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

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

**November 2007
Clinical Antimicrobial**

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

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1 **Guidance for Industry¹**
2 **Smallpox (Variola) Infection: Developing Drugs for**
3 **Treatment or Prevention**
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8 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current
9 thinking on this topic. It does not create or confer any rights for or on any person and does not operate to
10 bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of
11 the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA
12 staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call
13 the appropriate number listed on the title page of this guidance.
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18 **I. INTRODUCTION**
19

20 This guidance provides recommendations to potential sponsors (including industry, academic,
21 and government) on the development of drugs to treat or prevent infection caused by variola
22 virus, the etiological agent of smallpox.² The guidance focuses mainly on drugs that are
23 expected to act by inhibiting variola virus replication; however, sponsors of drugs proposed to
24 act against smallpox by other mechanisms are encouraged to consult this guidance for relevant
25 content, as well as to discuss questions and proposals directly with the appropriate review
26 division at the Food and Drug Administration (FDA). Most sponsors consulting this guidance
27 will wish to develop and file an investigational new drug application (IND) with the FDA, with
28 the eventual goal of submitting a new drug application (NDA) for these indications. Because of
29 the unique and challenging issues arising in this development area, we strongly encourage
30 beginning with pre-investigational new drug application (pre-IND) consultations between
31 sponsors and the FDA addressing the sequence and content of nonclinical and clinical study
32 proposals
33

34 This guidance does not address the following types of development:
35

- 36 • Drug development for the treatment of bacterial complications of smallpox
- 37
- 38 • Development of biological therapies such as vaccines or antisera to treat or prevent
39 variola

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

² For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

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- Drug development for infections from viruses other than variola

This guidance also does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E8 General Considerations for Clinical Trials* and *E9 Statistical Principles for Clinical Trials*.³ This guidance focuses on drug development and trial design issues that are specific to the study of smallpox (variola) infection.

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

II. BACKGROUND

For centuries, smallpox affected human populations. The most severe form, variola major, had reported mortality ranging from 5 percent to 50 percent in different outbreak situations (Fenner and Henderson et al. 1988). This form is the principal source of concern regarding potential bioterrorist uses of smallpox and, therefore, the most relevant to this guidance. A less severe variant, variola minor, caused a similar rash but generally less than 2 percent mortality. Worldwide efforts at case identification, containment, and vaccination improved smallpox control, and eventually clinical smallpox was declared eradicated in 1980 by the World Health Organization. Retention of variola virus stocks was limited by international agreement to two sites, one in Russia and the other at the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. However, concerns exist that variola virus could be used as a weapon of bioterrorism.

The first line of defense against smallpox infection is vaccination with vaccinia virus.⁴ Vaccination before exposure to variola provides substantial immunity against smallpox and it is thought likely to prevent or reduce the symptoms of smallpox if given a few days after exposure to variola (CDC 2001; CDC 2003a). Substantial protection generally is thought to last for at least a few years; information about any longer-term benefit is incomplete and controversial. Expectations about the usefulness of vaccination in a biothreat situation would depend upon the ability to vaccinate exposed and at-risk persons, and on assumptions about whether and to what extent immunity produced by vaccinia vaccine might be able to protect against a variola virus strain used in a terrorist attack.

³ We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at <http://www.fda.gov/cder/guidance/index.htm>.

⁴ See the Smallpox Response Plan and Guidelines on the CDC Web site at <http://www.bt.cdc.gov/agent/smallpox/response-plan/index.asp>.

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80 Routine smallpox vaccination in the United States was discontinued in the 1970s. Currently,
81 mass smallpox vaccination for civilians is not recommended, although some designated smallpox
82 response team health care and public health workers and members of the military have received
83 vaccinations. In addition, there are specific recommendations against nonemergency vaccine use
84 for certain segments of the population at elevated risk of adverse events (CDC 2003b; CDC
85 2003c). The discontinuation of mass vaccination, along with a lack of natural disease exposure,
86 means that most of the population is immunologically naïve to smallpox.⁵
87

88 Historically, treatment for smallpox was supportive (Dixon 1962). It is not known what effect
89 technologically advanced supportive care might have on mortality and morbidity. Generally, the
90 mode of death in fatal cases was considered unclear, and could have been multifactorial.
91 Superinfections may have accounted for some fatalities. A variety of hypotheses have been
92 proposed for other contributing factors. Antigen-antibody complex formation, fluid and
93 electrolyte imbalance, and direct cytopathic effects of replicating virus (in organs such as kidney,
94 liver, and lung) have been suggested. Terms such as *toxemia*, *sepsis*, and *cytokine storm* have
95 been invoked as potential contributors and might reflect combinations of such factors (see for
96 example Fenner and Henderson et al. 1988, Dixon 1962, and Jahrling and Hensley et al. 2004).
97

98 Antiviral drugs might prove to be a valuable adjunct for exposure situations in which vaccination
99 was not feasible or had failed to provide adequate protection if suitable evidence of drug benefit
100 can be established. Before the eradication of naturally occurring clinical smallpox, several drugs
101 were studied for therapy of established illness and postexposure prophylaxis of patient contacts.
102 Some of these drugs were reported to show effects in a variety of animal systems using
103 orthopoxviruses, and there were occasional reports of some reduction of human disease in
104 smallpox contacts, but none were found to provide reproducible protection of contacts or to be
105 reliably effective in humans with established smallpox illness (Fenner and Henderson et al.
106 1988). In addition, toxicity profiles of these drugs were limiting.
107

108 The approach to development programs to support the efficacy of drugs to treat smallpox is
109 affected by numerous distinctive features of smallpox and its history, including:
110

- 111 • The absence of smallpox cases for decades because of the success of the eradication
112 program
- 113
- 114 • Ethical issues that clearly preclude human challenge studies
115
- 116 • Restriction of variola virus to two designated maximum containment facilities with
117 stringent procedures to prevent any potential release
118
- 119 • The exceptionally narrow host range of variola virus
120

⁵ A submission for review of a new cell-culture-derived smallpox vaccine was discussed at an FDA advisory committee meeting on May 17, 2007. If new vaccine preparations come into use, recommendations for populations to be vaccinated could change. Updated FDA and CDC documents should be consulted where appropriate for current recommendations.

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- 121 • Disease differences between humans and nonhuman primates⁶ and lack of pathogenicity
122 for other host species after variola exposure
123
- 124 • The lack of any previously recognized effective drug, which severely limits any
125 conclusions that might be drawn regarding relationships between in vitro activity, blood
126 levels of the drug, and clinical effect from comparison of new agents against existing
127 ones
128
- 129 • The possibility of antiviral drug interference with effects of the live-virus vaccine
130
- 131 • The absence of detailed information on the pathophysiology of human smallpox itself,
132 including the mode of death
133
- 134 • The limited amount of additional information that potentially can be derived from
135 existing records
136
- 137 • The lack of readily encountered human diseases that can be considered as closely
138 analogous for purposes of preliminary investigation of potential treatments
139
- 140 • The differences between variola and other orthopoxviruses in disease characteristics,
141 drug susceptibility, and host range
142

143 Taken together, these characteristics affect drug development strategies and differentiate the
144 investigation of drugs for smallpox not only from assessment of drugs for common infectious
145 diseases, but also from study of vaccines against smallpox and study of drugs for other potential
146 agents of bioterrorism or biowarfare. For example, new smallpox vaccine candidates are likely
147 to be related to, and might be compared against, an existing vaccine with a long history of
148 successful use and a substantial amount of information on immunologic responses and protective
149 effects across host and viral species; the availability of this comparator, and of immunogenicity
150 measurements in human volunteers, might support development and licensure without use of a
151 variola-virus animal model (sponsors should contact the Office of Vaccine Research and Review
152 in the Center for Biologics Evaluation and Research (CBER) for information). As another
153 example, drug development for some bacterial biothreat agents can use accepted effective
154 comparator drugs, as well as animal models in which disease caused by the biothreat organism is
155 more similar to the human disease than has been observed with variola virus, and may be able to
156 relate results to human dose-response measurements in other bacterial infections. Therefore,
157 although based on common principles of drug development, many specifics of the approach to
158 drug development for smallpox are likely to differ even from the approaches to other situations
159 involving rare and life-threatening diseases.
160
161

⁶ Although a number of primate species can be infected, the typical illness in most nonhuman primates is mild relative to historical experience with human disease (Brinckerhoff and Tyzzer 1905; Hahon 1961), and mortality has been rare except for a few reports with added immunosuppression (Rao and Savithri Sukumar et al. 1968) or with intravenous injection of an extremely high viral inoculum (Jahrling and Hensley et al. 2004) suggesting major differences in host-pathogen interactions.

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162 **III. REGULATORY APPROACH REGARDING EARLY DRUG DEVELOPMENT**

163

164 **A. Selected Issues with Distinctive Impact**

165

166 As summarized in section II., Background, the unique characteristics of smallpox illness and
167 variola virus call for distinctive approaches to some aspects of drug development compared to
168 other viral diseases. For example, sponsors of potential antivariola drugs should prepare
169 appropriately for increased emphasis on the following issues: importance and extent of pre-IND
170 interactions with the FDA to facilitate the development process, special attention to procedures
171 for facilitating access to investigational drugs if an emergency situation were to occur during
172 development, and careful consideration of preliminary investigations using other related viruses
173 and discussion of their relevance to variola. The following sections briefly outline these issues
174 so that they can be revisited as appropriate in subsequent sections of this guidance.

175

176 In each topic area that follows, the amount and timing of the information recommended relative
177 to other steps in the development sequence may vary. Initial discussions with the FDA are
178 encouraged to address priorities and timelines for each proposed development plan.

179

180 *1. Pre-IND Consultations*

181

182 Before preparation of a protocol for human use of a drug under an IND, pre-IND consultations
183 with the FDA provide an opportunity to discuss the design and conduct of nonclinical studies
184 and approaches to development of human studies, when appropriate, based on nonclinical study
185 results. Some candidate antiviral drugs for smallpox may warrant repeated pre-IND
186 consultations as initial nonclinical data become available for review and contribute to the
187 discussion of additional studies. Pre-IND consultations might involve written responses to
188 sponsor submissions, telephone communications, and/or face-to-face meetings between sponsor
189 and FDA staff, as warranted and appropriate for review of preliminary proposals and data and for
190 efficient transmission of advice.

191

192 Plans for any human use of a drug directed against variola might depend in part on animal
193 studies greater in number and extent than is usual for drugs developed for other diseases.
194 Discussions of the design and use of such studies should take place at the pre-IND consultation
195 stage and early in the IND process. These issues highlight the importance of early interactions
196 with the FDA through pre-IND mechanisms, and pre-IND consultations and discussions might
197 be far more extensive than in many other areas of drug development. Potential studies to be
198 discussed in pre-IND and early IND phases might include studies of in vitro and in vivo activity
199 against a variety of poxviruses, animal toxicology studies, animal model pharmacokinetic
200 studies, human safety and pharmacokinetic studies, and consideration as to how human and
201 nonhuman pharmacokinetic data might be linked if an animal model is contemplated.

202 Preliminary studies of drug efficacy and safety in human patients with other diseases (that might
203 be performed under other INDs for other indications in some instances) also might be considered
204 to provide supportive information. Each of these components of preparation for an IND are
205 discussed further in subsequent sections of this guidance. As outlined in the following sections,
206 the selection and design of studies to obtain preliminary data will warrant interdisciplinary
207 assessment of a range of in vitro systems, animal models, and any available human data (e.g.,

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208 from use in nonsmallpox illnesses or in volunteer safety or pharmacokinetic studies) that might
209 prove to have indirect relevance to the use of a candidate drug if a smallpox outbreak were to
210 occur.

211
212 2. *Procedures for Facilitating Access to Investigational Drugs in Emergency*
213 *Situations*

214
215 One of the most important features distinguishing development of smallpox drugs from other
216 types of drug development is that the effect of the drug in humans infected with variola would
217 not be possible to assess unless cases of smallpox were to occur, but if even one case were to
218 occur, it would be responded to as a unique public health emergency. Therefore, it is particularly
219 important to develop a background of preliminary data providing evidence of safety and
220 potential benefit of the candidate drug to support development of protocols that might be used to
221 treat humans in such a public health emergency situation. Such a protocol might be planned and
222 reviewed as a controlled or uncontrolled study under a standard IND, or as a treatment IND,
223 depending on the circumstances and supporting information. Single-patient emergency IND
224 (EIND) proposals also might be considered if a case were to occur for which an investigational
225 drug would be considered potentially beneficial but no appropriate protocol was ready for use;
226 however, we prefer that sponsors give early attention to preparation of protocols for possible
227 outbreak situations, as such preparation should minimize the need for EIND consideration.

228
229 If drugs targeting smallpox are at appropriate more-advanced development stages with sufficient
230 data available at the time that a smallpox emergency occurs, consideration might be given to
231 using EUA provisions of the Project BioShield Act (P.L. 108-276). This authorization, issued by
232 the FDA Commissioner under section 564(b) of the Federal Food, Drug, and Cosmetic Act (the
233 Act), allows the introduction into interstate commerce of a drug, device, or biological product
234 intended for use in an actual or potential emergency during the effective period of an emergency
235 declaration. EUA candidates include products and uses that are not approved under the Act or
236 the Public Health Service Act. An EUA may be issued for a specific product if the totality of
237 available scientific evidence indicates that it may be effective for diagnosing, preventing, or
238 treating a serious or life-threatening condition that is caused by the agent that is the subject of the
239 emergency declaration; in addition, the known or potential benefits of the product must outweigh
240 its known or potential risks. Finally, there cannot be an adequate, approved, and available
241 alternative to the product for diagnosing, preventing, or treating the relevant serious or life-
242 threatening disease or condition.^{7,8}

243
244 The precise requirements for the issuance of an EUA are not as extensive as the requirements for
245 full approval, and the requirements for a given countermeasure cannot be determined in the
246 absence of the actual emergency because of the need for a risk-benefit assessment. However,
247 unapproved or unlicensed countermeasures in advanced stages of development that are expected
248 to have sufficiently promising risk-benefit information might be considered by the Strategic
249 National Stockpile and might be evaluated for investigational use under an IND or potentially

⁷ See 21 U.S.C. 564.

⁸ See the guidance for industry *Emergency Use Authorization of Medical Products* at <http://www.fda.gov/oc/guidance/emergencyuse.html>.

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250 under an EUA if a situation of sufficient magnitude arises in which criteria for such use are met.
251 In general, drugs proposed for consideration of potential use under an EUA should have
252 substantially more data available than usually required to support initial administration to
253 patients under an IND protocol, and should have evidence of sustained progress toward an NDA,
254 so that appropriate risk-benefit evaluations could be made to decide whether the interim use of
255 an EUA would be justified in a potential emergency situation. Sponsors who wish to propose
256 their drugs as potentially appropriate for use under an EUA are encouraged to discuss their
257 proposal with the review division as early as possible. To do so, we recommend sponsors
258 provide as much information as possible to the pre-IND or IND, as appropriate. Sponsors also
259 should provide frequent updates during the course of the development, proceeding toward
260 fulfillment of requirements for an NDA, while compiling summary information that might
261 support use under an IND or EUA, as appropriate, should an emergency arise before the
262 development process is complete.

263 3. *Use of Different Poxviruses and Assessment of Potential Relevance*

264
265 In the preliminary development of candidate antiviral drugs for potential use against variola,
266 initial studies of in vitro and in vivo antiviral activity should rely heavily on use of other related
267 viruses, principally the nonvariola orthopoxviruses. Although data obtained through the study of
268 nonvariola orthopoxviruses cannot directly substitute for studies using variola virus, they should
269 provide useful ancillary information about the safety and activity of experimental antivariola
270 compounds. Such studies are likely to be particularly important because of the restrictions on the
271 use of variola virus. Nonvariola orthopoxviruses can be used for initial investigations of in vitro
272 activity of candidate drugs, and for development and characterization of animal models for
273 preliminary assessment of in vivo activity. In addition, some nonvariola orthopoxviruses can
274 cause infections in humans (naturally or as complications of vaccination) in which therapeutic
275 investigations might contribute to supporting information for investigational treatment of
276 smallpox. Results from studies of nonvariola orthopoxviruses are not known to directly predict
277 activity or clinical benefit in treatment of smallpox, but accumulation of such data should be
278 important in evaluating the overall evidence base for drugs that potentially might be used in
279 human smallpox.
280

281
282 We recommend that candidate drugs that appear sufficiently promising to pursue development be
283 tested against several orthopoxvirus species, as no single virus has been identified as a best
284 approximation for variola in terms of specific prediction of drug effects. Viruses suitable for
285 preliminary studies can include a range of related nonvariola orthopoxviruses, with emphasis on
286 vaccinia and with additional consideration of other orthopoxviruses that have been reported as
287 causes of human disease (examples include monkeypox and cowpox) and viruses that can cause
288 virulent outbreaks in animal hosts (examples include ectromelia, rabbitpox, and camelpox). The
289 list of viruses to be studied should prominently include vaccinia because it has been more
290 extensively studied and characterized in the past than other orthopoxviruses. In addition,
291 vaccinia is in a group of orthopoxviruses closely related to variola, and studies of vaccinia also
292 might be relevant to the development of drugs to treat complications of vaccination. An
293 important factor in the evaluation of new drugs should be their ability to show substantial effects
294 consistently across different poxviruses and animal models.
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296 Evidence of activity against similar targets in multiple different poxviruses over a wide range of
297 drug doses and viral inoculum challenges should add some preliminary support to the likelihood
298 of activity against smallpox and also can contribute to other therapeutic goals. For example, a
299 drug that successfully treats vaccinia in animals might be studied to treat the complications of
300 smallpox vaccination,⁹ and studies of monkeypox might contribute to improving the treatment of
301 human monkeypox.

302
303 When undertaking studies of drug activity against nonvariola orthopoxviruses, sponsors should
304 provide evidence that the drug targets studied in the other orthopoxviruses are relevant to variola.
305 We recommend that even with such evidence regarding mechanism of action, extrapolations of
306 pathophysiological studies or treatment results across viral and host species be limited and
307 cautious, because fundamental characteristics of variola-related viruses can differ significantly
308 from those of variola. For example, although vaccinia is structurally similar enough to variola to
309 confer immunity through vaccination, drugs reported to be active against vaccinia in some
310 animal studies were not found to be useful against human smallpox (Fenner and Henderson et al.
311 1988). Similarly, although camelpox is virulent in camels and may have a closer genetic
312 relationship to variola than other poxviruses (Gubser and Smith 2002), it has not been reported as
313 a major human health problem in areas with substantial contact between humans and camels.

314
315 Evaluations of antiviral activity in the course of drug development typically should begin with
316 exploration of in vitro data, followed by animal data. Because smallpox is a potentially serious
317 threat but does not occur naturally (so clinical trials cannot be performed in field situations) and
318 human challenge studies would be unethical, animal models may provide important information
319 for the evaluation of treatment effect and may contribute directly to drug approval per 21 CFR
320 part 314, subpart I (the Animal Rule)¹⁰ if a suitable approach is agreed upon (see additional
321 discussion under section IV., Animal Models). It is important to obtain evidence of a therapeutic
322 effect using several species of animal models. The sponsor should make an effort to develop
323 animal models that resemble a range of variola-associated disease manifestations seen
324 historically in humans, and to generate evidence relevant to prediction of treatment responses in
325 humans. In addition to exploring antiviral activity, animal model data on pharmacokinetics and
326 pharmacodynamics can contribute toward selection of a preliminary drug dose range that might
327 be used to explore safety in humans, to facilitate exploration of treatment of other viral diseases
328 that might provide preliminary supporting information, and, if possible, to permit prediction of
329 an estimated dose range for optimal in vivo antiviral activity.

330
331 Human data from study of nonsmallpox illnesses also should play an important role in attempts
332 to develop a drug that might be useful against smallpox. Clinical studies might demonstrate

⁹ See the draft guidance for industry *Vaccinia Virus — Developing Drugs to Mitigate Complications from Smallpox Vaccination*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at <http://www.fda.gov/cder/guidance/index.htm>.

¹⁰ In some cases, therapeutic proteins or monoclonal antibodies may be evaluated using processes similar to antiviral drugs, but considered under the biologics version of the Animal Rule under 21 CFR part 601, subpart H. For ease of reference, to reflect regulations governing standard antiviral drug development, and because the primary focus of this guidance is on antiviral drugs, 21 CFR part 314 (and 312 where appropriate) citations are used throughout this guidance. Sponsors interested in developing therapeutic proteins or monoclonal antibodies for use against smallpox are encouraged to discuss their approach with the review division as early as possible in development.

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333 whether the drug is efficacious in any studies that can be performed in naturally occurring
334 infections with nonvariola orthopoxviruses such as vaccinia or monkeypox, or less closely
335 related poxviruses, such as molluscum contagiosum. Drug safety data should be evaluated using
336 the same types of human safety studies typically employed in other types of drug development,
337 as well as human clinical trials for other illnesses where investigation of the candidate drug may
338 be warranted. Sponsors should discuss with the FDA their plans and proposals for obtaining
339 safety data from sufficiently large and diverse study populations to support each successive
340 development stage.

341
342 The preliminary study of nonvariola orthopoxviruses is likely to warrant some differences in
343 approach, but should nevertheless be relevant, for development of products that are hypothesized
344 to act through mechanisms other than direct inhibition of viral replication. If a candidate drug is
345 proposed that is not considered to have an antiviral mechanism of action, the sponsor should
346 provide an adequate explanation of the mechanism of the drug's potential for utility in persons
347 who may be exposed to, or infected with, variola. The sponsor also should provide proposals for
348 early discussion to identify any differences in study approach that may be appropriate. Sponsors
349 of any such drug candidates should still provide data from evaluation of the effect of the drug on
350 viral replication, as part of the confirmation of the proposed mechanism of action and to assess
351 for any deleterious effects that might occur.

352
353 Sponsors should ensure that all studies and procedures incorporate adequate precautions to avoid
354 transmission of pathogenic virus or generation of novel biological hazards, including
355 containment measures and vaccination of study staff, as appropriate. Even beyond the
356 precautions warranted for other pathogens, it is critically important that the risk and benefit of
357 any investigation involving variola virus be carefully weighed, and that sponsors stringently
358 adhere to all measures to avoid any release or any increase in hazard associated with the virus.
359 Sponsors should give careful attention to observing all provisions of the Select Agent Rule (42
360 CFR part 73; also see <http://www.cdc.gov/od/sap/sitemap.htm>) and other applicable
361 governmental and institutional biosafety and biosecurity provisions.

B. Interactions Among Industry, Academic, and Government Sponsors

362
363
364
365 Because developing drugs for variola represents a unique situation, early and frequent
366 collaboration with government agencies is strongly encouraged, when appropriate to enhance
367 development in areas of unmet medical need or to facilitate suitable prioritization of access to
368 restricted resources such as containment facilities. As discussed earlier, substantial preliminary
369 data on the activity of candidate drugs for orthopoxvirus infections should be generated using
370 nonvariola orthopoxviruses. Early in the course of development, sponsors of candidate drugs
371 may find it useful to contact the National Institute of Allergy and Infectious Diseases, National
372 Institutes of Health, to identify sources of funding (e.g., grants and contracts) and to learn more
373 about collaborative programs where aspects of drug screening and development may be under
374 way. If, on the basis of study results with other orthopoxviruses, it appears appropriate to
375 consider studies using variola virus, pre-IND communications might address whether sponsors
376 should approach investigators at the CDC to explore potential collaborations with those who
377 work with variola virus and who are familiar with the biosafety level 4 (BSL-4) laboratories and
378 extensive precautions that are necessary for virus handling.

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379
380 If development of a candidate drug during pre-IND and early IND review processes yields
381 sufficiently promising results, we suggest that sponsors develop a protocol that would provide
382 for investigational use of the drug if a smallpox release were to occur. Discussions with the FDA
383 are strongly encouraged when developing a protocol to facilitate drug use by federal, state, and
384 local public health agencies in the event of a smallpox outbreak. Such communications can
385 contribute to ensuring that proposals for protocol sections (e.g., drug availability and data
386 collection) are adequate, and that investigator brochures contain all relevant material.

387
388 Because collaborative opportunities change over time, sponsors are encouraged to contact the
389 review division early during the pre-IND stage of drug development to obtain current
390 information regarding potential collaborative contacts.

391

C. Drugs with Previous or Concurrent Studies for Other Indications

392

393
394 Because smallpox is no longer a naturally occurring disease, data from studies of a candidate
395 drug in other human illnesses might play a more important role than usual in the preliminary
396 evaluation of both activity and safety. Useful information might be obtained either from studies
397 that have been used to support another indication, or from investigational study information
398 available to the sponsor.

399

400 If data concerning the use of the candidate drug for other diseases do not exist, sponsors should
401 consider whether the drug shows promise for treating other diseases, warranting pursuit of a
402 parallel line of development. This approach might provide safety and efficacy information
403 relevant to those other diseases, and safety information that might contribute to support of
404 investigational use if a smallpox emergency were to occur. In addition, if the other areas of
405 development include study of viral infections related to variola, such studies might provide
406 ancillary activity information to support investigational treatment of smallpox.

407

408 Some drug safety data should already exist if the drug under evaluation has previously
409 undergone substantial development, is currently or will be under study for other indications, or
410 has had approval sought for a nonvariola indication (whether orthopoxvirus-related or not), even
411 if it has not been previously approved by the FDA. In this case, depending on the extent of
412 already available safety information, the sponsor may not need to collect as much additional
413 information to complete the initial safety database.

414

415 In addition to safety data from healthy human volunteers, it can be particularly important to have
416 safety data from studies for other indications involving treatment of patients who are acutely and
417 severely ill. If a terrorist event involving smallpox were to occur, it is likely that a significant
418 proportion of patients would be severely ill, with organ system dysfunction and imbalances of
419 physiology that could increase the possibility of drug side effects. Safety data from previous
420 studies of the candidate drug used for treatment of any other disease should be provided to the
421 FDA, if available.

422

423 Information on drug safety, pharmacokinetics, and pharmacodynamics in special populations
424 (including studies in the pediatric population, the geriatric population, pregnant women, lactating

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425 women, and persons with renal and hepatic impairment) should be provided to the FDA, if
426 available. The sponsor should document the adequacy of the available data to support the safety
427 of a proposed clinical protocol. If the sponsor does not own the supporting safety data, and if
428 those data are not in the public domain, it is the sponsor's responsibility to obtain letters of
429 authorization allowing the FDA to refer to those studies in its evaluation of the proposed IND.
430

431 If the drug under evaluation has already been approved for other indications, the sponsor can
432 either obtain a right of reference to the safety data or rely on the FDA's previous finding of
433 safety of that drug. The sponsor also should provide any additional data that may be appropriate
434 to support the proposed investigational use (examples would include information sufficient to
435 support a different dose or patient population as compared with the approved use). However, if
436 the sponsor relies on the FDA's previous finding of safety, any future submission of an NDA
437 would be subject to the provisions of 21 CFR 314.54, Procedure for Submission of an
438 Application Requiring Investigations for Approval of a New Indication for, or other Change
439 from, a Listed Drug.
440

441 Early discussion with the FDA can help to identify planning strategies that can lead to the most
442 efficient design of overlapping development plans. For those drugs that are new chemical
443 entities, refer to section III.E., Nonclinical Toxicology, for information regarding the
444 recommended safety studies.
445

D. Chemistry, Manufacturing, and Controls

446 We recommend that the sponsor provide CMC information as described in the guidances for
447 industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1*
448 *Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products*
449 *and INDs for Phase 2 and Phase 3 Studies, Chemistry, Manufacturing, and Controls*
450 *Information*. We recommend that sponsors consult other relevant guidances and discuss plans
451 and questions with the review division.
452
453
454

E. Nonclinical Toxicology

455 A sponsor must supply information about the pharmacological and toxicological studies of a
456 drug performed in vitro or in animal studies adequate to support the safety of proposed clinical
457 investigations (21 CFR 312.23(a)(8)). The dose, duration, route, and overall design of animal
458 and other studies that should be submitted varies with the duration and nature of the proposed
459 clinical investigations. FDA guidances recommend how such requirements can be met. These
460 guidances are referenced in the following sections. Many of the elements listed as necessary in
461 IND submissions (see citations in the following paragraphs) also may be desirable in a pre-IND
462 submission to the extent that appropriate information is available.
463
464
465

466 The information submitted must include the identification and qualifications of the individuals
467 who evaluated the results of these studies and concluded that it is reasonably safe to begin the
468 proposed clinical investigations (§ 312.23(a)(8)). In addition, the sponsor must include a
469 statement detailing where the investigations were conducted and where the records are available

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470 for inspection (§ 312.23(a)(8)). As drug development proceeds, the sponsor should submit
471 nonclinical and clinical safety information as amendments to the IND or pre-IND.

472
473 Under § 312.23(a)(8), the sponsor must submit an integrated summary of the toxicological
474 effects of the drug in vitro and in animals. Depending on the nature of the drug and the phase of
475 the investigation, the summary should include the results of acute, subacute, and chronic toxicity
476 tests, safety pharmacology tests, tests of the drug's effects on reproduction and the developing
477 fetus, tests of the drug's genetic toxicity, any special toxicity test related to the drug's particular
478 mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology), and
479 any in vitro studies intended to evaluate drug toxicity. We also prefer that animal studies
480 describing the pharmacological effects and mechanisms of action of the drug and information on
481 the absorption, distribution, metabolism, and excretion of the drug be submitted. For each
482 toxicology study that is intended to support the safety of the proposed clinical investigation, a
483 full tabulation of data suitable for detailed review must be submitted (§ 312.23(a)(8)(ii)(b)).
484

485 Under § 312.23(a)(9)(i) and (iii), the sponsor must submit a summary of previous human
486 experience with the investigational drug. Detailed safety data as well as information relevant to
487 the rationale of drug development for any investigational drug marketed in the United States or
488 abroad should be submitted. A list of countries in which the drug has been marketed or
489 withdrawn from marketing for reasons related to its safety or efficacy also must be submitted.
490 Additionally, if the drug has been studied in controlled clinical trials, relevant data regarding the
491 drug's effectiveness for the proposed investigational trial should be submitted. Published
492 material relevant to the safety or effectiveness of the drug or clinical investigation must be
493 provided, whereas less-relevant published material should be provided as a bibliography.
494

495 Regulatory and pharmaceutical industry representatives from the United States, Europe, and
496 Japan (The International Conference on Harmonisation of Technical Requirements for
497 Registration of Pharmaceuticals for Human Use (ICH)) have written guidances for many of the
498 nonclinical requirements for safety studies. These guidances recommend international standards
499 for, and promote harmonization of, the nonclinical safety studies appropriate for supporting
500 human clinical trials of a given scope and duration.

501
502 *1. Timing of Nonclinical Studies to Support the Conduct of Human Clinical Trials*
503

504 Usually, once a drug has been shown in nonclinical studies to be sufficiently safe for clinical
505 trials to begin, such trials are conducted to demonstrate the drug's safety and efficacy in humans.
506 Phase 1 trials evaluate the safety and pharmacokinetic profile of the drug. These trials start with
507 relatively low drug exposure in a small number of subjects, often using healthy volunteers. The
508 pharmacokinetic data, together with activity data in vitro, should ideally demonstrate that a high
509 inhibitory quotient (IQ) can be expected at doses that are safe for the administration of the drug
510 (see section III.F.1.d., Inhibitory quotient). Efficacy evaluations generally are carried out in
511 trials of longer duration; therefore, phase 1 trials are usually followed by clinical trials in which
512 drug exposure increases by dose, duration, and/or size of the exposed patient population.
513

514 In trials of candidate drugs designed for potential future use against variola, studies to assess the
515 safety of the drug in humans typically can be conducted first in healthy volunteers. Thus,

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516 sufficient nonclinical studies usually would be carried out to support the safety of administration
517 of the drug for at least 2 weeks, or until pharmacokinetic measurements have demonstrated that
518 the drug has reached steady state in the healthy volunteers. In general, toxicology studies of 2
519 weeks duration in a rodent and a nonrodent species should support submission of protocols for
520 review for phase 1 clinical trials of up to 2 weeks. Upon the completion of studies to support a
521 dosing duration of up to 2 weeks, a 1-month (or longer) study, again in healthy volunteers, might
522 be appropriate to consider. However, to support the dosing of humans in clinical trials for a
523 period longer than 2 weeks, nonclinical toxicology studies of a longer duration should be
524 performed.¹¹ The clinical manifestations of variola infection suggest that some cases may
525 require treatment for longer than 2 weeks; therefore, we recommend that initial toxicology and
526 safety studies take this possibility into account.

2. *Acute and Subacute Toxicity Studies*

527
528
529
530 Acute toxicity studies are commonly the first studies carried out on a drug intended for humans
531 and use a single dose or multiple doses administered for no longer than a 24-hour period.
532 Subacute studies by definition are longer than acute studies, and are generally multiple-dose
533 studies carried out for no longer than 6 months. Most commonly, an acute study with drug
534 administration by the proposed clinical route of administration as well as a parenteral route
535 (usually intravenous) in a rodent and a nonrodent species is performed to set the doses for longer
536 term nonclinical studies and to evaluate the immediate toxicity profile of the drug. If the
537 proposed clinical route of administration will be intravenous, intravenous evaluations alone will
538 usually suffice. We recommend that observational evaluations, as well as clinical chemistry and
539 histopathologic evaluations, be performed at the end of 2 weeks for the acute studies.

3. *Safety Pharmacology Studies*

540
541
542
543 Safety pharmacology studies evaluate the interaction of the drug with organ systems such as the
544 central nervous system, cardiovascular system, and respiratory system. In some cases, the
545 sponsor can incorporate some safety pharmacology evaluations in animals into the design of
546 toxicology, kinetic, and clinical studies, whereas in other cases these endpoints are best evaluated
547 in specific safety pharmacology studies. Although the adverse effects of a substance might be
548 detectable at exposures that fall within the therapeutic range in appropriately designed safety
549 pharmacology studies, such effects may not be evident from observations and measurements
550 used to detect toxicity in conventional animal toxicity studies.¹²

4. *Genetic Toxicity*

551
552
553
554 We recommend that the sponsor perform a comprehensive assessment of a new drug's genotoxic
555 potential before its administration into humans. Since no single test is capable of detecting all
556 relevant genotoxic agents, the most common approach is to carry out a battery of in vitro and in
557 vivo tests for genetic toxicity. A standard test battery of studies has been selected under ICH to

¹¹ See the ICH guidance for industry *M3(R1) Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals* (<http://www.ich.org/cache/compo/276-254-1.html>).

¹² See the ICH guidance for industry *S7A Safety Pharmacology Studies for Human Pharmaceuticals*.

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558 evaluate a new drug for its ability to cause genetic toxicity. In general, two of the in vitro tests
559 should be completed before the initial submission of an IND. The remainder of the battery
560 should be completed before phase 2 studies.¹³

561
562 Detection of genetic toxicity can cause an ethical dilemma. Generally, no more than one dose of
563 a genetically toxic drug should be administered to a healthy volunteer. It is considered unethical
564 to subject a healthy volunteer, who does not stand to benefit from drug administration, to a drug
565 that might cause cancer. It is possible that a drug with potential for efficacy against variola also
566 can be a genetic toxin. We recommend that the sponsor confer with the review division
567 regarding such an issue as soon as possible.

568

569 5. *Reproductive Toxicity*

570

571 Reproductive toxicity studies assess the effect a drug can have on mammalian reproduction from
572 preming (adult male and female reproductive function) to sexual maturity of the offspring.
573 ICH guidances address the design of reproductive toxicity studies and offer a number of choices
574 for carrying out reproductive toxicity studies.¹⁴ The reproductive toxicity studies vary from
575 indication to indication, but they should be submitted before phase 3 trials. In studies of
576 poxvirus infections, risks that women entering the trials might be pregnant, and potential toxicity
577 to male and female fertility, are concerns. A study of fertility from conception to implantation
578 and at least one organogenesis study should be completed before the early studies in healthy
579 volunteers, and the full complement of studies preferably should be completed before the
580 administration of the drug in patients. The informed consent form should outline the potential
581 hazards associated with drug administration.

582

583 6. *Carcinogenicity Studies*

584

585 In general, we do not anticipate that carcinogenicity studies are likely to be necessary for drugs
586 that might be used only to treat established variola illness since the administration of such drugs
587 will not, in most cases, exceed 6 months. However, decisions regarding the performance of
588 carcinogenicity studies should be made on a case-by-case basis and depend upon the mutagenic
589 potential and/or possible structure-activity relationship of the test drug with other known
590 carcinogens.¹⁵ Further discussions also should take place if there is a possibility of longer-term
591 (and possibly recurrent) prophylactic use.

592

593 **F. Microbiology**

594

595 This section discusses important issues for consideration in the microbiological evaluation of
596 candidate drugs. Some components may change as more investigations take place in this field

¹³ See the ICH guidances for industry *S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals* and *S2A Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals*.

¹⁴ See the ICH guidance for industry *S5(R2) Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility* (<http://www.ich.org/cache/compo/276-254-1.html>).

¹⁵ See the ICH guidances for industry *S1A The Need for Carcinogenicity Studies of Pharmaceuticals* and *S1B Testing for Carcinogenicity of Pharmaceuticals* (<http://www.ich.org/cache/compo/276-254-1.html>).

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597 (e.g., increased opportunities to study cross-resistance or interactions with other antivariola virus
598 drugs). The sponsor should make available for review adequate information on sample
599 collection, assays performed, and on validation approaches for these assays. Use of a specific
600 procedure, method, or test system in an investigational protocol for a nonclinical laboratory
601 study, or as laboratory procedures supporting a clinical trial, does not constitute FDA
602 endorsement of that procedure, method, or test system, or FDA approval for clinical laboratory
603 use. This guidance addresses these points further in the following descriptions, and sponsors are
604 encouraged to discuss questions with the review division early in the drug development process.
605 Additional information on virology studies in some of the principal areas of antiviral drug
606 development can be found in the guidance for industry *Antiviral Product Development —*
607 *Conducting and Submitting Virology Studies to the Agency*. If a diagnostic assay proposed for
608 use in a clinical trial has not been previously cleared by the FDA but eventually may be
609 developed for commercial distribution, the sponsor should consider early discussions with the
610 Center for Devices and Radiological Health as well as the Center for Drug Evaluation and
611 Research (CDER) to facilitate collaborative or consultative review and comment as appropriate.
612

1. Components of Nonclinical Virology Studies and Reports

613
614
615 Nonclinical virology studies are an important component in the review process of a candidate
616 antivariola virus drug. These studies contribute to the evaluation of the antiviral activity and
617 safety of a candidate drug before its use in humans. Submitted study reports should identify the
618 mechanism of action, establish specific antiviral activity of the compound in cell culture and
619 animal models, and provide data on the development of viral resistance (or reduced susceptibility
620 of the virus) to the candidate drug. Distinctive factors affecting the generation of virology data
621 related to smallpox include limited access to the two approved smallpox laboratory facilities,
622 lack of an adequate animal model for smallpox (or animal host comparable to human disease),
623 and the critical importance of risk-benefit assessment and prioritization of resources for any
624 consideration of studies involving variola virus; therefore, information from related but more
625 common and less pathogenic viruses should be carefully compiled and analyzed, to a greater
626 extent than for the development of other antiviral products, before discussing potential
627 applicability to variola virus or actual study of variola virus.
628

629 Although data from other orthopoxviruses should not be considered definitive evidence of
630 antivariola activity, exploratory studies with such viruses can provide important adjunctive
631 information to the extent that these studies are safe and feasible to perform. Sponsors are
632 encouraged to assess activity of the candidate drug against several orthopoxviruses including
633 vaccinia virus. These nonclinical studies should be well advanced or completed before the
634 introduction of the candidate drug into humans. Pre-IND submissions should be used as an
635 opportunity for discussion of initial data obtained with nonvariola poxviruses and for
636 identification of additional studies that may be desirable with such viruses. They are also an
637 opportunity to discuss how and when it may be possible to generate data more directly applicable
638 to variola virus while maintaining experimental safety and appropriate prioritization of studies.
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640 a. Mechanism of action

641
642 A candidate drug might act directly by targeting a specific viral-encoded function (e.g., an
643 enzyme inhibitor) or act indirectly (e.g., interferon induction of the host cell response). Reports
644 of nonclinical virology studies should include background information describing the rationale
645 and data showing the mechanism of action of the candidate drug, and the sponsor should provide
646 complete publication copies of all key cited references. The sponsor also should provide
647 biochemical, structural, cellular, or genetic data to support the proposed mechanism of action.
648 Examples include data demonstrating receptor binding, inhibition of enzymatic activity, X-ray
649 crystallographic structure determination of bound inhibitor complex, and characterization of
650 resistance mutations in the gene encoding the target. The sponsor should demonstrate the
651 specificity of the candidate drug for the viral target over host proteins, especially when a viral
652 enzyme has a cellular counterpart. For example, if the candidate drug is designed to target the
653 variola DNA polymerase, specificity against the polymerase from related orthopoxviruses should
654 be shown in comparison with host DNA and RNA polymerases. If studies with polymerases
655 from more common and less pathogenic poxviruses are promising, applicable regulations or
656 guidances of relevant public health agencies at the time of drug development should be consulted
657 to determine whether assessment of specificity against recombinant variola polymerase is
658 appropriate. For nucleoside or nucleotide analogs, the intracellular half-life ($t_{1/2}$) of the
659 triphosphate form of the active drug moiety should be determined.

660
661 Immunomodulatory drugs might have unintended effects on the immune system that result in
662 activation of viral replication or in progression of clinical disease. Therefore, studies that only
663 show general immune stimulation by a candidate immunomodulatory drug are likely to be of
664 limited value, and sponsors should design studies to demonstrate whether an antiviral effect on
665 appropriate orthopoxviruses can be achieved.

666
667 b. In vitro antiviral activity

668
669 Cell culture systems and surrogate virus/animal models (e.g., vaccinia virus infection of mice
670 with congenital or induced immune compromise) should be used to show the candidate drug has
671 specific, quantifiable antiviral activity against an appropriate range of orthopoxviruses. The
672 FDA and organizations such as the Clinical and Laboratory Standards Institute (formerly the
673 National Committee on Clinical Laboratory Standards or NCCLS) do not recognize or
674 recommend a specific test system for assessing antiviral activity. Sponsors can consult published
675 work¹⁶ or present additional proposals for review.

676
677 We recommend that sponsors consider including vaccinia vaccine strains as well as other
678 laboratory strains (including any strains expected to be used in animal models) in
679 microbiological testing, not only as part of a broad-based orthopoxvirus testing strategy to screen
680 for potential relevance to variola, but also to assess the potential of the candidate drug for use in
681 clinical trials to treat vaccine complications.¹⁷ As outlined below, investigation of the treatment
682 of vaccination complications offers the opportunity to test the candidate variola drug in a human

¹⁶ Examples include Smee and Sidwell et al. 2002 and Kern and Hartline et al. 2002.

¹⁷ See note 9, *supra*.

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683 illness caused by a related virus (though the illnesses are not similar and extrapolation from one
684 to the other is likely to be limited), in addition to the intrinsic benefit that might arise from
685 development of treatments for vaccine complications. In addition, if a candidate drug has
686 suitable safety and in vitro activity profiles, studies of treatment effects in humans infected with
687 monkeypox virus also might offer useful preliminary information relevant to variola therapy as
688 well as possible direct benefit for future monkeypox treatments. We recommend that
689 information on antiviral activity also be generated for other related poxviruses, including any
690 nonvaccinia poxviruses that can be studied in animal models (e.g., cowpox, ectromelia,
691 monkeypox) to provide ancillary information on the effectiveness of the candidate drug.
692 Ultimately, the sponsor should explore the potential appropriateness of testing the antiviral
693 activity of the candidate drug against variola isolates if other data are sufficiently promising to
694 proceed to this stage.

695
696 We recommend that specific antiviral activity be determined using a quantitative assay to
697 measure virus replication in the absence and presence of increasing drug concentrations. The
698 drug concentration at which virus replication is inhibited 50 percent is the effective concentration
699 (EC_{50}) (also referred to as the inhibitory concentration (IC_{50})). We also recommend that the
700 sponsor document the sources of viruses (e.g., blood, plasma, defined laboratory strains, clinical
701 isolates), the method of isolation and the characterization, storage and stability, and cell culture
702 procedures and materials. Sponsors are encouraged to consult FDA and ICH guidances for
703 definitions on assay validation.¹⁸ For any assay developed or used for showing antiviral activity,
704 or other investigational assay used in the nonclinical and clinical studies, the sponsor should
705 provide sufficient information about the assay to assess the appropriateness of its use in the
706 specified study setting. Assays should be well-documented, and should adequately meet
707 requirements of 21 CFR part 58, Good Laboratory Practice for Nonclinical Laboratory Studies.
708 The test system should be standardized with well-defined control strains. The sponsor should
709 discuss with the FDA the specific information to be provided.

710
711 It is important to consider whether the inhibitory concentration is consistent with data supporting
712 the mechanism of action, such as a K_i or binding data. A candidate drug that inhibits virus
713 replication at a concentration much lower than is expected from the biochemical data supporting
714 the proposed mechanism suggests that another target may be affected or another mechanism of
715 inhibition may be operating.

c. In vitro antiviral activity in the presence of serum proteins

716
717
718
719 Serum proteins bind and sequester many drugs and might interfere with the antiviral activity of a
720 drug. Therefore, we recommend that the in vitro antiviral activity of a candidate drug be
721 analyzed both in the presence and absence of serum proteins. The effects of human serum (45 to
722 50 percent) and human plasma plus α -acidic glycoprotein on the in vitro antiviral activity of the
723 candidate drug should be evaluated by determining a median serum adjusted EC_{50} value and an
724 EC_{50} value in the presence of 2 mg/mL of α -acidic glycoprotein. For several well-defined strains
725 of orthopoxviruses appropriate for study, the sponsor should evaluate the effects of human serum

¹⁸ See the ICH guidance for industry *Q2(R1) Validation of Analytical Procedures: Text and Methodology* (<http://www.ich.org/cache/compo/276-254-1.html>) and the guidance for industry *Bioanalytical Method Validation*.

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726 (40 to 50 percent) and/or human plasma plus 2 mg/mL of α -acidic glycoprotein on the in vitro
727 antiviral activity of the candidate drug and determine a median serum adjusted EC₅₀ value.

728

729 d. Inhibitory quotient

730

731 Drug concentrations are an important factor in the response to viral therapy. Therefore, we
732 recommend that the sponsor determine an inhibitory quotient, $IQ = C_{\min}/\text{serum adjusted EC}_{50}$.
733 An IQ integrates plasma drug concentrations and resistance testing. A high IQ indicates the
734 potential that a drug concentration might be achieved in a patient that might effectively inhibit
735 the virus and minimize the development of drug resistance. A high IQ can help to identify
736 promising drugs for additional studies, and those additional studies in turn might make it
737 possible to obtain additional information on the relationship between IQ and outcome.

738

739 e. Cytotoxicity and therapeutic index

740

741 After drug exposure in a cell culture model, host cell death might be misinterpreted as antiviral
742 activity. Cytotoxicity tests use a series of increasing concentrations of the candidate drug to
743 determine what concentration results in the death of 50 percent of the host cells. This value is
744 referred to as the *median cellular cytotoxicity concentration* (CC₅₀ or CCIC₅₀). The relative
745 effectiveness of the candidate drug in inhibiting viral replication compared to inducing cell death
746 is referred to as the therapeutic index (i.e., CC₅₀/EC₅₀) or as the *selectivity index*. A high
747 therapeutic index is desired, as it represents maximum antiviral activity with minimal cell
748 toxicity. We recommend that the CC₅₀ be assessed both in stationary and dividing cells from
749 multiple human cell types and tissues for potential cell cycle, cell type, or tissue specific
750 toxicities. We also recommend that the effects of the candidate drug on mitochondrial toxicity in
751 cell culture be monitored by examining measures such as mitochondrial morphology, glucose
752 utilization, lactic acid production, and mitochondrial DNA content. These studies might reveal
753 the potential for toxicity in vivo.

754

755 f. In vitro combination activity analysis

756

757 Administration of multiple antiviral drugs might be more effective in inhibiting virus replication
758 than a single drug. Future treatments for variola virus might use combinations of drugs.
759 However, drug interactions are complex to study and interpret, and can result in antagonistic,
760 additive, or synergistic effects with respect to antiviral activity. For this reason, it is important to
761 test the in vitro antiviral activity of candidate drugs in combination with other drugs approved for
762 the same indication. We recommend in vitro drug combination activity studies be performed
763 with any investigational or approved drugs expected to be used with the candidate study drug to
764 treat variola infection at the time that a new candidate drug is entered into development. If other
765 drugs are approved for other poxvirus indications, we recommend in vitro combination activity
766 studies with those drugs as well. In vitro drug combination interactions can be evaluated using
767 analyses based on published work.¹⁹

768

¹⁹ Examples include Chou and Talalay 1984 and Prichard et al. 1993.

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769 g. Selection of resistant virus in vitro

770

771 The sponsor should assess the risk that variola virus might develop resistance to the candidate
772 drug. *Resistance*, as it is used herein, is a relative, not absolute, term. Because of the unique
773 hazards associated with variola virus, we recommend that the potential for emergence of
774 resistance be carefully explored using vaccinia virus and a variety of other nonvariola
775 orthopoxviruses. The evidence for applicability of these data to variola should be assessed and
776 presented to the FDA for further discussion. The sponsor should be prepared for how it might
777 assess the emergence of resistance if a smallpox emergency were to occur in which clinical use
778 of the candidate drug might be contemplated.

779

780 Two basic methods can be employed to isolate viruses in vitro that have reduced susceptibility to
781 the candidate drug. In the first, the virus is propagated for several passages at a fixed drug
782 concentration, using multiple cultures to test different concentrations. In the second, the virus is
783 passaged in the presence of increasing drug concentration starting at half the EC₅₀ value for the
784 parental virus. For both of these methods, virus production is monitored to detect the selection
785 of resistant virus. The former method is particularly useful for identifying drugs for which one
786 or two mutations can confer large shifts in susceptibility.

787

788 Selection in cell culture of virus resistant to the candidate drug can provide insight into whether
789 the genetic threshold for resistance development is high (three or more mutations) or low (one or
790 two mutations). The rate of appearance of resistant, mutant viruses depends on the rate of viral
791 replication, the number of virus genomes produced, and the fidelity of the viral replicative
792 machinery. Resistance is also a function of the IQ, as previously mentioned. Consideration of
793 these factors can help design tests to detect the appearance of virus resistant to high
794 concentrations of the drug in vitro. In cases when cell culture systems do not produce sufficient
795 virus titers and multiple mutations are required to develop resistance to high drug concentrations,
796 serial passage of the virus in the presence of increasing concentrations of the candidate drug
797 might lead to the isolation of resistant virus.

798

799 Well-characterized genotypic and phenotypic assays are important for detection of the
800 emergence of resistant virus during the development of candidate drugs. Sponsors can choose to
801 do phenotypic and genotypic characterization themselves or send samples to laboratories that are
802 registered under section 510 of the Act and use test systems with standard operating procedures.
803 In the former case, it is important that the investigational assay performance characteristics be
804 provided to the review division, and approved handling procedures for laboratory samples be
805 employed.²⁰

806

- 807 • **Genotypes** — Genotypic analysis of selected resistant viruses determines which
808 mutations might contribute to reduced susceptibility to the candidate drug. Identifying
809 resistance mutations can be useful in developing genotypic assays and analyzing their
810 ability to predict clinical outcomes and can provide data supporting the proposed
811 mechanism of action of the candidate drug. Frequently occurring mutations can be

²⁰ For definitions of assay validation, refer to the ICH guidance for industry *Q2(R1) Validation of Analytical Procedures: Text and Methodology* (<http://www.ich.org/cache/compo/276-254-1.html>) and the guidance for industry *Bioanalytical Method Validation*.

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812 identified by DNA sequence analysis of the relevant portions of the virus genome. We
813 recommend that the sponsor determine the complete coding sequence of the gene for the
814 target protein, and the pattern of mutations leading to resistance of a candidate drug, and
815 compare that pattern with the mutation pattern of other drugs in the same class. The
816 sponsor should report the details of the genotypic assays used along with the results for
817 controls used to standardize the assays. The report should include definition of the
818 lowest percentage for any one mutation present in a mixed population that the assay can
819 detect.

820

- 821 • **Phenotypes** — Phenotypic analysis determines if mutant viruses have reduced
822 susceptibility to the candidate drug. Once resistance mutations are identified, we
823 recommend evaluating their ability to confer phenotypic resistance in a recombinant virus
824 system (e.g., by using site-directed mutagenesis or polymerase chain reaction
825 amplification of relevant portions of the virus genome to introduce these mutations into a
826 standard laboratory genetic background). Construction of recombinants should use only
827 viral species and strains of suitably low risk to humans and should take place only under
828 adequate biosafety and biosecurity conditions (see section III.A., Selected Issues with
829 Distinctive Impact, and the Select Agent Rule). Then recombinant virus could be tested
830 for drug susceptibility in vitro. The shift in susceptibility, or fold resistant change, for a
831 clinical isolate is measured by determining the EC₅₀ values for both the isolate and a
832 reference virus under the same conditions and at the same time. The fold resistant change
833 is calculated as the EC₅₀ of isolate/EC₅₀ of reference strain. We recommend that a well-
834 characterized wild type laboratory strain grown in cell culture serve as a reference
835 standard.

836

837 The utility of a phenotypic assay depends on its sensitivity (i.e., its ability to measure
838 shifts in susceptibility (fold resistant changes) compared to reference strains or baseline
839 clinical isolates). Calculating the fold resistant change (EC₅₀ of isolate/EC₅₀ of reference
840 strain) makes comparisons between assays possible.

841

842 h. Cross-resistance

843

844 In the case of antiviral drugs targeting the same protein, cross-resistance (i.e., mutations leading
845 to reduced susceptibility to one drug resulting in decreased susceptibility to other drugs in the
846 same class) has been observed. Although no drugs are currently approved for the treatment of
847 variola infection, increased opportunities to study cross-resistance with other antivariola virus
848 drugs should emerge as more investigations take place in the field. Cross-resistance is not
849 necessarily reciprocal. For example, if virus X is resistant to drug A and shows cross-resistance
850 to drug B, virus Y, which is resistant to drug B, might still be susceptible to drug A. Cross-
851 resistance analysis can be important in the development of treatment strategies (i.e., establishing
852 the order in which drugs are given). The sponsor should evaluate the activity of the candidate
853 drug against viruses resistant to other approved drugs in the same class and the activity of
854 approved drugs against viruses resistant to the candidate drug.

855

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856 2. *Proposal for Monitoring Resistance Development*

857
858 Pre-IND and early IND discussions of candidate drugs for variola should consider studies that
859 will support the development of a protocol for investigational therapeutic use of the drug in the
860 event of a smallpox release. We recommend that these studies include evaluation of the in vitro
861 and in vivo antiviral activity using an appropriate range of poxviruses. With any such protocol,
862 the sponsor should include a plan to monitor the development of drug-resistant viruses if a
863 situation occurs in which individuals might be treated for smallpox. Animal studies with
864 nonvariola orthopoxviruses should make an important contribution to drug evaluation (see
865 section IV., Animal Models). Therefore, the sponsor should include proposals for the evaluation
866 of resistance in animal studies. We recommend that the resistance monitoring plan include a
867 description of the assays that will be used to monitor viral shedding and viral burden, methods of
868 sample collection and storage and for sample handling (frozen or ambient), and a description of
869 genotypic and phenotypic assays and the time points that will be analyzed (e.g., baseline, day 1,
870 additional specified on-treatment and post-treatment time points). The proposal should define
871 the parties responsible for each component.

872
873 We suggest that genotypic and phenotypic data be provided for baseline isolates from all patients
874 and endpoint isolates of patients who were virologic failures and discontinuations. Proposals for
875 resistance monitoring in animal studies should also give particular attention to changes from
876 baseline associated with clinical and laboratory manifestations of treatment failure. Furthermore,
877 we recommend that definitions of virologic failures and discontinuations be discussed with the
878 review division during protocol development. For example, in the more extensively studied
879 setting of therapy for HIV-1 infection, virologic failure definitions have been based on the course
880 of viral load measurements over time and on investigator evaluations of reasons for
881 discontinuation. We urge that information bases be developed to facilitate the assessment of the
882 relationship between clinical course and virologic findings in orthopoxvirus infections. Sponsors
883 are encouraged to consult with the review division on the preferred format for the submission of
884 resistance data.

885 3. *In Vivo Virology Study Reports (Clinical and/or Animal Studies)*

886
887
888 In addition to the nonclinical virology studies and reports discussed in the first part of the
889 Microbiology section, virology study reports from any clinical studies (and studies in animal
890 models where applicable) will be an important component of the overall evaluation of candidate
891 drugs as they reach later stages of development. We prefer that complete virology study reports
892 be extensive and include the raw and analyzed data as well as all the information necessary to
893 evaluate the procedures used to obtain those data. Virology study reports convey information on
894 in vivo antiviral activity of the candidate drug, development of resistance to the candidate drug in
895 treated patients and animal models, and cross-resistance with other drugs in the same drug class.
896 The format of a virology study report should be similar to that of a scientific publication and
897 typically should include the following sections: summary, introduction, materials and methods,
898 results, and discussion. The methods section should describe all the protocols employed and
899 include a description of the statistical analyses used. We recommend that sponsors also provide
900 copies of the publications of key references. For information regarding FDA materials on
901 reporting of virology study results, see the guidance for industry *Antiviral Product Development*

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902 — *Conducting and Submitting Virology Studies to the Agency*. Sponsors should discuss with the
903 FDA which aspects of these materials are applicable to orthopoxvirus studies and what
904 modifications may be warranted to address specific attributes of orthopoxvirus studies.
905

906 For some antiviral therapies in other settings, quantification of viral loads has been a good
907 measure of the clinical effectiveness of antiviral drugs and has provided insight into whether
908 these drugs have activity in vivo when the clinical benefit may not be apparent or may be
909 temporary because of the development of resistance. Such candidate drugs might prove useful
910 when studied in combination with other drugs. Development of methods for quantification of
911 viral burden or viral shedding, and evaluation of the relationship between these quantitative
912 measurements and clinical outcomes of disease and treatment, is encouraged for all
913 orthopoxvirus studies performed during the development of a candidate drug. However, it is
914 important to recognize that change in viral burden in the setting of variola infection is a
915 biomarker that may not fully capture the net treatment effect from the antiviral drug.²¹
916

917 As previously mentioned, we prefer that the sponsor provide a complete description of the
918 methodology and the quantitative assay performance characteristics, the specimen sources of
919 viruses (e.g., blood, plasma, defined lesion specimens), the storage and stability, and cell culture
920 procedures. We encourage efforts to collect specimens in sufficient quantities to allow reserve
921 amounts to be stored for possible re-evaluation by new or improved assays. Additionally, it is
922 important to examine the relationships between phenotypic and genotypic analyses and clinical
923 outcomes in any such studies, to assess the extent to which these assays may be predictive of the
924 utility of treating an individual with the candidate drug. We recommend using viral load and
925 genotypic and phenotypic assay analyses following the same criteria as described in previous
926 parts of the Microbiology section. Sponsors are encouraged to discuss their assays with the
927 review division. Genotypic analysis of baseline and failure isolates from patients failing to
928 respond to therapy or undergoing viral rebound can help identify mutations that contribute to
929 reduced susceptibility to the candidate drug. It is important that phenotypic analyses of baseline
930 and post-treatment isolates be completed to obtain information on the susceptibility of the
931 candidate drug and cross-resistance with other drugs. We recommend that genotypic and
932 phenotypic analysis of at least a subset of baseline isolates be performed to determine response
933 to therapy based on baseline genotype and baseline phenotypic drug susceptibilities. We
934 encourage sponsors to consult with the review division with respect to electronic submission of
935 resistance data.
936

G. Clinical Pharmacology

937 We recommend that sponsors study the relationship between in vitro and in vivo
938 pharmacokinetics and activity using animal models before the initiation of studies in humans
939 (see section IV., Animal Models). Sponsors also should consider developing models of drug
940 pharmacokinetics and pharmacodynamics to study drug dosage and drug regimens further, using
941 both in vitro systems and animals. Developing such models can help to expedite the selection of
942 an optimal drug dose regimen for human clinical studies.
943
944
945

²¹ See Fleming and DeMets 1996.

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946 Sponsors should provide human pharmacokinetic and pharmacodynamic information as soon as
947 it is available. If the candidate drug can be appropriately studied in any naturally occurring
948 human viral infection, these studies may provide relevant information about the relationship
949 between the drug's pharmacokinetics and a suitable pharmacodynamic endpoint. If no suitable
950 human pharmacodynamic endpoint is available, then any appropriate analyses of the relationship
951 between human pharmacokinetics and measurements of antiviral activity in animal models and
952 in vitro assays should be provided. Although the applicability to any potential occurrence of
953 human smallpox may not be directly assessable, the purpose of obtaining these data is to explore
954 the following issues:

- 955
- 956 • To demonstrate that the desired systemic drug concentration in humans actually can be
957 achieved after the anticipated dosage regimen is given
- 958
- 959 • To explore potential relationships between blood drug concentration and
960 pharmacodynamic response
- 961
- 962 • To select the appropriate dose
- 963
- 964 • To evaluate the relationship between drug exposure and subsequent development of viral
965 resistance (see section III.F.2., Proposal for Monitoring Resistance Development)
- 966

967 We recommend that sponsors perform exposure-response analyses where appropriate.²² These
968 analyses can help determine which drug exposure measures (e.g., area under the curve and
969 concentration at the end of the dosing interval) are relevant to a given outcome. For studies
970 conducted with animal models, the dose regimens used in animals to provide systemic exposure
971 comparable to humans may not be the same as the regimen for humans. Therefore, the sponsor
972 should consider what information it can generate and present to support an assumption that the
973 difference in dose regimens does not affect the drug's efficacy and/or safety. Examples of
974 studies that might contribute to this objective might include studies with infected animals across
975 a wide range of drug doses and dosing regimens showing whether the therapeutic effect is
976 regimen-sensitive, and pharmacokinetic-pharmacodynamic and treatment-outcome studies in
977 related human infections with comparable viral drug susceptibility.

978

979 A substantial percentage of the U.S. population older than 45 years has received immunization
980 with vaccinia, and it is possible that vaccine-induced residual immunity might confer prolonged
981 protective effect against variola infection, which might affect drug efficacy assessment. Vaccine
982 and drug interactions can be explored to a limited extent in animal models (see section IV.,
983 Animal Models). In addition, in data collection protocol plans for patients receiving drug
984 therapy if a smallpox emergency were to occur (see section V., Clinical Data), sponsors might
985 consider the possibility of obtaining samples to determine titers of antibodies against variola and
986 quantify antigen-specific T-cell responses. Such data should then be incorporated into exposure-
987 response analyses.

988

²² See the guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications*.

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989 The sponsor should fully characterize the metabolic profile (in vitro and in vivo) in humans, and
990 provide information comparing the plasma protein binding of the active drug components across
991 the range of expected concentrations in humans.

992
993 Recipients of the study drug may receive several medications concurrently. In vitro drug
994 metabolism studies can direct the investigation of potential human drug-drug interactions.²³ The
995 sponsor should provide drug interaction data; however, information regarding drug interactions
996 should not delay the submission of the IND.²⁴

997
998

999 IV. ANIMAL MODELS

1000

1001 When sponsors are developing drugs for potential use in treating or preventing smallpox, human
1002 data will be important in a number of ways, including (where appropriate) delineation of the
1003 drug's safety profile in healthy volunteers and observation of its safety and activity in other
1004 diseases (see section V., Clinical Data). No data from the use of the candidate drug in humans
1005 infected with variola virus will be available, unless an emergency involving bioterrorism or
1006 biowarfare or accidental release of the virus occurs. Under these unique development
1007 circumstances, data from animals, and further development and characterization of animal
1008 models, have the potential to provide much useful information in the evaluation of drugs to treat
1009 and prevent smallpox. Animal models can demonstrate drug activity in vivo (including the
1010 preliminary characterization of drug-drug or vaccine-drug interactions), provide exposure-
1011 response data to help estimate dosing regimens, and contribute to the design of a proposed
1012 protocol that can be available for investigational clinical use of a candidate drug if a smallpox
1013 release were to occur.

1014

1015 This section describes some types of animal studies that may be desirable to support
1016 investigational human use of a candidate drug, and provides a basis for discussion of what
1017 aggregate accumulation of data might lead to approval in the future. Because the availability of
1018 well-characterized animal models and the data supporting their use to predict human treatment
1019 responses is expected to change over time, sponsors are encouraged to consult with the review
1020 division early in the development process to review and discuss the status of existing models,
1021 prospects for studying newer models, and proposals for integrated use of animal and human
1022 studies. Sponsors should initiate such interactions at the pre-IND stage to discuss optimal use of
1023 resources in the initiation of development plans involving such animal studies.

1024

1025 A. Uses and Limitations of Different Orthopoxviruses

1026

1027 Currently, available data do not establish specific preferred, well-characterized animal models
1028 for smallpox, and no animal models have been shown to replicate or to predict human responses
1029 to therapy for smallpox. The ability of any animal model to predict human responses to therapy

²³ See the guidance for industry *Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro*.

²⁴ See the guidance for industry *In Vivo Drug Metabolism/Drug Interaction Studies — Study Design, Data Analysis, and Recommendations for Dosing and Labeling*.

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1030 for smallpox is difficult to assess, especially given the lack of any effective drugs that could be
1031 used to characterize models and to compare new drugs. The differences in both in vitro drug
1032 susceptibility and in vivo pathogenicity of different poxviruses for different hosts, and the
1033 immunomodulatory properties of the various orthopoxviruses themselves, add to the difficulty of
1034 extrapolating results from animal studies. However, using multiple nonvariola orthopoxviruses
1035 (see section III., Regulatory Approach Regarding Early Drug Development) in multiple models
1036 can provide useful information about the possibility of finding dose ranges that might offer
1037 benefit in human investigational use, particularly if a candidate drug is found to be highly active
1038 across a wide range of doses and treatment times relative to the disease course in animals.

1039
1040 To explore such possibilities, we recommend that compounds found to be active in vitro be
1041 studied in several animal models using multiple different orthopoxviruses initially, one of which
1042 should be vaccinia (animal models using vaccinia might provide information relevant to drug
1043 development for treatment of vaccine complications,²⁵ in addition to serving as part of the range
1044 of viruses used in exploration of potential applicability to smallpox treatment). The sponsor
1045 should discuss results from such studies with the FDA. These discussions also should include
1046 evaluation of the current status of various animal models at the time that drug development is
1047 ongoing. Based on data from initial studies and availability of suitably characterized models, the
1048 next step may be to assess the appropriateness of additional study in an animal model using
1049 variola (this step would require CDC collaboration; see section III.B., Interactions Among
1050 Industry, Academic, and Government Sponsors).

1051

B. Selection and Development of Animal Models

1052

1053
1054 We encourage using existing animal models to provide preliminary information on drug activity,
1055 as well as further development of models that resemble as closely as possible the
1056 pathophysiology and clinical manifestations of human smallpox. Detailed evaluation of the
1057 natural history of disease in the model and submission of data supporting such evaluation is
1058 important for selection of models and design of treatment studies. Because of the limitations of
1059 current understanding of human smallpox, sponsors should present the rationale for
1060 comparability of their proposed models based on available information about human smallpox,
1061 and also should present any information they can add regarding human smallpox (e.g., from
1062 written sources or pathology archives; see sections II., Background, and V., Clinical Data).

1063

1064 When considering the further development and characterization of animal models, it might be
1065 useful to study host and pathogen combinations including orthopoxviruses that are naturally
1066 virulent in the animal host species proposed as a model (e.g., ectromelia infection in mice or
1067 rabbitpox in rabbits) to explore the pathophysiological mechanism of toxicity in those models.
1068 Useful information also might arise from models that may have been more extensively
1069 developed using aggressive viral challenges to ensure reproducible serious disease
1070 manifestations, such as cowpox and vaccinia respiratory infection of mice, monkeypox
1071 respiratory exposure of nonhuman primates, and infection of immunocompromised animals
1072 (which also might have relevance for exploring the possible applicability of animal study results
1073 to human special populations likely to be considered for treatment). The sponsor should address
1074 the rationale for the route of administration in proposals for model development.

²⁵ See note 9, *supra*.

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1075
1076 Characterization and use of small animal models with a variety of nonvariola orthopoxviruses
1077 and challenge regimens can be especially important as an opportunity to explore the effects of a
1078 wide range of drug doses, dosing regimens, and treatment times relative to viral exposure and
1079 evolution of disease; differences in viral strain, inoculum, and route of exposure; and other
1080 variables. Results of such studies might help both in estimating the possible effect of these
1081 variations and in setting priorities for the use of resources (such as nonhuman primates and more
1082 pathogenic viruses) that are less readily available or more difficult to work with. We
1083 recommend that selection and assessment of nonhuman primate models receive careful
1084 consideration in later stages of animal investigations after initial results become available from
1085 small animal models. Assessing for similarity of pathologic mechanism and immune response
1086 (e.g., the mechanism of virus dissemination throughout the body, virus interactions with the
1087 immune system, and the pathologic process that leads to mortality) across different animal
1088 species using different orthopoxviruses and different doses and routes of virus inoculation might
1089 facilitate the determination of the pathophysiological mechanisms of various orthopoxviruses
1090 (Buller and Palumbo 1991; Smith and Kotwal 2002) and facilitate further development of animal
1091 models.

C. General Considerations in Study Design

1094
1095 The design of studies using animal models of orthopoxvirus infections should draw upon general
1096 principles of human clinical trial design as well as past experience with characterization of
1097 animal models and performance of nonclinical natural history and exposure-response studies.
1098 Protocols should include detailed clinical observations and laboratory studies in the animals,
1099 similar to clinical and laboratory monitoring that might be performed in human clinical trials in
1100 drug development programs for other types of serious illnesses. The purpose of such
1101 observations is to provide as much information as feasible about the relevance of the animal
1102 studies both for design of subsequent human clinical trials and for supplemental information to
1103 enhance the interpretability of sparse human clinical data.

1104
1105 In addition to the primary endpoints of mortality or major morbidity, sponsors are encouraged to
1106 identify as many secondary endpoints as possible that are associated with or predictive of
1107 outcome in the models under development. Other important considerations in refining animal
1108 studies include using a range of drug treatment doses, durations, and start times, including
1109 treatment started both before and after infection and symptomatology have become clinically
1110 established. Investigators should provide evidence that any drug target found is not unique to the
1111 virus or animal being studied, but is also applicable to variola and humans. Blinding of
1112 observers to treatment assignment may be of greater importance than in standard nonclinical
1113 studies.

D. Drug-Vaccine and Drug-Drug Interactions

1114
1115 We recommend that animal models be used to explore the potential effect the drug might have
1116 on vaccine efficacy, because vaccination would likely be a predominant part of the response to
1117 control any re-emergence of smallpox. Sponsors can propose and discuss the design of studies in
1118 which their candidate drug and an effective vaccine would be administered separately or together
1119
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1121 for pre-exposure or postexposure protection in a viral challenge animal model to compare the
1122 effects of separate and combination administration. Where appropriate, review of such study
1123 proposals and results can involve consultative collaboration between reviewers in different parts
1124 of the FDA responsible for review of the different products. Separate and combined effects of a
1125 candidate drug and passive immunotherapy should similarly be explored where appropriate.
1126 Any suspected drug-drug interactions that may have been noted in in vitro studies can be further
1127 studied in animal models as well. The sponsor should obtain viral load measurements and virus
1128 susceptibilities during animal studies to assess pharmacokinetic and pharmacodynamic
1129 relationships and correlates of outcome and to assist in the determination of the emergence of
1130 drug resistance. This information also can contribute to the assessment of combinations of
1131 antiviral drugs that may be beneficial if drug resistance develops with monotherapy. If there are
1132 suitable viral strains identified as resistant to other antiviral drugs or vaccines, the sponsor should
1133 also address the potential appropriateness of animal studies using such strains.

E. Sequence and Uses of Studies in Animal Models

1134
1135
1136
1137 The sponsor should discuss initial animal data and plans for further animal studies with the FDA
1138 to facilitate priority setting and identification of additional studies that can be useful and feasible.
1139 The initial focus should be on accumulation of sufficient in vivo evidence of activity, together
1140 with human safety data from early IND studies or from other uses of the candidate drug, to
1141 support the development of a protocol that will be available for investigational use if a smallpox
1142 emergency were to occur. These discussions can include consideration of studies that may be
1143 warranted to support risk-benefit assessment and dosing strategies. If preliminary data are
1144 sufficiently promising, the sponsor should present to the FDA for discussion an outline of issues
1145 to be considered in moving toward the possibility of submitting an application. In some
1146 instances, it may be preferable to pursue approval for other indications that can actually be
1147 studied in humans, with refinement of plans for investigational use if a smallpox emergency
1148 arises. In other instances, initial discussions might suggest that a sufficient aggregate body of
1149 evidence can be assembled to warrant consideration of approval under 21 CFR part 314, subpart
1150 I (the Animal Rule)²⁶ if well-characterized animal models predictive of human treatment
1151 responses can be developed. Consideration under 21 CFR part 314, subpart I is limited to drugs
1152 used to treat serious or life-threatening conditions that meet the following criteria:

- 1153
- 1154 • There is a reasonably well-understood pathophysiological mechanism of the toxicity of
1155 the substance and its prevention or substantial reduction by the product
1156
 - 1157 • The effect is demonstrated in more than one animal species expected to react with a
1158 response predictive for humans, unless the effect is demonstrated in a single animal
1159 species that represents a sufficiently well-characterized animal model for predicting the
1160 response in humans
1161
 - 1162 • The animal study endpoint is clearly related to the desired benefit in humans, generally
1163 the enhancement of survival or prevention of major morbidity
1164

²⁶ See note 10, supra.

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- 1165 • The data or information on the kinetics and pharmacodynamics of the product or other
1166 relevant data or information, in animals and humans, allows selection of an effective dose
1167 in humans
1168

1169 If a sponsor believes that a candidate drug can be developed toward potential approval using
1170 these criteria, the sponsor should present its rationale to the review division and should also
1171 provide supporting data and a proposed development approach, so that identification and design
1172 of an appropriate base of studies can be discussed prospectively in pre-IND or early IND
1173 interactions and can be suitably revised as initial results become available. Sponsors also should
1174 discuss with the FDA any anticipated difficulties in complying with the requirements of the good
1175 laboratory practices regulations (21 CFR part 58) where applicable, so that consultation can be
1176 provided on how to address these difficulties. If there is a situation in which animal studies are
1177 designed and agreed upon as the principal component of efficacy studies for approval, and if
1178 results of such studies are then found to be sufficient to support approval under Subpart I, then
1179 clinical trials are required to be conducted after such an approval if and when they are feasible as
1180 field trials (e.g., after an accidental or hostile exposure), and suitable protocols should be
1181 submitted for review during the drug development process. Safety evaluation is not covered
1182 under Subpart I but should be conducted under pre-existing requirements for development of
1183 new drugs and, therefore, should include appropriate human data.
1184
1185

V. CLINICAL DATA

1186
1187
1188 The approach to acquiring clinical data in drug development for smallpox depends on the unique
1189 characteristics of the situation and the intended uses of the drug, as well as on previously
1190 established principles of drug assessment. The sponsor should discuss with the FDA during pre-
1191 IND communications and early IND processes the prospects for obtaining initial human data and
1192 the plans for later stages of development if initial findings are sufficiently promising. We
1193 recommend that discussions address generation of initial human safety data, use of the drug for
1194 non-smallpox purposes, and in selected cases, development of plans for use of an investigational
1195 drug, such as under an IND or EUA as appropriate to the development stage and the extent of the
1196 emergency (see section III., Regulatory Approach Regarding Early Drug Development), if a
1197 smallpox event were to occur. We also recommend that the sponsor consider any additional
1198 support it can provide for such a clinical approach through examination of human data from
1199 existing records of the smallpox era that might contribute to elucidation of the poorly understood
1200 pathophysiology of human smallpox. In addition, the sponsor should present plans for study of
1201 drug-drug interactions (see section III.G., Clinical Pharmacology). Evaluation of the advisability
1202 of, and strategies for, developing clinical protocols typically should involve interdisciplinary
1203 assessment of a broad range of initial nonclinical data including in vitro and in vivo studies with
1204 nonvariola orthopoxviruses (see section III., Regulatory Approach Regarding Early Drug
1205 Development).
1206

1207 Expectations for human data to support investigational use of a drug in the event of a smallpox
1208 emergency might differ substantially according to the proposed circumstances of its use. For
1209 example, both the likelihood of benefit and the degree of acceptable risk might be different for
1210 treatment of established serious illness, for postexposure prophylaxis by persons who have been

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1211 exposed to smallpox (before they develop illness or at the first signs of incipient illness) in the
1212 hope of preventing or attenuating disease, or for prophylactic use before and throughout a period
1213 of exposure risk if vaccine is not available or is believed to be ineffective. Risk-benefit
1214 evaluations thus might vary substantially in each of these situations and should be discussed on a
1215 case-by-case basis.

1216
1217 If a candidate drug has not been previously studied in humans but has an acceptable risk profile
1218 based on nonclinical studies, the initial human protocol for pre-IND discussion and for review in
1219 the initial IND submission typically is a phase 1 safety study in healthy volunteers (see sections
1220 III.E., Nonclinical Toxicology, and III.G., Clinical Pharmacology). For a candidate drug with
1221 greater toxicity (based on nonclinical or any available clinical data), typical phase 1 studies in
1222 healthy volunteers may not be appropriate. If despite this greater toxicity a satisfactory risk-
1223 benefit balance can be estimated in an existing patient population that might benefit from the
1224 treatment (in contrast to healthy volunteers), it may be appropriate to perform early studies in
1225 that patient population. Because of the challenges of designing such a drug development
1226 program and the greater toxicity of drugs developed using this approach, sponsors are strongly
1227 encouraged to take advantage of the opportunity for early consultation with the FDA regarding
1228 the design of these studies. This consultation also can include discussion of whether a single
1229 IND can be appropriate for the intended range of studies or whether, in some instances, more
1230 than one IND may be more suitable. Selection of and supporting data for appropriate dosing,
1231 population, and timing of initial human studies can be important to address in later stages of pre-
1232 IND consultations. There also might be agents with promising activity data for which, because
1233 of greater toxicity or lack of alternative potential uses, it may not be possible to identify a
1234 population appropriate for clinical studies to characterize the pharmacokinetics (and also safety)
1235 of the candidate drug. In such circumstances, we suggest sponsors discuss potential approaches
1236 to drug development with the FDA.

1237
1238 Under some circumstances, development under the IND should include preparation of a clinical
1239 protocol that could be available for use if a bioterrorism-associated release of variola were to
1240 occur and lead to consideration of using the drug under an IND. Submission and review of such
1241 a protocol and its supporting information also can contribute to efficient consideration of a drug
1242 for EUA status if warranted. Protocol development for such situations should proceed on a case-
1243 by-case basis, taking into consideration such particulars as in vitro and animal activity data and
1244 safety data. We recommend that pre-IND discussions be held to address the type of information
1245 that should be obtained to justify development of a protocol. The sponsor should provide
1246 separate protocols to address the use of the candidate drug for treatment or for prophylaxis if
1247 initial discussion suggests these different uses might be appropriate on the basis of preliminary
1248 data.

1249
1250 Additional important information regarding the safety and efficacy of the candidate drug can
1251 come from studies investigating its use for other indications (see section III.C., Drugs with
1252 Previous or Concurrent Studies for Other Indications). If the initial data suggest that the drug
1253 can be useful for a nonsmallpox indication, in some instances it can be appropriate to pursue
1254 development for such an alternative indication and in the process assemble supporting
1255 information for investigational use in the event of a smallpox emergency. In addition to any
1256 other indications with previous or concomitant studies, we recommend that investigators seek

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1257 out other viral illnesses in humans in which the drug can be appropriately studied. Results of
1258 these studies might further contribute to evidence of drug safety and efficacy in the illness
1259 studied, and also simultaneously provide ancillary supporting information for smallpox studies.
1260 An example of this would be study of the drug for other poxvirus infections such as molluscum
1261 contagiosum, vaccinia, or monkeypox. It is particularly important to identify settings in which
1262 controlled trials can be conducted appropriately. The IND protocol previously mentioned for use
1263 in a smallpox outbreak can be further refined after gathering information from the use of a
1264 similar protocol during an outbreak caused by a related virus (see section III., Regulatory
1265 Approach Regarding Early Drug Development). We encourage early interaction with the review
1266 division to discuss the relevance of any such studies for potential use in variola.
1267

A. Safety Data

1268
1269
1270 The amount and type of safety data available at the time of the initial IND submission depends
1271 upon the candidate drug's development history. Candidate drugs that have been developed for
1272 other indications may have human safety data available, whereas other candidate drugs may have
1273 only nonclinical data available at the time of the initial IND submission. Safety data that have
1274 already been acquired during the development of a candidate drug for other indications can help
1275 to expedite the development process (see section III.C., Drugs with Previous or Concurrent
1276 Studies for Other Indications).
1277

1278 If the candidate drug does not have human safety data from studies in other diseases, the sponsor
1279 should propose plans for acquiring initial safety data for discussion through initial studies under
1280 the IND. Typically, the initial study can be a single-dose phase 1 study in healthy volunteers.
1281 The actual first study in humans will depend on what is known about the candidate drug from
1282 nonclinical studies and any available clinical data. An additional noteworthy consideration
1283 regarding the candidate drug's safety profile is that the side effect profile can depend in part
1284 upon the underlying clinical condition of the study subjects. For example, the side effect profile
1285 in patients who are acutely and severely ill may more accurately reflect that of a smallpox-
1286 infected individual than a study in healthy volunteers. Efforts to characterize the safety profile as
1287 it would be in the target population should be considered and discussed with the FDA.
1288

1289 If a candidate drug were to be used emergently in the setting of a smallpox event, it is likely that
1290 persons exposed to the drug also would be recent vaccinees or candidates for vaccination.
1291 Historically, there have been expert opinions that replication of vaccinia virus at the vaccination
1292 site may be important to development of optimal immunity, especially when vaccination is
1293 offered after smallpox exposure (Dixon 1962). Interference with the immunization response is a
1294 potentially serious concern, particularly if the candidate drug is under consideration for use to
1295 prevent disease rather than only for treating established illness. Therefore, it is important that the
1296 sponsor evaluate for the potential and degree of effect the drug may have on vaccine efficacy.
1297 We recommend that this potential interaction be addressed to the extent feasible in animal
1298 studies before IND submission, and the possibility of further investigations be discussed early in
1299 the IND process as appropriate. Depending on review of available information, in some
1300 instances such additional investigations can include a human immunogenicity study, similar to
1301 those used in evaluating new vaccines, to assess the effect of the antiviral on the immunologic

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1302 responses of vaccinated volunteers as well as on viral shedding, with collaborative and
1303 consultative review as appropriate from FDA staff in both CDER and CBER.

1304
1305 The amount and type of safety data preferred as support for a protocol for use in humans in an
1306 emergency setting depends on the risk-benefit profile of the candidate drug in the context of its
1307 potential uses (e.g., for prophylaxis or treatment). If smallpox were to develop in an
1308 unvaccinated individual, it might be appropriate to allow the use of a drug with significant
1309 toxicity if the drug appears promising for treatment of established variola major smallpox illness,
1310 which historically has a high fatality rate. However, the same level of toxicity might be
1311 inappropriate for postexposure prophylaxis in a vaccinated individual or an individual with no
1312 contraindications to vaccinia vaccination. Therefore, for clinical trial proposals, the use for
1313 which the drug is being considered, and the potential toxicity profile (see section III.E.,
1314 Nonclinical Toxicology) of the drug should be clearly described in the protocol.

1315
1316 Data collection during the clinical use of the drug is crucial, and can help to identify previously
1317 unrecognized safety issues relating to the investigational drug. We recommend including a case
1318 report form (CRF) as part of a protocol for a specific proposed use that facilitates the collection
1319 of safety data. The CRF should provide a tool for efficiently capturing complete safety data, and
1320 include specific provisions for ascertaining manifestations of any toxicity the drug may have
1321 demonstrated in vitro or in animal studies. The sponsor should provide separate CRFs to address
1322 different proposed uses of the candidate drug (e.g., use for treatment versus prophylaxis). We
1323 recommend that long-term follow-up also be included, as appropriate, to look for delayed
1324 outcomes such as genetic or reproductive toxicity. Some patients with variola infection could
1325 receive medications that interact with the candidate drug. Therefore, we also recommend that
1326 concomitant medication use be recorded on the CRF. An example of the type of data that should
1327 be collected includes, but is not limited to:

- 1328
- 1329 • Demographics (patient age, sex, race, and ethnicity)
 - 1330 • History of smallpox vaccination and description of whether there was an adequate take
1331 (skin response to the vaccine)
 - 1332 • Patient's past medical history
 - 1333 • Physical examinations
 - 1334 • Serum laboratory tests (e.g., hematology panel, chemistry profile, renal and liver function
1335 tests)
 - 1336 • Other therapies specific for smallpox that have been used before or concomitant with the
1337 study drug, and outcome
 - 1338 • General supportive therapies that can affect outcome (e.g., fluid replacement)
 - 1339 • Other medications taken concomitantly for unrelated conditions
 - 1340 • Adverse events (including severity, suspected drug relationship, treatment and response)
 - 1341 • Ultimate outcome (principal and subsidiary clinical and laboratory assessments)

1342
1343 Characterization of the metabolic profile for the candidate drug and the potential for drug
1344 interactions is important to the evaluation of the safety profile and management of potential risks
1345 associated with the candidate drug. Types of studies to address these issues are referenced in
1346 section III.G., Clinical Pharmacology.

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1348 As more safety data are acquired, the risk-benefit assessment associated with a specific candidate
1349 drug can change over time. Therefore, the sponsor should provide for ongoing reassessment
1350 through a system such as a data and safety monitoring board during the administration of a
1351 protocol. Collaborations between sponsors and public health agencies are encouraged to
1352 facilitate optimal ascertainment and use of clinical experiences if a protocol were to be used in an
1353 emergency situation (see section III.B., Interactions Among Industry, Academic, and
1354 Government Sponsors).

B. Efficacy Data

1356
1357
1358 During the planning stages of smallpox drug development, and during discussion and
1359 development of studies of in vitro and in vivo activity and of human safety, we recommend that
1360 sponsors also begin to consider how they will prepare to assess efficacy if a human smallpox
1361 outbreak were to occur. There are numerous reasons to design protocols for maximal capture of
1362 efficacy data as well as safety data, despite the constraints on study design and conduct that can
1363 be inherent in such a situation. Advance consideration of the range of possible actions in
1364 response to any smallpox event can facilitate both emergency readiness and effective data
1365 collection. Data collection will be important for the direct benefit of patients in an emergency
1366 situation to guide informed decisions about the continuation or modification of treatment
1367 interventions. If a candidate drug were used under IND in such a setting, collection of efficacy
1368 data also will be important to support revisions of ongoing protocols and informed development
1369 of future protocols, as well as to satisfy requirements for any contemplated application for
1370 approval. In addition, even if a drug goes through the development process to the point of
1371 approval under 21 CFR part 314, subpart I, Subpart I requires that clinical trials be performed if
1372 circumstances arise in which they would be feasible.

1373
1374 The scenarios in which health care professionals or public health officials might consider use of
1375 a candidate drug could range across a spectrum of possibilities including, but not limited to, the
1376 following:

- 1377
1378 • A high-mortality mass casualty situation in which vaccine is unavailable or believed
1379 ineffective
- 1380
1381 • A release with substantial initial mortality, after which vaccination and containment
1382 measures appear effective in limiting spread
- 1383
1384 • A limited release with few cases and/or a strain of unexpectedly lower virulence
- 1385
1386 • A situation in which treatment or prophylaxis may be started on the basis of a preliminary
1387 diagnosis that turns out to be inaccurate
- 1388

1389 It may be unclear, at the time of a decision to activate a prepared protocol, where on this
1390 spectrum an outbreak might eventually fall. Factors such as those listed could strongly affect not
1391 only the feasibility of systematic data collection and strength of any conclusions drawn from the
1392 data, but also the acceptability of risks (including drug toxicity or lack of efficacy) associated
1393 with the protocol, effect of perceived risks on drug acceptance by patients, availability of

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1394 supportive interventions or any other specific therapies under development at the time, and
1395 ability to implement other intervention and control measures such as quarantine and ring
1396 vaccination. We recommend that each protocol take into account the range of potential uses as
1397 the candidate drug begins to be studied.²⁷
1398

1399 We suggest that sponsors consider the possible designs of a protocol to be available for use in the
1400 event of an emergency, taking into account both the likely constraints on data collection and the
1401 limited interpretability of uncontrolled data. Additional considerations on the approach to
1402 clinical studies can be based on published FDA guidance.²⁸ We also suggest that the range of
1403 proposed drug uses, and the effect of each use on appropriate study design, be taken into
1404 account. Placebo-controlled trials are unlikely to find acceptance for treatment of established
1405 serious smallpox illness unless the candidate drug has safety concerns that are thought to be as
1406 important as the preliminary evidence suggesting potential benefit. However, mortality has
1407 varied so much among historical outbreaks that comparisons to historical data might well be
1408 misleading.
1409

1410 If a proposed drug is shown to have a human safety profile and animal activity results that
1411 suggest potential use for prophylaxis or pre-emptive treatment, we recommend that the study
1412 design take into account the primary role of vaccine. Even if there are preliminary animal data
1413 exploring drug and vaccine interactions, many uncertainties about the uses of drug and vaccine
1414 together in an outbreak situation can remain. For example, even a small inhibitory effect of drug
1415 on vaccinia virus might be cause for concern if a maximal immunologic stimulus were needed to
1416 provide protection by postexposure vaccination; on the other hand, if an outbreak were to occur
1417 with a viral strain against which the vaccine was suspected to protect poorly or not at all,
1418 adjunctive drug therapy might assume increased importance (although drug effects against such a
1419 strain also can be unpredictable). If other drugs have reached similar stages of development, the
1420 design of a candidate drug protocol should consider possible comparisons between treatments or
1421 combinations of treatments. Comparison of different dosing regimens also should be considered
1422 if supported by available risk-benefit information. The sponsor should include all of these issues
1423 in IND discussions if development reaches a stage at which development of a protocol for
1424 investigational clinical use or use under an EUA appears appropriate.
1425

1426 A key component in the collection of quality data can be a pre-existing protocol that can be
1427 rapidly activated in a post-terrorism event setting. We recommend that the protocol include a
1428 system for data collection that incorporates appropriate forms to facilitate thorough data

²⁷ For example, potential smallpox scenarios are most often discussed using the hypothesis of a massive epidemic that could rapidly overwhelm efforts at data collection. Even in this setting, availability of a protocol might be useful to remind health care professionals of dose adjustments and basic safety follow-up that can contribute directly to patient management. The other possible scenarios include the possibility of a few cases receiving intensive medical management, or an unexpectedly mild disease form in which occasional severe drug toxicities have a major effect on future attitudes toward treatment and control measures (the 1976 experience with H1N1 swine influenza vaccination provides a relevant example of the difficulty in predicting evolution of a potential public health threat). Availability of adequate data collection systems can be important to balanced assessment of ongoing and future interventions in the event of a smallpox outbreak anywhere on the spectrum of potential extent and severity.

²⁸ See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

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1429 collection. Some of the types of data that should be collected are outlined in section V.A., Safety
1430 Data. The design of data forms and data collection systems should take into account the range of
1431 circumstances in which they might be used, as previously outlined; the use of electronic rather
1432 than paper-based technologies might facilitate collection, quality assurance, and/or analysis of
1433 such data.

1434
1435 Study design should allow patients to receive fully situation-appropriate supportive care.
1436 Depending on the circumstances of an outbreak, normal medical care processes might generate
1437 many of the desired data elements.²⁹ CRF design should take into account the potential
1438 spectrum of supportive care and, where appropriate, provide for selected information to be
1439 transcribed after the fact from medical records if such provisions might facilitate the most
1440 efficient use of emergency resources.

1441
1442 We recommend that data collection plans provide for appropriate clinical samples that can be
1443 useful in evaluating activity of the candidate drug. These samples can include viral load
1444 measurements and virus susceptibilities, to assess for activity in vivo and for the emergence of
1445 drug resistance. In addition to characterizing the frequency and rapidity of resistance emergence,
1446 such information can contribute to identifying combinations of antiviral drugs that might be
1447 beneficial if viral resistance occurs using single drug treatment.

1448
1449 Ideally, protocols with strategies to maximize accuracy and completeness of variola drug
1450 efficacy data collection should be prepared in advance, as it would be important to have them
1451 available if a smallpox event were to occur, not only to assess the outcomes associated with use
1452 of an investigational drug but also to facilitate disease assessment, treatment, and monitoring.
1453 Clinical and public health expert authorities might recommend standardized patient evaluation
1454 and management strategies in an emergency situation. Therefore, sponsors should consider the
1455 possibilities for such recommendations and their implications for patient care as well as data
1456 collection. Advance discussions between potential sponsors and public health officials can be
1457 useful to design investigational protocols and methods for case ascertainment and enrollment for
1458 candidate drugs that might be used in such a situation (see section III.B., Interactions Among
1459 Industry, Academic, and Government Sponsors).

1460
1461 Because mortality and major morbidity are the greatest concerns when the possibility of a
1462 smallpox threat is considered, these outcomes will be the measurements most readily associated
1463 with direct demonstration of clinical benefit, and, therefore, should be the most appropriate
1464 endpoints in any study of a candidate treatment in the event of a smallpox outbreak. As with the

²⁹ In the past, supportive care for smallpox patients could be both intensive and extensive, including interventions related to nutrition, hydration, fluid and electrolyte balance, pain control, skin care, attempt to prevent or treat superinfections (both superficial and systemic), and psychosocial support. The potential effects of technological advances in these areas and others such as renal and respiratory support, plus possible attempts to counter the immune modifying properties of the virus, are unknown; experience with severe acute respiratory syndrome shows that supportive modalities continue to have a prominent role, together with outbreak control measures, even when health care workers are confronted with a contagious and potentially fatal disease with no specific treatment or vaccine available. If serious smallpox cases were to occur in a setting permitting intensive management, it is likely that frequent clinical and laboratory assessments would be documented in the hospital record, and drug study protocols and procedures should be designed to reflect appropriate provisions for collection and utilization of such information.

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1465 use of animal models, sponsors should try to identify clinical correlates that might be studied to
1466 assess whether they are associated with or predictive of clinical outcome. If alternative or
1467 surrogate endpoints can be identified that are reasonably likely to predict benefit, we recommend
1468 that the possibility of using such markers in clinical trials, if this proves feasible, be discussed
1469 with the review division (21 CFR 314.510). A range of secondary endpoints (e.g., skin lesion
1470 progression and scarring, measurements of viral burden, duration of illness, and specific organ
1471 system involvement) also may be appropriate to assess, depending on the circumstances in which
1472 studies might be carried out.³⁰

1473
1474 For some drugs, it may be appropriate to discuss preliminary information available from human
1475 infections with poxviruses from other genera such as molluscum contagiosum or orf, although
1476 applicability of this information to orthopoxviruses cannot be assumed. We recommend that
1477 studies involving treatment of human vaccinia complications,³¹ or any studies of other human
1478 orthopoxvirus infections such as monkeypox, also be considered as potentially contributory.
1479 Information available from studies for other indications also may contribute useful supplemental
1480 information to overall evaluations of the candidate drug (see section III.C., Drugs with Previous
1481 or Concurrent Studies for Other Indications).

1482

1483

1484 **VI. SUMMARY**

1485

1486 Development of drugs to treat or prevent infection by variola virus presents many challenges that
1487 are not common in standard drug development. Sponsors should pursue pre-IND and early IND
1488 interactions with the review division to discuss the role of nonvariola orthopoxviruses, animal
1489 models, and other aspects of the drug development plan. If drug development progresses to a
1490 stage warranting development of a clinical protocol that can be available if a smallpox
1491 emergency were to occur, the sponsor should plan for accurate and thorough data collection.

1492

³⁰ The relationship of an alternative or surrogate endpoint to the primary outcome of interest cannot be assumed a priori (see Fleming and DeMets 1996). One illustrative example is the known historical differences in mortality between variola major and variola minor despite clinically similar nature and extent of skin lesions. Therefore, defining such relationships should be an important element in data collection and analysis.

³¹ See note 9, supra.

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