacodynamics, pharmacokinetics, and pharmacological similarity to other pharmaceuticals
- Aspects of the general biology of the pharmaceutical target, or known roles of the target in reproduction or development

FDA Oncology DART Guidance (2019)



- “In general, when the weight of evidence (WOE) indicates clear adverse reproductive effects, additional reproductive toxicology studies may not be warranted.”
- Does not address safe margins of exposure [clinical exposures typically overlap with adverse exposures in animals]
- Does not address the potential risks to a developing embryo or fetus *during clinical trials* because pregnancy testing and use of highly effective methods of birth control are usually adequate to minimize the risk of unintentional exposure of the embryo or fetus when including women of reproductive potential in clinical trials
 - Many oncology drugs are expected to be EFD toxicants

FDA Oncology DART Guidance (2019)

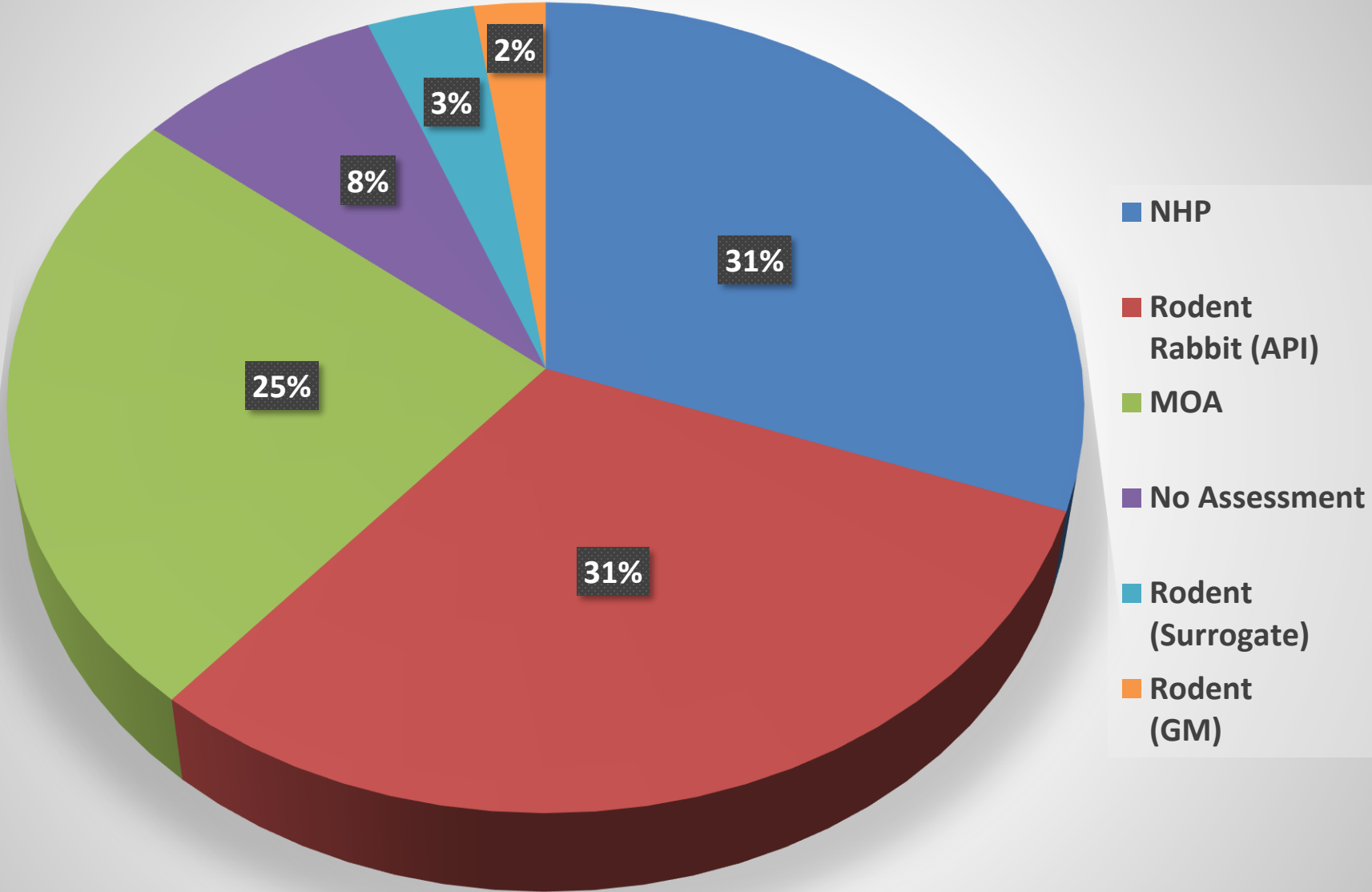


- Data to inform on WOE may include:
 - Reproductive findings in humans, such as when a drug is in a class of pharmaceuticals with extensive publicly available information on potential reproductive effects
 - Reproductive findings from genetically-modified animals or models employing pharmacologic inhibition, as appropriate
 - Information from a surrogate molecule, when a surrogate is available and the target biology in the animal species is relevant to humans
 - Literature-based assessment of target biology in humans or animal species, which can describe the following:
 - Expression and the role of the molecular target during embryo-fetal development
 - Any other relevant information, such as the role of the target in placental development, placental transfer, maternal tolerance, etc.
 - Use of alternative assays, such as fit-for-purpose *in vitro* or *ex vivo*, or nonmammalian *in vivo* assays can be used

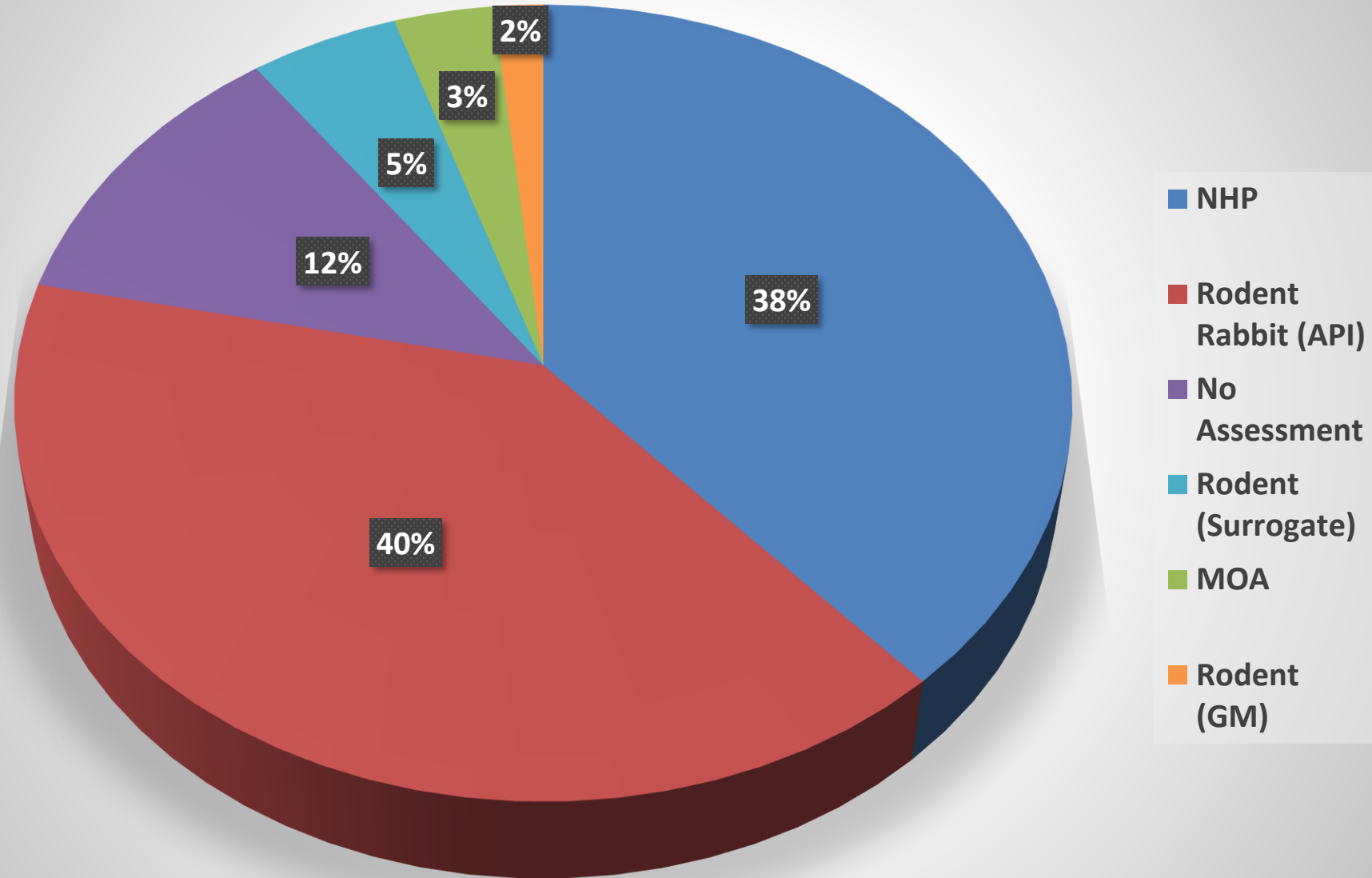
How Have We Been Doing?

Source of Risk Information in Section 8.1?

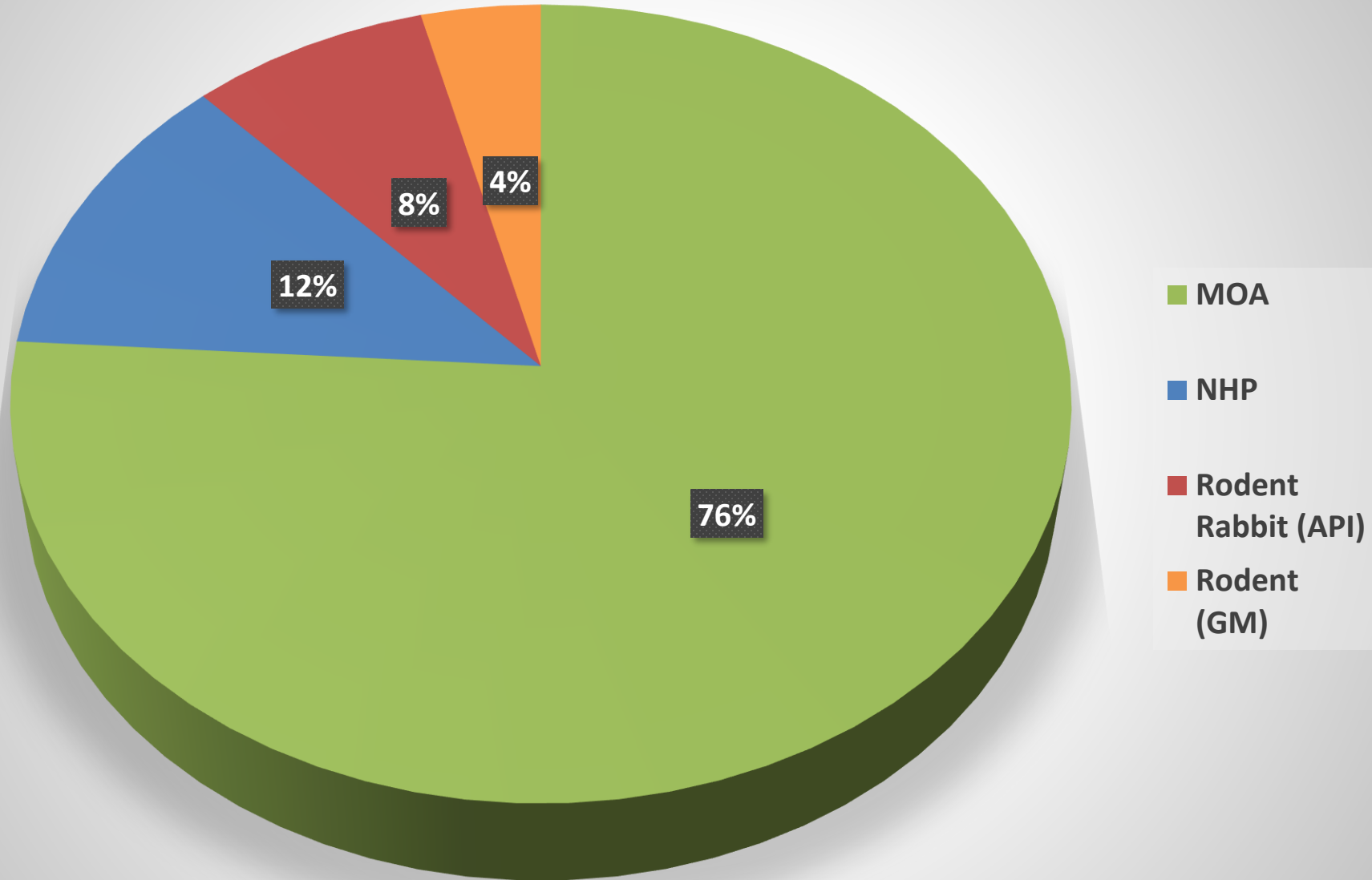
All Indications (2015–2021)



Non-oncology Indications (2015–2021)



Oncology Indications (2015–2021)



Recap, by the Numbers, for 2015–2021

- More than two-thirds of labels for BLAs approved in this period do not rely on EFD/ePPND data from NHPs
 - 62% of non-oncology products
 - 88% of oncology products
- Labeling was based on a weight-of-evidence assessment
 - 22% of non-oncology products
 - 80% of oncology products

Why the Difference Between Oncology and Non-oncology for WOE Labeling (80% vs. 22%)



- By their very nature, biotherapeutics to treat advanced cancer are generally expected to have teratogenic activity
 - ADCs with payloads that are toxic to rapidly dividing cells (6)
 - mAbs that disrupt immune tolerance (4)
 - mAbs that deplete immune cells or progenitors (3)
 - Inhibitors of kinases involved in embryofetal development (3)
 - Cytotoxic mAb directed to cells of the neuroectoderm (1)
 - Approved only for coadministration with products with known adverse effects on EFD (1)

Why the Difference Between Oncology and Non-oncology for WOE Labeling (76% vs. 15%)



- Not generally necessary to identify safe margins of exposure for oncology products
 - Therapeutic exposures expected to have adverse effects (including EFD toxicity)
 - Qualitative assessment of risk more acceptable

Characteristics of Non-oncology BLAs Relying on WOE for 8.1 Risk Assessment



- Enzyme replacement therapy (2)
- Exogenous target (e.g., virus or bacteria) (4)
- Male-only treatment population (X-linked recessive trait) (1)
- VEGF Inhibitor (1)
- Interferon alfa (1)

Summary

- During the last seven-year period, two-thirds of approved BLAs have product labeling that does not rely on NHP data for section 8.1
 - Non-oncology relied on the NHP 38% of time, oncology 12% of the time
- 80% of labels for oncology product BLAs, but only 22% of non-oncology product BLAs, rely on a weight-of-evidence approach for the risk assessment for section 8.1
 - Largely a function of the different types of targets and mechanisms of action between oncology and non-oncology products
- Existing guidance fully supports the use of weight-of-evidence and other non-NHP alternative assessments of EFD risk

The Future of NHP Use in Drug Testing (1)

- Alternatives to the NHP
 - Other nonrodent animal models (dogs, mini-pigs, rabbits, ?)
 - Rodent-only general toxicology assessment
 - “where the biological activity of the biopharmaceutical is well understood”
 - Modified rodent model systems
 - Genetically modified rodents
 - Mimic effect of target engagement
 - Partially humanized to render pharmacologically relevant
 - Rodent-specific surrogate

Guidances only discusses the use of such models for specific endpoints (e.g., DART studies), not general toxicity studies

The Future of NHP Use in Drug Testing (2)

- Weight-of-evidence assessments (DART)
- New Approach Methodologies
 - Current approaches are primarily focuses on chemicals and small molecule drugs
 - Suitability for biologics testing unknown
 - No NAM is currently able to provide all of the safety information provided by whole animal studies

The Future of NHP Use in Drug Testing (3)

- NHPs are likely to remain a key animal model for some classes of pharmaceuticals for the foreseeable future.
- The key to reducing the numbers of NHPs used in pharmaceutical testing is to only use NHPs in those programs that have no other scientifically reasonable approach to nonclinical safety testing.



U.S. FOOD & DRUG
ADMINISTRATION