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

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact Jeff Murray at 301-796-1500.

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

July 2018
Clinical/Antimicrobial

Revision 1

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TABLE OF CONTENTS

Smallpox (Variola Virus) Infection: Developing Drugs for Treatment or Prevention Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment or prevention of smallpox (variola virus) infection.[2] Clinical efficacy trials of drugs for the treatment or prevention of smallpox are not feasible[3] 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 This draft guidance is intended to serve as a focus for continued discussions among the Division of Antiviral Products (DAVP), pharmaceutical sponsors, the academic community, and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 act by inhibiting variola virus replication. Although the primary focus of this guidance is on antiviral drugs, therapeutic proteins or monoclonal antibodies also may be eligible for evaluation under the animal rule. Sponsors interested in developing small molecules, therapeutic proteins, or monoclonal antibodies for use

[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 over time. 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 treatment or prevention of smallpox.

against smallpox are encouraged to discuss their approach with the FDA as early as possible in development and are encouraged to communicate with the FDA through the Pre-IND Consultation Program.[5]

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

This guidance also does not contain discussion of 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* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.[6]

This guidance revises the draft guidance for industry *Smallpox (Variola) Infection: Developing Drugs for Treatment or Prevention* issued in November 2007. This revised draft guidance includes modifications pertaining to the following: key study design considerations for animal efficacy studies; selection of an effective dose in humans; nonclinical virology issues; key pharmacology and toxicology issues; and chemistry, manufacturing, and controls for drugs developed for smallpox. These revisions intend to streamline the guidance and incorporate input from a public workshop in 2009 and an advisory committee meeting in 2011.

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

The most severe form of smallpox, variola major, had reported mortality 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

[5] 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/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm#preIND.

[6] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

eventually led the World Health Organization in 1980 to declare that smallpox was eradicated. Retention of variola virus stocks was 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 be used as a weapon of bioterrorism.

The first line of defense against smallpox infection is vaccination with vaccinia virus (CDC 2015; CDC 2016).[7] However, the usefulness of vaccination in a biothreat situation depends on the ability to vaccinate exposed and at-risk persons and on whether vaccine immunity will be able to protect against a variola 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 programs to evaluate the safety and efficacy of smallpox treatment or prevention are affected by numerous distinctive features of smallpox and its history, including:

- 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
- 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
- Current nonhuman primate (NHP) models using variola virus are not consistently reproducible and do not mimic what is known about human smallpox disease
- The possibility of antiviral drug interference with effects of the live-virus vaccine

[7] 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).

- The 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-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.[8] 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.[9]

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 non-variola orthopoxviruses, including vaccinia virus and other orthopoxviruses with the greatest homology to variola virus for the drug target. 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. Consideration should be given to conducting studies in vaccinia virus-infected immunocompromised/immunosuppressed animals to support the use of the drug in immunocompromised people with either variola virus infection or complications caused by vaccination.

Small animal models should be used 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, 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 the use of resources (such as NHPs and/or more pathogenic viruses) that are less readily available or more

[8] Materials for the 2011 Antiviral Drugs Advisory Committee are available at https://wayback.archive-it.org/7993/20170404145348/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/ucm247236.htm.

[9] 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.

difficult to work with. We recommend that selection and assessment of NHP models receive consideration 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

The selection of the animal models in which to test the efficacy of an investigational drug is critically important for drugs developed under the animal rule.[10] 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 study initiation.

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 lethal 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 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 (including the aforementioned 2011 Antiviral Drugs Advisory Committee meeting), DAVP recommends the following: (1) data from at least two lethal animal models of non-variola orthopoxvirus infection should be obtained to evaluate drug efficacy; (2) non-variola 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 use of multiple non-variola 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*, "euthanasia criteria should be prospectively specified" and agreed to by DAVP before conduct of animal studies intended to support regulatory decision-making. A detailed documentation of the euthanasia decision should be included in the study report for each animal euthanized during the course of 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 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*

[10] 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*.

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 characterization of 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 based on antibody assays. 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, demonstration of 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 (that is, 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 outcome 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.

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

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

3. Selection of an Effective Dose in Humans

To support human dose selection for an investigational drug, the sponsor should characterize the PK profile of the drug in healthy humans and both the PK profile and the PD 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 to the PK profile of the drug in healthy animals to determine whether the specific orthopoxvirus infection affects the drug's PK. 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, interspecies differences in absorption, distribution (including plasma protein binding), metabolism, and excretion should be considered when determining the human dose.

As described in the guidance for industry *Product Development Under the Animal Rule*, human doses that provide exposures that exceed the exposures in animals associated with the fully effective dose (ideally by several-fold, if the drug's safety profile supports such dosing) should be selected. This 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* or for biologics as outlined in the ICH guidance for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*. 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 *Providing Regulatory Submissions in Electronic Format — Standardized Study Data* 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), 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*.

We recommend that sponsors evaluate the investigational drug's antiviral activity against a broad panel of orthopoxviruses, including vaccinia virus, orthopoxviruses with the greatest homology to the variola virus drug target, and 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. 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. Sponsors should include plans in their resistance analyses to distinguish between nucleotide sequence changes caused by their resistance assay and those occurring in vivo.

Sponsors should submit information on sample collection, assays performed, and on validation approaches for these assays. Use of 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.[11]

The FDA performs independent assessments of virologic and resistance data. Sponsors should consult with DAVP before submission of virology datasets to obtain information on the most recent format and, in the case of Next Generation Sequence analysis, the procedure for submission of FASTQ files.

Laboratory work with certain orthopoxviruses must comply with applicable regulations (e.g., the select agent regulations found at 42 CFR part 73)[12] 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.[13]

D. Clinical Considerations

For the FDA to approve a drug for treatment or prevention of smallpox under the animal rule, the safety of the drug must be established (21 CFR part 314, subpart I, for drugs and 21 CFR part 601, subpart H, for biologics). However, the animal rule does not provide special provisions for the evaluation of 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. Evaluation of 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 through the use of investigational smallpox drugs in clinical field trials. For drugs

[11] 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.

[12] Information on the Federal Select Agent Program can be found at https://www.selectagents.gov.

[13] Information on biosafety can be found at https://www.cdc.gov/biosafety/publications/bmbl5/index.htm and https://www.nih.gov/research-training/safety-regulation-guidance.

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 the treatment of smallpox or smallpox prevention 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 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. Safety signals identified from animal studies or human trials should be characterized and, if necessary, specific study design elements should be incorporated in the proposed nonclinical and clinical protocols.

The evaluation of certain drug-drug interactions also may involve healthy volunteer studies. 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 studies 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, this 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. Because clinical studies 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.[14]

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(s) should be designed to evaluate the most appropriate therapeutic use(s) 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.

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 time frame 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.[15] If a situation arises in which it is necessary to treat a patient under an expanded access IND for emergency use, a sponsor 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, efforts should be made to develop an appropriate clinical trial protocol.

[14] Sponsors are strongly encouraged to discuss drug development for non-variola 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.

[15] 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*.

405 *5. Emergency Use Authorization*
406
407 In the event of a smallpox emergency, the FDA may issue an emergency use authorization
408 (EUA)[16] to provide emergency access to unapproved drugs (or approved drugs with unapproved
409 indications) after the Secretary of Health and Human Services issues the requisite declaration[17]
410 that circumstances exist justifying the authorization of emergency use of the drugs, provided
411 other statutory criteria are met. For example, the FDA must conclude that based on the totality
412 of scientific evidence available, it is reasonable to believe that a drug may be effective to treat or
413 prevent smallpox, the known and potential benefits outweigh the known and potential risks of
414 the drug, and there is no adequate, approved, and available alternative. Sponsors that think that
415 their drugs may warrant EUA consideration are encouraged to submit relevant information and
416 initiate pre-EUA discussions rather than waiting for a potential emergency to arise; however, the
417 issuance of an EUA is not considered an appropriate final goal for drug development or a
418 substitute for generating data to support an NDA or BLA.
419
420 **E. Clinical Pharmacology Considerations**
421
422 See section III.A.3., Selection of an Effective Dose in Humans, for a discussion on obtaining
423 exposure-response data for the investigational drug from at least two well-characterized animal
424 models to aid in determining a human effective dose. Sponsors should follow the standard drug
425 development paradigms for clinical pharmacology. Intrinsic and extrinsic factors (such as organ
426 impairment, food effect, or drug interactions) that may affect the pharmacokinetics of an
427 investigational drug should be well characterized and the effective dose in humans should be
428 adjusted if necessary. Because of human subject protection considerations in the conduct of
429 clinical trials in specific populations, such as pregnant women and pediatric patients (45 CFR
430 part 46, subparts B and D), administration of an investigational drug solely for the purpose of
431 collecting PK data may not be ethical. For such specific populations, it may be possible to
432 obtain PK data if there are situations in which a drug is already being used for reasons other than
433 solely for obtaining PK data. In some circumstances, modeling and simulation methods can be
434 used to determine effective doses; the use of such methods should be discussed with the FDA.
435
436 **F. Chemistry, Manufacturing, and Controls Considerations**
437
438 Sponsors should pay particular attention to developing formulations for patients who are unable
439 to swallow solid oral dosage formulations (e.g., development of oral solutions and powders for
440 pediatric patients, parenteral formulations for extremely ill patients).
441
442 It is likely that drugs for the treatment or prevention of smallpox infection may be stockpiled for
443 long periods of time in anticipation of a sudden outbreak and therefore an expiration dating

[16] 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* (available at https://www.fda.gov/regulatoryinformation/guidances/ucm125127.htm).

[17] 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))).

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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