#278

Human User Safety in New and Abbreviated New Animal Drug Applications

Guidance for Industry

Draft Guidance

This guidance document is being distributed for comment purposes only.

Submit comments on this draft guidance by the dated provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with docket number FDA-2023-D-0592.

For further information regarding this document, contact Dr. Karen Sussman, Center for Veterinary Medicine (HFV-114), Food and Drug Administration, 7500 Standish Place, Rockville MD 20855, 240-402-0876, karen.sussman@fda.hhs.gov.

Additional copies of this draft guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville MD 20855, and may be viewed on the Internet at https://www.fda.gov/animal-veterinary, https://www.fda.gov/regulatory-information/search-fda-guidance-documents, or http://www.regulations.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine (CVM)
April 2023

Table of Contents

Human User Safety in New and Abbreviated New Animal Drug Applications

Draft Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. Introduction

Human User Safety (HUS) is an integral component of the overall safety evaluation of proposed new animal drugs.[1] The FD&C Act does not provide specific guidance on data requirements or assessment methods to identify the risks or the risk mitigation measures for human users of new animal drugs. FDA is issuing this draft Guidance for Industry (GFI) to clarify the current approaches and recommendations of the Food and Drug Administration's (FDA's) Center for Veterinary Medicine (CVM) for HUS assessment and submission of HUS information to support the overall safety of proposed new animal drugs prior to approval.[2]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Abbreviations

Abbreviation	What It Means
ACTP	Animal Cells, Tissues, and Cell- and Tissue-Based Products
ANADA	Abbreviated New Animal Drug Application

[1] As noted in section 572(c)(1)(F) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), when we evaluate the safety of a proposed new animal drug under section 512(d) of the FD&C Act (the provision that outlines the approval criteria for new animal drug applications as well as the safety standards for applications for conditional approval (see section 571(a)(1)(D) of the FD&C Act), we consider information that supports "the conclusion that the proposed use of the new animal drug is safe with respect to individuals exposed to the new animal drug through its manufacture or use."

[2] This guidance addresses HUS considerations for dosage form new animal drugs and animal drugs for use in animal feed. This guidance does not address HUS of food additives or animal food, or processes for post-approval reporting or monitoring of human user safety related adverse events. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at https://www.fda.gov/animal-veterinary/report-problem/how-report-animal-drug-and-device-side-effects-and-product-problems.

Abbreviation	What It Means
API	Active Pharmaceutical Ingredient
CDER	Center for Drug Evaluation and Research
CVM	Center for Veterinary Medicine
FAO	Food and Agricultural Organization of the United Nations
FDA	US Food and Drug Administration
GFI	Guidance for Industry
HUS	Human User Safety
IGA	Intentional Genomic Alteration
INAD	Investigational New Animal Drug
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JINAD	Generic Investigational New Animal Drug
NADA	New Animal Drug Application
NOAEL	No-Observed-Adverse-Effect Level
OTC	Over the Counter
ONADE	Office of New Animal Drug Evaluation
PPE	Personal Protective Equipment
PM	Project Manager
RLNAD	Reference Listed New Animal Drug
Rx	Prescription
SDS	Safety Data Sheet
TAS	Target Animal Safety
VFD	Veterinary Feed Directive
WHO	World Health Organization

III. Background and Scope

This draft guidance is intended for sponsors interested in pursuing the approval, or conditional approval, of new animal drugs (including new generic animal drugs). This guidance is also intended for FDA staff, veterinary health professionals, and the general public interested in understanding the general principles of HUS assessment for new animal drugs. This guidance addresses general principles of HUS assessment for new animal drugs, sources of data, mitigation strategies for proposed new animal drugs, potential recommendations to address HUS concerns, and how HUS information should be submitted to CVM.[3] This guidance provides transparency to our stakeholders and is part of CVM's ongoing practice of providing relevant guidance on the new animal drug application process for sponsors.

[3] There may be other Federal occupational health and safety regulations as well as other relevant State or local laws that may apply to the manufacture or use of veterinary drugs.

CVM evaluates HUS under the regulatory framework of the Target Animal Safety (TAS) technical section for new animal drugs. HUS covers human exposures to a new animal drug or its metabolites resulting from expected or anticipated conditions of use or from foreseeable accidents associated with the use of the new animal drug. CVM does not routinely expect HUS assessment for new animal drugs to address conditions of exposure that may result from deliberate extralabel use, misuse, or abuse of a drug. However, for new animal drugs that contain active substances categorized as "controlled substances,"[4] or that may otherwise be deliberately misused, it may be warranted for drug sponsors to include additional considerations or mitigation strategies (e.g., special packaging conditions) to limit or prevent access or intentional misuse of the drug. Because each proposed new animal drug and the intended use of the proposed drug may pose unique HUS-related considerations or challenges, CVM's recommendations for the type of information necessary to evaluate HUS are specific to each new animal drug and its proposed use. Therefore, recommendations and information in this guidance are not all inclusive, but rather are intended to provide general guidance to address HUS prior to approval for new animal drugs.

Drug sponsors' evaluation of HUS should be an ongoing process that continues throughout the development and lifecycle of a new animal drug as new information becomes available. Prior to approval of a new animal drug, drug sponsors should submit information to allow CVM to understand the drug's HUS profile and associated risks. CVM recommends drug sponsors consider and discuss the components and methodology of HUS assessment described in this guidance early during the development of their drug. CVM recommends that sponsors have additional discussions as new information pertaining to HUS becomes available during product development. Discussions may be especially important when considering HUS for novel classes or dosage forms of new animal drugs, previously unapproved uses or use conditions of an approved animal drug (e.g., novel routes of administration or target animal species), the impact of formulation or dosage form changes for generic new animal drugs, and during development of applicable drug labeling. In all cases, sponsors are encouraged to contact CVM to discuss the types of information that are recommended to support the HUS assessment of an animal drug or to discuss other questions related to this assessment.

Agreement on the acceptability of HUS information and the proposed mitigations (i.e., labeling, packaging, marketing status, etc.) is most often determined under the TAS technical section. However, the final decision on the HUS of a new animal drug is based on all the information in the (Generic) Investigational New Animal Drug file ((J)INAD)/(Abbreviated) New Animal Drug application ((A)NADA) as a whole.

[4] Such drugs are required to be scheduled by the United States Drug Enforcement Administration. See 21 U.S.C. §§ 811 and 812.

Typically, generic new animal drugs do not present novel HUS considerations.[5, 6] Sponsors of generic new animal drugs are encouraged to use the suitability petition review process to determine if changes from the pioneer Reference Listed New Animal Drug (RLNAD) would result in significant changes to the HUS assessment for their generic new animal drug. Special considerations for generic new animal drugs are discussed in section IX. *Special Considerations for Generic New Animal Drugs (ANADA)*.

IV. Terminology

Controlled Substance: Active substances that are regulated by the United States Drug Enforcement Administration for availability and access in the United States under the Controlled Substances Act.[7]

Drug product: A finished dosage form, for example, tablet, capsule, or solution, etc., that contains an active ingredient generally, but not necessarily, in association with inactive ingredients.[8]

Formulation: The formulation is considered to be the components and composition of the drug product as described in 21 CFR 514.1(b)(4). A component is any ingredient and its grade used in the manufacture of a drug product, including those ingredients that may not appear in the drug product (e.g., those components that are removed or react during the manufacturing process). The composition is the per unit dose quantities (amounts and/or percentages) of all components.

Foreseeable accidents: The exposure of a human user to new animal drugs outside the scope of labeled instructions for use (e.g., spills, accidental ingestion or self-injection, etc.) or without the use of some or all common and specific technical, operational, and personal protective measures (e.g., inadequate dilution of a veterinary medicinal product, use without adequate personal protective equipment, etc.).

Human User: For the purposes of this guidance and the assessment of HUS, human user is any person who may come into contact with the new animal drug or components of the manufactured product before, during, or after its application or administration to the animal. Human user may also be referred to as user and/or end-user.

---

[5] The suitability petition process under section 512(n)(3) of the FD&C Act allows a generic drug sponsor to seek approval for a generic new animal drug that differs from the pioneer reference listed new animal drug (RLNAD) in certain permissible ways (e.g., change in route of administration or dosage form). However, such a petition cannot be approved if the proposed change requires additional safety or effectiveness information. If such a change raises a novel HUS concern that requires additional safety information, CVM cannot approve the suitability petition.

[6] Section 512(c)(2)(A)(viii) of the FD&C Act requires that generic sponsors ensure the safety of the inactive ingredients in their proposed formulations.

[7] See 21 U.S.C. §§ 811 and 812

[8] See 21 CFR § 210.3(b)(4)

Label: For the purposes of this guidance, the label refers to the component of labeling that is associated with the immediate container.[9]

Labeling: For the purposes of this guidance, labeling refers to all packaging and instructional components accompanying the new animal drug, including the label.[10]

Labeling Language: For the purposes of this guidance, labeling language refers to the specific wording used in labeling to convey information relevant to the safe and effective use of the drug.

New Animal Drug: A new animal drug is defined, in part, as any drug intended for use in animals other than man, including any drug intended for use in animal feed but not including the animal feed, the composition of which is such that the drug is not generally recognized as safe and effective for the use under the conditions prescribed, recommended, or suggested in the labeling of the drug.[11]

Personal Protective Equipment: Equipment that is designed and used to protect the wearer from exposure to a new animal drug. Personal protective equipment may include, but is not limited to, head, eye, respiratory, body, hand, and/or foot protection. Personal protective equipment may also be referred to as individual protective equipment.

V. Principles of HUS Assessment

Understanding the underlying risk of use of an animal drug is a critical component of HUS. During the new animal drug approval process, sponsors should present an assessment of the risk to those human users involved in handling and administering the new animal drug. This should also include risks from exposure to metabolites, as well as treated animals and bodily fluids/excreta such as urine, feces, vomit, and saliva. This HUS assessment may vary depending on multiple factors, including, but not limited to:

- The toxicity profile of the new animal drug (Active Pharmaceutical Ingredient (API) and inactive ingredients)
- The dosage form of the new animal drug (tablet, suspension, gel, injectable solution, etc.)
- The route of administration (including any delivery device) of the new animal drug
- The characteristics of the expected human users of the new animal drug (e.g., residential or home user vs. occupational or professional user)
- The overall risk to the human user posed by the use of the new animal drug

A. Human User Safety Assessment

There are three basic overarching components of a HUS assessment. The first is hazard, which encompasses information based on the potential adverse effects that a new animal

[9] See section 201(k) of the FD&C Act

[10] See section 201(m) of the FD&C Act

[11] See section 201(v) of the FD&C Act.

drug may have on a human user. The second is exposure, which encompasses information on how much (volume or amount), by what route, and with what frequency a human user may come into contact with the animal drug. The third component of HUS assessment is risk characterization. CVM uses hazard and exposure to help estimate the risk to the human user from a given new animal drug. Risk is the likelihood of an adverse event to the human user following exposure to a new animal drug (API and/or inactive ingredients). Hazard and exposure may be pre-defined by the characteristics of the new animal drug, dosage form, or the route of administration. Therefore, mitigation strategies (see section VII. *Potential HUS Recommendations*) may represent valuable methods to address concerns from the risk to the human user associated with the potential exposure to the new animal drug.

1. Hazard

Hazard represents the intrinsic potential for adverse health events that is posed by a given new animal drug. Hazard, as part of a HUS assessment, is made up of two subcomponents: hazard identification and hazard characterization.

a. Hazard Identification

Hazard identification focuses on determining the specific component(s) of the new animal drug that may elicit a toxicological response. The factors that go into identifying the hazard include, but are not limited to:

- New animal drug components (API and inactive ingredients)
- Chemical properties of the components of the new animal drug
- Chemical class of the new animal drug (including structurally related compounds) and/or known mechanism of action
- Drug delivery device or method

b. Hazard Characterization

Hazard characterization is defined by the understanding of the relationship between the dose of the hazardous material a person is exposed to and the probability of an adverse health event occurring at that dose. This is sometimes known as the "dose-response" relationship. It is not always necessary or reasonable to determine a dose-response relationship, for example when chemicals behave in idiosyncratic fashions where dose is not related to response. It may also not be necessary or reasonable to determine a dose-response relationship when available data or information is insufficient to establish such a relationship and/or CVM determines that such information is not materially relevant to address potential HUS concerns. Please refer to the section on risk characterization below (section V.A.3. *Risk Characterization*).

Hazard characterization may be determined by reviewing toxicological data and literature for the identified hazards. This review of available information should

focus on the potential adverse human health effects and their severity. Potential sources of toxicity data are found in section VI. *Sources of Information* of this GFI.

Sponsors may also consider the mode of action (the key events at the molecular level that propagate into organ level effects) and/or toxicokinetics (how the human and/or animal body is expected to absorb, distribute, metabolize, and eliminate a chemical) when evaluating the potential hazards.

2. Exposure

Exposure assessment in many cases is the component of the HUS assessment that drives what mitigation measures may be needed to ensure safe use of a new animal drug for human users. When conducting an exposure assessment, the sponsor should describe the exposure scenarios and define the likelihood of these exposure scenarios.

The supporting information for the exposure scenarios should describe the following:

c. The Characteristics of the Human User Population Likely to be Exposed

The exposure assessment should define who is the primary human user for a given new animal drug. Human users may include, but are not limited to, veterinarians and/or their assistants, occupational workers, or pet-owners and/or household members. Subpopulations that are at special risk may include children, pregnant and nursing women, women of child-bearing age, and women who may be pregnant or are attempting to become pregnant.

For products intended for use in companion animals,[12] CVM recommends that the exposure assessment specifically consider potential exposures of household members. Household members may include young children and persons who may be exposed to the new animal drug via a secondary route such as handling the animal or the animal's bodily fluids/excreta after drug administration. In some instances, other exposure scenarios may be considered, such as accidental exposure following improper storage or disposal of unused product.

Sponsors are encouraged to include data or information on the probability of exposure in human users. CVM encourages sponsors to consider known adverse events or existing pharmacovigilance data when assessing possible exposure probabilities.

d. How the Human User May be Exposed to the New Animal Drug

Exposure may occur during any or all of the following three phases: pre-administration, administration, and post-administration. The pre-administration phase includes activities related to storage, opening, preparing, or mixing the new animal drug. The pre-administration phase may include, but is not limited to, activities such as: assembling dosing equipment, setting/locking pre-filled oral syringes, or loading

[12] CVM considers companion animals to include dogs, cats, and horses.

an administration or drug delivery device such as a balling gun or syringe. Exposure scenarios may also include accidental exposures to pre-drawn doses of an animal drug. The administration phase is when the animal drug is actually administered to the animal. Exposure during the administration phase may encompass many scenarios including, but not limited to, accidental exposure while restraining an animal during dosing, leakage of drug from the animal's oral cavity or dosing device, or touching topically applied drugs. The post-administration phase includes disassembly and/or cleaning of dosing equipment, disposal, handling the animal or its waste or bodily fluids after drug administration, or cleaning the treatment stall or area that was used for drug administration.

In general, the most common exposure routes for human users include oral, dermal, inhalation, ocular, and injection. The route of exposure for the human user may be influenced by the dosage form of the new animal drug and the drug delivery device (if one is used). New animal drugs may be dispensed in a variety of dosage forms such as a powder, tablet, solution, spray, impregnated collar, etc. The use of an animal drug may be associated with multiple routes of human user exposure. Human exposure routes may differ from the intended route of drug administration in the animal.

The exposure analysis should consider both the frequency of administration and the duration of exposure. Different dosage forms may be associated with different durations and frequencies of exposure.

Frequency is how often an exposure event occurs. Frequency is generally broken into one of three time-factors: acute, sub-chronic, and chronic. Acute exposures are generally considered to be single exposures, such as accidental injection, dermal contact, eye contact, or oral ingestion. Sub-chronic exposures are generally considered to be those where there are multiple (often daily) exposures events, and this series of exposures may occur over a timeframe up to 90 days in length. Chronic exposures are generally considered to be those where there are multiple (often daily) exposures events, and this series of exposures may occur over a period of 91 days up to the lifetime of the human user.

The duration of exposure is how long a single exposure event lasts following initial exposure to the drug product. The duration of exposure to the human user may affect the likelihood of a toxic effect occurring. One example is an animal drug administered by a topical route of administration to a companion animal. A topical exposure may increase the duration of exposure per exposure event for the human user and other household members because it may be absorbed by the user or other household members if not immediately washed off.

Another example is that the duration of exposure resulting from an accidental injection may last for multiple drug half-lives because once the drug is injected there are not typically methods to remove this exposure.

3. Risk Characterization

A risk characterization should communicate the overall determination of the risk or risks to the human user associated with use of an animal drug product. The risk characterization should describe all of the assumptions used in making the risk determination as well as any uncertainties that may exist within the risk assessment. The risk characterization may also describe what potential mitigations exist to reduce the overall HUS risk for an animal drug product. There are three main types of risk characterization for human user safety: qualitative, semi-quantitative, and quantitative. CVM will evaluate the HUS risk of a new animal drug product in a qualitative, semi-quantitative, or quantitative manner, based on the toxicity profile (hazard) of the new animal drug product and reasonably likely human exposure scenario(s). A quantitative risk assessment may not be necessary for all new animal drugs, as not all exposure patterns lend themselves to this type of assessment. Sponsors are encouraged to consider which type of assessment is most appropriate for the new animal drug under review.

a. Qualitative Risk Characterization

Qualitative risk characterization is focused on a descriptive analysis of hazard and exposure. An example of an exposure scenario whereby a qualitative risk characterization might be appropriate is the administration of a tablet dosage form. In this case, hazard is variable, the likelihood of exposure is low, and mitigation is reasonably likely to be adequately addressed by labeling language indicating that handwashing after administration is advised. Additional language in this scenario might also include instructions on what to do in case of accidental ingestion.

b. Semi-Quantitative Risk Characterization

A semi-quantitative risk characterization is predominantly used when sufficient information exists to help determine quantitatively either the hazard or exposure, but not both. An example might be a dermally applied animal drug product. If the hazard is well-defined, assumptions may be made about the exposure, even in the absence of specific exposure data. These exposure assumptions typically incorporate the use of maximal potential exposure which can give some information as to the overall risk profile for a new animal drug product and allow a HUS assessment to be conducted.

c. Quantitative Risk Characterization

A quantitative risk characterization may be used where sufficient information exists to quantitatively define both the hazard and exposure for a given animal drug product. This generally includes sufficient hazard information to identify the No-Observed-Adverse-Effect Level (NOAEL) as well as information on exposure estimates. Exposure information may come from default values that are scientifically justifiable

or from exposure studies conducted with the drug product, such as dislodgeable residue studies[13] for a topical product.

A risk characterization may include a quantitative evaluation such as a calculation of the margin of exposure (MOE) and its relationship to the uncertainty factors for a drug and its exposure scenario. The MOE is the ratio of the NOAEL to the estimated human exposure of a drug. Assessing whether the MOE value calculated represents acceptable user risk considers the uncertainty factors for the toxicity profile of a drug and exposure estimates. Uncertainty factors represent the uncertainty in the understanding of the data available to describe the adverse effect of a drug in an intended population. This may include the uncertainty in the difference of toxicity of an animal drug between humans and the animals used in a toxicity study (the interspecies factor), in the difference in sensitivity to an animal drug between humans (the intraspecies factor), in the difference of effects of studies of different exposure length (duration factor), or in other factors that are necessary to account for uncertainty in the knowledge base. The most common approach to applying uncertainty factors to a toxicological assessment is to consider a factor of 100X which represents both the intra- and inter-species uncertainty factors. The MOE should be higher than the uncertainty factors for a given drug product exposure scenario to ensure that there is a sufficient margin of safety to account for possible unknowns in exposure or toxicity of the animal drug product relative to the human user.

B. Other Considerations

Certain new animal drugs, such as drugs used in or on animal feeds, oncology drugs, controlled substances, emerging technology products, and protein-based drug products may have unique HUS safety concerns. Specific information, concerns, or types of studies may be relevant to the HUS assessment of these types of new animal drugs. Considerations for these types of new animal drugs are discussed below. Similar to other new animal drugs, HUS information for drugs used in or on animal feed, oncology drugs, controlled substances, emerging technology products, and protein-based drug products should be of sufficient depth to allow an adequate risk assessment by CVM.

1. Animal Drugs Used In or On Animal Feed[14]

The HUS risks associated with animal drugs used in or on animal feed may depend on factors such as the physical characteristics of the medicated article or Type B or C medicated feed (e.g., likelihood of dust generation during handling or the concentration of drug in the Type A medicated article versus that in the finished Type C medicated feed), or the type of feed in which the medicated article is proposed to be mixed (e.g., dry versus liquid, or pelleted versus mash feed, etc.). Routes of exposure to Type A

[13] Dislodgeable residue studies may also be referred to as transferrable residue studies, "wipe" test or studies, "petting with white gloves" studies, "stroking" studies, or "petting" studies.

[14] A sponsor may seek approval for a medicated feed for use in companion animals. In such a case, sponsors may also need to address factors relevant to companion animal exposure scenarios. Sponsors are encouraged to contact CVM to discuss HUS for such proposed products.

medicated articles and drugs in Type B or C medicated feeds may include inhalation, ingestion, and exposure of skin and eyes.

Relevant differences in overall exposure and mitigation strategies are drug and formulation dependent and evaluation of this information occurs on a case-by-case basis. For animal drugs used in or on animal feed, Type A medicated articles contain higher concentrations of the API than the medicated feed. Hazards, routes of exposure, and mitigation strategies for a Type A medicated article may be different than those for a Type B and/or C medicated feed containing that Type A medicated article. The HUS assessment for new animal drug applications for Type A medicated articles should address both the concerns relevant to the use and handling of the Type A medicated article as well as the concerns relevant to the preparation, handling, and feeding of the resulting medicated feed(s) when prepared at the maximum inclusion rates proposed for the labeling.

2. Oncology Drugs for Use in Animals

The narrow therapeutic margin of safety for many oncology drugs for use in animals presents unique HUS considerations for the person(s) administering these types of drugs and those exposed to the treated animal via residual drug or active metabolites on the animal or in bodily fluids/excreta such as urine, feces, vomit, and saliva. The HUS assessment for oncology drugs may necessitate evaluations of the pharmacokinetics, pharmacodynamics, and excretion of the drug product and active metabolites. These evaluations may be necessary to: 1) estimate the potential exposure to excreted drug or active metabolites, and 2) guide labeling recommendations for safe handling of the animal and bodily fluids/excreta after treatment. Refer to CVM GFI #237, "Oncology Drugs for Companion Animals,"[15] for specific recommendations regarding HUS for oncology drugs.

3. Controlled Substances

New chemical entities with the potential for abuse, as well as drugs that are scheduled under the Controlled Substances Act, are candidates for an assessment of abuse potential. These drugs may have unique HUS concerns associated with accidental exposure or intentional misuse. Sponsors may refer to the CDER GFI, "Assessment of Abuse Potential of Drugs,"[16] (January 2017) for additional guidance. Specific information on controlled substances may also be found in the Controlled Substances Act.[17]

Specific HUS concerns related to controlled substances depend on factors such as the active ingredient, dosage form, route of administration, and whether the new animal drug is intended to be used on farms/within animal production facilities, dispensed for administration at home to a companion animal, or limited to use within veterinary

[15] https://www.fda.gov/media/98399/download

[16] https://www.fda.gov/media/116739/download

[17] See 21 U.S.C. § 13

practices. Sponsors should contact CVM early in the development process to determine if an assessment of abuse potential is needed and how best to address potential HUS concerns associated with the proposed new animal drug.

4. Emerging Technology Products

Products that utilize an emerging technology often have novel mechanisms of action or other characteristics and may have unique HUS considerations. Examples of these products may include animal cells, tissues, and cell- and tissue-based products (ACTPs), intentional genomic alterations (IGAs), and gene therapy-based animal drugs. HUS assessments for products that utilize an emerging technology may differ from assessments of traditional new animal drugs; for example, the "dose-response" relationship may not apply to the risks of some ACTPs and IGAs.

- HUS considerations for ACTPs may include, but are not limited to:
    - Exposure to donor infectious disease agents
    - Exposure to toxins produced by the ACTP
    - Hypersensitivity to the ACTP or excipients
    - Handling coolants such as liquid nitrogen and solid carbon dioxide
- HUS considerations for IGAs may include, but are not limited to:
    - Human exposure in the environment to any substances produced by the IGA in animals, such as toxins, allergens, or substances that may contribute to antimicrobial resistance
    - Infectious agents if the animals are modified to serve as infectious disease models or are intended to be resistant to zoonotic pathogens, and
    - Risks associated with handling the construct, vector, or other material used to create the IGA
- HUS considerations for gene therapy-based products may include, but are not limited to:
    - Viral shedding
    - Immunogenicity
    - Handling viral vectors
    - Specific risks related to inadvertent gene expression in the human user

5. Protein-based drug products

Protein-based drug products (e.g., proteins, modified proteins, and peptide products) for use in animals may pose a risk to the human user due to their potential to induce an adverse immune system response subsequent to accidental exposure. Examples of

adverse immune system responses may be anaphylactoid reactions, immunogenicity, or immune system activation. Additionally, if the animal drug protein is highly homologous to a human protein, it may cross-react with human protein receptors and potentially result in an effect in humans that is similar to the desired effect in the target animal or adversely affect an endogenous protein.

HUS assessments for protein-based drug products may differ somewhat from assessments of traditional new animal drugs. While the "dose-response" relationship may not apply to the hazard characterization of some protein-based animal drugs, there may be safety concerns associated with accidental exposure to these drugs that should be factored into the overall risk to the human user.

VI. Sources of Information

A variety of sources of information may be used to support a HUS assessment. Sponsors should consider how the quality and relevance of the information submitted for evaluation may impact the HUS assessment. If foreign language documents are used to support the HUS assessment, complete and accurate English translations of such documents must be included in the submission. Sponsors may consider including, but are not limited to providing, the following types of information:

A. Sponsor Generated Studies

1. Toxicity Studies

Toxicity studies are studies conducted *in vivo* or *in vitro* to demonstrate hazards associated with exposure to an animal drug. These studies may be conducted in a variety of non-human species or cell-based models. Toxicity information should typically focus on studies using standard laboratory animal species. Toxicity studies can be used to identify if the API, inactive ingredients, or drug product possesses a potential human health hazard. The information provided by these studies may be extrapolated to estimate the effects of human exposure. These studies may include acute lethal toxicity studies (oral, dermal and inhalation), irritation studies (dermal and ocular), and skin sensitization studies, in addition to longer term subchronic, chronic, reproductive, developmental, carcinogenicity, and genotoxicity studies. For new animal drugs intended for use in food-producing animals, the studies conducted to determine human food safety may also provide information that can be used when determining HUS.

2. Target Animal Studies

a. Target Animal Safety Studies

Target animal safety studies are studies conducted in the target animal species to provide information on the safety of an investigational product in the intended species under the proposed conditions of use. These studies are typically conducted under laboratory conditions and include reports of adverse findings in animals after drug administration which may provide information relevant to various routes of exposures

(i.e., oral, skin eye, etc.) consistent with accidental human exposure(s) and/or resultant clinical signs. These studies may also capture data on accidental exposure(s) in humans administering the drug and handling the animals during the study and resultant clinical signs observed during the study.

b. Field Studies:

Field studies are studies conducted in the target animal species to demonstrate effectiveness and safety of a proposed new animal drug when it is used under typical or expected conditions of use and according to the proposed labeling. These studies also include reports of adverse events in animals and may include information on any accidental human exposure(s) and resultant clinical signs observed during the study.

3. Post-Administration Studies:

Post-administration studies are studies conducted in the target animal species to determine the likely exposure of a human user to a new animal drug, or metabolized component of the new animal drug, after the animal drug has been administered. Post-administration studies may include, but are not limited to, the use of pharmacological modeling or evaluation of excretion data or physical evaluation of drug residues. One type of post-administration study that CVM may recommend is the dislodgeable residue study for topical products. Dislodgeable residue studies for topical products can provide information to estimate the dermal exposure levels of users after administration of the new animal drug. Dislodgeable residue studies may also be used to help determine the seclusion time[18] (time the animal should be secluded without human contact) needed following treatment of the animal to mitigate human exposure to the drug. CVM generally recommends sponsors submit study protocols for dislodgeable residue studies for review prior to study conduct.

4. Human Factor Studies

Human factor studies can provide information regarding risk of accidental human exposure during animal drug administration. Human factor studies are conducted with representative users to assess the adequacy of the product-user interface design to eliminate or mitigate potential use-related hazards. Human factor studies may be recommended when administration of the new animal drug includes a proprietary dosing device (e.g., syringe). The human factor study primarily evaluates: (i) the ability of the user to perform critical tasks necessary for the safe and effective administration and use of the new animal drug, and (ii) the ability of the user to understand labeling language critical to the safe and effective use of the new animal drug. Additional information or data may be collected during these studies as needed.

B. Previously Approved Drug Information

[18] Seclusion time may also be referred to as "no contact" time.

This includes, but is not limited to, animal drug labeling, human drug labeling, Freedom of Information summaries, adverse drug event reports (for the same or similar drugs or APIs used in veterinary or human medicine), and pharmacovigilance reports (e.g., periodic safety update reports or periodic drug experience reporting) for previously approved drugs.

C. Literature

Use of scientific literature is of interest because it makes use of existing knowledge and may reduce or eliminate the need for additional animal studies, or *in vitro* studies, to support HUS. While publications may describe an animal drug's safety, effectiveness, and chemical or pharmacological characteristics, individual publications may be insufficient to define all the relevant HUS risks of a given animal drug. However, when used in aggregate, literature may provide significant inferential value on the HUS risks posed by a new animal drug. Considerations for the use of literature, including types of review methods to synthesize information from a single or multiple publications, as well as other information on the use of literature to support drug approval, may be found in CVM GFI #106, "The Use of Published Literature in Support of New Animal Drug Approvals."[19]

D. Safety Data Sheets (SDS)

SDS may provide information on the physical properties of chemical components of an animal drug product or the API, health and environmental hazards, protective measures, and safety precautions for handling and storing the drug product, its API, or excipients. If SDS are submitted by sponsors, they should contain the information required by Occupational Safety and Health Administration and the United Nations Global Harmonization System. Sponsors should provide the source of SDS submitted to CVM.

E. Reports

Use of published reports may provide relevant supporting information. These reports may come from sources such as, but not limited to:

- Other Federal regulatory authorities (e.g., Environmental Protection Agency, United States Department of Agriculture).
- International bodies (e.g., FAO/WHO JECFA) or regulatory authorities (e.g., European Medicines Agency).

In combination with the information provided by the sponsor, CVM may also consider information from other sources, including, but not limited to, independent literature searches, opinions published or communicated by other regulatory agencies (US or foreign countries), other submissions to the INAD or NADA file, professional conferences and communication with subject matter experts, similarity to drugs approved for human use, and adverse drug experience reports of the same or similar drugs used in veterinary or human medicine.

[19] https://www.fda.gov/media/70056/download (April 2022).

VII. HUS Recommendations

The HUS concerns identified for each new animal drug help determine which mitigation strategies are appropriate to address potential risks to human users. CVM recommends that sponsors use all available data and information to consider how to appropriately address the HUS risk for a proposed new animal drug.

Mitigation strategies may incorporate the use of labeling language and/or other non-labeling-based strategies such as marketing status, packaging (including special storage conditions), or other physical mitigations (including dosing equipment). Proposed risk mitigation strategies should reduce human user exposure to an acceptable level and should be reasonable to implement for a given animal drug. Sponsors should consider that more than one strategy may be necessary to sufficiently minimize the HUS risk. Sponsors should be aware that risk mitigation strategies for a new animal drug may be different across various animal species and classes, as well as with different dosage forms and conditions of use. These risk mitigation strategies may also differ from risk mitigation strategies implemented for human drug products. Sponsors are encouraged to proactively examine what risks may occur during use or exposure to the new animal drug and propose appropriate mitigation strategy(ies).

A. Non-Labeling Based Strategies

Some non-labeling based strategies by which HUS risk may be mitigated include, but are not limited to, the following:

1. Marketing (Dispensing) Status (Rx, OTC or VFD):

HUS is part of the determination of marketing status. A new animal drug that has HUS concerns, such that adequate directions for safe lay use cannot be written, is not eligible for approval for OTC use.

2. Selection of Packaging:

The primary (immediate) and secondary containers (packaging surrounding the immediate container) are instrumental in mitigating risk to the human user, as are the volume or amount of the new animal drug in the immediate container and how the new animal drug is removed or withdrawn from the container. Modification of packaging is a mechanism by which risk may be reduced for a new animal drug. Examples of risk mitigating packaging include, but are not limited to, child safe packaging, blister packs, or pre-loaded syringes. Furthermore, a new animal drug may pose a risk only when the exposure reaches a certain dose. In these cases, risk might be reduced by limiting the volume or amount of the drug in the primary container, vial, or syringe.

3. Administration Method

Drug delivery equipment (e.g., a safety syringe or other dosing device) may be important to limit or prevent exposures of concern to human users. In the new animal drug application, sponsors should include information on the use of appropriate drug delivery

equipment, if applicable. If a specific dosing device is necessary to administer a new animal drug, the dosing device will be evaluated as part of the overall new animal drug approval. Instructions may be necessary to direct the safe use of drug specific dosing devices. If non-specific administration devices are used (e.g., non-proprietary oral syringes), risk mitigation might include, for example, limiting the volume or amount of drug to be administered at each dosing.

4. Use of PPE:

The use of PPE, where appropriate, during any phase of new animal drug administration may be important to limit or prevent exposures of concern to human users. PPE may include, but is not limited to, goggles, face shields, respirators of varying types, long sleeves and long pants, lab coats, gloves, and boot covers. Another time when PPE use might be appropriate may be when handling animal waste from treated animals. Proposed PPE should be reasonable to implement for a given animal drug under expected conditions of use.

B. Labeling Strategies:

Specific labeling elements (e.g., labeling statements, boxed warnings, client information sheet, etc.) may be appropriate as mitigation strategies to direct the safe use of the product and convey HUS concerns related to risk (hazard and/or exposure) to the human user that are not otherwise mitigated through non-labeling based strategies. New animal drugs with novel chemical entities or routes of administration in a given species may benefit from use of specific labeling statements or incorporation of other labeling elements (e.g., client information sheets, instructional media, etc.) to adequately direct their safe use. In addition, some animal drugs (e.g., oncology drugs or gene therapy-based drugs) should include specific HUS related language on investigational labeling or other documents (e.g., informed consent sheets) used during investigational studies prior to approval. Sponsors should contact CVM if there are questions regarding labeling or related documents.

HUS-related labeling language from similar animal drugs/drug classes may be applicable to a proposed new animal drug. Final labeling will reflect current scientific knowledge and supportive data in the drug submission file(s) for the new animal drug as well as general best practices related to risk communication. Therefore, HUS-related language for certain new animal drugs might not be identical to other similar approved products.

For new animal drugs with approved counterparts for human use that have HUS warning, precaution, or contraindication language, CVM recommends that sponsors use all of the appropriate warning, precaution, and contraindication HUS language related to human exposures for these drugs.[20] Such HUS labeling language of a new animal drug should be consistent with the language present on approved human drugs; however, labeling language

[20] See CDER/CBER GFI, "Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format."

may be adapted to reflect applicable differences between the animal drug and human drug (e.g., formulation, dosage and administration, etc.).

If HUS risks and mitigation strategies associated with a Type A medicated article apply to the Type B and/or C medicated feed at the proposed inclusion rates, then relevant HUS labeling statements may be appropriate for the medicated feed Blue Bird label for that product. Conversely, there may also be risks and mitigation strategies associated with the Type B and/or Type C medicated feed that are not applicable to the Type A medicated article. Applicable HUS statements should be included on the representative labeling[21] for Type B and/or Type C medicated feed, including free-choice medicated feed.

Applicable HUS product warnings and safety measures are communicated in the User Safety Warnings section of the package insert, as well as the FOI summary document for all approved new animal drugs. This information may also be presented on other labeling components (e.g., the label, client information sheets, product cartons, and shipping containers) if needed. Labeling language to address HUS concerns should clearly convey the specific risks associated with use of the product and safety measure descriptions for mitigation of those risks. Applicable labeling language should be expressed using simple terminology where possible and should consider the end-user reading the label. In addition to the warning language, the placement, size, and prominence of these warnings may also aid in mitigation of risk.

Boxed warnings *[21 CFR §201.57(c)(1)]* might be appropriate in the case of serious warnings, particularly human user exposures or adverse events that may lead to death or serious injury of the human user. These practices generally follow recommendations made in Section IV. *Boxed Warning (§ 201.57(c)(5))* of the CDER/CBER 2011 GFI, "Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescriptions Drug and Biological Products—Content and Format."[22]

CVM recommends that sponsors include the following HUS related information on new animal drug labeling:

1. In the User Safety Warnings section:
    a. Begin the User Safety Warnings section of labeling with: "Not for use in humans. Keep out of reach of children."
    b. Describe how to obtain a copy of the SDS for the product.

2. In the Contact Information section: Describe how to report suspected adverse drug experiences associated with product use. We recommend the following language: "To report suspected adverse drug experiences, contact [insert name of business] at [insert business telephone number]. For additional information about reporting

[21] See Guidance for Industry #181, "Blue Bird Medicated Feed Labels." The guidance provides recommendations on the content and format of the representative Blue Bird labeling proposed to be used for Type B and Type C medicated feed only.

[22] https://www.fda.gov/media/71866/download

adverse drug experiences for animal drugs, contact FDA at [insert current FDA telephone number for voluntary reporting of adverse drug experiences] or http://www.fda.gov/reportanimalae."

To further protect human health, additional descriptive warnings and safety measures are sometimes used on new animal drug labeling. The following are examples of other HUS information that might appear on labeling:

1. Words, icons, and/or graphics to identify specific product risks or to illustrate mitigation procedures.
2. Statements addressing use and handling of the new animal drug by sensitive populations (e.g., women who are pregnant or may become pregnant, women who are breastfeeding, children, persons who are immunocompromised, or persons with hypersensitivity to a drug or drug class). If handling of an animal drug may result in increased risk to certain populations, then labeling statements recommending extra caution for those administering or coming into contact with the animal drug or treated animals should be considered.
3. Labeling statement(s) to identify the types of exposure that should be avoided to minimize the identified risk(s) and what safety measures should be taken to avoid such exposures (e.g., use of PPE during product handling or administration, avoiding contact with the treated area of an animal after application of transdermal drug products).
    a. This information typically focuses on the most likely routes of accidental or inadvertent exposure for a given animal drug.
    b. If PPE is recommended for use with a new animal drug, then it should be available to the end-user and able to be used appropriately when handling or administering the new animal drug.
4. Recommended steps for medical attention in the event of human exposure. These may include, but are not limited to:
    a. Specific first aid measures that can be undertaken to reduce potential harm (e.g., washing hands, flushing eyes, or inducing vomiting).
    b. How to seek professional medical help (e.g., contact poison control or a human physician).
    c. Information for physicians or poison control centers on specific treatment procedures that should or can be employed after potential or confirmed exposure, if defined care options are known.
5. Considerations for handling bodily fluids/excreta or animal carcasses of treated animals in special situations. Examples of such special situations may include, but are not limited to:
    a. Oncology drugs for animals: For oncology drugs proposed for use in animals, CVM recommends that sponsors refer to the CVM GFI #237, "Oncology

Drugs for Companion Animals," for specific recommendations for the client information sheet and labeling.

b. Emerging Technologies: Waste and carcasses from animals with IGAs and animals treated with ACTPs or gene therapy products may necessitate special disposal procedures.

When the immediate container and/or outer packaging for a new animal drug cannot fully accommodate HUS warnings from the package insert due to space considerations, sponsors should ensure that relevant information is communicated to the user on the animal drug label and outer packaging. In such cases, an abbreviated User Safety Warning referring the human user to the package insert should be added to the immediate container label and secondary container (e.g., packaging that surrounds the immediate container) for the animal drug. Sponsors should also consider the need for User Safety Warning language on shipping labeling.

CVM's Office of New Animal Drug Evaluation (ONADE) considers, on a case-by-case basis, requests to provide a translation of significant HUS related language into another language (typically Spanish) in situations where non-English speaking farm personnel are likely to administer the new animal drug and significant harm could come to the worker(s) if accidentally exposed to the new animal drug or if the new animal drug is used inappropriately. Sponsors are responsible for the accuracy of the foreign-language translation.

VIII. How HUS Information Should Be Submitted to CVM

Sponsors are encouraged to contact CVM if unsure of when to submit HUS information, what information and data should be submitted together, or how to make a HUS submission (including those related to devices necessary for drug administration). The ONADE project managers (PMs) serve as a central point of contact for pioneer drug sponsors and can provide information about the new animal drug review process and ONADE's regulatory procedures. If sponsors have questions and do not have an ONADE PM assigned to their company, sponsors can contact the PMs through the CVM mailbox CVM.ONADE.PM@fda.hhs.govmailto:AskCVM@fda.hhs.gov. Sponsors of generic new animal drugs should contact the Division of Generic Animal Drugs at CVMDGADMGT@fda.hhs.gov.

HUS information can be discussed with CVM at various points in the development process. Correspondingly, HUS information may be submitted to ONADE for review under various submission types. CVM recommends considering what HUS concerns a new animal drug may have as early in the drug approval process as possible. Information relevant to the HUS assessment for a new animal drug can be submitted with the initial submission (A-0000) to the INAD file or JINAD file, with a request for a presubmission conference (Z-submission), or as a data submission (P-submission) to the INAD file or as a part of the NADA file. In certain circumstances, HUS information can also be submitted under other submission types. If HUS information is submitted under a data submission it can be submitted as a stand-alone submission to the INAD file (under the TAS technical section) or in conjunction with TAS data. While

CVM generally requests that substantive HUS information be submitted as part of a data submission, CVM encourages sponsors to discuss during the presubmission conference, or other relevant meetings, what HUS information should be submitted and when the HUS information should be submitted.

CVM recommends sponsors use the initial presubmission conference process to discuss plans to address HUS or unique aspects of the new animal drug or conditions of use that impact HUS. The amount of information provided and the level of detail of the information provided should be commensurate with the submission type. If substantive HUS information and/or study report(s) commensurate with a major technical section will be submitted, this information should be submitted as a data submission (P-submission; TAS technical section submission) or in a NADA. Sponsors should consult with CVM prior to submitting substantial HUS information outside of a major technical section. The assessment of abuse potential for veterinary products can be addressed as part of the HUS assessment under the Target Animal Safety technical section or as agreed upon with CVM.

When submitting HUS information as part of a technical section, sponsors should include a cohesive justification of appropriate mitigation measures that incorporate aforementioned HUS components (exposure, hazard, user population, target animal population, etc.). If HUS information is submitted under multiple submissions, sponsors should bring this to the attention of CVM. CVM recommends sponsors submit all relevant draft labeling statements pertaining to HUS with the HUS information as it is submitted to CVM for review. Any additional relevant HUS information that becomes apparent subsequent to the initial review of HUS information may be included in the next TAS technical section submission, if applicable, or in the All Other Information technical section. If this situation occurs, sponsors should inform CVM of the presence of this new information in the cover letter for the submission.

IX. Special Considerations for Generic New Animal Drugs (ANADA)

CVM cannot approve an ANADA that necessitates the conduct of novel safety studies to support HUS. Deviations from the RLNAD that generate questions on the comparability of HUS between the RLNAD and the proposed generic drug are typically not permissible. If a generic new animal drug sponsor submits a suitability petition that requires review of additional HUS considerations, CVM will review the petition and determine if additional labeling language (e.g., warning language) is necessary. It is not possible for CVM to grant a suitability petition if the change requested necessitates completion of additional safety studies to support the generic new animal drug approval. As early in product development as possible, sponsors with a suitability petition granted for a change in route of administration or dosage form should consider discussing with CVM if there is a need to modify HUS language due to the change.

During the generic new animal drug approval process, HUS warnings or related labeling language are evaluated as part of the labeling review. In general, generic labeling must include all HUS labeling language and HUS warnings that are present on all RLNAD labeling.[23] However, for some generic drugs (e.g., generic versions of older drugs), CVM may recommend

[23] See section 512(c)(2)(A)(vii) of the FD&C Act.

the use of updated HUS labeling language to reflect current thinking or general labeling improvements that CVM is recommending for all products. To update HUS labeling language for an approved generic new animal drug, sponsors should submit a supplemental application for review to the Division of Generic Animal Drugs.

Packaging for generic drugs should generally incorporate the same risk mitigation techniques as the RLNAD. However, generic drug sponsors may employ different risk mitigation techniques provided the alternative method has demonstrated the desired safety properties and achieves the same goal as those used for the RLNAD product. CVM recommends that generic drug sponsors discuss proposed mitigation methods with CVM as early as possible in the product development.

For further questions regarding HUS for generic new animal drugs, sponsors should contact the Division of Generic Animal Drugs at: CVMDGADMGT@fda.hhs.gov.