Guidance for Industry
Vaccinia Virus — Developing Drugs to Mitigate Complications from Smallpox Vaccination

DRAFT GUIDANCE

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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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Guidance for Industry

Vaccinia Virus — Developing Drugs to Mitigate Complications from Smallpox Vaccination

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Vaccinia Virus — Developing Drugs to Mitigate Complications from Smallpox Vaccination

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 recommendations on the development of drugs to be used to treat complications that may occur from smallpox vaccination with vaccinia virus. It is intended to help commercial and research sponsors plan and design appropriate nonclinical and clinical studies during the development of these drugs. This guidance does not make recommendations about the development of drugs to treat smallpox. That issue will be addressed separately in a future guidance document. This guidance also does not address the development of biological therapies, such as vaccinia immune globulin (VIG).

The development of drugs to mitigate vaccinia virus complications raises unique and challenging issues. Many of the previous studies done on the topic were performed prior to the 1970s, before the United States abandoned routine vaccinia vaccination for smallpox. A concern that smallpox may be used as a bioterrorism agent has led to a limited reintroduction of smallpox vaccination, with the potential for widespread vaccination should an attack with smallpox occur. Therefore, it is critical that we develop drugs to treat the complications associated with the vaccine. Currently, there are no FDA-approved drugs indicated for treatment of vaccinia vaccine complications. We would like to strongly encourage the submission of pre-investigational new drug applications (pre-INDs) to promote discussions between sponsors and FDA addressing the sequence and content of nonclinical and clinical study proposals.

[1] This guidance has been prepared by the Division of Counter-Terrorism and the Division of Antiviral Drug Products in the Center for Drug Evaluation and Research (CDER) in cooperation with the Division of Dermatologic and Dental Drug Products and the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products, CDER; the Center for Biologics Evaluation and Research (CBER); and the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration.

To facilitate drug development, the sponsor may find it advantageous to collaborate with governmental agencies and academic centers. These collaborations may provide resources such as drug screening, improved access to target populations for clinical trials, and funding. Drug development also may be facilitated by investigating drugs that already have undergone substantial development and have a mature safety database.

This guidance first summarizes appropriate nonclinical studies recommended during early drug development. The section on chemistry, manufacturing and controls (CMC) refers the sponsor to relevant guidances for CMC information. A nonclinical toxicology section outlines required and recommended in vitro and animal safety studies used to support the safety of clinical investigations. A microbiology section details both nonclincal and clinical issues important during drug development, such as identifying drug mechanism of action, antiviral activity, cytotoxicity, drug activity in combination with other drugs, and drug resistance. A clinical pharmacology section discusses analyses the sponsor should perform to elucidate an understanding of drug pharmacokinetics and pharmacodynamics, including data that should be obtained from special populations.

Next, the guidance focuses on the acquisition of in vivo data through the use of animal models. Because the rate of serious vaccinia complications in the vaccinated population is low, the amount of efficacy data adequate for drug approval may not be obtainable through clinical trials. Therefore, animal models may provide a source of supportive efficacy data, or possibly contribute directly to drug approval under 21 CFR part 314, subpart I (the Animal Efficacy Rule). The guidance discusses the requirements of the Animal Efficacy Rule.

The guidance concludes with sections addressing the acquisition of human efficacy and safety data. Issues surrounding the design of clinical trials are discussed. In addition, sections detailing data collection requirements and recommendations, along with consideration of long-term patient follow-up and special population data collection, are presented. A sample case report form is provided as an example of a data collection format.

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.

II. BACKGROUND

Naturally occurring smallpox was declared eradicated in 1980 following a global campaign initiated by the World Health Organization (WHO) that incorporated use of case identification, containment, and vaccination. The United States abandoned the routine use of smallpox vaccination in the civilian population in the early 1970s (Breman and Henderson 2002) due to concerns that the risks of developing an adverse event secondary to vaccinia inoculation outweighed the risk of developing smallpox. Although clinical smallpox has been eradicated, there are concerns that variola virus, the etiological agent of smallpox, could be used as a

weapon of bioterrorism. Therefore, proposals for smallpox vaccination have been discussed and public health advisory groups have issued recommendations for administration of vaccine to selected groups (CDC 2003a).

According to advisory panel evaluations and recommendations (CDC 2003a; 2001), vaccinia virus vaccine administered prior to exposure to variola virus produces substantial immunity against smallpox that usually lasts for at least several years. In addition, if performed within a few days after initial variola exposure, it may prevent disease or decrease the symptoms of smallpox.

The currently licensed smallpox vaccine uses live vaccinia virus. According to the Dryvax package insert, the vaccine is contraindicated for routine non-emergency use for persons who are immunosuppressed, persons with eczema or a past history of eczema, persons with other acute, chronic, or exfoliative skin conditions, and pregnant women due to the potential development of complications secondary to the vaccine itself. Household contacts of such persons should not be vaccinated. Also, the Contraindications section of the package insert (non-emergency use) was updated to include persons with cardiac disease or certain risk factors for cardiac disease. (Please see the package insert for a complete listing of contraindications.) Important complications associated with the smallpox vaccine include, but are not limited to:

- Generalized vaccinia
- Erythema multiforme and Stevens-Johnson syndrome
- Eczema vaccinatum
- Other rashes (e.g. folliculitis)
- Inadvertent autoinoculation or transmission to close contacts
- Secondary infection of skin complications
- Ocular vaccinia
- Progressive vaccinia
- Postvaccinial central nervous system disease (encephalitis, encephalomyelitis, and encephalopathy)
- Myo/pericarditis[2] (CDC 2003b)
- Fetal vaccinia (a very rare complication caused by the exposure of pregnant women to vaccinia)
- Anaphylaxis

Vaccinia virus exposure may occur via vaccination, accidental person-to-person spread from a vaccinated individual to a close contact, or exposure from use of the virus as a recombinant

[2] Myo/pericarditis was reported rarely following smallpox vaccination (Karjalainen et al., 1983). In the current civilian and military smallpox vaccine programs, myo/pericarditis has been reported recently in vaccinees (CDC 2003b). Therefore, current recommendations state that persons with known underlying heart disease or who have three or more known major cardiac risk factors should also be excluded from smallpox vaccination pending further assessment of causality (CDC 2003c).

vector for another investigational vaccine. For data on smallpox vaccine adverse event rates from 10 state-wide surveys see Table 1 (Lane et al., 1970).

Available rates of vaccinia vaccination adverse events come mainly from studies done prior to 1970 (Lane et al. 1970; Lane et al. 1969). Current complication rates from vaccination may be difficult to predict accurately. Rates for certain complications could be anticipated to be higher now due to the larger number of at-risk individuals in today's population.

Table 1. Adverse event rates associated with vaccinia vaccination (cases/million vaccinations)

	Primary Vaccination	Revaccination
Inadvertent Inoculation	529.2	42.1
Generalized Vaccinia	241.5	9.0
Eczema Vaccinatum	38.5	3.0
Progressive Vaccinia	1.5	3.0
Post-vaccinial Encephalitis	12.3	2.0

Adapted from: Lane MJ, Ruben FL, Neff JM, et al., 1970, "Complications of Smallpox Vaccination, 1968: Results of Ten Statewide Surveys," *Journal of Infectious Diseases*, 122:303-309.

For example, there are an estimated 8.5 million persons with cancer, 850,000 persons with HIV/AIDS and 184,000 solid-organ transplant recipients in the United States (Kempner et al. 2002). In addition, many persons today who would receive a primary vaccination are at an older age compared to the majority who received vaccinations during the previous smallpox vaccination program era. This change in age distribution could increase the occurrence or detection of certain adverse events while possibly decreasing others. Alternatively, rigorous screening for persons with contraindications to the vaccine in a pre-event vaccination campaign could result in fewer adverse events. In addition, new smallpox vaccines are being developed that may cause complications that differ in scope and number from the previous profile.

Currently, VIG, which is not FDA approved, is recommended by the Centers for Disease Control and Prevention (CDC) under an investigational protocol for specific vaccinia complications. Treatment is recommended for (1) eczema vaccinatum, (2) progressive vaccinia, (3) generalized vaccinia that is severe or occurs in a patient with an underlying illness that may increase risk of severity, and (4) in limited cases of severe lesions secondary to inadvertent autoinoculation. VIG is not recommended for benign self-limited complications or complications that are not believed to be associated with viral replication (CDC 2003d). To date, there are no drugs with FDA approval to treat vaccinia complications. However, the availability of therapies used to treat these complications may change, and investigators should address questions regarding this issue to FDA on a real-time basis.

III. REGULATORY APPROACH REGARDING DRUG DEVELOPMENT

In each topic area below, the amount and timing of the information recommended relative to other steps in the development sequence may vary. We encourage initial discussions with FDA to address priorities and timelines for each proposed development plan. Pre-IND submissions are encouraged at an early stage of development to facilitate such discussions, to address questions about the development sequence, and to provide an opportunity for feedback on nonclinical and clinical study proposals. Sponsors should contact the appropriate review division for advice on the procedure for a pre-IND submission.[3] For other, more general information on development of approaches to medical countermeasures, the Division of Counter-Terrorism may be a useful resource.

This guidance focuses on drugs designed to treat the complications associated with vaccinia virus replication. If candidate drugs are proposed that are not considered to have an antiviral mechanism of action, it is important that sponsors provide an adequate rationale and that they address other specific aspects of their proposed actions. For example, any product directed principally at treating bacterial superinfections of vaccination sites may be more appropriate for principal evaluation as an antibacterial therapy for complicated bacterial skin infections, and any product directed principally at characteristics of wound healing may call for consideration of wound-specific issues. If such cases occur, other guidances may prove useful.[4] However, we expect sponsors of such drug candidates to provide data from evaluation of the effect of the drug on viral replication and from assessment of drug-drug interactions with antiviral drugs targeted for vaccinia complications. Sponsors will want to ensure that all studies and procedures incorporate adequate precautions to avoid transmission of pathogenic virus or generation of novel biologic hazards, including containment measures and vaccination of study staff, as appropriate.

A. Interactions Among Industry, Academic, and Government Sponsors

Sponsors are encouraged to explore areas of interaction and collaboration to increase the efficiency of drug development and resource use. For example, contacting the National Institute of Allergy and Infectious Diseases, National Institutes of Health, may be useful early in the course of development to identify sources of grants and contracts, and to learn about collaborative programs where aspects of drug development may be under way. For products in the development stage for which clinical trials are appropriate,

[3] For example, contact the Division of Antiviral Drug Products for systemic therapies, the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products for ophthalmic products, or the Division of Dermatologic and Dental Drug Products for topical products that have no systemic formulation.

[4] Draft guidances on *Uncomplicated and Complicated Skin and Skin Structure Infections – Developing Antimicrobial Drugs for Treatment* and *Chronic Cutaneous Ulcer and Burn Wounds – Developing Products for Treatment* were issued in July 1998 and June 2000, respectively. If and when finalized, they will represent the Agency's thinking on these topics.

discussions with public health programs through the CDC or state and local public health agencies may facilitate identification of target populations and setting priorities for resource use. In some circumstances, collaborations between sponsors of drugs and developers of new vaccine candidates may be beneficial.

Opportunities, such as funding programs or collaborative efforts, may change substantially over time. Therefore, we recommend that the sponsor identify contacts for collaboration at the relevant stage of product development.

B. Drugs with Previous or Concurrent Studies for Other Indications

If the drug under evaluation has not been previously approved but has already undergone substantial development and is currently under study for other indications (or for which such studies are planned) or has had approval sought for a nonvaccinia indication, it may be possible to expedite the development process. In this situation, some safety data will already exist, and the applicant may not need to collect as much additional data to complete the safety database. Furthermore, results of studies for other similar indications may provide ancillary supporting data for the evaluation of efficacy for vaccinia-related indications. It is the responsibility of the sponsor to document the adequacy of the available safety data to support the safety of the clinical protocol under consideration.

If the sponsor does not own the supporting safety data and if those data are not in the public domain, it is the sponsor's responsibility to get letters of authorization allowing FDA to refer to those studies during its evaluation of the proposed clinical trial.

If the drug under evaluation has already been approved for other indications, the sponsor can either obtain a right of reference to the safety data or rely on the Agency's previous finding of safety of that drug and provide any additional supportive data, as appropriate, to support the proposed investigational use (e.g., due to different dose or patient population as compared with the approved use). If the sponsor relies on the Agency's previous finding of safety, however, any future submission of an NDA would be subject to the provisions of 21 CFR 314.54.

Early discussion with the Agency may help to identify planning strategies that could lead to the most efficient design of overlapping development plans. For those drugs that are new chemical entities, please refer to section D of this section (Nonclinical Toxicology) for information regarding the recommended safety studies.

C. Chemistry, Manufacturing, and Controls

We recommend that the sponsor submit chemistry, manufacturing, and controls (CMC) information as described in the guidances *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs* and *INDs for Phase 2 and 3 Studies Chemistry, Manufacturing, and Controls Information*. Depending on the situation, we recommend that sponsors consult other relevant guidances.

D. Nonclinical Toxicology

A sponsor must supply information about the pharmacological and toxicological studies of a drug performed in vitro or in animal studies adequate to support the safety of proposed clinical investigations (21 CFR 312.23(a)(8)). The kind, duration, and scope of animal and other studies that should be submitted varies with the duration and nature of the proposed clinical investigations. Guidance documents are available from FDA that make recommendations about ways such requirements can be met; they are referenced in the following sections.

The information submitted must include the identification and qualifications of the individuals who evaluated the results of these studies and concluded that it is reasonably safe to begin the proposed clinical investigations (§ 312.23(a)(8)). In addition, the sponsor must include a statement detailing where the investigations were conducted and where the records are available for inspection (§ 312.23(a)(8)). As drug development proceeds, the sponsor will be expected to submit nonclinical and clinical safety informational amendments.

The sponsor must submit an integrated summary of the toxicological effects of the drug in vitro and in animals (§ 312.23(a)(8)(ii)(a)). Depending on the nature of the drug and the phase of the investigation, the summary should include the results of acute, subacute, and chronic toxicity tests, safety pharmacology tests, tests of the drug's effects on reproduction and the developing fetus, tests of the drug's genetic toxicity, any special toxicity test related to the drug's particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology), and any in vitro studies intended to evaluate drug toxicity. We also expect that animal studies describing the pharmacological effects and mechanisms of action of the drug and information on the absorption, distribution, metabolism, and excretion of the drug will be submitted. For each toxicology study that is intended to support the safety of the proposed clinical investigation, a full tabulation of data suitable for detailed review must be submitted (§ 312.23(a)(8)(ii)(b)).

The sponsor must submit a summary of previous human experience with the investigational drug (§ 312.23(a)(9)). A sponsor is required to submit detailed safety data as well as information relevant to the rationale of drug development for any investigational drug marketed in the United States or abroad (§ 312.23(a)(9)(i)). A list of countries in which the drug has been marketed or withdrawn from marketing for reasons related to its safety or efficacy must also be provided (§ 312.23(a)(9)(iii). Additionally, if the drug has been studied in controlled clinical trials, relevant data regarding the drug's effectiveness for the proposed investigational trial should be submitted (§ 312.23(a)(9)(i)). Published material relevant to the safety or effectiveness of the drug or clinical investigation must be provided while less relevant published material should be provided as a bibliography.

Regulatory and pharmaceutical industry representatives from the United States, Europe and Japan (The International Conference on Harmonisation of Technical Requirements of

Registration for Pharmaceuticals for Human Use (ICH)) have written guidance documents for many of the nonclinical requirements for safety studies. These guidance documents recommend international standards for, and promote harmonization of, the nonclinical safety studies needed to support human clinical trials of a given scope and duration.

1. Timing of Nonclinical Studies to Support the Conduct of Human Clinical Trials

Usually, once a drug has been shown in nonclinical studies to be sufficiently safe for clinical trials to begin, trials are conducted to demonstrate the drug's safety and efficacy in humans. Phase 1 trials evaluate the safety and pharmacokinetic profile of the drug. These trials start with relatively low drug exposure in a small number of subjects, often using healthy volunteers. The pharmacokinetic data, together with activity data in vitro, should ideally demonstrate that a high inhibitory quotient (IQ, see relevant section in III.E.2.d), can be expected at doses that are safe for the administration of drug. Efficacy evaluations are carried out in trials of longer duration. Therefore phase 1 trials are usually followed by clinical trials in which drug exposure increases by dose, duration, and/or size of the exposed patient population.

In trials of drugs designed to treat vaccinia complications, we expect that studies to assess the safety of the drug in humans will be conducted first in healthy volunteers. Sufficient nonclinical studies should be carried out to support the safety of administration of the drug for at least 2 weeks, or until pharmacokinetic measurements have demonstrated that the drug has reached steady state in the normal volunteers. In general, toxicology studies of 2 week duration in a rodent and a nonrodent species will support submission of protocols for review for phase 1 clinical trials of up to 2 weeks. Upon the completion of such studies, a 1 month (or longer) study, again in healthy volunteers, might be considered. However, to support the dosing of humans in clinical trials for a period longer than 2 weeks, nonclinical toxicology studies of a longer duration should be performed.[5] The clinical spectrum of serious vaccinia complications suggests that some cases may require treatment for longer than 2 weeks, and therefore we recommend that initial toxicology and safety studies take this possibility into account.

2. Acute and Subacute Toxicity Studies

Acute toxicity studies are often the first studies carried out on a drug intended for humans and use a single dose or multiple-doses administered for no longer than a 24-hour period. Subacute studies are multiple-dose studies carried out for no longer than 6 months. Most commonly, an acute study with drug administration by the proposed clinical route of administration as well as a parenteral route (usually intravenous) is performed in a rodent and a nonrodent species to set the doses for longer term nonclinical studies and to evaluate the immediate toxicity profile of the drug. If the proposed clinical route of administration is to be intravenous, intravenous evaluations alone will usually suffice.

[5] See ICH guidance on *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals*

We recommend that observational evaluations, as well as clinical chemistry and histopathologic evaluations, be performed at the end of 2 weeks.

3. Safety Pharmacology Studies

Safety pharmacology studies evaluate the interaction of the drug with organ systems such as the central nervous system, cardiovascular system and respiratory system. In some cases, the sponsor can incorporate some safety pharmacology evaluations in animals into the design of toxicology, kinetic, and clinical studies, while in other cases these endpoints are best evaluated in specific safety pharmacology studies. Although the adverse effects of a substance may be detectable at exposures that fall within the therapeutic range in appropriately designed safety pharmacology studies, such effects may not be evident from observations and measurements used to detect toxicity in conventional animal toxicity studies.[6]

4. Genetic Toxicity

Prior to the administration of a new drug into humans, we recommend that the sponsor perform a comprehensive assessment of its genotoxic potential. Since no single test is capable of detecting all relevant genotoxic agents, the usual approach has been to carry out a battery of in vitro and in vivo tests for genetic toxicity. A standard test battery of studies has been selected under ICH to evaluate a new drug for its ability to cause genetic toxicity. In general, two of the in vitro tests should be completed prior to the initial submission of an IND, and the remainder of the battery should be completed prior to phase 2 studies.[7]

If genetic toxicity is detected, one is confronted with an ethical dilemma. Generally, a genetically toxic drug is not administered to a healthy volunteer for greater than one dose. It is considered unethical to subject a healthy volunteer, who does not stand to benefit from drug administration, to a drug that might cause cancer. It is possible that some drugs with efficacy against vaccinia could also be genetic toxins. We recommend that the sponsor confer with the review division regarding such an issue as soon as possible.

5. Reproductive Toxicity

Reproductive toxicity studies assess the effect a drug may have on mammalian reproduction from premating (adult male and female reproductive function) to sexual maturity of the offspring. ICH guidances address the design of reproductive toxicity studies and offer a number of choices for carrying out reproductive toxicity studies.[8] The

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[6] See ICH guidance *on S7A Safety Pharmacology Studies for Human Pharmaceuticals*.

[7] See ICH guidances *S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals and S2A Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals*.

[8] See ICH guidances *S5A Detection of Toxicity to Reproduction for Medicinal Products* and *S5B Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility*.

reproductive toxicity studies vary from indication to indication, but they are all expected to be submitted before phase 3 trials. In trials of vaccinia complications, women entering the trials while pregnant and toxicity to male and female fertility are concerns. We expect that a study of fertility from conception to implantation and at least one organogenesis study would be completed prior to the early studies in healthy volunteers, and the full complement of studies would be completed prior to the administration of the drug in patients. The informed consent should outline the hazards associated with drug administration.

6. Carcinogenicity Studies

In general, carcinogenicity studies would not be expected for drugs used to treat vaccinia complications since the administration of the drug would not, in most cases, exceed 6 months. However, decisions regarding the performance of carcinogenicity studies would need to be made on a case-by-case basis and would depend on the mutagenic potential and/or possible structure-activity relationship of the test drug with other known carcinogens.[9]

E. Microbiology

This section discusses issues that are important to consider during the microbiologic evaluation of candidate drugs. Some components may change as more investigations take place in this field (for example, increased opportunities to study cross-resistance or interactions with other anti-vaccinia drugs). The sponsor will be expected to make available for review adequate information on sample collection and 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 does not constitute FDA endorsement of that procedure, method, or test system, or FDA approval for clinical laboratory use. This guidance addresses these points further in the following descriptions, and sponsors are strongly encouraged to bring questions for discussion with the review division early in the drug development process.

1. Nonclinical Virology Reports

Nonclinical virology reports are an important component in the review process of a candidate anti-vaccinia drug. They contribute to the evaluation of a candidate drug's safety concerns and activity prior to its use in humans. We request that submitted reports identify the mechanism of action, establish specific antiviral activity of the compound in a model system, and provide data on the development of viral resistance (or reduced susceptibility of the virus) to the candidate drug. We would expect that these studies be well advanced or completed prior to the introduction of the candidate drug into humans.

[9] See ICH guidances *S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals* and *S1B Testing for Carcinogenicity of Pharmaceuticals*.

2. Components of Nonclinical Virology Reports

a. Mechanism of Action

A candidate drug may act directly by targeting a specific viral-encoded function, (e.g., an enzyme inhibitor), or act indirectly (e.g., interferon induction of the host cell response). We request that nonclinical virology reports include background information describing the rationale and data showing the mechanism of action of the candidate drug and that the sponsor provide photocopies of all key cited references. We also expect that biochemical, structural, cellular, or genetic data will be presented to support the proposed mechanism of action. Examples include data demonstrating receptor binding, inhibition of enzymatic activity, X-ray crystallographic structure determination of bound inhibitor complex, and characterization of resistance mutations in the gene encoding the target. The sponsor will want to demonstrate the specificity of the candidate drug for the viral target over host proteins, especially when a viral enzyme has a cellular counterpart. For example, if the candidate drug targets a viral polymerase, specificity against the viral polymerase should be shown in comparison with host DNA and RNA polymerases. For nucleoside or nucleotide analogs, the sponsor will want to determine the intracellular half-life ($t_{1/2}$) of the triphosphate form of the active drug moiety.

We will look to see whether immunomodulatory drugs may have unintended adverse effects that result from a drug's actions on the immune system or from activation of viral replication. We will also look to see whether sponsors show a specific immune activation targeting vaccinia virus, not general immune stimulation.

b. In Vitro Antiviral Activity

For vaccinia virus, we expect that cell culture systems and animal models (e.g., infection of immunosuppressed or SCID mice) will be used to show the candidate drug has specific, quantifiable antiviral activity. FDA and organizations such as NCCLS do not recognize or recommend a specific test system for assessing antiviral activity. Sponsors can consult published work[10] or present additional proposals for review. We recommend that the antiviral activity of the candidate drug be tested against multiple vaccinia virus isolates, to demonstrate the candidate drug's activity for the most divergent isolates. The tested isolates should include vaccinia vaccine strains contained in licensed smallpox vaccines, other laboratory strains (including any strains expected to be used in animal models), and recent clinical isolates, if available. The sponsor will want to submit information that demonstrates that the data collected is relevant to the vaccine strains that may be targets for treatment in the clinical setting. We recommend that information on antiviral activity also be generated for related poxviruses, including any nonvaccinia poxviruses that may be studied in animal models (such as cowpox or monkeypox) or used as sources of ancillary information in the overall evaluation of the effectiveness of the candidate drug.

[10] For example, Kern et al., 2002, or Smee et al., 2002.

We recommend that specific antiviral activity be determined using a quantitative assay to measure virus replication in the absence and presence of increasing concentrations of the drug. The concentration of the drug at which virus replication is inhibited 50 percent is the inhibitory concentration, IC_{50}, or effective concentration, EC_{50}. We also recommend that the sponsor document the sources of viruses (such as blood, plasma, defined laboratory and vaccine strains), their method of isolation and their characterization, storage and stability, and cell culture procedures and materials. Sponsors are encouraged to consult FDA, ICH and NCCLS guidance documents for approaches to standardizing and controlling method parameters and definitions on assay validation. For any assay developed or used for showing antiviral activity, or other investigational assay used in the nonclinical and clinical studies, the sponsor should provide sufficient information about the assay to assess the appropriateness of its use in the specified study setting. Assays should be well documented, and should adequately meet requirements of 21 CFR part 58. The test system should be standardized with well-defined control strains. The sponsor should discuss with the Agency the specific information to be provided.

It is important to consider whether the inhibitory concentration is consistent with data supporting the mechanism of action, such as K_i (inhibitory constant) or binding data. A drug candidate that inhibits virus replication at a concentration much lower than would be expected from the biochemical data supporting the proposed mechanism suggests that another target may be affected or another mechanism of inhibition may be operating.

c. In Vitro Antiviral Activity in the Presence of Serum Proteins

Serum proteins bind and sequester many drugs and may interfere with a drug's antiviral activity. Therefore, we recommend that the in vitro antiviral activity of a candidate drug be analyzed both in the presence and absence of serum proteins. For multiple laboratory and clinical isolates of vaccinia, the sponsor will want to evaluate the effects of human serum (45-50 percent) and/or human plasma plus α-acidic glycoprotein on the in vitro antiviral activity of the candidate drug and determine a mean serum adjusted IC_{50} or EC_{50} value.

d. Inhibitory Quotient

Drug concentrations are an important factor in the response to viral therapy. Therefore, we recommend that the sponsor determine an inhibitory quotient (IQ) = C_{min}/serum adjusted IC_{50}. An IQ integrates plasma drug concentrations and resistance testing. A high IQ indicates the potential that a drug concentration may be achieved in a patient that will effectively inhibit the virus and minimize the development of drug resistance. A high IQ may help to identify promising drugs for further studies. Additional information on the relationship between IQ and outcome may be obtainable in such studies.

e. Cytotoxicity

After drug exposure in a cell culture model, host cell death may be misinterpreted as antiviral activity. Cytotoxicity tests use a series of increasing concentrations of the candidate drug to determine what concentration results in the death of 50 percent of the host cells. This value is referred to as the median cellular cytotoxicity concentration and is identified by the initializations

CC_{50} or $CCIC_{50}$. The relative effectiveness of a candidate drug in inhibiting viral replication compared to inducing cell death is referred to as the therapeutic index, (i.e., CC_{50}/IC_{50}), or as the selectivity index. A high therapeutic index is desired, as this represents maximum antiviral activity with minimal cell toxicity. We recommend that the CC_{50} be assessed both in stationary and dividing cells from multiple human cell types and tissues for potential cell cycle, cell type, or tissue specific toxicities. We also recommend that the effects of the candidate drug on mitochondrial toxicity in cell culture be monitored by examining measures such as mitochondrial morphology, glucose utilization, lactic acid production, and mitochondrial DNA content. These studies may reveal the potential for toxicity in vivo.

f. In Vitro Combination Activity Analysis

Administration of multiple antiviral drugs may be more effective in inhibiting virus replication than a single drug. Future treatments for vaccinia complications may use combinations of drugs. However, drug interactions are complex and may result in antagonistic, additive, or synergistic effects with respect to antiviral activity. For this reason, it is important to test the in vitro antiviral activity of candidate drugs in combination with other drugs approved for the same indication. In the case of vaccinia, for which there are no currently FDA approved drugs, we recommend that in vitro combination activity studies be considered with any other investigational drugs expected to be used with the candidate study drug, as well as with any drugs approved for the indication at the time that a new candidate drug is entered into development. Drug interactions can be evaluated using analyses based on published work such as Chou and Talalay (1984).

g. Selection of Resistant Virus In Vitro

We expect that the sponsor will assess the potential of a target virus to mutate and develop resistance to the candidate drug. *Resistance* as it is used here is a relative, not absolute, term.

Two basic methods can be employed to isolate viruses that have reduced susceptibility to the candidate drug. In the first, the virus is propagated for several passages at a fixed drug concentration, using multiple cultures to test different concentrations. Alternatively, the virus is passaged in the presence of increasing drug concentration starting at half the IC_{50} value for the parental virus. For both of these methods, virus production is monitored to detect the selection of resistant virus. The former method is particularly useful to identify drugs for which one or two mutations can confer large shifts in susceptibility.

Selection in cell culture of virus resistant to the candidate drug can provide insight into whether the genetic threshold for resistance development is high (≥3 mutations) or low (1 or 2 mutations). The rate of appearance of resistant, mutant viruses depends on the rate of viral replication, the number of virus genomes produced, and the fidelity of the viral replicative machinery. Resistance is also a function of the inhibitory quotient, as mentioned above. Consideration of these factors may help design tests to detect the appearance of virus resistant to high concentrations of the drug in vitro. In cases when cell culture systems do not produce sufficient virus titers and multiple mutations are required to develop resistance to high drug concentrations,

serial passage of the virus in the presence of increasing concentrations of the candidate drug may lead to the isolation of resistant virus.

Genotypes

Genotypic analysis of selected resistant viruses determines which mutations might contribute to reduced susceptibility to the candidate drug. Identifying resistance mutations can be useful in developing genotypic assays and analyzing their ability to predict clinical outcomes and can provide data supporting the proposed mechanism of action of the candidate drug. Frequently occurring mutations can be identified by DNA sequence analysis of the relevant portions of the virus genome. We recommend that the complete coding sequence of the gene for the target protein be determined. Furthermore, we recommend that the pattern of mutations leading to resistance of a candidate drug be documented and compared with the mutation pattern of other drugs in the same class. We recommend that the details of the genotypic assays used be reported along with the results for controls used to standardize the assays. Finally, we recommend that the sponsor define the lowest percentage for any one mutation present in a mixed population that can be detected with a particular genotypic assay.

Phenotypes

Phenotypic analysis determines if mutant viruses have reduced susceptibility to the candidate drug. Once resistance mutations are identified, we recommend that their ability to confer phenotypic resistance be evaluated in a recombinant virus system (e.g., by using site-directed mutagenesis or PCR amplification of relevant portions of virus genome to introduce these mutations into a standard laboratory genetic background). One could then test recombinant virus for drug susceptibility in vitro. The shift in susceptibility, or fold resistant change, for a clinical isolate is measured by determining the IC_{50} or EC_{50} values for both the isolate and a reference virus under the same conditions and at the same time. The fold resistant change is calculated as the IC_{50} of isolate/IC_{50} of reference strain. We recommend that a well-characterized wild type laboratory strain grown in cell culture serve as a reference standard and multiple isolates of vaccinia be examined by phenotypic assays, including clinical isolates, when possible. Clinical isolates should be representative of the breadth of diverse mutations and combinations known (if known) to confer reduced susceptibility. Due to the small number of vaccinia complications likely to be available for analysis during any one drug development program, potential sponsors are encouraged to consider establishment of a bank of clinical isolates that could be made available for assessment of future candidate drugs.

The utility of a phenotypic assay will depend upon its sensitivity, (i.e. its ability to measure shifts in susceptibility (fold resistant changes) compared to reference strains or baseline clinical isolates). Calculating the fold resistant change (IC_{50} of isolate/IC_{50} of reference strain) allows for comparisons between assays.

Well-characterized genotypic and phenotypic assays are important for detection of the emergence of resistant virus during the development of candidate drugs. Applicants can choose to do phenotypic and genotypic characterization or send samples to laboratories that are registered under section 510 of the Federal Food, Drug, and Cosmetic Act and use test systems

with standard operating procedures. In the former case, it is important that the investigational assay's performance characteristics be provided to the review division, and in the latter case, we urge that approved handling procedures for laboratory samples be employed.

h. Cross-Resistance

In the case of antiviral drugs targeting the same protein, cross-resistance, (i.e. mutations leading to reduced susceptibility to one drug resulting in decreased susceptibility to other drugs in the same class) has been observed. Cross-resistance is not necessarily reciprocal. For example, if virus X is resistant to drug A and shows cross-resistance to drug B, virus Y, which is resistant to drug B, may still be sensitive to drug A. Cross-resistance analysis may be important in the development of treatment strategies (i.e., establishing the order in which drugs are given). The sponsor will want to evaluate the effectiveness of the candidate drug against viruses resistant to other approved drugs in the same class and the effectiveness of approved drugs against viruses resistant to the candidate drug.

3. Proposal for Monitoring Resistance Development

Prior to the initiation of clinical studies in patients with vaccinia complications, a sponsor is urged to submit a plan to monitor for the development of resistant viruses with the nonclinical reports in the IND. If animal studies are expected to make a salient contribution to drug evaluation (see section IV on Animal Models),we also urge that proposals for the evaluation of resistance in the appropriate parts of the animal studies be submitted. The resistance monitoring plan would generally include the assays that will be used to monitor viral shedding and viral burden, methods of sample collection and storage, methods for sample handling (frozen or ambient), genotypic and phenotypic assays, timepoints that will be analyzed (e.g., baseline, day 1, and additional specified on-treatment and post-treatment time points), and the names of the parties responsible for each of these. In addition, we recommend that plans for genotypic and phenotypic baseline studies and additional substudies be considered and submitted. We recommend that genotypic and phenotypic analyses of at least a subset of baseline isolates be performed to determine outcomes based on baseline mutations and baseline phenotypic drug susceptibilities.

We suggest that genotypic and phenotypic data be provided (at a minimum) for baseline isolates from all patients and the endpoint isolates of virologic failures and discontinuations. Furthermore, we recommend that definitions of virologic failures and discontinuations be discussed with the review division during protocol development. For example, in the more extensively studied setting of therapy for HIV-1 infection, virologic failure definitions have been based on the course of viral load measurements over time and on investigator evaluations of reasons for discontinuation. We urge that information bases be developed to facilitate the assessment of the relationship between clinical course and virologic findings in vaccinia complications.

4. In Vivo Virology Study Reports (Clinical and/or Animal Studies)

In addition to the nonclinical virology reports discussed in the first part of the Microbiology section above, virology study reports from clinical studies (and studies in animal models where applicable) will be an important component of the overall evaluation of candidate drugs as they reach later stages of development. We expect that complete virology study reports, such as those submitted with a new drug application (NDA), will be extensive and will include the raw and analyzed data as well as all the information to evaluate the procedures used to obtain those data. Virology study reports convey information on in vivo antiviral activity of the candidate drug, development of resistance to the candidate drug in treated patients and animal models, and cross-resistance with other drugs in the same drug class. The format of a virology study report is similar to a scientific paper and typically includes summary, introduction, materials and methods, results, and discussion sections. The methods section will typically describe all the protocols employed and include a description of the statistical analyses used. We recommend that sponsors also provide photocopies of key references.

For some antiviral therapies in other settings, quantification of viral loads has been a good measure of the clinical effectiveness of antiviral drugs and has provided insight into whether these drugs have activity in vivo when the clinical benefit may not be apparent or may be temporary due to the development of resistance. Such candidate drugs may prove useful when studied in combination with other drugs. Development of methods for quantification of viral burden or viral shedding, and evaluation of the relationship between these quantitative measurements and clinical outcomes of disease and treatment, is encouraged for vaccinia studies. As mentioned above, we expect the sponsor to provide a complete description of the methodology and the quantitative assay performance characteristics, the specimen sources of viruses (such as blood, plasma, defined lesion specimens), their storage and stability, and cell culture procedures. We encourage efforts to collect sufficient specimen to allow reserve amounts to be stored for possible re-evaluation by new or improved assays. Additionally, it will be important to examine the relationships between phenotypic and genotypic analyses and clinical outcomes in vaccinia studies, to assess the extent to which these assays may be predictive of the utility of treating an individual with the candidate drug. We recommend using viral load, genotypic, and phenotypic assays analyses following the same criteria as described above in the Microbiology section (section III.E). Sponsors are encouraged to discuss their assays with the review division. Genotypic analysis of baseline and failure isolates from patients failing to respond to therapy or undergoing viral rebound can help identify mutations that contribute to reduced susceptibility to the candidate drug. It is important that phenotypic analyses of baseline and posttreatment isolates be completed to obtain information on the susceptibility of the candidate drug and cross-resistance with other drugs. We recommend that genotypic and phenotypic analysis of at least a subset of baseline isolates be performed to determine response to therapy based on baseline mutations and baseline phenotypic drug susceptibilities. Please consult the review division with respect to electronic submission of resistance data.

F. Clinical Pharmacology

We recommend that sponsors study the relationship between in vitro activity and in vivo activity using animal models prior to the initiation of studies in humans (see section IV on Animal Models). Sponsors should also consider developing models of drug pharmacokinetics and/or pharmacodynamics to study drug dosage and drug regimens further, using both in vitro systems

and animals. Developing such models could expedite the selection of an optimal drug dose regimen for human clinical studies.

Please submit human pharmacokinetic and pharmacodynamic information as soon as available. The purpose of obtaining these data is as follows:

1. To demonstrate that the desired systemic drug level in humans can actually be achieved after the anticipated dosage regimen is given
2. To explore the relationship between blood drug concentration and pharmacodynamic response
3. To select the appropriate dose
4. To evaluate the relationship between drug exposure and subsequent development of viral resistance (see section III.E.3 on Proposal for Monitoring Resistance Development).

We recommend that you perform exposure-response analyses where appropriate.[11] These analyses may help to determine which drug exposure measures, for example, area-under-the curve (AUC) and concentration at the end of the dosing interval, are relevant to a given outcome. For studies conducted with animal models, the dose regimens used in animals to provide systemic exposure comparable to humans may not be the same as the regimen for humans. Therefore, the sponsor should consider conducting studies demonstrating that the difference in dose regimens does not affect the drug's efficacy and/or safety.

We expect that the sponsor will characterize fully the metabolic profile (in vitro and in vivo) in humans and will submit information comparing the plasma protein binding of the active drug components across the range of expected concentrations in humans.

We would expect to receive pharmacokinetic data for special populations, including pediatric patients,[12] elderly patients (= 65 years), and patients with renal and hepatic impairment.[13] Please submit available pharmacokinetic data in pregnant women and available data for drug excretion into human breast milk as soon as available. However, if the information base is otherwise sufficient for an NDA, we would not advise delaying submission while awaiting the special population data.

Since vaccinia complications tend to occur in persons with underlying illnesses, recipients of the study drug may be receiving several medications concurrently (e.g., antiretrovirals and immunosuppressants). In vitro drug metabolism studies may direct the investigation of potential

[11] See FDA guidance *Exposure–Response Relationships — Study Design, Data Analysis, and Regulatory Applications* .

[12] A draft guidance on *General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biologics* issued in November 1998. Once finalized, it will represent the Agency's perspective on this issue.

[13] See FDA guidance on *Pharmacokinetics in Patients with Impaired Renal Function* and *Pharmacokinetics in Patients with Impaired Hepatic Function*

human drug-drug interactions.[14] The sponsor should submit drug interaction data. However, information regarding drug interactions should not delay the submission of the NDA.[15]

Sponsors are encouraged to refer to other FDA guidances that may be appropriate.[16]

IV. ANIMAL MODELS

The acquisition of human data is very important and is expected to be a major focus of development plans. However, data from animals have much to offer in the evaluation of drugs for vaccinia complications. Due to the low rate of serious vaccinia complications, it may not be possible to acquire clinical data from trials sufficiently large enough to serve as the sole basis of approval. Animal models may provide supportive information for the design of clinical protocols, support the use of a candidate drug under an investigational protocol in an emergency situation, and possibly contribute directly to the basis for approval in combination with obtainable human data.

Historically, there have been no accepted, well-characterized animal models shown to replicate or to predict human responses to therapy for vaccinia complications. Currently, the ability of any animal model to predict human responses to vaccinia therapy is difficult to assess, especially given the lack of any drugs previously established as effective that could be used to characterize models and to compare new drugs. Use of existing animal models to provide preliminary information on drug activity is encouraged, as is further development of models that resemble as closely as possible the apparent predisposing risk factors (such as immune compromise or dermatologic disease), pathophysiology, and clinical manifestations of disease associated with specific vaccinia complications in humans, and with differing viral strains.

If well-characterized animal models predictive of human treatment responses can be developed and if there is agreement that adequate clinical trials would not be ethical as deliberate challenge studies and would be infeasible as field studies, circumstances may exist where drug approval may be based upon evidence of effectiveness obtained from studies done in animals (see the Animal Efficacy Rule, 21 CFR part 314, subpart I[17]). A determination that adequate clinical trials could not ethically be conducted as challenge studies might be made if it were determined that no suitable endpoint (surrogate measurement) could be established to obtain adequate information in studies of healthy volunteers who could ethically be vaccinated for the purpose of a drug study and that challenge studies of clinical endpoints (mortality or major morbidity) in serious vaccine complications would require deliberate vaccine exposure of individuals at high risk of serious adverse events who should avoid vaccine in nonemergency situations. A determination that adequate clinical trials would be infeasible as field trials could be made if it is determined that a new drug is being developed in circumstances in which it is not possible to

[14] See FDA guidance *Drug Metabolism/Drug Interaction Studies*.

[15] See FDA guidance *In Vivo Metabolism/Drug Interaction Studies*.

[16] See FDA guidance *Population Pharmacokinetics*.

[17] *Federal Register* 67(105): 37995-37996, May 31, 2002.

obtain appropriate information from studies of adverse events occurring during vaccination activities carried out for reasons other than drug studies. We will rely on evidence from studies in animals to provide substantial evidence of the effectiveness of a product directed against a serious or life-threatening condition only when:

1. The pathophysiological mechanism of the toxicity of vaccinia virus and its prevention or substantial reduction by the drug are reasonably well understood.
2. The effect is demonstrated in more than one animal species expected to be predictive of the response in humans unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized model for predicting the response in humans.
3. The endpoint studied in the animal model is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity.
4. Data on the kinetics and pharmacodynamics of the drug in both animals and humans are available and sufficiently well understood to recommend an effective dose in humans.

If there is a situation in which animal studies are designed and agreed to as the principal component of the efficacy evaluation, clinical trials in humans are required to be conducted with due diligence when feasible and ethically appropriate, and suitable protocols must be submitted for review during the development process (21 CFR part 314, subpart I). Thus, it is important to plan timely studies of treatment of any serious complications occurring during ongoing use of vaccinia for purposes such as public health vaccination campaigns and development of alternative vaccines. If drug development is undertaken for the treatment of less serious, self-limited vaccinia complications, clinical trials will be expected as the principal determination of efficacy. Even if there are circumstances in which evidence of effectiveness in animal studies can appropriately be used for approval, these provisions for use of animal studies do not apply to safety evaluation (21 CFR part 314, subpart I), which will follow preexisting requirements for new drug products (*Federal Register* 67*:*37989, May 31, 2002). Therefore, safety data from human studies will also be expected.

The contribution of animal data to efficacy evaluations will vary according to numerous factors. Important considerations in refining animal studies include using a range of treatment start times and durations, including treatment started after a vaccinia complication has become clinically established. Blinding of observers to treatment assignment may be of greater importance than in standard nonclinical studies.

Because the availability of well-characterized animal models and the data supporting their use to predict human treatment responses is expected to change over time, potential sponsors are encouraged to consult with the applicable FDA review division early in the developmental process to review and discuss the status of existing models, prospects for studying newer models, and proposals for integrated use of animal and human studies.

V. CLINICAL DATA

A. Clinical Trials

The decision to proceed to clinical trials in patients with vaccinia complications will depend on a drug nonclinical toxicity profile, activity in cell culture and animal studies, and human adverse events in phase 1 studies and/or data available from other uses of the drug. When appropriate drugs are identified for study, general considerations on the approach to clinical studies can be based on a combination of published FDA guidance[18] and discussion with the review division. The risk/benefit profile of the drug determines what types of clinical trials are appropriate. For example, a drug with frequent serious toxicities is unlikely to be suitable for treatment of self-resolving minor complications, whereas a drug with few toxicities might be evaluated if there is interest in attempting to reduce the duration of this type of vaccinia complication. Alternatively, a drug with known major risks of toxicity that is highly active and has sufficiently positive preliminary data to suggest a meaningful benefit may be suitable for study in patients with severe life-threatening vaccinia complications who lack alternative therapy.

For development of clinical trial proposals, it would be wise to clearly define the type of vaccinia complication for which a drug is being considered for therapy. If treatment is being considered to decrease duration and symptoms of generally self-limited vaccinia complications, such as minor autoinoculations and most generalized vaccinia events (for which specific treatment has not been considered necessary or recommended in the past), human data would likely be the principal or sole source of information on the outcomes of interest and placebo-controlled trials will likely be called for. However, the ability to draw secure conclusions may be limited unless treatment effects are dramatic enough to allow an adequately powered study with a small sample. For serious and potentially life-threatening vaccinia complications, such as eczema vaccinatum and progressive vaccinia, (which have traditionally been treated with VIG), placebo-controlled trials are unlikely to be either feasible or acceptable, and alternative approaches may be considered. Noninferiority comparisons against VIG are likely to be of limited value because of the lack of quantitative information on VIG efficacy and because of the inability to identify enough cases for an adequately powered comparison. If a candidate drug is studied in the context of a large-scale vaccination campaign in which substantial numbers of serious vaccinia complications occur, it may be possible to consider studies designed to show superiority to VIG (or other accepted therapies at the time studies are initiated), or to assess the contribution of the candidate drug when added to previously established therapy, or to assess use as a rescue treatment for failures following use of VIG or other accepted therapy. Endpoints in studies of serious vaccinia complications are generally expected to be measurements of mortality or major morbidity with direct demonstration of clinical benefit. If alternative or surrogate endpoints can be identified that are reasonably likely to predict benefit, the sponsor may want to discuss with the appropriate review division the possibility of using such markers in pivotal clinical trials, with the

[18] See FDA guidance *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

expectation that if this proves feasible, subsequent studies would be planned to confirm clinical benefit (21 CFR 314.510).

Even in circumstances when the likelihood of accruing enough serious vaccinia complications for the rigorous statistical assessment of a variety of treatments may be low, we encourage the design of pilot studies to facilitate data collection about disease course and response to therapy. These data may not lead to firm conclusions regarding the efficacy of a new treatment. However, small numbers of vaccinia complications with systematic data collection may contribute to the design of further nonhuman studies and assist in defining the emergence of viral resistance. In addition, data collection may help to identify previously unrecognized safety issues relating to the investigational drug. Because the risk/benefit assessment associated with a study may change as the study progresses, we recommend that the sponsor provide for ongoing reassessment through a system such as a Data Safety Monitoring Board (DSMB).

If an approach to treatment might be used prior to full development of the vaccination response (for example, systemic treatment for an autoinoculation lesion developing synchronously with the primary vaccination lesion) the sponsor would want to evaluate for potential and degree of interference with vaccine efficacy.

Depending on the drug toxicity, studies in normal human vaccinated volunteers can be considered to provide preliminary or ancillary evidence to support design of clinical trials or to contribute to a compilation of efficacy and safety data. For example, if meaningful measurements of circulating or local viral burden can be developed (see section III.E.4 on In Vivo Virology Study Reports), it may be justifiable and reasonable to perform preliminary studies of activity in human vaccinia infection by examining drug effects on response to vaccination in healthy volunteers. Potential parameters include lesion development and viral shedding. These studies may also contribute to the characterization of proposed surrogate markers for use in further clinical trials as discussed above. Development of a standardized method of diagnosis and viral burden assessment is encouraged. It is recommended that sample collection techniques be well documented. In such a study, the sponsor will also want to address uncertainties regarding the status of volunteers' vaccine-related immunity to smallpox after administration of the drug and investigate other correlates of the immune response or response to re-vaccination at a suitable time.

For a drug with a problematic safety profile that could not be ethically introduced into healthy human volunteers, obtainment of human pharmacokinetic, pharmacodynamic, and safety data may have to wait until complications from vaccination arise. In addition, the sponsor will want to consider collecting preliminary safety and efficacy information available from human infections with other orthopoxviruses or poxviruses from other genera such as molluscum contagiosum or orf. However, applicability to vaccinia cannot be assumed.

Treatment of ocular vaccinia (blepharitis, conjunctivitis, keratitis, and iritis) has been approached somewhat differently than the treatment of cutaneous or systemic

complications in the past (CDC 2003d). We recommend that studies involving drugs designed to address this complication be discussed in consultation with ophthalmology experts, as well as with the Division of Anti-inflammatory, Analgesic, and Ophthalmologic Drug Products.

Treatment of complications not generally thought to involve ongoing viral replication, such as erythema multiforme and postvaccinial encephalitis, is not specifically addressed in this guidance. However, proposals can be submitted to the appropriate review division for review and discussion.

B. Data Collection

1. Pre-Terrorism Event

In a nonemergent vaccination program, there are advisory panel recommendations for prevaccination screening to identify persons with a contraindication to receiving vaccinia vaccination (CDC 2003a). There will likely be small numbers of people who experience vaccine-associated complications that will require treatment, and it is expected that vaccine exposures and complications will be identifiable through efforts to track and record them. To maximize the likelihood that information from these experiences can be used to improve future treatment decisions, it is essential that data on the use of any candidate drug to treat vaccine complications be captured completely and accurately. Types of data to be collected include, but are not limited to:

- Demographics (e.g. patient age, gender, race/ethnicity)
- The nature of vaccinia exposure (vaccination vs. contact)
- Physical examinations detailing the type and extent of complication
- The patient's underlying condition
- Serum laboratory tests (for example, hematology panel, chemistry profile, renal and liver function tests)
- Other therapies used and outcome
- Drug toxicity
- Ultimate outcome
- Timing, specimen type, and results for all specimens obtained for virologic studies, including pre- and post-treatment blood samples for detection and quantification of viremia
- Serum drug levels where appropriate

We recommend designing a comprehensive case report form to assist in the accurate collection of data that will be used to assess the safety and efficacy of the drug (see Attachment A; although perhaps not all-inclusive, this example can be used as a starting point for such designs). Other guidances that address the assessment of skin lesions may provide additional suggestions regarding parameters to be followed during clinical

trials.[19] Investigators are encouraged to submit a case report form specifically designed to address their drug. Collaborations between sponsors and public health agencies are encouraged to facilitate optimal ascertainment and use of clinical experiences (see section III.A on Interactions Between Industry, Academic, and Government Sponsors and Investigators).

2. Post-Terrorism Event

In the event that vaccinia vaccine is administered under the circumstances of a variola bioterrorism attack, there may be more complications associated with vaccination. In this situation, no absolute contraindications have been established regarding the use of the vaccine if a patient has a high-risk exposure to variola, on the premise that those at greatest risk of developing a serious vaccinia complication are also at greatest risk for death from smallpox (CDC 2001). Because of the extensive use of resources in implementing a response to a smallpox event and also because of potential confusion between clinical manifestations of vaccinia complications and those of early smallpox, both case ascertainment and follow-up may be seriously compromised. Investigators should be aware that pre-event design of strategies to maximize accuracy and completeness of post-event data collection may be very important not only to assess the safety and outcomes of any investigational drug that may be used, but also to facilitate disease assessment, treatment, and monitoring. Clinical and public health expert authorities may recommend standardized patient evaluation and management in an emergency situation. Therefore, sponsors may want to consider such recommendations and their implications for patient care as well as data collection when designing a case report form (as above, material in Attachment A may provide a starting point). Sponsors should have a data collection system already in place. See section V.B.1 on Pre-Terrorism Event, for a brief discussion regarding the types of data that should be collected. Advance discussions between potential sponsors and public health officials would be useful to design investigational protocols and methods for case ascertainment and enrollment for candidate drugs that might be used in such a situation (see section III.A on Interactions Between Industry, Academic, and Government Sponsors and Investigators). As above, investigators are encouraged to design and submit a case report form designed to address the specific needs of their drug. Sponsors should refer to the National Defense Authorization Act for Fiscal Year 2004 (Pub. L. No. 108-136, sec. 1603, 117 Stat. 1392, 1684 (2003)) concerning planning the emergency use of unapproved drugs, or drugs unapproved for counterterrorism indications in the setting of a terrorism event. If the cited provisions in this act appear potentially applicable to a candidate drug, we encourage the sponsor to initiate early discussions with the Agency regarding the proposed use.

[19] For example, draft guidances on *Uncomplicated and Complicated Skin and Skin Structure Infections – Developing Antimicrobial Drugs for Treatment* and *Chronic Cutaneous Ulcer and Burn Wounds – Developing Products for Treatment* were issued in July 1998 and June 2000, respectively. If and when finalized, they will represent the Agency's thinking on these topics.

3. Post-Approval Studies

Post-approval studies should be considered to add to safety and efficacy data, especially given the likelihood that small clinical trials will have provided data for drug approval. There are certain circumstances that require the use of post-approval studies. For example, if the drug is granted accelerated approval using a surrogate endpoint to demonstrate efficacy, confirmatory clinical studies will be expected for verification of the clinical benefit of the drug and for confirmation that the observed clinical benefit is related to ultimate outcome (21 CFR 314.510). Also, if approval is given based upon efficacy data from animal models, postmarketing studies must be conducted to demonstrate efficacy in human patients whenever this becomes possible (21 CFR part 314, subpart I). Applicants must provide a plan or approach to the postmarketing study commitments to be used when the clinical studies become feasible (21 CFR part 314, subpart I).[20] In any of these situations, proposals and plans for appropriate postmarketing studies should be submitted for discussion during design of the overall clinical development plan, and plans would generally be expected to be in place and ready for implementation prior to any approval action. Postmarketing data collection may take place during or after a bioterrorism attack and may not be a conventional postmarketing study. However, opportunities for data collection may arise without an emergency situation, and we urge that they be used appropriately. FDA emphasizes the importance of having a means and a plan in place for rapidly identifying potential drug recipients, as well as a complete and thorough data collection system.

C. Long-Term Follow-Up

We recommend that follow-up analysis after administration of a candidate drug address durability of the therapeutic regimen, as well as the possible emergence of drug resistance. In addition, investigators should plan for long-term follow-up after drug administration if there are specific safety concerns associated with the drug, for example, carcinogenicity. If the drug is administered to pregnant women, we recommend that follow up include an assessment of the outcomes of pregnancy. Although we would expect that scarring or any other permanent sequelae of the vaccinia complication would be recorded in treatment follow-up, these phenomena may be particularly important and may warrant more detailed assessment for topical products or products that claim to expedite the epidermal healing process.

D. Special Populations

We recommend that information on drug safety, drug pharmacokinetics, and pharmacodynamics (including the necessary dose modifications), in the pediatric population, the geriatric population, pregnant women, lactating women, and persons with renal and hepatic impairment be submitted to FDA as soon as it is available. However, if overall safety and efficacy information is developed to a stage warranting discussions of submission of an NDA, an NDA should not be delayed to await inclusion of this special

[20] See the *Federal Register* 67(105): 37995-37996, May 31, 2002.

population data. In addition, many of the patients susceptible to vaccinia complications will be on medications that may interact with the candidate drug. Studies addressing these drug-drug interactions would also be of interest to the FDA (see section III.F on Clinical Pharmacology).

VI. SUMMARY

The number of smallpox vaccine complications requiring treatment is expected to be small, and plans for drug development should be carefully designed to make optimal use of the human data that can be collected. In this setting, development and study of animal models, to augment sparse human data, may also make important contributions to evidence of drug efficacy (see section IV on Animal Models). Evidence of safety will still require collection of safety data in humans, however. Sponsors are advised to contact FDA at an early stage of drug development to discuss proposals for the design of animal studies; proposals for clinical outcome, safety, and efficacy measures; and for the development of possible surrogate endpoints.

Data collection from the treatment of complications secondary to both nonemergent and emergent vaccination programs will yield important information regarding the safety and efficacy of the drug. We recommend that carefully planned, thorough data collection systems be put in place as early in the drug development process as possible.

ATTACHMENT: SAMPLE CASE REPORT FORM

This sample case report may not be all-inclusive. Investigators are encouraged to contact FDA at an early stage of plan development for data collection to discuss plan details and subsequently to discuss development of a case report form specifically designed to address the concerns of their drug, the vaccinia complication(s) to be studied, and the circumstances of the study.

Page 1

Treatment Center*: _____ Treatment Center ID Number: _____

Patient Name*: _____ Patient ID Number: _____

Date of Birth: _____ Gender: ____ Race/Ethnicity: _____

<u>Vaccinia Exposure</u> (Check One):
_____Vaccination Date: _____
_____Contact with Vaccinee Date:_____
Nature of contact (household, office, school, etc.): **_____**
_____Other

<u>Vaccine History</u>:
Vaccine Lot Number: _____
Vaccine Type: _____
Vaccine Manufacturer:_____
Concomitant Vaccinations:_____
Where Was Vaccination provided?:_____
History of Previous Smallpox Vaccination: Yes_____ No_____
If yes, date of previous smallpox vaccinations(s) _____
Does patient have previous smallpox vaccination scar?_____

*** Personal identifiers should be removed to protect patient confidentiality after completion of data collection**

SAMPLE CASE REPORT FORM

This sample case report may not be all-inclusive. Investigators are encouraged to contact FDA at an early stage of plan development for data collection to discuss plan details and subsequently to discuss development of a case report form specifically designed to address the concerns of their drug, the vaccinia complication(s) to be studied, and the circumstances of the study.

Page 2 **Patient ID Number: _____**

Patient's Underlying Condition (Check those that apply):

Chronic Skin Condition: **Atopic Dermatitis _____**
Eczema (active)_____(history of/currently inactive)___
Other (describe, e.g. psoriasis, severe acne, etc.) _____

HIV/AIDS_____ **If Patient HIV+:**
Most recent CD4 Count: _____ Date of test:_____
Most recent Viral Load: _____ Date of test: _____

Immunosuppressive Medication (detail in "Additional Medications" below)_____
Diagnosis Requiring Immunosuppressive Medication:
Organ Transplant:_____
Autoimmune disease (describe, e.g. rheumatoid arthritis, lupus, etc.)_____
Other (describe):_____

Cancer (Include type and stage if known):_____

Congenital Immune Deficiency (describe): _____

History of Underlying Heart Disease or Cardiac Risk Factors (describe):_____

Pregnant: ____ **Estimated Gestational Age:_____**

Other (describe) :_____

Patient's Additional Medications (Prescription as well as over-the-counter, dietary supplements, and herbal supplements. Include dose and length of time on immunosuppressants and chemotherapeutic drugs if applicable):

_____ _____ _____
_____ _____ _____
_____ _____ _____

SAMPLE CASE REPORT FORM

This sample case report may not be all-inclusive. Investigators are encouraged to contact FDA at an early stage of plan development for data collection to discuss plan details and subsequently to discuss development of a case report form specifically designed to address the concerns of their drug, the vaccinia complication(s) to be studied, and the circumstances of the study.

Page 3 **Patient ID Number:_____**

Vaccinia Complication (Check Those That Apply):

Autoinoculation _____
Generalized Vaccinia _____
Eczema Vaccinatum _____
Progressive Vaccinia _____
Ocular Vaccinia (blepharitis, conjunctivitis, keratitis, iritis) _____
Other (describe) _____

Date of Onset of Complication: _____

Describe Previous Treatments as Follows (e.g. VIG, etc):

Treatment:_____
Date:_____Dose:_____Route: _____Outcome:_____
Date:_____Dose:_____Route: _____Outcome:_____
Date:_____Dose:_____Route: _____Outcome:_____
Date:_____Dose:_____Route: _____Outcome:_____

Treatment:_____
Date:_____Dose:_____Route: _____Outcome:_____
Date:_____Dose:_____Route: _____Outcome:_____
Date:_____Dose:_____Route: _____Outcome:_____
Date:_____Dose:_____Route: _____Outcome:_____

[List And Indicate Inclusion And Exclusion Criteria For This Specific Study**]**

SAMPLE CASE REPORT FORM

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Page 4 **Patient ID Number:_____**

Study Treatment (Note Any Missed Doses):

Date/Time:_____ Dose/Route:_____
Date/Time:_____ Dose/Route:_____
Date/Time:_____ Dose/Route:_____
Date/Time:_____ Dose/Route:_____
Date/Time:_____ Dose/Route:_____
Date/Time:_____ Dose/Route:_____
Date/Time:_____ Dose/Route:_____
Date/Time:_____ Dose/Route:_____

Study Drug Levels When Appropriate:

Date/Time:_____ Peak (P) or Trough (T):_____Drug Level (units):_____
Date/Time:_____ Peak (P) or Trough (T):_____Drug Level (units):_____

Medications Added During Study:

Date:_____Dose/Route:_____Indication:_____
_____
Date:_____Dose/Route:_____Indication:_____
_____
Date:_____Dose/Route:_____Indication:_____
_____
Date:_____Dose/Route:_____Indication:_____
_____
Date:_____Dose/Route:_____Indication:_____
_____

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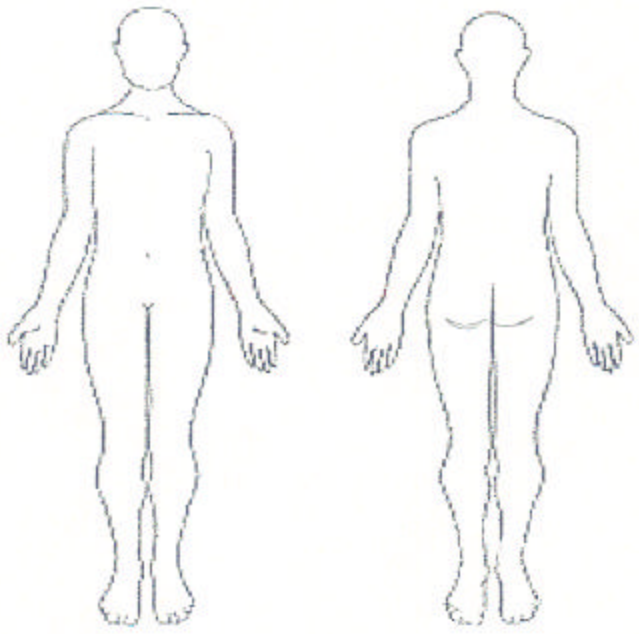
Page 5 **Patient ID Number: _____**

Physical Examination (Make additional copies of this page for each assessment scheduled per protocol and any additional assessments needed)

Date:_____

General Description of Lesion(s): _____
Distribution of Lesion(s): _____
Number of Lesions: _____
Document Size of Largest Lesion and Note if Lesion Size Varies at This Visit:_____

Drawing and mapping of lesion(s):



SAMPLE CASE REPORT FORM

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Page 6 **Patient ID Number: _____**

Physical Examination, continued

Photograph of lesion(s)(Document Body Site Photographed):

Date/Time: _____
Date/Time: _____
Date/Time: _____
Date/Time: _____
Date/Time: _____
Date/Time: _____

Tmax: _____
BP: _____
Pulse: _____
RR: _____
I/O: _____
General:_____
HEENT:_____
Pulmonary:_____
Cardiac:_____
Abdomen:_____
Extremities:_____
Neurologic:_____
Psychiatric:_____
Other :_____

SAMPLE CASE REPORT FORM

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Page 7 **Patient ID Number: _____**

Laboratory Results (Make additional copies of this page for each assessment scheduled per protocol and any additional assessments needed**)**

Date

WBC (Differential)								
Hgb/Hct								
Platelets								
Sodium								
Potassium								
Chloride								
Bicarbonate								
Phosphorus								
Magnesium								
Calcium								
Glucose								
BUN								
Creatinine								
Total Bilirubin								
Alkaline Phosphatase								
AST								
ALT								
Total Protein								
Albumin								
LDH								
Amylase								
PT								
PTT								
CD4 count*								
HIV viral load*								
Other								

*** Monitor CD4 count and HIV viral load if patient is HIV positive.**

SAMPLE CASE REPORT FORM

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Page 8 **Patient ID Number: _____**

Viral Culture to Screen for Resistance (if applicable):

Site of Culture: _____
Date:_____
Result (e.g., viral load if applicable)**: _____**
Genotype Performed: Yes____ (attach results) **No_____**

Assessment for evidence of bacterial superinfection (physical exam, cultures if applicable)

Other Tests/ X-rays (Include Date)_____
_____

Pregnancy test: Pos._____ Neg. _____ (Place here if not part of inclusion/exclusion criteria; risk/benefit assessment of study enrollment should be documented)

SAMPLE CASE REPORT FORM

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Page 9 **Patient ID Number: _____**

Investigational Drug Adverse Events Reporting Table

	AE Event Description	Date/ Time of Onset	Date/ Time of Resolution	Severity 1 – mild 2- moderate 3- severe	Continuous (C) Vs. Intermittent (I)	Relationship to the study drug 0 – unknown 1- NR 2- Probably NR 3- Possibly R 4- Probably R	Intervention/ Treatment
AE # 1							
AE # 2							
AE # 3							
AE # 4							
AE # 5							

Abbreviations: AE, adverse event; NR, not related; R, related (serious events should be reported in accordance with expedited procedures even if relationship to treatment is considered unlikely)

SAMPLE CASE REPORT FORM

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Page 10 **Patient ID Number: _____**

Post-Treatment Follow-Up (Make additional copies of this page for each assessment scheduled per protocol and any additional assessments needed)

Include Current Medications/Treatments
Physical Examination
Laboratory Tests
Complications and Subsequent Courses of Action

(Refer to previous case report form for sample of layout design)

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