
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DRAFT GUIDANCE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)
Center for Devices and Radiological Health (CDRH)**

**March 2004
Clinical Antimicrobial**

Guidance for Industry

Vaccinia Virus — Developing Drugs to Mitigate Complications from Smallpox Vaccination

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1 **Guidance for Industry¹**
2 **Vaccinia Virus — Developing Drugs to Mitigate**
3 **Complications from Smallpox Vaccination**
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7 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current
8 thinking on this topic. It does not create or confer any rights for or on any person and does not operate to
9 bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of
10 the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA
11 staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call
12 the appropriate number listed on the title page of this guidance.
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18 **I. INTRODUCTION**
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20 This guidance provides recommendations on the development of drugs to be used to treat
21 complications that may occur from smallpox vaccination with vaccinia virus. It is intended to
22 help commercial and research sponsors plan and design appropriate nonclinical and clinical
23 studies during the development of these drugs. This guidance does not make recommendations
24 about the development of drugs to treat smallpox. That issue will be addressed separately in a
25 future guidance document. This guidance also does not address the development of biological
26 therapies, such as vaccinia immune globulin (VIG).
27

28 The development of drugs to mitigate vaccinia virus complications raises unique and challenging
29 issues. Many of the previous studies done on the topic were performed prior to the 1970s, before
30 the United States abandoned routine vaccinia vaccination for smallpox. A concern that smallpox
31 may be used as a bioterrorism agent has led to a limited reintroduction of smallpox vaccination,
32 with the potential for widespread vaccination should an attack with smallpox occur. Therefore, it
33 is critical that we develop drugs to treat the complications associated with the vaccine. Currently,
34 there are no FDA-approved drugs indicated for treatment of vaccinia vaccine complications. We
35 would like to strongly encourage the submission of pre-investigational new drug applications
36 (pre-INDs) to promote discussions between sponsors and FDA addressing the sequence and
37 content of nonclinical and clinical study proposals.
38

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.

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

44
45 This guidance first summarizes appropriate nonclinical studies recommended during early drug
46 development. The section on chemistry, manufacturing and controls (CMC) refers the sponsor
47 to relevant guidances for CMC information. A nonclinical toxicology section outlines required
48 and recommended in vitro and animal safety studies used to support the safety of clinical
49 investigations. A microbiology section details both nonclinical and clinical issues important
50 during drug development, such as identifying drug mechanism of action, antiviral activity,
51 cytotoxicity, drug activity in combination with other drugs, and drug resistance. A clinical
52 pharmacology section discusses analyses the sponsor should perform to elucidate an
53 understanding of drug pharmacokinetics and pharmacodynamics, including data that should be
54 obtained from special populations.

55
56 Next, the guidance focuses on the acquisition of in vivo data through the use of animal models.
57 Because the rate of serious vaccinia complications in the vaccinated population is low, the
58 amount of efficacy data adequate for drug approval may not be obtainable through clinical trials.
59 Therefore, animal models may provide a source of supportive efficacy data, or possibly
60 contribute directly to drug approval under 21 CFR part 314, subpart I (the Animal Efficacy
61 Rule). The guidance discusses the requirements of the Animal Efficacy Rule.

62
63 The guidance concludes with sections addressing the acquisition of human efficacy and safety
64 data. Issues surrounding the design of clinical trials are discussed. In addition, sections detailing
65 data collection requirements and recommendations, along with consideration of long-term
66 patient follow-up and special population data collection, are presented. A sample case report
67 form is provided as an example of a data collection format.

68
69 FDA's guidance documents, including this guidance, do not establish legally enforceable
70 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should
71 be viewed only as recommendations, unless specific regulatory or statutory requirements are
72 cited. The use of the word *should* in Agency guidances means that something is suggested or
73 recommended, but not required.

74

75

76 II. BACKGROUND

77

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

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

88
89 According to advisory panel evaluations and recommendations (CDC 2003a; 2001), vaccinia
90 virus vaccine administered prior to exposure to variola virus produces substantial immunity
91 against smallpox that usually lasts for at least several years. In addition, if performed within a
92 few days after initial variola exposure, it may prevent disease or decrease the symptoms of
93 smallpox.

94
95 The currently licensed smallpox vaccine uses live vaccinia virus. According to the Dryvax
96 package insert, the vaccine is contraindicated for routine non-emergency use for persons who are
97 immunosuppressed, persons with eczema or a past history of eczema, persons with other acute,
98 chronic, or exfoliative skin conditions, and pregnant women due to the potential development of
99 complications secondary to the vaccine itself. Household contacts of such persons should not be
100 vaccinated. Also, the Contraindications section of the package insert (non-emergency use) was
101 updated to include persons with cardiac disease or certain risk factors for cardiac disease.
102 (Please see the package insert for a complete listing of contraindications.) Important
103 complications associated with the smallpox vaccine include, but are not limited to:

- 104
- 105 • Generalized vaccinia
 - 106 • Erythema multiforme and Stevens-Johnson syndrome
 - 107 • Eczema vaccinatum
 - 108 • Other rashes (e.g. folliculitis)
 - 109 • Inadvertent autoinoculation or transmission to close contacts
 - 110 • Secondary infection of skin complications
 - 111 • Ocular vaccinia
 - 112 • Progressive vaccinia
 - 113 • Postvaccinial central nervous system disease (encephalitis, encephalomyelitis, and
114 encephalopathy)
 - 115 • Myo/pericarditis² (CDC 2003b)
 - 116 • Fetal vaccinia (a very rare complication caused by the exposure of pregnant
117 women to vaccinia)
 - 118 • Anaphylaxis

119
120
121 Vaccinia virus exposure may occur via vaccination, accidental person-to-person spread from a
122 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).

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

125
126 Available rates of vaccinia vaccination adverse events come mainly from studies done prior to
127 1970 (Lane et al. 1970; Lane et al. 1969). Current complication rates from vaccination may be
128 difficult to predict accurately. Rates for certain complications could be anticipated to be higher
129 now due to the larger number of at-risk individuals in today's population.

130
131 **Table 1. Adverse event rates associated with vaccinia vaccination (cases/million**
132 **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

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

136
137
138 For example, there are an estimated 8.5 million persons with cancer, 850,000 persons with
139 HIV/AIDS and 184,000 solid-organ transplant recipients in the United States (Kempner et al.
140 2002). In addition, many persons today who would receive a primary vaccination are at an older
141 age compared to the majority who received vaccinations during the previous smallpox
142 vaccination program era. This change in age distribution could increase the occurrence or
143 detection of certain adverse events while possibly decreasing others. Alternatively, rigorous
144 screening for persons with contraindications to the vaccine in a pre-event vaccination campaign
145 could result in fewer adverse events. In addition, new smallpox vaccines are being developed
146 that may cause complications that differ in scope and number from the previous profile.

147
148 Currently, VIG, which is not FDA approved, is recommended by the Centers for Disease Control
149 and Prevention (CDC) under an investigational protocol for specific vaccinia complications.
150 Treatment is recommended for (1) eczema vaccinatum, (2) progressive vaccinia, (3) generalized
151 vaccinia that is severe or occurs in a patient with an underlying illness that may increase risk of
152 severity, and (4) in limited cases of severe lesions secondary to inadvertent autoinoculation.
153 VIG is not recommended for benign self-limited complications or complications that are not
154 believed to be associated with viral replication (CDC 2003d). To date, there are no drugs with
155 FDA approval to treat vaccinia complications. However, the availability of therapies used to
156 treat these complications may change, and investigators should address questions regarding this
157 issue to FDA on a real-time basis.

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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.

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

199
200 Opportunities, such as funding programs or collaborative efforts, may change
201 substantially over time. Therefore, we recommend that the sponsor identify contacts for
202 collaboration at the relevant stage of product development.

B. Drugs with Previous or Concurrent Studies for Other Indications

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204
205
206 If the drug under evaluation has not been previously approved but has already undergone
207 substantial development and is currently under study for other indications (or for which
208 such studies are planned) or has had approval sought for a nonvaccinia indication, it may
209 be possible to expedite the development process. In this situation, some safety data will
210 already exist, and the applicant may not need to collect as much additional data to
211 complete the safety database. Furthermore, results of studies for other similar indications
212 may provide ancillary supporting data for the evaluation of efficacy for vaccinia-related
213 indications. It is the responsibility of the sponsor to document the adequacy of the
214 available safety data to support the safety of the clinical protocol under consideration.

215
216 If the sponsor does not own the supporting safety data and if those data are not in the
217 public domain, it is the sponsor's responsibility to get letters of authorization allowing
218 FDA to refer to those studies during its evaluation of the proposed clinical trial.

219
220 If the drug under evaluation has already been approved for other indications, the sponsor
221 can either obtain a right of reference to the safety data or rely on the Agency's previous
222 finding of safety of that drug and provide any additional supportive data, as appropriate,
223 to support the proposed investigational use (e.g., due to different dose or patient
224 population as compared with the approved use). If the sponsor relies on the Agency's
225 previous finding of safety, however, any future submission of an NDA would be subject
226 to the provisions of 21 CFR 314.54.

227
228 Early discussion with the Agency may help to identify planning strategies that could lead
229 to the most efficient design of overlapping development plans. For those drugs that are
230 new chemical entities, please refer to section D of this section (Nonclinical Toxicology)
231 for information regarding the recommended safety studies.

C. Chemistry, Manufacturing, and Controls

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233
234
235 We recommend that the sponsor submit chemistry, manufacturing, and controls (CMC)
236 information as described in the guidances *Content and Format of Investigational New*
237 *Drug Applications (INDs) for Phase 1 Studies of Drugs* and *INDs for Phase 2 and 3*
238 *Studies Chemistry, Manufacturing, and Controls Information*. Depending on the
239 situation, we recommend that sponsors consult other relevant guidances.

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D. Nonclinical Toxicology

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

250
251 The information submitted must include the identification and qualifications of the
252 individuals who evaluated the results of these studies and concluded that it is reasonably
253 safe to begin the proposed clinical investigations (§ 312.23(a)(8)). In addition, the
254 sponsor must include a statement detailing where the investigations were conducted and
255 where the records are available for inspection (§ 312.23(a)(8)). As drug development
256 proceeds, the sponsor will be expected to submit nonclinical and clinical safety
257 informational amendments.

258
259 The sponsor must submit an integrated summary of the toxicological effects of the drug
260 in vitro and in animals (§ 312.23(a)(8)(ii)(a)). Depending on the nature of the drug and
261 the phase of the investigation, the summary should include the results of acute, subacute,
262 and chronic toxicity tests, safety pharmacology tests, tests of the drug's effects on
263 reproduction and the developing fetus, tests of the drug's genetic toxicity, any special
264 toxicity test related to the drug's particular mode of administration or conditions of use
265 (e.g., inhalation, dermal, or ocular toxicology), and any in vitro studies intended to
266 evaluate drug toxicity. We also expect that animal studies describing the
267 pharmacological effects and mechanisms of action of the drug and information on the
268 absorption, distribution, metabolism, and excretion of the drug will be submitted. For
269 each toxicology study that is intended to support the safety of the proposed clinical
270 investigation, a full tabulation of data suitable for detailed review must be submitted
271 (§ 312.23(a)(8)(ii)(b)).

272
273 The sponsor must submit a summary of previous human experience with the
274 investigational drug (§ 312.23(a)(9)). A sponsor is required to submit detailed safety data
275 as well as information relevant to the rationale of drug development for any
276 investigational drug marketed in the United States or abroad (§ 312.23(a)(9)(i)). A list of
277 countries in which the drug has been marketed or withdrawn from marketing for reasons
278 related to its safety or efficacy must also be provided (§ 312.23(a)(9)(iii)). Additionally, if
279 the drug has been studied in controlled clinical trials, relevant data regarding the drug's
280 effectiveness for the proposed investigational trial should be submitted (§ 312.23(a)(9)(i)).
281 Published material relevant to the safety or effectiveness of the drug or clinical
282 investigation must be provided while less relevant published material should be provided
283 as a bibliography.

284
285 Regulatory and pharmaceutical industry representatives from the United States, Europe
286 and Japan (The International Conference on Harmonisation of Technical Requirements of

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

292

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

294

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

305

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

319

2. Acute and Subacute Toxicity Studies

321

322 Acute toxicity studies are often the first studies carried out on a drug intended for humans
323 and use a single dose or multiple-doses administered for no longer than a 24-hour period.
324 Subacute studies are multiple-dose studies carried out for no longer than 6 months. Most
325 commonly, an acute study with drug administration by the proposed clinical route of
326 administration as well as a parenteral route (usually intravenous) is performed in a rodent
327 and a nonrodent species to set the doses for longer term nonclinical studies and to
328 evaluate the immediate toxicity profile of the drug. If the proposed clinical route of
329 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*

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

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3. Safety Pharmacology Studies

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

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4. Genetic Toxicity

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

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357

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

364
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366

5. Reproductive Toxicity

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

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*.

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

377 378 6. *Carcinogenicity Studies*

379
380 In general, carcinogenicity studies would not be expected for drugs used to treat vaccinia
381 complications since the administration of the drug would not, in most cases, exceed 6
382 months. However, decisions regarding the performance of carcinogenicity studies would
383 need to be made on a case-by-case basis and would depend on the mutagenic potential
384 and/or possible structure-activity relationship of the test drug with other known
385 carcinogens.⁹

386 387 **E. Microbiology**

388
389 This section discusses issues that are important to consider during the microbiologic evaluation
390 of candidate drugs. Some components may change as more investigations take place in this field
391 (for example, increased opportunities to study cross-resistance or interactions with other anti-
392 vaccinia drugs). The sponsor will be expected to make available for review adequate information
393 on sample collection and assays performed and on validation approaches for these assays. Use
394 of a specific procedure, method, or test system in an investigational protocol for a nonclinical
395 laboratory study does not constitute FDA endorsement of that procedure, method, or test system,
396 or FDA approval for clinical laboratory use. This guidance addresses these points further in the
397 following descriptions, and sponsors are strongly encouraged to bring questions for discussion
398 with the review division early in the drug development process.

399 400 1. *Nonclinical Virology Reports*

401
402 Nonclinical virology reports are an important component in the review process of a candidate
403 anti-vaccinia drug. They contribute to the evaluation of a candidate drug's safety concerns and
404 activity prior to its use in humans. We request that submitted reports identify the mechanism of
405 action, establish specific antiviral activity of the compound in a model system, and provide data
406 on the development of viral resistance (or reduced susceptibility of the virus) to the candidate
407 drug. We would expect that these studies be well advanced or completed prior to the introduction
408 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*.

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410 2. *Components of Nonclinical Virology Reports*

411

412 a. Mechanism of Action

413

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

428

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

433

434 b. In Vitro Antiviral Activity

435

436 For vaccinia virus, we expect that cell culture systems and animal models (e.g., infection of
437 immunosuppressed or SCID mice) will be used to show the candidate drug has specific,
438 quantifiable antiviral activity. FDA and organizations such as NCCLS do not recognize or
439 recommend a specific test system for assessing antiviral activity. Sponsors can consult published
440 work¹⁰ or present additional proposals for review. We recommend that the antiviral activity of
441 the candidate drug be tested against multiple vaccinia virus isolates, to demonstrate the candidate
442 drug's activity for the most divergent isolates. The tested isolates should include vaccinia
443 vaccine strains contained in licensed smallpox vaccines, other laboratory strains (including any
444 strains expected to be used in animal models), and recent clinical isolates, if available. The
445 sponsor will want to submit information that demonstrates that the data collected is relevant to
446 the vaccine strains that may be targets for treatment in the clinical setting. We recommend that
447 information on antiviral activity also be generated for related poxviruses, including any
448 nonvaccinia poxviruses that may be studied in animal models (such as cowpox or monkeypox) or
449 used as sources of ancillary information in the overall evaluation of the effectiveness of the
450 candidate drug.

451

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

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452 We recommend that specific antiviral activity be determined using a quantitative assay to
453 measure virus replication in the absence and presence of increasing concentrations of the drug.
454 The concentration of the drug at which virus replication is inhibited 50 percent is the inhibitory
455 concentration, IC₅₀, or effective concentration, EC₅₀. We also recommend that the sponsor
456 document the sources of viruses (such as blood, plasma, defined laboratory and vaccine strains),
457 their method of isolation and their characterization, storage and stability, and cell culture
458 procedures and materials. Sponsors are encouraged to consult FDA, ICH and NCCLS guidance
459 documents for approaches to standardizing and controlling method parameters and definitions on
460 assay validation. For any assay developed or used for showing antiviral activity, or other
461 investigational assay used in the nonclinical and clinical studies, the sponsor should provide
462 sufficient information about the assay to assess the appropriateness of its use in the specified
463 study setting. Assays should be well documented, and should adequately meet requirements of
464 21 CFR part 58. The test system should be standardized with well-defined control strains. The
465 sponsor should discuss with the Agency the specific information to be provided.
466

467 It is important to consider whether the inhibitory concentration is consistent with data supporting
468 the mechanism of action, such as K_i (inhibitory constant) or binding data. A drug candidate that
469 inhibits virus replication at a concentration much lower than would be expected from the
470 biochemical data supporting the proposed mechanism suggests that another target may be
471 affected or another mechanism of inhibition may be operating.
472

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

473
474
475 Serum proteins bind and sequester many drugs and may interfere with a drug's antiviral activity.
476 Therefore, we recommend that the in vitro antiviral activity of a candidate drug be analyzed both
477 in the presence and absence of serum proteins. For multiple laboratory and clinical isolates of
478 vaccinia, the sponsor will want to evaluate the effects of human serum (45-50 percent) and/or
479 human plasma plus α -acidic glycoprotein on the in vitro antiviral activity of the candidate drug
480 and determine a mean serum adjusted IC₅₀ or EC₅₀ value.
481

d. Inhibitory Quotient

482
483
484 Drug concentrations are an important factor in the response to viral therapy. Therefore, we
485 recommend that the sponsor determine an inhibitory quotient (IQ) = C_{min}/serum adjusted IC₅₀.
486 An IQ integrates plasma drug concentrations and resistance testing. A high IQ indicates the
487 potential that a drug concentration may be achieved in a patient that will effectively inhibit the
488 virus and minimize the development of drug resistance. A high IQ may help to identify
489 promising drugs for further studies. Additional information on the relationship between IQ and
490 outcome may be obtainable in such studies.
491

e. Cytotoxicity

492
493
494 After drug exposure in a cell culture model, host cell death may be misinterpreted as antiviral
495 activity. Cytotoxicity tests use a series of increasing concentrations of the candidate drug to
496 determine what concentration results in the death of 50 percent of the host cells. This value is
497 referred to as the median cellular cytotoxicity concentration and is identified by the initializations

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498 CC₅₀ or CCIC₅₀. The relative effectiveness of a candidate drug in inhibiting viral replication
499 compared to inducing cell death is referred to as the therapeutic index, (i.e., CC₅₀/IC₅₀), or as the
500 selectivity index. A high therapeutic index is desired, as this represents maximum antiviral activity
501 with minimal cell toxicity. We recommend that the CC₅₀ be assessed both in stationary and
502 dividing cells from multiple human cell types and tissues for potential cell cycle, cell type, or tissue
503 specific toxicities. We also recommend that the effects of the candidate drug on mitochondrial
504 toxicity in cell culture be monitored by examining measures such as mitochondrial morphology,
505 glucose utilization, lactic acid production, and mitochondrial DNA content. These studies may
506 reveal the potential for toxicity in vivo.

f. In Vitro Combination Activity Analysis

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

g. Selection of Resistant Virus In Vitro

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

527 Two basic methods can be employed to isolate viruses that have reduced susceptibility to the
528 candidate drug. In the first, the virus is propagated for several passages at a fixed drug
529 concentration, using multiple cultures to test different concentrations. Alternatively, the virus is
530 passaged in the presence of increasing drug concentration starting at half the IC₅₀ value for the
531 parental virus. For both of these methods, virus production is monitored to detect the selection of
532 resistant virus. The former method is particularly useful to identify drugs for which one or two
533 mutations can confer large shifts in susceptibility.

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

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

545

546 Genotypes

547

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

560

561 Phenotypes

562

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

579

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

584

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

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

592 h. Cross-Resistance

593
594
595 In the case of antiviral drugs targeting the same protein, cross-resistance, (i.e. mutations leading
596 to reduced susceptibility to one drug resulting in decreased susceptibility to other drugs in the
597 same class) has been observed. Cross-resistance is not necessarily reciprocal. For example, if
598 virus X is resistant to drug A and shows cross-resistance to drug B, virus Y, which is resistant to
599 drug B, may still be sensitive to drug A. Cross-resistance analysis may be important in the
600 development of treatment strategies (i.e., establishing the order in which drugs are given). The
601 sponsor will want to evaluate the effectiveness of the candidate drug against viruses resistant to
602 other approved drugs in the same class and the effectiveness of approved drugs against viruses
603 resistant to the candidate drug.

604 3. *Proposal for Monitoring Resistance Development*

605
606
607 Prior to the initiation of clinical studies in patients with vaccinia complications, a sponsor is
608 urged to submit a plan to monitor for the development of resistant viruses with the nonclinical
609 reports in the IND. If animal studies are expected to make a salient contribution to drug
610 evaluation (see section IV on Animal Models), we also urge that proposals for the evaluation of
611 resistance in the appropriate parts of the animal studies be submitted. The resistance monitoring
612 plan would generally include the assays that will be used to monitor viral shedding and viral
613 burden, methods of sample collection and storage, methods for sample handling (frozen or
614 ambient), genotypic and phenotypic assays, timepoints that will be analyzed (e.g., baseline, day
615 1, and additional specified on-treatment and post-treatment time points), and the names of the
616 parties responsible for each of these. In addition, we recommend that plans for genotypic and
617 phenotypic baseline studies and additional substudies be considered and submitted. We
618 recommend that genotypic and phenotypic analyses of at least a subset of baseline isolates be
619 performed to determine outcomes based on baseline mutations and baseline phenotypic drug
620 susceptibilities.

621
622 We suggest that genotypic and phenotypic data be provided (at a minimum) for baseline isolates
623 from all patients and the endpoint isolates of virologic failures and discontinuations.

624 Furthermore, we recommend that definitions of virologic failures and discontinuations be
625 discussed with the review division during protocol development. For example, in the more
626 extensively studied setting of therapy for HIV-1 infection, virologic failure definitions have been
627 based on the course of viral load measurements over time and on investigator evaluations of
628 reasons for discontinuation. We urge that information bases be developed to facilitate the
629 assessment of the relationship between clinical course and virologic findings in vaccinia
630 complications.

631
632 4. *In Vivo Virology Study Reports (Clinical and/or Animal Studies)*

633

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

647
648 For some antiviral therapies in other settings, quantification of viral loads has been a good
649 measure of the clinical effectiveness of antiviral drugs and has provided insight into whether
650 these drugs have activity in vivo when the clinical benefit may not be apparent or may be
651 temporary due to the development of resistance. Such candidate drugs may prove useful when
652 studied in combination with other drugs. Development of methods for quantification of viral
653 burden or viral shedding, and evaluation of the relationship between these quantitative
654 measurements and clinical outcomes of disease and treatment, is encouraged for vaccinia studies.
655 As mentioned above, we expect the sponsor to provide a complete description of the
656 methodology and the quantitative assay performance characteristics, the specimen sources of
657 viruses (such as blood, plasma, defined lesion specimens), their storage and stability, and cell
658 culture procedures. We encourage efforts to collect sufficient specimen to allow reserve amounts
659 to be stored for possible re-evaluation by new or improved assays. Additionally, it will be
660 important to examine the relationships between phenotypic and genotypic analyses and clinical
661 outcomes in vaccinia studies, to assess the extent to which these assays may be predictive of the
662 utility of treating an individual with the candidate drug. We recommend using viral load,
663 genotypic, and phenotypic assays analyses following the same criteria as described above in the
664 Microbiology section (section III.E). Sponsors are encouraged to discuss their assays with the
665 review division. Genotypic analysis of baseline and failure isolates from patients failing to
666 respond to therapy or undergoing viral rebound can help identify mutations that contribute to
667 reduced susceptibility to the candidate drug. It is important that phenotypic analyses of baseline
668 and posttreatment isolates be completed to obtain information on the susceptibility of the
669 candidate drug and cross-resistance with other drugs. We recommend that genotypic and
670 phenotypic analysis of at least a subset of baseline isolates be performed to determine response
671 to therapy based on baseline mutations and baseline phenotypic drug susceptibilities. Please
672 consult the review division with respect to electronic submission of resistance data.

F. Clinical Pharmacology

673
674
675
676 We recommend that sponsors study the relationship between in vitro activity and in vivo activity
677 using animal models prior to the initiation of studies in humans (see section IV on Animal
678 Models). Sponsors should also consider developing models of drug pharmacokinetics and/or
679 pharmacodynamics to study drug dosage and drug regimens further, using both in vitro systems

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

682
683 Please submit human pharmacokinetic and pharmacodynamic information as soon as available.
684 The purpose of obtaining these data is as follows:

- 685
- 686 1. To demonstrate that the desired systemic drug level in humans can actually be
687 achieved after the anticipated dosage regimen is given
 - 688 2. To explore the relationship between blood drug concentration and
689 pharmacodynamic response
 - 690 3. To select the appropriate dose
 - 691 4. To evaluate the relationship between drug exposure and subsequent development
692 of viral resistance (see section III.E.3 on Proposal for Monitoring Resistance
693 Development).
- 694

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

702
703 We expect that the sponsor will characterize fully the metabolic profile (in vitro and in vivo) in
704 humans and will submit information comparing the plasma protein binding of the active drug
705 components across the range of expected concentrations in humans.

706
707 We would expect to receive pharmacokinetic data for special populations, including pediatric
708 patients,¹² elderly patients (= 65 years), and patients with renal and hepatic impairment.¹³ Please
709 submit available pharmacokinetic data in pregnant women and available data for drug excretion
710 into human breast milk as soon as available. However, if the information base is otherwise
711 sufficient for an NDA, we would not advise delaying submission while awaiting the special
712 population data.

713
714 Since vaccinia complications tend to occur in persons with underlying illnesses, recipients of the
715 study drug may be receiving several medications concurrently (e.g., antiretrovirals and
716 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*

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

719
720 Sponsors are encouraged to refer to other FDA guidances that may be appropriate.¹⁶

721

722

IV. ANIMAL MODELS

724

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

733

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

743

744 If well-characterized animal models predictive of human treatment responses can be developed
745 and if there is agreement that adequate clinical trials would not be ethical as deliberate challenge
746 studies and would be infeasible as field studies, circumstances may exist where drug approval
747 may be based upon evidence of effectiveness obtained from studies done in animals (see the
748 Animal Efficacy Rule, 21 CFR part 314, subpart I¹⁷). A determination that adequate clinical
749 trials could not ethically be conducted as challenge studies might be made if it were determined
750 that no suitable endpoint (surrogate measurement) could be established to obtain adequate
751 information in studies of healthy volunteers who could ethically be vaccinated for the purpose of
752 a drug study and that challenge studies of clinical endpoints (mortality or major morbidity) in
753 serious vaccine complications would require deliberate vaccine exposure of individuals at high
754 risk of serious adverse events who should avoid vaccine in nonemergency situations. A
755 determination that adequate clinical trials would be infeasible as field trials could be made if it is
756 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.

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

- 761
- 762 1. The pathophysiological mechanism of the toxicity of vaccinia virus and its prevention or
763 substantial reduction by the drug are reasonably well understood.
 - 764 2. The effect is demonstrated in more than one animal species expected to be predictive of
765 the response in humans unless the effect is demonstrated in a single animal species that
766 represents a sufficiently well-characterized model for predicting the response in humans.
 - 767 3. The endpoint studied in the animal model is clearly related to the desired benefit in
768 humans, generally the enhancement of survival or prevention of major morbidity.
 - 769 4. Data on the kinetics and pharmacodynamics of the drug in both animals and humans are
770 available and sufficiently well understood to recommend an effective dose in humans.

771

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

785

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

791

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

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799 **V. CLINICAL DATA**

800

801 **A. Clinical Trials**

802

803 The decision to proceed to clinical trials in patients with vaccinia complications will
804 depend on a drug nonclinical toxicity profile, activity in cell culture and animal studies,
805 and human adverse events in phase 1 studies and/or data available from other uses of the
806 drug. When appropriate drugs are identified for study, general considerations on the
807 approach to clinical studies can be based on a combination of published FDA guidance¹⁸
808 and discussion with the review division. The risk/benefit profile of the drug determines
809 what types of clinical trials are appropriate. For example, a drug with frequent serious
810 toxicities is unlikely to be suitable for treatment of self-resolving minor complications,
811 whereas a drug with few toxicities might be evaluated if there is interest in attempting to
812 reduce the duration of this type of vaccinia complication. Alternatively, a drug with
813 known major risks of toxicity that is highly active and has sufficiently positive
814 preliminary data to suggest a meaningful benefit may be suitable for study in patients
815 with severe life-threatening vaccinia complications who lack alternative therapy.

816

817 For development of clinical trial proposals, it would be wise to clearly define the type of
818 vaccinia complication for which a drug is being considered for therapy. If treatment is
819 being considered to decrease duration and symptoms of generally self-limited vaccinia
820 complications, such as minor autoinoculations and most generalized vaccinia events (for
821 which specific treatment has not been considered necessary or recommended in the past),
822 human data would likely be the principal or sole source of information on the outcomes
823 of interest and placebo-controlled trials will likely be called for. However, the ability to
824 draw secure conclusions may be limited unless treatment effects are dramatic enough to
825 allow an adequately powered study with a small sample. For serious and potentially life-
826 threatening vaccinia complications, such as eczema vaccinatum and progressive vaccinia,
827 (which have traditionally been treated with VIG), placebo-controlled trials are unlikely to
828 be either feasible or acceptable, and alternative approaches may be considered.

829 Noninferiority comparisons against VIG are likely to be of limited value because of the
830 lack of quantitative information on VIG efficacy and because of the inability to identify
831 enough cases for an adequately powered comparison. If a candidate drug is studied in the
832 context of a large-scale vaccination campaign in which substantial numbers of serious
833 vaccinia complications occur, it may be possible to consider studies designed to show
834 superiority to VIG (or other accepted therapies at the time studies are initiated), or to
835 assess the contribution of the candidate drug when added to previously established
836 therapy, or to assess use as a rescue treatment for failures following use of VIG or other
837 accepted therapy. Endpoints in studies of serious vaccinia complications are generally
838 expected to be measurements of mortality or major morbidity with direct demonstration
839 of clinical benefit. If alternative or surrogate endpoints can be identified that are
840 reasonably likely to predict benefit, the sponsor may want to discuss with the appropriate
841 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*.

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

844
845 Even in circumstances when the likelihood of accruing enough serious vaccinia
846 complications for the rigorous statistical assessment of a variety of treatments may be
847 low, we encourage the design of pilot studies to facilitate data collection about disease
848 course and response to therapy. These data may not lead to firm conclusions regarding
849 the efficacy of a new treatment. However, small numbers of vaccinia complications with
850 systematic data collection may contribute to the design of further nonhuman studies and
851 assist in defining the emergence of viral resistance. In addition, data collection may help
852 to identify previously unrecognized safety issues relating to the investigational drug.
853 Because the risk/benefit assessment associated with a study may change as the study
854 progresses, we recommend that the sponsor provide for ongoing reassessment through a
855 system such as a Data Safety Monitoring Board (DSMB).

856
857 If an approach to treatment might be used prior to full development of the vaccination
858 response (for example, systemic treatment for an autoinoculation lesion developing
859 synchronously with the primary vaccination lesion) the sponsor would want to evaluate
860 for potential and degree of interference with vaccine efficacy.

861
862 Depending on the drug toxicity, studies in normal human vaccinated volunteers can be
863 considered to provide preliminary or ancillary evidence to support design of clinical trials
864 or to contribute to a compilation of efficacy and safety data. For example, if meaningful
865 measurements of circulating or local viral burden can be developed (see section III.E.4 on
866 In Vivo Virology Study Reports), it may be justifiable and reasonable to perform
867 preliminary studies of activity in human vaccinia infection by examining drug effects on
868 response to vaccination in healthy volunteers. Potential parameters include lesion
869 development and viral shedding. These studies may also contribute to the
870 characterization of proposed surrogate markers for use in further clinical trials as
871 discussed above. Development of a standardized method of diagnosis and viral burden
872 assessment is encouraged. It is recommended that sample collection techniques be well
873 documented. In such a study, the sponsor will also want to address uncertainties
874 regarding the status of volunteers' vaccine-related immunity to smallpox after
875 administration of the drug and investigate other correlates of the immune response or
876 response to re-vaccination at a suitable time.

877
878 For a drug with a problematic safety profile that could not be ethically introduced into
879 healthy human volunteers, obtainment of human pharmacokinetic, pharmacodynamic,
880 and safety data may have to wait until complications from vaccination arise. In addition,
881 the sponsor will want to consider collecting preliminary safety and efficacy information
882 available from human infections with other orthopoxviruses or poxviruses from other
883 genera such as molluscum contagiosum or orf. However, applicability to vaccinia cannot
884 be assumed.

885
886 Treatment of ocular vaccinia (blepharitis, conjunctivitis, keratitis, and iritis) has been
887 approached somewhat differently than the treatment of cutaneous or systemic

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

892
893 Treatment of complications not generally thought to involve ongoing viral replication,
894 such as erythema multiforme and postvaccinial encephalitis, is not specifically addressed
895 in this guidance. However, proposals can be submitted to the appropriate review division
896 for review and discussion.

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B. Data Collection

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1. Pre-Terrorism Event

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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:

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- 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

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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

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

936 937 2. *Post-Terrorism Event*

938
939 In the event that vaccinia vaccine is administered under the circumstances of a variola
940 bioterrorism attack, there may be more complications associated with vaccination. In this
941 situation, no absolute contraindications have been established regarding the use of the
942 vaccine if a patient has a high-risk exposure to variola, on the premise that those at greatest
943 risk of developing a serious vaccinia complication are also at greatest risk for death from
944 smallpox (CDC 2001). Because of the extensive use of resources in implementing a
945 response to a smallpox event and also because of potential confusion between clinical
946 manifestations of vaccinia complications and those of early smallpox, both case
947 ascertainment and follow-up may be seriously compromised. Investigators should be aware
948 that pre-event design of strategies to maximize accuracy and completeness of post-event data
949 collection may be very important not only to assess the safety and outcomes of any
950 investigational drug that may be used, but also to facilitate disease assessment, treatment, and
951 monitoring. Clinical and public health expert authorities may recommend standardized
952 patient evaluation and management in an emergency situation. Therefore, sponsors may
953 want to consider such recommendations and their implications for patient care as well as data
954 collection when designing a case report form (as above, material in Attachment A may
955 provide a starting point). Sponsors should have a data collection system already in place.
956 See section V.B.1 on Pre-Terrorism Event, for a brief discussion regarding the types of data
957 that should be collected. Advance discussions between potential sponsors and public health
958 officials would be useful to design investigational protocols and methods for case
959 ascertainment and enrollment for candidate drugs that might be used in such a situation (see
960 section III.A on Interactions Between Industry, Academic, and Government Sponsors and
961 Investigators). As above, investigators are encouraged to design and submit a case report
962 form designed to address the specific needs of their drug. Sponsors should refer to the
963 National Defense Authorization Act for Fiscal Year 2004 (Pub. L. No. 108-136, sec. 1603,
964 117 Stat. 1392, 1684 (2003)) concerning planning the emergency use of unapproved drugs,
965 or drugs unapproved for counterterrorism indications in the setting of a terrorism event. If
966 the cited provisions in this act appear potentially applicable to a candidate drug, we
967 encourage the sponsor to initiate early discussions with the Agency regarding the proposed
968 use.

969
970

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.

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971 3. *Post-Approval Studies*

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973 Post-approval studies should be considered to add to safety and efficacy data, especially
974 given the likelihood that small clinical trials will have provided data for drug approval.
975 There are certain circumstances that require the use of post-approval studies. For
976 example, if the drug is granted accelerated approval using a surrogate endpoint to
977 demonstrate efficacy, confirmatory clinical studies will be expected for verification of the
978 clinical benefit of the drug and for confirmation that the observed clinical benefit is
979 related to ultimate outcome (21 CFR 314.510). Also, if approval is given based upon
980 efficacy data from animal models, postmarketing studies must be conducted to
981 demonstrate efficacy in human patients whenever this becomes possible (21 CFR part
982 314, subpart I). Applicants must provide a plan or approach to the postmarketing study
983 commitments to be used when the clinical studies become feasible (21 CFR part 314,
984 subpart I).²⁰ In any of these situations, proposals and plans for appropriate postmarketing
985 studies should be submitted for discussion during design of the overall clinical
986 development plan, and plans would generally be expected to be in place and ready for
987 implementation prior to any approval action. Postmarketing data collection may take
988 place during or after a bioterrorism attack and may not be a conventional postmarketing
989 study. However, opportunities for data collection may arise without an emergency
990 situation, and we urge that they be used appropriately. FDA emphasizes the importance
991 of having a means and a plan in place for rapidly identifying potential drug recipients, as
992 well as a complete and thorough data collection system.

993

994 **C. Long-Term Follow-Up**

995

996 We recommend that follow-up analysis after administration of a candidate drug address
997 durability of the therapeutic regimen, as well as the possible emergence of drug
998 resistance. In addition, investigators should plan for long-term follow-up after drug
999 administration if there are specific safety concerns associated with the drug, for example,
1000 carcinogenicity. If the drug is administered to pregnant women, we recommend that
1001 follow up include an assessment of the outcomes of pregnancy. Although we would
1002 expect that scarring or any other permanent sequelae of the vaccinia complication would
1003 be recorded in treatment follow-up, these phenomena may be particularly important and
1004 may warrant more detailed assessment for topical products or products that claim to
1005 expedite the epidermal healing process.

1006

1007 **D. Special Populations**

1008

1009 We recommend that information on drug safety, drug pharmacokinetics, and
1010 pharmacodynamics (including the necessary dose modifications), in the pediatric
1011 population, the geriatric population, pregnant women, lactating women, and persons with
1012 renal and hepatic impairment be submitted to FDA as soon as it is available. However, if
1013 overall safety and efficacy information is developed to a stage warranting discussions of
1014 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.

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1015 population data. In addition, many of the patients susceptible to vaccinia complications
1016 will be on medications that may interact with the candidate drug. Studies addressing these
1017 drug-drug interactions would also be of interest to the FDA (see section III.F on Clinical
1018 Pharmacology).
1019

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VI. SUMMARY

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1023 The number of smallpox vaccine complications requiring treatment is expected to be small, and
1024 plans for drug development should be carefully designed to make optimal use of the human data
1025 that can be collected. In this setting, development and study of animal models, to augment
1026 sparse human data, may also make important contributions to evidence of drug efficacy (see
1027 section IV on Animal Models). Evidence of safety will still require collection of safety data in
1028 humans, however. Sponsors are advised to contact FDA at an early stage of drug development to
1029 discuss proposals for the design of animal studies; proposals for clinical outcome, safety, and
1030 efficacy measures; and for the development of possible surrogate endpoints.
1031

1032

1033 Data collection from the treatment of complications secondary to both nonemergent and
1034 emergent vaccination programs will yield important information regarding the safety and
1035 efficacy of the drug. We recommend that carefully planned, thorough data collection systems be
1036 put in place as early in the drug development process as possible.

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ATTACHMENT: SAMPLE CASE REPORT FORM

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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:** _____

Vaccinia Exposure (Check One):

____ **Vaccination** **Date:** _____

____ **Contact with Vaccinee** **Date:** _____

Nature of contact (household, office, school, etc.): _____

____ **Other**

Vaccine History:

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**

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SAMPLE CASE REPORT FORM

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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):

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SAMPLE CASE REPORT FORM

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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]

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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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SAMPLE CASE REPORT FORM

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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: _____

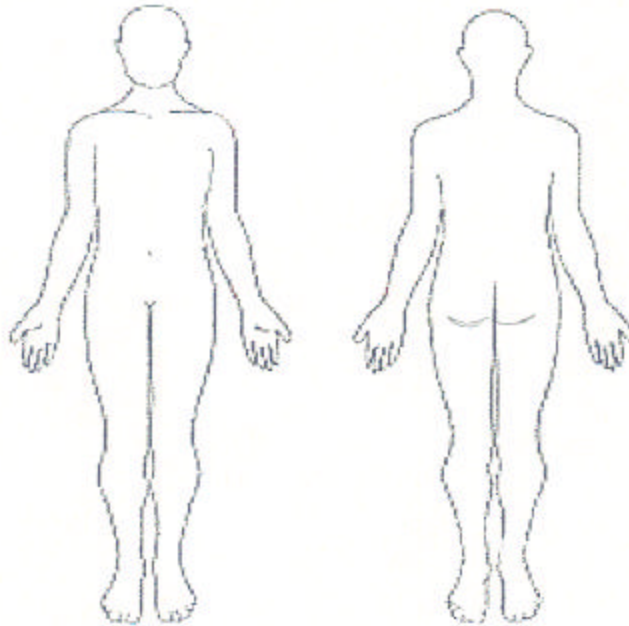
General Description of Lesion(s): _____

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):



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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 : _____

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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								

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

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SAMPLE CASE REPORT FORM

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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 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)

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SAMPLE CASE REPORT FORM

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Page 9

Patient ID Number: _____

Investigational Drug Adverse Events Reporting Table

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	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							

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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)

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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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REFERENCES

- 1367
1368
1369 Breman JG, Henderson DA, 2002, “Diagnosis and Management of Smallpox,” *New England*
1370 *Journal of Medicine*, 346:1300-1308.
1371
1372 Centers for Disease Control and Prevention (CDC), 2003a, “Recommendations for Using
1373 Smallpox Vaccine in a Pre-Event Vaccination Program,” *Morbidity and Mortality Weekly*
1374 *Report*, 52(RR07):1-16.
1375
1376 CDC, 2003b, “Update: Cardiac-Related Events During the Civilian Smallpox Vaccination
1377 Program — United States, 2003,” *Morbidity and Mortality Weekly Report*, 52(21):492-496.
1378
1379 CDC, 2003c, “Notice to Readers: Supplemental Recommendations on Adverse Events Following
1380 Smallpox Vaccine in the Pre-Event Vaccination Program: Recommendations of the Advisory
1381 Committee on Immunization Practices,” *Morbidity and Mortality Weekly Report*,
1382 52(13):282-284.
1383
1384 CDC, 2003d, “Smallpox Vaccination and Adverse Reactions: Guidance for Clinicians,”
1385 *Morbidity and Mortality Weekly Report*, 52(RR04):1-28.
1386
1387 CDC, 2001, “Vaccinia (Smallpox) Vaccine Recommendations of the Advisory Committee on
1388 Immunization Practices (ACIP),” *Morbidity and Mortality Weekly Report*, 50(RR10): 1-25.
1389
1390 Chou TC, Talalay P, 1984, “Quantitative Analysis of Dose-Effect Relationships: The combined
1391 Effects of Multiple Drugs or Enzyme Inhibitors”, *Advances in Enzyme Regulation*, 22:27-55.
1392
1393 Dryvax® (Smallpox Vaccine, Dried, Calf Lymph Type) package insert (Wyeth Laboratories,
1394 Inc.), Rev 6/26/2003.
1395
1396 Karjalainen J, Heikkila J, Nieminen MS, et al., 1983, “Etiology of Mild Acute Infectious
1397 Myocarditis. Relation to Clinical Features,” *Acta Medica Scandinavica*, 213(1):65-73.
1398
1399 Kempner AR, Davis MM, Freed GL, 2002, “Expected Adverse Events in a Mass Smallpox
1400 Vaccination Campaign,” *Effective Clinical Practice*, 5:84-90.
1401
1402 Kern E, Hartline C, Harden E, et al., 2002, “Enhanced Inhibition of Orthopoxvirus Replication *In*
1403 *Vitro* by Alkoxyalkyl Esters of Cidofovir and Cyclic Cidofovir,” *Antimicrobial Agents and*
1404 *Chemotherapy*, 46: 991-995.
1405
1406 Lane MJ, Ruben FL, Neff JM, et al., 1970, “Complications of Smallpox Vaccination, 1968:
1407 Results of Ten Statewide Surveys,” *Journal of Infectious Diseases*, 122:303-309.
1408
1409 Lane MJ, Ruben FL, Neff JM, et al., 1969, “Complications of Smallpox Vaccination, 1968,
1410 National Surveillance in the United States,” *New England Journal of Medicine*, 281:1201-
1411 1208.
1412

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1413 Smee D, Sidwell R, Kefauver D, et al., 2002, “Characterization of Wild-Type and Cidofovir-
1414 Resistant Strains of Camelpox, Cowpox, Monkeypox and Vaccinia Viruses,” *Antimicrobial*
1415 *Agents and Chemotherapy*, 46:1329-1335.