
Smallpox (Variola Virus) Infection: Developing Drugs for Treatment or Prevention Guidance for Industry

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

**November 2019
Clinical/Antimicrobial**

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Smallpox (Variola Virus) Infection: Developing Drugs for Treatment or Prevention Guidance for Industry¹

This guidance represents 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 office responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for treatment or prevention of smallpox (variola virus) infection.² Clinical efficacy trials of drugs for treating or preventing smallpox are not feasible³ and challenge studies in healthy subjects are unethical; therefore, drugs for these indications should be developed and approved under the regulations commonly referred to as the *Animal Rule* (21 CFR part 314, subpart I, for drugs and 21 CFR part 601, subpart H, for biologics). This guidance serves as a focus for continued discussions among the Division of Antiviral Products (DAVP), pharmaceutical sponsors, the academic community, and the public.⁴

This guidance focuses on drugs that are expected to inhibit variola virus replication. Although antiviral drugs are the primary focus of this guidance, therapeutic proteins or monoclonal antibodies also may be eligible for evaluation under the *Animal Rule*.⁵ Sponsors interested in developing small molecules, therapeutic proteins, or monoclonal antibodies for use against

¹ This guidance has been prepared by the Division of Antiviral Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

² For the purposes of this guidance, unless otherwise specified, all references to *drugs* include both human drugs and therapeutic biological products (such as therapeutic proteins and monoclonal antibodies) that are regulated by CDER. References to *approval* include new drug application approval for drugs or biologics license application licensure for therapeutic proteins and monoclonal antibodies.

³ The determination of infeasibility of field trials can change. Should circumstances change such that field trials become feasible (e.g., after accidental exposure to or intentional release of variola virus occurs), the sponsor should discuss its development plans with CDER's Division of Antiviral Products.

⁴ In addition to consulting guidances, sponsors are encouraged to contact DAVP to discuss specific issues that arise during the development of drugs for treating or preventing smallpox.

⁵ See 21 CFR 601.91(a).

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smallpox are encouraged to discuss their approach with the FDA as early as possible in development and to communicate with the FDA through the Pre-IND Consultation Program.⁶

This guidance does not address the treatment of bacterial complications of smallpox or the development of biological therapies (other than monoclonal antibodies) to treat or prevent smallpox. Sponsors interested in developing other types of biological products, such as vaccines and immunoglobulin preparations (other than monoclonal antibodies), should contact the appropriate review division in the Center for Biologics Evaluation and Research.

Nor does this guidance address the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* (September 1998) and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001), respectively.⁷

This guidance finalizes the draft guidance of the same name issued on July 11, 2018. This guidance also clarifies the recommended immunological characterization of animals in key studies and includes minor editorial changes.

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. BACKGROUND

Ordinary smallpox, the most common form of smallpox caused by infection with variola major virus, had a reported mortality rate ranging from 5 percent to 50 percent in different outbreak situations (Fenner et al. 1988). This form is the principal source of concern regarding potential bioterrorist uses of smallpox and therefore is the most relevant to this guidance. Worldwide efforts at case identification, containment, and vaccination eventually led the World Health Organization in 1980 to declare that smallpox was eradicated. Retention of variola virus stocks is limited by international agreement to two sites, one in Russia and the other at the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. However, concerns exist that variola virus could remain in undeclared or unknown locations or could be developed and used as a weapon of bioterrorism.

⁶ For more information, see the Getting Started with the Division of Antiviral Products Pre-IND Process web page at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/ucm077546.htm> and the Investigational New Drug (IND) Application web page at <https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application>.

⁷ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

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The first line of defense against smallpox infection is vaccination with vaccinia virus (Petersen et al. 2015; Petersen et al. 2016).⁸ However, the usefulness of vaccination in a biothreat situation depends on the safety profile of the vaccine, on the ability to vaccinate exposed and at-risk persons in a timely manner, and on whether vaccine immunity will be able to protect against a variola virus strain used in a terrorist attack. Because routine smallpox vaccination in the United States was discontinued in the 1970s and there is no natural disease exposure, most of the U.S. population is immunologically naïve to smallpox.

Historically, treatment for smallpox was supportive (Dixon 1962). It is not known what effect technologically advanced supportive care might have on mortality and morbidity. Generally, the mode of death in fatal cases was unclear and could have been multifactorial (Fenner et al. 1988; Dixon 1962).

Antiviral drugs may be a valuable adjunct for exposure situations in which vaccination is not feasible or fails to provide adequate protection. Drug development to evaluate the safety and efficacy of treating or preventing smallpox has numerous challenges, including the following:

- The absence of smallpox cases for decades because of the successful smallpox eradication program
- The absence of detailed information on the pathophysiology of human smallpox itself, including the mode of death
- The lack of any previously recognized effective drug in controlled clinical trials conducted prior to the eradication of smallpox
- Ethical issues that preclude human smallpox challenge studies
- Restriction of variola virus samples to two designated maximum containment facilities
- The exceptionally narrow host range of variola virus, which contributes to a lack of pathogenicity in most animal species after variola virus exposure
- Lack of consistent reproducibility of data from current nonhuman primate (NHP) models using variola virus, and failure to mimic what is known about human smallpox disease
- The possibility of antiviral drug interference with effects of the live-virus vaccine
- The known and potential differences between variola virus and other orthopoxviruses in disease characteristics, drug susceptibility, and host range

In light of these challenges, many specifics of the approaches to drug development for smallpox are likely to differ even from the approaches to other situations involving rare and life-

⁸ These citations contain recommendations for vaccination of certain personnel considered to be at risk of occupational exposure to orthopoxviruses (2016) and for broader use if a smallpox event were to occur (2015).

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threatening diseases. Because of the unique complexities of drug development in this area, extensive discussion with multiple stakeholders has taken place, including a public workshop in 2009 and an advisory committee meeting in 2011.⁹ These discussions helped the FDA formulate the regulatory pathway for smallpox drug development that is described in this guidance.

III. DEVELOPMENT PROGRAM

A. Multidisciplinary Considerations for Studies in Animal Models Using Orthopoxvirus

Because of the unique characteristics of smallpox disease and variola virus mentioned above and discussed further below, animal studies with several related viruses play a much larger role in drug development for smallpox than is the case for many other infectious diseases.¹⁰

1. Considerations for Preliminary Assessments of Antiviral Activity in Animal Models

We recommend that compounds found to be active in cell culture be studied in several lethal animal models using multiple different orthopoxviruses, including vaccinia virus, monkeypox virus, and other orthopoxviruses as appropriate depending on the breadth of antiviral activity in cell culture.

Vaccinia virus should be studied because it is related to variola virus, and studies of vaccinia virus also might be relevant to the development of drugs to treat complications of vaccination. Sponsors should consider conducting studies in vaccinia virus-infected immunocompromised or immunosuppressed animals to support using the drug in immunocompromised people with either variola virus infection or complications caused by vaccination.

Antiviral activity against monkeypox virus should also be studied in one or more animal models. Monkeypox virus infection of NHPs is a potentially useful model of human smallpox for establishing drug efficacy. In addition, human monkeypox itself can be severe and is endemic in certain regions, and preliminary studies in monkeypox virus-infected animals may inform the design of studies evaluating the drug as a treatment for human monkeypox.

Sponsors should initially use small animal models to characterize the preliminary antiviral activity of the drug and should evaluate the effects of a wide range of study variables, including drug doses, dosing regimens, treatment times relative to viral exposure and evolution of disease,

⁹ See 2011 advisory committee materials at <https://wayback.archive-it.org/7993/20170404145348/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/ucm247236.htm>.

¹⁰ Approval under the Animal Rule requires adequate and well-controlled animal efficacy studies; however, we support the principles of the 3Rs, to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with the FDA if they wish to use a nonanimal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

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differences in viral species, strain and inoculum, and route of viral exposure. Results of such studies may help both in estimating the possible effect of these variations and in setting priorities for using resources (such as NHPs and/or more pathogenic viruses) that are less readily available or more difficult to work with. We recommend that sponsors consider selecting and assessing NHP models in later stages of animal investigations after initial results become available from small animal models.

2. Key Study Design Considerations for Animal Efficacy Studies to Support Potential NDA Submission Under the Animal Rule

Selecting the animal models in which to test the efficacy of an investigational drug is critically important for drugs developed under the Animal Rule.¹¹ Sponsors are strongly encouraged to obtain concurrence from DAVP on the animal models and the design of the adequate and well-controlled efficacy studies before initiating a study.

During the December 14–15, 2011, Antiviral Drugs Advisory Committee meeting on the development of drugs to treat variola virus infection, the advisory committee agreed with the FDA’s assessment that current NHP models using variola virus are not consistently reproducible and do not mimic what is known about human smallpox disease. Because scientific limitations of these available variola virus models preclude definitive efficacy assessments, and uncertainty exists whether an adequate variola virus model can be developed, the FDA and the advisory committee agreed that data from a combination of other lethal animal models using surrogate orthopoxviruses (e.g., NHP studies with monkeypox virus, rabbit studies with rabbitpox virus, mouse studies with ectromelia virus) could be used as evidence along with, or potentially instead of, animal studies using variola virus.

Based on multiple discussions with stakeholders, DAVP recommends the following: (1) data from at least two lethal animal models of orthopoxvirus infection should be obtained to evaluate drug efficacy; (2) orthopoxvirus animal models proposed for use in adequate and well-controlled efficacy studies should be well-characterized and generate reproducible results that are reasonably expected to predict efficacy in variola virus–infected or exposed humans; and (3) mortality, based on prospectively defined criteria for euthanasia, should be the primary endpoint for efficacy studies. The recommendation for using multiple orthopoxvirus animal models acknowledges the unique challenges and uncertainties associated with smallpox drug development and the fact that no single orthopoxvirus animal model is known to be the best predictor of human responses to treatments for smallpox.

As discussed in the guidance for industry *Product Development Under the Animal Rule*, (October 2015) “[e]uthanasia criteria should be prospectively specified” and agreed to by DAVP before sponsors conduct animal studies intended to support regulatory decision-making. Sponsors should include a detailed documentation of the euthanasia decision in the study report for each animal euthanized during the study. The documentation should include, but is not limited to, how the animal met the euthanasia criteria and whether there were any deviations from the prespecified criteria. The euthanasia documentation and methods for ensuring data

¹¹ For general discussion of the Animal Rule and general guidance for developing products under this regulation, see the guidance for industry *Product Development Under the Animal Rule*.

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quality and integrity (including modifications to data handling due to high-containment facility requirements) should also be discussed with DAVP before study conduct. See the guidance for industry *Product Development Under the Animal Rule* regarding data quality and integrity expectations for the adequate and well-controlled animal efficacy studies and the pharmacokinetic (PK) and/or pharmacodynamic (PD) studies used to select a dose and regimen in humans.

The design of these animal studies should be based on the general principles of human clinical trial design as well as past experience with characterizing animal models and results from the nonclinical natural history and exposure-response studies. Animals used in natural history and efficacy studies should have been demonstrated to be immunologically naïve to the orthopoxvirus challenge agent. Sponsors should perform this assessment by direct serologic analysis for larger animals or by indirect approaches (e.g., using sentinel animals) for rodents with low blood volume to monitor for any prior orthopoxvirus exposures in the test animals. Assessments based on cellular immune assays should also be considered when feasible and appropriate. Animal study protocols should include detailed clinical observations and laboratory evaluations in the animals, similar to clinical and laboratory monitoring that might be performed in human clinical trials in drug development programs for other types of serious illnesses. Furthermore, demonstrating consistency and reproducibility of results using the same model at different animal facilities can assist in characterizing the model. Blinding for studies should follow recommendations outlined in the guidance for industry *Product Development Under the Animal Rule*. The protocol should also include details about treatment assignment and randomization procedures.

In addition to the primary endpoint of mortality (i.e., proportion of animals succumbing to rather than recovering from disease), sponsors are encouraged to evaluate secondary endpoints that could be associated with or predictive of outcomes in the animal models under development.

Other important study design considerations include using a range of drug doses, durations, and start times, including treatment started both before and after infection and symptomatology have become clinically established. In addition, differences in the time course of disease development between human smallpox and orthopoxvirus animal models should be considered in protocol design.

Animal study protocols should also include methods for quantifying viral burden or viral shedding (both virus and viral DNA) and evaluating the relationship between these quantitative measurements and clinical outcomes of disease and treatment. Viral isolates from animals failing treatment or with extended virus shedding should be evaluated for the development of drug resistance.

The goal of the adequate and well-controlled animal studies is to demonstrate that the investigational drug is statistically significantly superior to placebo and confers a treatment or prevention effect considered likely to be clinically meaningful. Sponsors should discuss power considerations and a proposed statistical analysis plan with the FDA before initiating planned studies.

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3. Selection of an Effective Dosing Regimen in Humans

To support human dose selection for an investigational drug, sponsors should characterize the PK profile of the drug in healthy humans and both the PK profile and the PD profile of the drug in the surrogate orthopoxvirus animal models that are used to demonstrate efficacy. In addition, the PK profile of the drug in infected animals should be compared with the PK profile of the drug in healthy animals to determine whether the specific orthopoxvirus infection affects the drug's PK profile. It is critical that the PK data in humans and the PK and PD data in animals are obtained in well-controlled studies using fully validated bioanalytical assays for determining drug concentrations. For each of the surrogate orthopoxvirus animal models used to establish efficacy, the exposure-response relationship of the drug should be established and the fully effective dose and the drug exposure associated with the fully effective dose should be determined. Furthermore, sponsors should consider interspecies differences in absorption, distribution (including plasma protein binding), metabolism, and excretion when determining the human dose.

The determination of treatment duration will depend on several factors including, but not limited to, the pharmacokinetic characteristics of the drug, the proposed indication (i.e., treatment or prophylaxis), and the pathophysiology and disease course in animal models of orthopoxvirus infection versus humans with smallpox.

As described in the guidance for industry *Product Development Under the Animal Rule*, sponsors should select human doses that provide exposures that exceed the exposures in animals associated with the fully effective dose (ideally by severalfold if the drug's safety profile supports such dosing). This selection serves to accommodate any uncertainties relating to the similarity of the exposure-response relationship between humans and animals.

B. Pharmacology/Toxicology Considerations

Pharmacology/toxicology considerations for safety evaluation should follow the standard drug development paradigms for small molecules as outlined in the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010) or for biologics as outlined in the ICH guidance for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (July 1997). Historical clinical data suggest that some patients (e.g., immunocompromised) with variola virus infection may have had clinical disease lasting longer than 2 weeks; therefore, we recommend that initial toxicology and safety studies take this possibility into account. Duration of studies to support investigational new drug application (IND) and new drug application (NDA)/biologics license application (BLA) filings are outlined in the respective ICH guidances.

We do not anticipate that carcinogenicity studies will be needed for drugs that might be used only to treat established smallpox because the administration of such drugs will not, in most cases, exceed 6 months. However, if there is a cause for concern (e.g., positive genotoxicity or other risks for carcinogenicity), then follow-up discussions with DAVP may be warranted. Lastly, see the guidances for industry *Product Development Under the Animal Rule* and

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Providing Regulatory Submissions in Electronic Format — Standardized Study Data (December 2014) regarding requirements for electronic submission of nonclinical pharmacology/toxicology as well as nonclinical efficacy datasets.

C. Nonclinical Virology Considerations

Study reports for the investigational drug should provide results and analyses describing its mechanism of action, establish its specific antiviral activity in cell culture and animal models, provide data on the development and potential mechanisms of viral drug resistance (or reduced susceptibility of the virus to the drug) in cell culture and animal models, and assess its cytotoxicity and mitochondrial toxicity. Additional information on virology studies can be found in the guidance for industry *Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency* (June 2006).

We recommend that sponsors evaluate the investigational drug's antiviral activity against a broad panel of orthopoxviruses, including vaccinia virus and other orthopoxviruses expected to be used in animal models (e.g., monkeypox virus, rabbitpox virus, ectromelia virus). Such assessments constitute a broad-based orthopoxvirus testing strategy to screen for potential relevance to variola virus and assess the potential of the investigational drug to treat vaccine complications or human monkeypox. Ultimately, sponsors should explore the potential appropriateness of testing the antiviral activity of the investigational drug against variola virus isolates if other data are sufficiently promising to proceed to this stage.

Orthopoxvirus DNA polymerases replicate their viral genomes with high fidelity, complicating the genotypic analysis of resistance in animal studies. To aid in the interpretation of drug resistance results from animal studies, sponsors should include plans to evaluate the performance of their nucleotide sequencing assay(s) to help distinguish between nucleotide sequence changes caused by their resistance assay versus those occurring in vivo and possibly contributing to drug resistance.

Sponsors should submit information on sample collection, assays performed, and validation approaches for these assays. Using a specific procedure, method, or test system in an investigational protocol for a nonclinical laboratory study, or as a laboratory procedure supporting a clinical trial, does not constitute FDA endorsement of that procedure, method, or test system, or FDA approval for clinical laboratory use.¹²

The FDA performs independent assessments of virologic and resistance data. Sponsors should consult with DAVP before submitting virology datasets to obtain information on the most recent recommended formats. In the case of next-generation sequence analysis, sponsors should refer to the guidance for industry and technical specification document *Submitting Next Generation Sequencing Data to the Division of Antiviral Products* (July 2019), which describes the

¹² Submission of an investigational device exemption to the Center for Devices and Radiological Health may be warranted if an investigational assay is used in a clinical trial.

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procedure for submission of files in the FASTQ format (containing sequence nucleotides and quality information).

Laboratory work with certain orthopoxviruses must comply with applicable regulations (e.g., the select agent regulations found at 42 CFR part 73)¹³ and should incorporate relevant biosafety and biosecurity procedures as appropriate to the viruses studied. Sponsors should contact relevant government agencies, such as the CDC and the National Institutes of Health, for more information regarding biosafety procedures.¹⁴ Sponsors should also be aware that all studies of variola virus must be conducted in collaboration with CDC and will require approval from the World Health Organization.

D. Clinical Considerations

For the FDA to approve a drug for treating or preventing smallpox under the Animal Rule, the safety of the drug must be established.¹⁵ However, the Animal Rule does not provide specific provisions for evaluating safety. Therefore, the FDA evaluates these drugs under preexisting NDA/BLA regulations for establishing the safety of new drugs or biological products. Under most conditions, the human safety data for smallpox drugs will come from healthy volunteer studies and/or relevant human safety data for the same drugs developed for other indications. Evaluating important drug-drug interactions also may involve healthy volunteer studies. In the event of a smallpox public health emergency, human safety and efficacy data also can be obtained by using investigational smallpox drugs in clinical field trials. For drugs approved under the Animal Rule, postmarketing clinical trials are required when feasible and ethical (21 CFR part 314, subpart I, for drugs and 21 CFR part 601, subpart H, for biologics).

1. Healthy Volunteer Safety Trials

Outside of a public health emergency, the safety evaluation of drugs developed solely for treating or preventing smallpox largely depends on safety trials in healthy volunteers. Nonclinical safety and activity data of the investigational drug should be available before the initiation of human trials to support safety and to guide clinical trial design (e.g., dose, duration), as outlined in the respective ICH guidances for small molecules (ICH M3(R2)) or biologics (ICH S6(R1)). Sponsors should discuss any concerns related to the safety or ethics of healthy volunteer trials with the FDA early in the drug development program.

The size and composition of the human safety database needed to support smallpox drug approval depend on issues such as the indication (e.g., treatment, post-exposure prophylaxis, or prophylaxis), the drug's toxicity, and the extent of the FDA's experience with a particular drug (and possibly with related drugs). For a drug intended to treat smallpox, greater known risks or greater uncertainty about undefined risks may be acceptable if a drug offers a potential for benefit to smallpox patients, given the serious nature of the disease. In general, a safety database

¹³ Information on the Federal Select Agent Program can be found at <https://www.selectagents.gov>.

¹⁴ Information on biosafety can be found at <https://www.cdc.gov/biosafety/publications/bmb15/index.htm> and <https://www.nih.gov/research-training/safety-regulation-guidance>.

¹⁵ See 21 CFR 314.610(a) and 601.91(a).

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of at least 300 individuals is needed for a 95 percent confidence interval to rule out a 1 percent rate of a specific adverse reaction if that specific adverse reaction did not occur in the population studied. For drugs intended to prevent smallpox infection that might therefore be administered to large numbers of healthy individuals with uncertain risk of smallpox disease, a larger safety database may be needed. Sponsors should discuss with DAVP the appropriate safety database size for their drugs.

The adverse-event grading scale used in safety trials should be appropriate for healthy adult human volunteers. Sponsors should characterize safety signals identified from animal studies or human trials and, if necessary, incorporate specific study design elements in the proposed nonclinical and clinical protocols.

Evaluating certain drug-drug interactions also may involve healthy volunteer trials. Sponsors should be prepared to address the potential interaction between a smallpox therapeutic and smallpox vaccination and should discuss with DAVP the conduct and timing of animal studies and any appropriate human trials for this purpose.

2. Safety Data from Non-Smallpox Clinical Experience

Safety information to support approval of a smallpox drug can be derived from clinical trials of the same drug for a non-smallpox indication. In the case of approved drugs, safety information can include safety data generated both pre- and postapproval. For drugs in development for non-smallpox indications, safety data acquired in all stages of development can support approval under the Animal Rule. Because patients with smallpox disease may be expected to be acutely ill, safety data from clinical trials for non-smallpox indications associated with acute illness may be particularly relevant. And because clinical trials in related viruses may provide additional support for a drug's activity as well as its safety, sponsors can consider simultaneously developing a drug for another poxvirus infection such as molluscum contagiosum virus, vaccinia virus, or monkeypox virus.¹⁶

3. Clinical Trials in the Event of a Public Health Emergency

Sponsors developing smallpox drugs under the Animal Rule should design one or more clinical trials to assess the safety and efficacy of the investigational drugs in the event of a human smallpox outbreak. Sponsors should discuss important trial design elements and potential smallpox emergency scenarios with the FDA and other relevant stakeholders early in the trial design process. The trial or trials should be designed to evaluate the most appropriate therapeutic use or uses for the drug (treatment, post-exposure prophylaxis, or prophylaxis) based on results of nonclinical studies. Depending on the strength of the data, efficacy and safety results from an emergency clinical trial could be used to support approval of a drug that was in the process of being developed under the Animal Rule.

¹⁶ Sponsors are strongly encouraged to discuss drug development for nonvariola indications with DAVP as early as possible, especially in circumstances in which the drug has potential to fill an unmet need by pursuing those other indications.

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The Animal Rule stipulates that all drugs approved using the Animal Rule should be evaluated for efficacy and safety through clinical trials if circumstances arise in which that would be feasible and ethical. Therefore, smallpox drug approval under the Animal Rule will include a requirement to conduct one or more human postmarketing trials if a smallpox outbreak occurs, and the marketing application must include a plan or approach to meet this requirement (21 CFR part 314, subpart I, for drugs and 21 CFR part 601, subpart H, for biologics). The drug-approval letter will include a milestone date for submission of the final clinical protocol, ready for implementation should the need arise.

4. Expanded Access IND for Emergency Use

For sporadic events such as smallpox vaccine complications or accidental laboratory exposures to orthopoxviruses, treatment of a patient under an individual patient expanded access IND for emergency use may be appropriate if the drug under development is expected to have activity against the orthopoxvirus and if the patient is not able to participate in a clinical trial.¹⁷ If a situation arises in which it is necessary to treat a patient under an expanded access IND for emergency use, sponsors should collect data to the extent feasible while recognizing that the data collected may be of limited utility. If frequent sporadic uses of an investigational drug are anticipated, sponsors should develop an appropriate clinical trial protocol.

5. Emergency Use Authorization

In the event of a smallpox emergency, the FDA may issue an emergency use authorization (EUA)¹⁸ to provide emergency access to unapproved drugs (or approved drugs for unapproved indications) after the Secretary of Health and Human Services issues the requisite declaration¹⁹ that circumstances exist justifying the authorization of emergency use of the drugs, provided other statutory criteria are met. For example, the FDA must conclude that based on the totality of scientific evidence available, it is reasonable to believe that a drug may be effective to treat or prevent smallpox, the known and potential benefits outweigh the known and potential risks of the drug, and there is no adequate, approved, and available alternative. Sponsors who think their drugs may warrant EUA consideration are encouraged to submit relevant information and initiate pre-EUA discussions rather than wait for a potential emergency to arise; however, the issuance of an EUA is not considered an appropriate final goal for drug development or a substitute for generating data to support an NDA or a BLA.

¹⁷ The requirements and procedures for expanded access INDs for emergency use can be found in 21 CFR part 312, subpart I, and in the guidance for industry *Expanded Access to Investigational Drugs for Treatment Use — Questions and Answers* (June 2016).

¹⁸ The requirements and procedures for EUAs can be found in section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360bbb-3) and in the guidance for industry and other stakeholders *Emergency Use Authorization of Medical Products and Related Authorities* (January 2017).

¹⁹ The declaration of the Secretary of Health and Human Services must be based on one of four determinations (including a material threat determination), as described in statute (section 564(b)(1) of the FD&C Act (21 U.S.C. 360bbb-3(b)(1))).

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E. Clinical Pharmacology Considerations

See section III. A. 3, Selection of an Effective Dose in Humans, for a discussion on obtaining exposure-response data for the investigational drug from at least two well-characterized animal models to aid in determining an effective dose in humans. Sponsors should follow the standard drug development paradigms for clinical pharmacology. Intrinsic and extrinsic factors (such as organ impairment, food effect, or drug interactions) that may affect the pharmacokinetics of an investigational drug should be well characterized and the effective dose in humans should be adjusted if necessary. Because of human subject protection considerations for conducting clinical trials in specific populations, such as pregnant women and pediatric patients (45 CFR part 46, subparts B and D and 21 CFR part 50 subpart D), administering an investigational drug solely for the purpose of collecting PK data may not be ethical. For such specific populations, it may be possible to obtain PK data if there are situations in which a drug is already being used for reasons other than solely for obtaining PK data. In some circumstances, modeling and simulation methods can be used to determine effective doses; sponsors should discuss using such methods with the FDA.

F. Chemistry, Manufacturing, and Controls Considerations

Sponsors should pay particular attention to developing formulations for patients who are unable to swallow solid oral dosage formulations (e.g., development of oral solutions and powders for pediatric patients, parenteral formulations for extremely ill patients).

It is likely that drugs for treating or preventing smallpox infection may be stockpiled for long periods of time in anticipation of a sudden outbreak, so an expiration dating period (shelf life) that is longer than usual may be desirable. To generate the stability data needed to support a long expiration dating period, it may be advantageous to place in the long-term stability testing program larger amounts of drug than is usual.

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