Guidance for Industry

Animal Models — Essential Elements to Address Efficacy Under the Animal Rule

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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TABLE OF CONTENTS

I. INTRODUCTION **4**

II. BACKGROUND **5**

III. ANIMAL RULE CONSIDERATIONS **5**

IV. DISCUSSION OF ESSENTIAL DATA ELEMENTS OF AN ANIMAL MODEL **7**

A. Characteristics of CBRN Agent that Influence the Disease or Condition **7**

1. The Challenge Agent *7*
2. Pathogenic Determinants *8*
3. Route of Exposure *8*
4. Quantification of Exposure *8*

B. Host Susceptibility and Response to Etiologic Agent **8**

C. Natural History of Disease: Pathophysiologic Comparability **9**

1. Time to Onset of Disease/Condition *10*
2. Time Course of Progression of Disease/Condition *10*
3. Manifestations (signs and symptoms) *10*

D. Trigger for Intervention **11**

E. Characterization of Medical Intervention **11**

1. Product Class *11*
2. Mechanism of Action *12*
3. In vitro Activity *12*
4. Activity in Disease/Condition of Similar Pathophysiology *12*
5. Pharmacokinetics (PK) in Unaffected Animals/Humans *12*
6. PK/PD (Pharmacokinetics/Pharmacodynamics) in Affected Animals/Humans *12*
7. PK Interactions with Medical Products Likely to Be Used Concomitantly *13*
8. Synergy or Antagonism of Medical Products Likely to Be Used in Combination *13*

F. Design Considerations for Animal Efficacy Studies **13**

1. Endpoints *14*
2. Timing of intervention *14*
3. Route of Administration *15*
4. Dosing Regimen *15*

V. HUMAN SAFETY INFORMATION **16**

VI. ESSENTIAL DATA ELEMENTS OF AN ANIMAL MODEL **16**

ATTACHMENT A: ACRONYMS AND ABBREVIATIONS **18**

REFERENCES **19**

Guidance for Industry[1]
Animal Models — Essential Elements to Address Efficacy Under the Animal Rule

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides information to potential sponsors (industry, academia, and government) on the development of animal models to study efficacy. The guidance focuses on the identification of the critical characteristics (essential data elements) of an animal model to be addressed when developing drug or biological products for approval or licensure, respectively, under the Animal Rule (see 21 CFR 314.600 for drugs; 21 CFR 601.90 for biological products).

This guidance does not address:

- The preclinical pharmacology/toxicology studies necessary for early drug or biological product development
- The details of study design and conduct for either animal efficacy studies or human safety studies
- The development of animal models for other purposes, such as for assessment of toxicology
- The threshold for determining that human efficacy studies are not ethical and/or not feasible

FDA's guidance documents, including this guidance, 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.

[1] This guidance has been prepared by the Animal Model Characterization Working Group in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

II. BACKGROUND

FDA's regulations concerning the approval of new drugs or biological products when human efficacy studies are neither ethical nor feasible are known as "the Animal Rule" (21 CFR 314.600 for drugs; 21 CFR 601.90 for biological products). The Animal Rule states that in selected circumstances, when it is neither ethical nor feasible to conduct human efficacy studies, FDA may grant marketing approval based on adequate and well-controlled animal studies when the results of those studies establish that the drug or biological product is reasonably likely to produce clinical benefit in humans. Demonstration of the product's safety in humans is still necessary (see section V.).

The purpose of this guidance is to identify the critical characteristics of an animal model that should be addressed when efficacy of the product under development will be established under the Animal Rule.

The critical characteristics discussed in section IV identify the essential elements to be considered and fully explored as part of the development of an animal model. All elements may not be achievable for each etiologic agent[2] and intervention[3] being studied. Early and frequent interactions between FDA and the sponsor are recommended to discuss these elements and any issues encountered by the sponsor. Current FDA requirements for establishing the safety of a product in humans continue to apply. Although the discussion in this guidance touches on clinical safety, it is not meant to address all requirements for assurance of human safety.

III. ANIMAL RULE CONSIDERATIONS

To develop an animal model to demonstrate efficacy, the sponsor should obtain information on the natural history of the disease or condition in both humans and animals, on the etiologic agent, and on the proposed intervention. Data from the human experience with the etiologic agent and/or with the intervention, if available, may support applicability of the animal model.

The Animal Rule states that FDA can rely on the evidence from animal studies to provide substantial evidence of effectiveness only when:

1. There is a reasonably well-understood pathophysiological mechanism of the toxicity of the (chemical, biological, radiological, or nuclear) substance and its prevention or substantial reduction by the product
2. The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal

[2] For this document the terms *agent*, *threat agent*, or *etiologic agent* refer to lethal or permanently disabling toxic chemical, biological, radiological or nuclear (CBRN) substances regarding which efficacy studies in humans are neither ethical nor feasible. The term *challenge agent* refers to the CBRN material used in the animal studies.

[3] The terms *treatment* and *therapy* refer to any intervention that prevents or mitigates the toxicity of these etiologic agents.

species that represents a sufficiently well-characterized animal model[4] for predicting the response in humans

3. The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity
4. The data or information on the (pharmaco) kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans

(21 CFR 314.610(a)(1)-(4); 21 CFR 601.91(a)(1)-(4))

If these criteria are met, it is reasonable to expect the effectiveness of the product in animals to be a reliable indicator of its effectiveness in humans.

The Animal Rule allows approval based on a single animal species, if the animal model is sufficiently well-characterized; however the usual expectation is that efficacy will be demonstrated in more than one species. In order to support approval based on one animal species, in general more than one efficacy study using that species should be conducted to demonstrate reproducibility of the results.

Data from animal studies to demonstrate dose-response and to support the dose selected for the animal efficacy studies are expected as is the case for traditional product development. Sponsors of products approved for other indications may be asked to provide additional nonclinical and/or clinical data to support approval/licensure of the proposed product for the indication under consideration.

If another regulatory pathway to approval (i.e., one using human data) is feasible and ethical, that pathway must be used (21 CFR 314.600 and 601.90). Although the Animal Rule allows development of products that would otherwise not have any route to approval, the rule reflects the Agency's recognition that many treatments that appeared effective in animals have not proved to be effective in humans. Consequently, developing animal models that will yield efficacy results that can be expected to be predictive for humans is challenging. The animal studies must be adequate and well-controlled (21 CFR 314.610 and 601.91), and should use the pertinent features of an adequate and well-controlled clinical study, such as a detailed protocol with randomization and adequate blinding and a statistical plan as described in 21 CFR 314.126.

Early and frequent interactions between FDA and the sponsor are recommended to discuss the applicability of the Animal Rule and specific areas of concern, as well as to enable the review of, and comment on, protocols prior to study initiation. FDA may seek Advisory Committee consultation before approval and/or early in the development process to discuss whether the concept of using certain animal data to support efficacy is reasonable.

All studies intended to support approval under the Animal Rule must be carried out under the procedures and controls outlined in FDA's Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies regulations (21 CFR Part 58). FDA recognizes that conforming to GLP regulations in the conduct of studies on CBRN agents may present challenges. Such issues and

[4] A "sufficiently well-characterized animal model" is one for which the model has been adequately evaluated for its responsiveness.

their possible impact on study results and conclusions, should be discussed with the review division prior to conduct of the studies. In addition, the studies must comply with the Animal Welfare Act (7 U.S.C. 2131). For certain infectious agents, sponsors must adhere to the Select Agent Rule[5] and should comply with standards on the use of Biosafety Level (BSL) laboratory facilities.[6]

The animal efficacy studies conducted to support approval under the Animal Rule are likely to use a significant number of animals. Sponsors should submit detailed protocols (see 21 CFR 312.23(a)(6)) and provide for frequent monitoring throughout the study period. FDA strongly encourages sponsors to submit a development plan and to communicate frequently with the Agency when developing products under the Animal Rule. The protocols for the animal efficacy studies should be discussed with FDA, with sufficient time for FDA review and comment, prior to the study being conducted.

IV. DISCUSSION OF ESSENTIAL DATA ELEMENTS OF AN ANIMAL MODEL

This section provides further information on the Table, Essential Data Elements of an Animal Model, found in section VI.

A. Characteristics of CBRN Agent that Influence the Disease or Condition

Some characteristics of the specific chemical, biological, radiological, and/or nuclear (CBRN) agent that influence the disease or condition under study include: the challenge agent, pathogenic determinants, the route of exposure, and quantification of exposure.

1. The Challenge Agent

The challenge agent used in animal studies generally should be identical to the etiologic agent that causes the human disease. The purity of the challenge preparation should be documented when appropriate. If the challenge agent is different from the etiologic agent known to cause human disease, the sponsor should provide justification for the use of this challenge agent and explain why, when used in the proposed animal model, it should be considered suitable for establishing effectiveness of the intervention in humans. For example, for an animal efficacy study to support approval of a radiation countermeasure, a sponsor may not be able to predict the actual radiation exposure that would follow a nuclear detonation or the subsequent fallout. In such a case, the sponsor should provide a detailed explanation of the appropriateness of the type of radiation and dose used in the study and its relevance to the clinical situation. FDA strongly recommends that the scientific approach under consideration be discussed with FDA prior to the start of the animal studies.

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[5] See Select Agent Rule (42 CFR Parts 72 & 73) available at http://www.cdc.gov/od/sap/final_rule.htm.

[6] See 5th Edition of Biosafety in Microbiological and Biomedical Laboratories (BMBL), available at http://www.cdc.gov/od/ohs/biosfty/bmbl5/bmbl5toc.htm.

2. Pathogenic Determinants

It should be demonstrated that the pathogenic determinants of disease in the animal model are similar to those understood for humans. Pathogenic determinants can include toxin production, target organs or enzyme systems, or type of radiation. For example, although mice and guinea pigs are susceptible to *Bacillus anthracis*, the pathogenesis and mechanism of toxicity are different from those in humans, so that these rodent species may not be appropriate efficacy models for anthrax.[7] Animal species that are not susceptible to the agent, or do not demonstrate the endpoint of interest (i.e., potential for mortality or major morbidity that might be reduced or prevented by sufficiently effective interventions) are not suitable for the efficacy studies.

3. Route of Exposure

In general, the animal models developed should use a route of exposure to the challenge agent that is the same as the anticipated human exposure route. This is especially important for conditions for which the route of exposure is directly related to pathogenesis. For example, human infection with *Yersinia pestis* through flea bite, the intravenous (IV) route, or aerosol exposure results in the development of bubonic, septicemic, or pneumonic plague, respectively. If a sponsor is proposing a route of exposure to the etiologic agent in animals that is different from what is expected in humans, adequate scientific justification should be provided. FDA strongly recommends that if such an approach is being considered, it should be discussed with FDA before the start of the animal studies.

4. Quantification of Exposure

Reliable quantification and reproducibility of the challenge dose should be demonstrated. When appropriate, the sponsor should describe the scalar relationship of the animal dose to that anticipated in human disease. If large differences are observed, then potential implications for interpretation of comparative pathogenesis, pathophysiology, and study results should be discussed with FDA. Standardization of the challenge dose may be a consideration in the future to ensure robust evaluation of data in the determination of effectiveness.

B. Host Susceptibility and Response to Etiologic Agent

The animal model chosen for development should be susceptible to the threat agent. FDA recognizes there may be species differences. For example, an animal species being used to study efficacy for a radiation countermeasure may require a different threshold of radiation exposure to develop acute radiation syndrome, but the animal species may still be appropriate for study if the resulting illness and course are similar in the animal species and humans. However, if this threshold differs greatly from the human threshold, the suitability of the animal model may be

[7] Leffel, E.K. and Pitt, L.M., Anthrax. In *Biodefense: Research Methodology and Animal Models*. Swearengen, J.R. ed. Boca Raton, FL. CRC Press, 2006, 77-93.

called into question. The factor that determines differences in susceptibility to the threat agent should be described to the best extent possible (e.g., see the discussion of pyridostigmine and soman in section E.2).

The response to the etiologic agent (resulting illness or injury) manifested by the animal species exposed to that agent should be similar to the illness or injury seen in humans. For example, mustard gas typically produces extensive blistering to exposed human skin. If the animal species evaluated does not have blistering as a prominent feature of exposure to mustard gas, it is unlikely that this animal model would be acceptable to the Agency. If the sponsor believes that such a model is supportive to the study of its investigational drug, the model should be discussed with the Agency and a justification should be provided

C. Natural History of Disease: Pathophysiologic Comparability

The natural history of disease in animals and in humans should be characterized, compared, and discussed with the Agency before the sponsor initiates intervention studies in animals. In some instances, use of several different models in the same development plan can be considered. Experimental parameters may need to be modified to create a condition that more closely mimics the disease in humans. For example, variola virus causes human smallpox, and humans are the only known natural host. Nonhuman primate animal models that have been studied using variola virus as the challenge agent require a large inoculum, and often the IV route of administration is used. FDA recommends that compounds found to be active in vitro against orthopoxviruses be studied in several animal models using multiple different orthopoxviruses initially. Based on data from initial studies and availability of suitably characterized models, the next step may be to assess the appropriateness of additional study in an animal model using variola.[8] Sponsors who plan to use an animal model that involves exposure to a challenge agent that is different from the known etiologic agent in humans should discuss this with the Agency along with their planned protocols and any major differences in, or limitations of, the animal model.

When comparing the disease in animals with the disease in humans, sponsors should include time to onset of disease/condition; time course of progression of disease; and manifestations, that is, signs and symptoms (severity, progression, clinical and pathologic features, laboratory parameters, the extent of organ involvement, morbidity, and outcome of disease). A single animal model may not reflect the entire spectrum of human disease. The time to onset of disease, progression of disease, and the manifestations/outcome can be influenced by many factors, including concentration and type of etiologic agent, virulence or lethal potential of the etiologic agent, route of exposure, and other host factors including immune status.

[8] See FDA's draft guidance for industry *Smallpox (Variola) Infection: Developing Drugs for Treatment or Prevention.* Once finalized this guidance will represent the Agency's thinking on this topic.
Also, we update guidances periodically. To make sure you have the most recent version of a guidance, check the appropriate (CDER or CBER) guidance Web site, listed on the second title page of the guidance.

1. Time to Onset of Disease/Condition

The time to onset of disease/condition in animals should be reasonably similar to that in humans. Factors such as strain of the infective microorganism, route of exposure, and/or the level of exposure (i.e., concentration of the chemical, biological, radiological, or other etiologic agent) can influence time to disease/condition onset.

2. Time Course of Progression of Disease/Condition

The progression of the disease/condition in animals should be similar to that of the disease in humans to allow for observation of the effects of intervention. For example, hamsters challenged with anthrax have an extremely rapid disease progression. Thus, this species is not useful for testing the efficacy of products for the treatment of anthrax in humans. Furthermore, the clinical course of disease in the animal may be more rapid than that in the human as a result of experimental conditions, such as the route of exposure (e.g., an IV route of exposure may alter many characteristics including the time course of disease). The change in the clinical course may result in making disease recognition, intervention, and assessment of outcome more difficult. Showing the effect of an intervention may be more challenging when the time between onset of disease and death is short.

3. Manifestations (signs and symptoms)

The disease manifestations, including clinical signs and their known time course, laboratory parameters, histopathology, gross pathology, and the outcome (morbidity or mortality), should be compared between untreated animals and untreated humans (e.g., historical information). Differences should be clearly noted and explained based on the understanding of the pathophysiologic differences between the species, with due acknowledgment of the limitations that may arise where this level of understanding is limited. Because certain disease manifestations in humans (e.g., fever and shortness of breath) may be difficult to discern in animals through clinical observation, a sponsor may need to use more refined techniques, such as telemetry, to evaluate affected animals. Animals in the natural history studies as well as animals in the efficacy studies should be observed with greater frequency over the entire course of the day than would be typical of most nonclinical (pharmacology/toxicology) animal studies. This is especially true when the primary endpoint is mortality and animals are being evaluated in the context of prospectively-defined euthanasia criteria. With a mortality endpoint, animal welfare and sample integrity need to be addressed. Sample integrity (e.g., cultures, histology) may be compromised if not obtained just prior to or immediately after death or euthanasia. Study results may be influenced by the criteria used. Study personnel should be blinded to treatment and should follow observation and euthanasia criteria to minimize the possibility of unnecessary suffering of moribund animals.[9]

[9] Refer to Animal Welfare Act (7 U.S.C. 2131).

D. Trigger for Intervention

Identification of the trigger for intervention in the animal studies is critical to defining the timing of the intervention. Because animals cannot simulate the health-seeking behavior manifested by humans, the trigger for intervention should be accurately defined in the animal model. If signs and symptoms in the animal model closely resemble those in humans, these can serve as the trigger for intervention when they are recognized in the individual animal. However, in the absence of disease-defining manifestations, certain biological parameters should be used to identify the time for initiation of treatment if they are known to be relevant to the diagnosis of human disease and if a relationship to the likely diagnostic process and timing in human use of the product can be shown. For example, presence of bacteremia has been used in some efficacy studies in humans for initiation of intervention with antimicrobial drug products.[10] The utility of biological parameters/biomarkers should be demonstrated, including an analysis of the time course of the appearance of the biomarkers in animals and the onset of disease and availability of diagnostic information in humans.

When a biomarker is used as a trigger for intervention in animal studies, both the assay methodology for the biomarker and its performance characteristics should be adequately characterized. The materials and methods for the assay, as well as the raw data and results from the actual testing, should be provided for FDA review. Summary data are not sufficient. Sponsors are encouraged to initiate early discussion with FDA regarding the utility of the chosen triggers for intervention, particularly when the signs and symptoms of disease in the animal differ from those in humans.

E. Characterization of Medical Intervention

Efficacy studies should reflect the expected clinical use and indication. A particular dosage form may not be suitable for the proposed indication, so the product's dosage form should be considered in planning the development of the product. For example, an oral dosage form is preferred for postexposure prophylaxis for large populations, while an IV dosage form may be necessary for seriously ill patients. If the product is already approved for human use, there may be information on which to base the expected dose and regimen, but if there is no approved human use, the animal result will need to be translated for human use, generally requiring some PK/PD assessment. The following specific information should be submitted on the product and its characteristics in humans and in animals.

1. Product Class

The product's therapeutic class should be identified. Information that is available about other members of the class can be used to help identify potential animal models and predict/evaluate safety and efficacy issues in the proposed animal model.

[10] Refer to package insert for Cubicin, NDA No. 021572, accessible at Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.

2. Mechanism of Action

Understanding the mechanism of action may help to identify specific safety and efficacy issues in the proposed animal model and to identify what additional studies should be performed. The animal studies to support the approval of pyridostigmine as a pretreatment for exposure to the nerve agent soman highlight the importance of understanding the mechanism of action of the drug and host factors in each animal species evaluated. Pretreatment with pyridostigmine was shown to decrease the lethality of soman in rhesus monkeys. However, pretreatment with pyridostigmine produced small and inconsistent effects on mortality in studies using rats, mice, and rabbits. The effect of pyridostigmine was masked in these latter species because of high serum levels of the enzyme carboxylesterase, which eliminates soman from the blood and makes these species naturally highly resistant to the nerve agent. Rhesus monkeys and humans have little or no carboxylesterase. To elucidate the mechanism of pyridostigmine and bridge the data to the human experience, a study was conducted in rats pretreated with pyridostigmine as well as a carboxylesterase inhibitor prior to exposure to soman. In this study, pyridostigmine demonstrated a mortality benefit in the rats similar to that seen in the rhesus monkeys.

3. In vitro Activity

Understanding the in vitro activity of the product will supplement known information on the mechanism of action and provide early screening information.

4. Activity in Disease/Condition of Similar Pathophysiology

If a candidate product is targeted at a common pathway in the pathophysiologic cascade, information may be available on the candidate product's use for diseases that possess a similar pathway. For example, information for a product approved for the treatment of neutropenia secondary to chemotherapy in cancer patients may provide useful data to support studying this product for the reduction of mortality in patients with neutropenia secondary to acute radiation syndrome. This information on the related condition, although not required, lends further support to the candidate product's efficacy for the indication to be studied.

5. Pharmacokinetics (PK) in Unaffected Animals/Humans

PK studies should be done in unaffected animals and humans to characterize the PK profile in each and to propose dosing regimens that provide comparable drug exposures in the animals and humans. Early interaction with FDA is critical to justify and establish the appropriate dosing regimen for the pivotal animal studies.

6. PK/PD (Pharmacokinetics/Pharmacodynamics) in Affected Animals/Humans

PK information in affected animals should be compared to PK information obtained from unaffected animals to establish whether the pathophysiology of a disease affects the PK

(e.g., changes in metabolic parameters may alter the pharmacokinetics). Measures of treatment response (PD measurements such as clinical outcome or exploratory biomarkers) should be proposed for discussion based on both animal studies and any available human information. If a candidate product has been used in humans for other indications, PK/PD information for the alternate indications may be supportive. It should be noted that the animal model may not predict specific disease/drug interactions. Such interactions may not be observed until the disease is treated in humans, reinforcing the critical need for postmarket clinical studies in the event of human disease.

7. PK Interactions with Medical Products Likely to Be Used Concomitantly

The absorption, distribution, metabolism, and excretion (ADME)[11, 12] of a candidate product should be studied and understood.[13] The sponsor, with knowledge of the ADME of the investigational product, should discuss with FDA other medical products that are likely to be co-administered based on the clinical scenario. Potential combinations should be considered for interaction studies that may affect the PK of either product. For example, if a candidate drug is metabolized via the cytochrome P450 system, safety or efficacy of the candidate drug could be compromised by the concomitant use of cytochrome P450 inhibitors or inducers. Such drug/drug interactions should be evaluated.

8. Synergy or Antagonism of Medical Products Likely to Be Used in Combination

Candidate products should be evaluated within the context that reflects anticipated clinical use. The sponsor, in consultation with FDA, should consider other products that are likely to be used and evaluate whether the activity of either product, when used in combination, is affected (i.e., synergy or antagonism). Examples of potential interactions include drug/drug interactions and drug/vaccine interactions. For example, it should be known whether the use of an anthrax antitoxin monoclonal will have an effect on the activity of the antimicrobials used for the treatment of disseminated anthrax disease. This potential interaction should therefore be evaluated in the animal model. This information is especially important when the therapeutic intervention is expected to include more than one medical product.

F. Design Considerations for Animal Efficacy Studies

Assessment of efficacy in animals should be robust. Adequate and well-controlled animal efficacy studies, with endpoints that demonstrate substantial clinical benefit, generally the enhancement of survival or prevention of major morbidity, are required. The time course of observation should be optimized to assess the true treatment effect. At a minimum, placebo-

[11] See *guidance for industry: Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro.*

[12] See *guidance for industry: Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling.*

[13] Biodistribution and elimination should be studied for products that are not biologically amenable to traditional ADME measures (e.g., many biologics such as vaccines, and cell and gene therapies).

controlled animal studies should be performed. If a product approved for the same indication is available, it should be used as an active comparator in addition to the investigational drug and placebo arms. The study should also be blinded to the extent feasible; any situation in which study staff might become aware of treatment assignments should be discussed with FDA in advance in view of the potential for major effects on study interpretability. Animals of both sexes should be included. FDA recognizes that there are significant supply constraints on using mature or older animals of certain animal species. The issue of the age and the immune status of the animals used in efficacy studies as compared to the intended human population should be addressed by the sponsor, when relevant. Study procedures should be uniformly applied to all study groups, and potential bias should be reduced by prespecifying the criteria for euthanasia and discussing their potential effects on interpretation of results.

Studies should be designed to mimic the clinical scenario and achieve meaningful outcomes comparable to the endpoints desired in humans. In some instances, supportive care should be administered to the animals as part of the study design. In such cases, demonstration of a product's benefit over supportive care (i.e., supportive care plus investigational drug arm should be demonstrated to be superior to the supportive care plus placebo arm) will be necessary for approval or licensure. Early discussion between the sponsor and the review division regarding the type, timing, and choice of supportive care to be administered is highly recommended.

In addition to the design characteristics already discussed in this section, the following parameters should also be addressed in the study protocols:

1. Endpoints

The product studied in the animal model should demonstrate a beneficial effect analogous to the intended outcome in humans. Primary study endpoints, which should be specifically discussed with the review division, generally are the enhancement of survival or prevention of major morbidity. The dose response for these endpoints should be explored fully and established. Although secondary endpoints can provide useful information about the animal model and the activity of the product as studied in the animal model, ordinarily, only primary endpoints can serve as the basis of approval.

2. Timing of intervention

The time to initiate intervention should support the specific indication sought for a product. If the intent is to develop the product for a treatment indication, intervention before disease is established may overestimate the effect that is likely to be seen in humans and may indeed show an effect when none would be seen in humans. A reasonable understanding of the disease course and a trigger for intervention defined by the natural history studies will be needed to design the animal efficacy studies for a treatment indication; it is important to establish the relationship of time after exposure to effectiveness. With this information, the timing for intervention can be defined, thus differentiating postexposure prophylaxis from treatment. A product to be used for postexposure prophylaxis should be administered within a reasonable window after exposure to the threat agent, but before onset of disease, with a time relationship that is

adequately justified with respect to administration of the product to humans. Proposals for pre-exposure prophylaxis should be described and discussed in advance on a case-by-case basis.

3. Route of Administration

The route of administration should reflect the indication being sought and the anticipated clinical scenario, such as mass casualty. For example, if a large number of people were exposed to anthrax, an oral dosage form would be preferred over an injectable for postexposure prophylaxis. It may be important to study multiple routes.

4. Dosing Regimen

<u>Drugs, monoclonals, and small therapeutic proteins:</u>

The determination of the dosing regimen should rely on sufficient PK and PD data or other relevant product information in animals and/or humans. The goals should be to (a) determine a regimen in animals that is safe and effective for the indication studied; (b) determine the corresponding exposure (i.e., AUC, Cmax) in animals that is yielded by that dosing regimen; and (c) calculate a dosing regimen in humans that will give an equivalent exposure to that seen in the animal. This will enable initial extrapolation from a dosing regimen found to be efficacious in the animal model to one expected to produce a similar benefit in humans, assuming similar exposure–response relationships. Different dosing regimens in animals and humans may be needed to provide equivalent exposure to the product and thus should be discussed with the Agency.

<u>Vaccines:</u>

The goal should be to develop a regimen that provides a protective immune response and that is safe. For vaccines, the dose(s) used in the animal should induce an immune response that allows for appropriate extrapolation of the animal protection data to humans based on solid scientific principles. A shorter dosing interval between inoculations as compared to the proposed clinical dosing interval may be acceptable with appropriate scientific justification.

In summary, the indication being sought drives the study design. The desired outcomes of the study (i.e., product's effect) should be determined early and carefully factored into the study design to ensure that the study meets both scientific and regulatory objectives. The Agency recommends that study protocols be prepared and submitted to FDA with enough time for FDA to review the protocols and provide feedback to the sponsor before the animal studies are initiated. The sponsor can submit these protocols (i.e., the adequate and well-controlled animal efficacy studies) with a request for review under the Special Protocol Assessment (SPA) provisions.[14]

[14] See guidance for industry: *Special Protocol Assessment.*

V. HUMAN SAFETY INFORMATION

The body of available human safety data, including data from the product's evaluation and use in other indications, is a critical component of any product's development plan and influences the risk/benefit considerations. FDA may ask for additional human safety trials to complete the safety profile of the product. Healthy human volunteers should be enlisted when there is no known significant risk in the administration of the product. If the risk is significant, study in a patient population with a similar disease should be considered if a population can be identified for which the risk/benefit balance of the study is appropriate. Sponsors should propose selection and justification of the appropriate study population in advance for FDA review and feedback.

The size of the required clinical safety database depends on many factors. Existing safety data would generally be satisfactory for products that are already marketed for another indication and known to have an acceptable safety profile in the populations that would receive the product for the new indication. When the new indication requires a longer duration of use or higher dose, additional safety data must be obtained (21 CFR 314.50(d)(5)(vi)). The type of indication being sought is another factor. For example, a product that will be used as prophylaxis in large numbers of people should have a larger safety database than a product developed for treatment of patients who are symptomatic with a disease of known high mortality. In prophylaxis scenarios, it is likely that some proportion of humans will receive the product without having been exposed to the threat agent. An adequate safety database is needed to reduce the risk of serious harm in a healthy population.

The timing and design of clinical safety studies should be coordinated with exploration of the efficacious dose and regimen in animals, in order to plan adequate studies to characterize the safety of the intended human dose, formulation, route of administration, and duration of use. Preclinical safety information should guide the choice of additional safety assessments of interest in the human safety studies. This is particularly useful for products with no prior human safety data, or when the anticipated human dosing regimen has not been previously studied or approved.

VI. ESSENTIAL DATA ELEMENTS OF AN ANIMAL MODEL

The essential data elements for the development and evaluation of animal models are listed in the table below. These elements serve as a guide. They may be modified or revised as new scientific information relevant to the condition under study becomes available. Early and frequent interactions between the sponsor and FDA are critical for feedback on proposals and appropriate discussion of uncertainties and the risk/benefit balance.

Table: Essential Data Elements of an Animal Model

DATA ELEMENTS	Animal(s)	Human
A. Characteristics of the CBRN Agent that Influence the Disease or Condition		
1. The challenge agent		
2. Pathogenic determinants		
3. Route of exposure		
4. Quantification of exposure		
B. Host Susceptibility and Response to Etiologic Agent		
C. Natural History of Disease: Pathophysiologic Comparability		
1. Time to onset of disease/condition		
2. Time course of progression of disease/condition		
3. Manifestations (signs and symptoms)		
D. Trigger for Intervention		
E. Characterization of the Medical Intervention		
1. Product class		
2. Mechanism of action		
3. In vitro activity		
4. Activity in disease/condition of similar pathophysiology		
5. PK in unaffected animals/humans		
6. PK/PD in affected animals/humans		
7. PK interactions with medical products likely to be used concomitantly		
8. Synergy or antagonism of medical products likely to be used in combination		
F. Design Considerations for Animal Efficacy Studies		
1. Endpoints		
2. Timing of intervention		
3. Route of administration		
4. Dosing regimen		
HUMAN SAFETY INFORMATION		

ATTACHMENT A: ACRONYMS AND ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AUC	Area under plasma concentration-time curve from zero to infinity
BSL	Biosafety Level
CBER	Center for Biologics Evaluation and Research
CBRN	Chemical, Biological, Radiological, or Nuclear
CDER	Center for Drug Evaluation and Research
Cmax	Maximum (peak) plasma drug concentration after single dose administration
FDA	Food and Drug Administration
GLP	Good Laboratory Practices
IV	Intravenous
PD	Pharmacodynamics
PK	Pharmacokinetics
SPA	Special Protocol Assessment

REFERENCES

21 CFR, Part 58. Good Laboratory Practice for Nonclinical Laboratory Studies (accessible at http://www.nal.usda.gov/awic/legislat/21cfr97.htm).

42 CFR, Parts 72 and 73. "Possession, Use and Transfer of Select Agents and Toxins," (CDC) *Federal Regist*er 70 (March 18, 2005): 13293 – 13325. (accessible at http://www.cdc.gov/od/sap/final_rule.htm)

FDA, "New Drug and Biological Drug Products; Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical and Feasible," *Federal Register 67* (31 May 2002): 37988-37998.

FDA, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, guidance for industry, *Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling.*

FDA, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, guidance for industry, *Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies in Vitro.*

FDA, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, guidance for industry, *Special Protocol Assessment*.

FDA, Center for Drug Evaluation and Research, draft guidance for industry, *Smallpox (Variola) Infection: Developing Drugs for Treatment or Prevention.*

Leffel, E.K. and Pih, L.M. (2006), Anthrax. In Swearengen, J.R. (Ed.). Biodefense: Research Methodology and Animal Models. (pp. 77-93). Boca Raton, FL: CRC Press.

USDA Animal Welfare Act, Public Law 89-544, as amended, 7 U.S.C. 2131 *et.seq.* (accessible at http://www.nal.usda.gov/awic/legislat/awa.htm).

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WHO guidelines on nonclinical evaluation of vaccines, Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 927, Annex 1) (accessible at http://www.who.int/biologicals/publications/trs/areas/vaccines/nonclinical_evaluation/en/).