

Animal Models — Essential Elements to Address Efficacy Under the Animal Rule

CONCEPT PAPER

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3 **Concept Paper**
4 **Animal Models — Essential Elements to Establish**
5 **Efficacy Under the Animal Rule**

6 **I. INTRODUCTION**
7

8 FDA's regulations concerning the approval of new drugs or biological products when human
9 efficacy studies are not ethical or feasible are known as "the Animal Rule" (21 CFR 314.600 for
10 drugs; CFR 601.90 for biologics). The Animal Rule states that in selected circumstances, when it
11 is unethical or infeasible to conduct human efficacy studies, the FDA may grant marketing
12 approval based on adequate and well-controlled animal studies when the results of those studies
13 establish that the drug or biological product is reasonably likely to produce clinical benefit in
14 humans. Demonstration of the product's safety in humans is still necessary (see section IV.G).
15

16 This concept paper is intended to identify the critical characteristics of an animal model that
17 should be addressed when efficacy of the product under development will be established under
18 the Animal Rule. It should also help determine whether an animal model can be considered
19 sufficiently well-characterized to propose that the effect demonstrated in a single animal species
20 can be used to support approval/licensure. We anticipate that this concept paper will be further
21 developed and issued as a draft guidance for public input.
22

23 The critical characteristics discussed in section III of the concept paper identify the elements to
24 be fully explored as an animal model is developed. All elements may not be achievable for each
25 etiologic agent¹ and intervention² being studied. Early and frequent interactions between the
26 FDA and the sponsor are recommended to discuss these elements and any issues encountered by
27 the sponsor. Current FDA requirements for establishing the safety of a product in humans
28 continue to apply. Although the following discussion touches on clinical safety, it is not meant to
29 address all requirements for assurance of human safety.
30

31 **II. ANIMAL RULE CONSIDERATIONS**
32

33 To develop an animal model to demonstrate efficacy, the sponsor should obtain information on
34 the natural history of the disease or condition in both humans and animals, on the etiologic agent,
35 and on the proposed intervention. Data from the human experience with the etiologic agent or
36 with the intervention, if available, may support applicability of the animal model.
37

38 The Animal Rule states that FDA can rely on the evidence from animal studies to provide
39 substantial evidence of effectiveness only when:

¹ For this document the terms *agent*, *threat agent*, or *etiologic agent* refer to chemical, biological, radiological or nuclear (CBRN) substances, as well as to any potentially lethal or permanently disabling toxic substance or organism in which efficacy studies in humans are not ethical or feasible. The term *challenge agent* refers to the CBRN material used in the animal studies.

² The terms *treatment* and *therapy* refer to any intervention that prevents or mitigates the toxicity of these etiologic agents.

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1. There is a reasonably well-understood pathophysiological mechanism of the toxicity of the (chemical, biological, radiological, or nuclear) substance and its prevention or substantial reduction by the product
2. The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model (meaning the model has been adequately evaluated for its responsiveness) for predicting the response in humans
3. The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity
4. The data or information on the (pharmaco) kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans allows selection of an effective dose in humans

(21 CFR 314.610(a)(1)-(4); 601.91(a)(1)-(4))

If these criteria are met, it is reasonable to expect the effectiveness of the product in animals to be a reliable indicator of its effectiveness in humans.

Although the Animal Rule allows approval based on a single animal species, if the animal model is sufficiently well-characterized, the usual expectation is that efficacy will be demonstrated in more than one species. If one animal species is to be considered sufficient, in general more than one efficacy study using that species should be conducted to demonstrate reproducibility of the results.

Data from animal studies to demonstrate dose-response and to support the dose selected for the animal efficacy studies are expected as is the case for traditional product development. Sponsors of products approved for other indications may be asked to provide additional nonclinical and/or clinical data to support approval/licensure of the proposed product for the indication under consideration.

If another regulatory pathway to approval (i.e., one using human data) is feasible, that pathway must be used (21 CFR 314.600; 601.90). Although the Animal Rule allows development of products that would otherwise not have any route to approval, the rule reflects the Agency's recognition that many treatments that appeared effective in animals have not proved to be effective in humans. Consequently, developing animal models that will yield efficacy results that can be expected to be predictive for humans is challenging. The animal studies should use the pertinent features of an adequate and well-controlled clinical study, such as a detailed protocol with randomization and adequate blinding and a statistical plan as described in 21 CFR 314.126.

Early and frequent interactions between the FDA and the sponsor are recommended to discuss the applicability of the Animal Rule and specific areas of concern, as well as to enable the review of, and comment on, protocols prior to study initiation. FDA may seek Advisory Committee

85 consultation before approval and/or early in the development process to discuss whether the
86 concept of using certain animal data to support efficacy is reasonable (67 FR 37992).

87
88 All studies subject to the Animal Rule must be carried out under the procedures and controls
89 outlined in the good laboratory practices (GLP) regulations (21 CFR 58). FDA recognizes that
90 conforming to GLP regulations in the conduct of studies on CBRN agents may present
91 challenges. Such issues and their possible impact on study results and conclusions, should be
92 discussed with the review division prior to conduct of the studies. In addition, the studies must
93 comply with the Animal Welfare Act (7 U.S.C. 2131). For certain infectious agents, sponsors
94 should adhere to the Select Agent Rule³ and comply with standards on the use of Biosafety
95 Level (BSL) laboratory facilities.⁴

96
97 The number of animals available for research, especially nonhuman primates (NHP), is finite.
98 The animal efficacy studies conducted under the Animal Rule will use a significant number of
99 animals. Sponsors should submit detailed protocols and provide for frequent monitoring
100 throughout the study period (see 21 CFR 312.23(a)(6)). The FDA strongly encourages sponsors
101 to submit a development plan and to communicate frequently with the Agency when developing
102 products under the Animal Rule. The protocols for the animal efficacy studies should be
103 discussed with the FDA, with sufficient time for FDA review and comment, prior to the study
104 being conducted.

105 **III. DISCUSSION OF ESSENTIAL DATA ELEMENTS OF AN ANIMAL MODEL**

106
107 This section provides further information on the Table, Essential Data Elements of Animal
108 Model, found in section IV.

109 **A. Characteristics of CBRN Agent that Influence the Disease or Condition**

110
111 Some characteristics of the specific chemical, biological, radiological, and/or nuclear (CBRN)
112 agent that influence the disease or condition under study include: the challenge agent, pathogenic
113 determinants, the route of exposure, and quantification of exposure.

114 *1. The Challenge Agent*

115
116
117 The challenge agent used in animal studies should be identical to the etiologic agent that
118 causes the human disease. The purity of the challenge preparation should be documented
119 when appropriate. If the challenge agent is different from the etiologic agent known to
120 cause human disease, the sponsor should provide justification for the use of this challenge
121 agent and explain why, when used in the proposed animal model, it should be considered
122 suitable for establishing effectiveness of the intervention in humans. For example, for an
123 animal efficacy study to support approval of a radiation countermeasure, a sponsor will
124 probably not be able to predict the actual radiation exposure that would follow a nuclear
125
126

³ See Select Agent Rule (42 CFR Parts 72 & 73) available at http://www.cdc.gov/od/sap/final_rule.htm.

⁴ See 5th Edition of Biosafety in Microbiological and Biomedical Laboratories (BMBL), available at <http://www.cdc.gov/od/ohs/biosfty/bmb15/bmb15toc.htm>.

127 detonation or the subsequent fallout. In such a case, the sponsor should provide a detailed
128 explanation of the appropriateness of the type of radiation and dose used in the study and
129 its relevance to the clinical situation.

130
131 2. *Pathogenic Determinants*
132

133 It should be demonstrated that the pathogenic determinants of disease in the animal
134 model are similar to those understood for humans. Pathogenic determinants can include
135 toxin production, target organs or enzyme systems, or type of radiation. For example,
136 although mice and guinea pigs are susceptible to *Bacillus anthracis*, the pathogenesis and
137 mechanism of toxicity are different from those in humans, so that these rodent species
138 may not be appropriate efficacy models for anthrax.⁵ Animal species that are not
139 susceptible to the agent, or do not demonstrate the endpoint of interest (i.e., potential for
140 mortality or major morbidity that might be reduced or prevented by sufficiently effective
141 interventions) are not suitable for the efficacy studies.
142

143 3. *Route of Exposure*
144

145 In general, the animal models developed should use a route of exposure to the challenge
146 agent that is the same as the anticipated human exposure route. This is especially
147 important for conditions for which the route of exposure is directly related to
148 pathogenesis. For example, human infection with *Yersinia pestis* through flea bite, the
149 intravenous (IV) route, or aerosol exposure results in the development of bubonic,
150 septicemic, or pneumonic plague, respectively. If a sponsor is proposing a route of
151 exposure to the etiologic agent in animals that is different from what is expected in
152 humans, scientific justification should be provided. The FDA strongly recommends that
153 if such an approach is being considered, it should be discussed with the FDA before the
154 start of the animal studies.
155

156 4. *Quantification of Exposure*
157

158 Reliable quantification and reproducibility of the challenge dose should be demonstrated.
159 If appropriate, the sponsor should describe the scalar relationship of the animal dose to
160 that anticipated in human disease. If large differences are observed, then potential
161 implications for interpretation of comparative pathogenesis, pathophysiology, and study
162 results should be discussed with the FDA. It is possible that there may be standardization
163 of the challenge dose in the future such that comparison studies can be conducted.
164

165 **B. Host Susceptibility and Response to Etiologic Agent**
166

167 The animal model chosen for development should be susceptible to the threat agent. FDA
168 recognizes there may be species differences. For example, an animal species being used to study
169 efficacy for a radiation countermeasure may require a different threshold of radiation exposure to
170 develop acute radiation syndrome, but the animal species may still be appropriate for study if the

⁵ Leffel, E.K. and Pitt, L.M., Anthrax. In *Biodefense: Research Methodology and Animal Models*. Swearingen, J.R. ed. Boca Raton, FL. CRC Press, 2006, 77-93.

171 resulting illness and course are similar in the animal species and humans. However, if this
172 threshold differs greatly from the human threshold, the suitability of the animal model may be
173 called into question. The factor that determines differences in susceptibility to the threat agent
174 should be described to the best extent possible (e.g., see the discussion of pyridostigmine and
175 soman in section E.2).

176
177 The response to the etiologic agent (resulting illness or injury) manifested by the animal species
178 exposed to the threat agent should be similar to the illness or injury seen in humans. For
179 example, mustard gas typically produces extensive blistering to exposed human skin. If the
180 animal species evaluated does not have blistering as a prominent feature of exposure to mustard
181 gas, it is unlikely that this animal model would be acceptable to the Agency. If the sponsor
182 believes that such a model is supportive to the study of their investigational drug, the model
183 should be discussed with the Agency and a justification should be provided.

184 185 **C. Natural History of Disease: Pathophysiologic Comparability**

186
187 The natural history of disease in animals and in humans should be characterized, compared, and
188 discussed with the Agency before the sponsor initiates intervention studies in animals. In some
189 instances, use of several different models in the same development plan can be considered.
190 Experimental parameters may need to be modified to create a condition that more closely mimics
191 the disease in humans. For example, variola virus causes human smallpox, and humans are the
192 only known natural host. Nonhuman primate animal models that have been studied using variola
193 virus as the challenge agent require a large inoculum, and often the IV route of administration is
194 used. FDA recommends that compounds found to be active in vitro against orthopoxviruses be
195 studied in several animal models using multiple different orthopoxviruses initially. Based on data
196 from initial studies and availability of suitably characterized models, the next step may be to
197 assess the appropriateness of additional study in an animal model using variola.⁶ Sponsors who
198 plan to use an animal model that involves exposure to a challenge agent that is different from the
199 known etiologic agent in humans should discuss this with the Agency along with their planned
200 protocols and any major differences in, or limitations of, the animal model.

201
202 When comparing the disease in animals with the disease in humans, sponsors should include
203 time to onset of disease/condition; time course of progression of disease; and manifestations, that
204 is, signs and symptoms (severity, progression, clinical and pathologic features, laboratory
205 parameters, the extent of organ involvement, morbidity, and outcome of disease). A single
206 animal model may not reflect the entire spectrum of human disease. The time to onset of disease,
207 progression of disease, and the manifestations/outcome can be influenced by many factors,
208 including concentration and type of etiologic agent, virulence or lethal potential of the etiologic
209 agent, route of exposure, and other host factors including immune status.

210

⁶ See FDA's draft guidance for industry *Smallpox (Variola) Infection: Developing Drugs for Treatment or Prevention*. Once finalized this guidance will represent the Agency's thinking on this topic. Also, we update guidances periodically. To make sure you have the most recent version of a guidance, check the appropriate (CDER or CBER) guidance Web site.

211 *1. Time to Onset of Disease/Condition*

212
213 The time to onset of disease/condition in animals should be reasonably similar to that in
214 humans. Factors such as strain of the infective microorganism, route of exposure, and/or
215 the level of exposure (i.e., concentration of the chemical, radiological, or other etiologic
216 agent(s)) may influence time to onset.

217
218 *2. Time Course of Progression of Disease/Condition*

219
220 The progression of the disease/condition in animals should be similar to the disease in
221 humans to allow for observation of the effects of intervention. Hamsters challenged with
222 anthrax have an extremely rapid disease progression. Thus, this species is not useful for
223 testing the efficacy of products for the treatment of anthrax. Furthermore, the clinical
224 course of disease in the animal may be more rapid than that in the human as a result of
225 experimental conditions, such as the route of exposure. For example, an IV route of
226 exposure may alter many characteristics including the time course of disease. The change
227 in the clinical course may result in making disease recognition, intervention, and
228 assessment of outcome more difficult. Showing the effect of an intervention may be
229 more challenging when the time between onset of disease and death is short.

230
231 *3. Manifestations (signs and symptoms)*

232
233 The disease manifestations, including clinical signs and their known time course,
234 laboratory parameters, histopathology, gross pathology, and the outcome (morbidity or
235 mortality), should be compared between untreated animals and untreated humans (e.g.,
236 historical information). Differences should be clearly noted and explained based on the
237 understanding of the pathophysiologic differences between the species, with due
238 acknowledgment of the limitations that may arise where this level of understanding is
239 limited. Because certain disease manifestations in humans (e.g., fever and shortness of
240 breath) may be difficult to discern in animals through clinical observation, a sponsor may
241 need to use more refined techniques, such as telemetry, to evaluate affected animals.
242 Animals in the natural history as well as the efficacy studies should be observed with
243 greater frequency over the entire course of the day than would be typical of most
244 nonclinical (pharmacology/toxicology) animal studies. This is especially true when the
245 primary endpoint is mortality and animals are being evaluated in the context of
246 prospectively-defined euthanasia criteria. With a mortality endpoint, animal welfare and
247 sample integrity need to be addressed. Sample integrity (e.g., cultures, histology) may be
248 compromised if not obtained just prior to or immediately after death or euthanasia. Study
249 results may be influenced by the criteria used. Study personnel should be blinded to
250 treatment and should follow observation and euthanasia criteria to minimize the
251 possibility of unnecessary suffering of moribund animals.⁷

252
253 **D. Trigger for Intervention**

254

⁷Refer to Animal Welfare Act (7 U.S.C. 2131).

255 Identification of the trigger for intervention in the animal studies is critical to defining the timing
256 of the intervention. Because animals cannot simulate the health-seeking behavior manifested by
257 humans, the trigger for intervention should be accurately defined in the animal model. If signs
258 and symptoms in the animal model closely resemble those in humans, these can serve as the
259 trigger for intervention when they are recognized in the individual animal. However, in the
260 absence of disease-defining manifestations, certain biological parameters should be used to
261 identify the time for initiation of treatment if they are known to be relevant to the diagnosis of
262 human disease and if a relationship to the likely diagnostic process and timing in human use of
263 the product can be shown. For example, presence of bacteremia has been used in some efficacy
264 studies in humans for initiation of intervention with antimicrobial drug products.⁸ The utility of
265 biological parameters/biomarkers should be demonstrated, including an analysis of the time
266 course of the appearance of the biomarkers in animals and the onset of disease and availability of
267 diagnostic information in humans.

268
269 When a biomarker is used as a trigger for intervention in animal studies, both the assay
270 methodology for the biomarker and its performance characteristics should be adequately
271 characterized. The materials and methods for the assay, as well as the raw data and results from
272 the actual testing, should be provided for FDA review. Summary data are not sufficient.
273 Sponsors are encouraged to initiate early discussion with the FDA regarding the utility of the
274 chosen triggers for intervention, particularly when the signs and symptoms of disease in the
275 animal differ from those in humans.

276 277 **E. Characterization of Medical Intervention**

278
279 Efficacy studies should reflect the expected clinical use and indication. A particular dosage form
280 may not be suitable for the proposed indication, so the product's dosage form should be
281 considered in planning the development of the product. For example, an oral dosage form is
282 preferred for postexposure prophylaxis for large populations, while an IV dosage form may be
283 necessary for seriously ill patients. If the product is already approved for human use, there may
284 be information on which to base the expected dose and regimen, but if there is no proven human
285 use, the animal result will need to be translated for human use, generally requiring some PK/PD
286 assessment. The following specific information should be submitted on the product and its
287 characteristics in humans and in animals.

288 289 *1. Product Class*

290
291 The product's therapeutic class should be identified. Information that is available about
292 other members of the class can be used to help identify potential animal models and
293 predict/evaluate safety and efficacy issues in the proposed animal model.

294 295 *2. Mechanism of Action*

296
⁸ Refer to package insert for Cubicin, NDA No. 021572, accessible at Drugs@FDA:
<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>.

297 Understanding the mechanism of action may help to identify specific safety and efficacy
298 issues in the proposed animal model and to identify what additional studies should be
299 performed. The animal studies to support the approval of pyridostigmine as a
300 pretreatment for exposure to the nerve agent soman highlight the importance of
301 understanding the mechanism of action of the drug and host factors in each animal
302 species evaluated. Pretreatment with pyridostigmine was shown to decrease the lethality
303 of soman in rhesus monkeys. However, pretreatment with pyridostigmine produced small
304 and inconsistent effects on mortality in studies using rats, mice, and rabbits. The effect of
305 pyridostigmine was masked in these latter species because of high serum levels of the
306 enzyme carboxylesterase, which eliminates soman from the blood and makes these
307 species naturally highly resistant to the nerve agent. Rhesus monkeys and humans have
308 little or no carboxylesterase. To elucidate the mechanism of pyridostigmine and bridge
309 the data to the human experience, a study was conducted in rats pretreated with
310 pyridostigmine as well as a carboxylesterase inhibitor prior to exposure to soman. In this
311 study, pyridostigmine demonstrated a mortality benefit in the rats similar to that seen in
312 the rhesus monkeys.

313 3. *In vitro Activity*

314 Understanding the in vitro activity of the product will supplement known information on
315 the mechanism of action and provide early screening information.

316 4. *Activity in Disease/Condition of Similar Pathophysiology*

317 If a candidate product is targeted at a common pathway in the pathophysiologic cascade,
318 information may be available on the candidate product's use for diseases that possess a
319 similar pathway. Information for a product approved for the treatment of neutropenia
320 secondary to chemotherapy in cancer patients may provide useful data to support
321 studying this product for the reduction of mortality in patients with neutropenia
322 secondary to acute radiation syndrome. This information in the related condition,
323 although not required, lends further support to the candidate product's efficacy for the
324 indication to be studied.

325 5. *Pharmacokinetics (PK) in Unaffected Animals/Humans*

326 PK studies should be done in unaffected animals and humans to characterize the PK
327 profile in each and to propose dosing regimens that provide comparable drug exposures
328 in the animals and humans. Early interaction with the FDA is critical to justify and
329 establish the appropriate dosing regimen for the pivotal animal studies.

330 6. *PK/PD (Pharmacokinetics/Pharmacodynamics) in Affected Animals/Humans*

331 PK information in affected animals should be compared to PK information obtained from
332 unaffected animals to establish whether the pathophysiology of a disease affects the PK
333 (e.g., changes in metabolic parameters may alter the pharmacokinetics). Measures of
334 treatment response (PD measurements such as clinical outcome or exploratory
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343 biomarkers) should be proposed for discussion based on both animal studies and any
344 available human information. If a candidate product has been used in humans for other
345 indications, PK/PD information for the alternate indications may be supportive. It should
346 be noted that the animal model may not predict specific disease/drug interactions. Such
347 interactions may not be observed until the disease is treated in humans, reinforcing the
348 critical need for postmarket clinical studies in the event of human disease.

349
350 7. *PK Interactions With Medical Products Likely to Be Used Concomitantly*

351
352 The absorption, distribution, metabolism, and excretion (ADME)^{9, 10} of a candidate
353 product should be studied and understood. The sponsor, with knowledge of the ADME
354 of the investigational product, should discuss with the FDA other medical products that
355 are likely to be co-administered based on the clinical scenario. Potential combinations
356 should be considered for interaction studies that may affect the PK of either product. If a
357 candidate drug is metabolized via the cytochrome P450 system, safety or efficacy of the
358 candidate drug could be compromised by cytochrome P450 inhibitors or inducers used
359 concomitantly. Such drug/drug interactions should be evaluated.

360
361 8. *Synergy or Antagonism of Medical Products Likely to Be Used in Combination*

362
363 Candidate products should be evaluated within the context that reflects anticipated
364 clinical use. The sponsor, in consultation with FDA, should consider other products that
365 are likely to be used and evaluate whether the activity of either product, when used in
366 combination, is affected (i.e., synergy or antagonism). Examples of potential interactions
367 include drug/drug interactions and drug/vaccine interactions. For example, it should be
368 known whether the use of an anthrax antitoxin monoclonal will have an effect on the
369 activity of the antimicrobials used for the treatment of disseminated anthrax disease. This
370 potential interaction should therefore be evaluated in the animal model. This information
371 is especially important when the therapeutic intervention is expected to include more than
372 one medical product.

373
374 **F. Design Considerations for Efficacy Studies**

375
376 Assessment of efficacy in animals should be as robust as possible. Adequate and well-controlled
377 animal efficacy studies, with endpoints that demonstrate substantial clinical benefit, generally the
378 enhancement of survival or prevention of major morbidity, are expected. The time course of
379 observation should be optimized to assess the true treatment effect. At a minimum, placebo-
380 controlled animal studies should be performed. If a product approved for the same indication is
381 available, it should be used as an active comparator in addition to the investigational drug and
382 placebo arms. The study should also be blinded to the extent feasible; any situation in which
383 study staff might become aware of treatment assignments should be discussed in advance in view

⁹ See *guidance for industry: Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro*.

¹⁰ See *guidance for industry: Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling*.

384 of the potential for major effects on study interpretability. Animals of both sexes should be
385 included. FDA recognizes that there are significant supply constraints on using mature or older
386 animals of certain animal species. The issue of the age and the immune status of the animals used
387 in efficacy studies as compared to the intended human population should be addressed by the
388 sponsor, when relevant. Study procedures should be uniformly applied to all study groups, and
389 potential bias should be reduced by prespecifying the criteria for euthanasia and discussing their
390 potential effects on interpretation of results.

391
392 Studies should be designed to mimic the clinical scenario and achieve meaningful outcomes
393 comparable to the endpoints desired in humans. In some instances, supportive care should be
394 administered to the animals as part of the study design. In such cases, demonstration of a
395 product's benefit over supportive care (i.e., supportive care plus investigational drug arm should
396 be demonstrated to be superior to the supportive care plus placebo arm) will be required for
397 approval or licensure. Early discussion between the sponsor and the review division regarding
398 the type, timing, and choice of supportive care to be administered is highly recommended.

399
400 In addition to the design characteristics discussed above, the following parameters should be
401 addressed in the study protocols. We recommend that study protocols be prepared and submitted
402 to FDA with enough time for FDA to review the protocols and provide feedback to the sponsor
403 before the animal studies are initiated. The sponsor can submit these protocols with a request for
404 review under the Special Protocol Assessment (SPA) provisions.¹¹

405
406 *1. Endpoints*

407
408 The product studied in the animal model should demonstrate a beneficial effect analogous
409 to the intended outcome in humans. Primary study endpoints, which should be
410 specifically discussed with the review division, generally are the enhancement of survival
411 or prevention of major morbidity. The dose response for these endpoints should be
412 explored fully and established. Although secondary endpoints can provide useful
413 information about the animal model and the activity of the product as studied in the
414 animal model, ordinarily, only primary endpoints can serve as the basis of approval.

415
416 *2. Timing of intervention*

417
418 The time to initiate intervention should support the specific indication sought for a
419 product. If the intent is to develop the product for a treatment indication, intervention
420 before disease is established may overestimate the effect that is likely to be seen in
421 humans and may indeed show an effect when none would be seen in humans. A
422 reasonable understanding of the disease course and a trigger for intervention defined by
423 the natural history studies will be needed to design the animal efficacy studies for a
424 treatment indication; it is important to establish the relationship of time after exposure to
425 effectiveness. With this information, the timing for intervention can be defined, thus
426 differentiating postexposure prophylaxis from treatment. A product to be used for

¹¹ See guidance for industry: *Special Protocol Assessment*.

427 postexposure prophylaxis should be administered within a reasonable window after
428 exposure to the threat agent, but before onset of disease, with a time relationship that is
429 adequately justified with respect to administration of the product to humans. Proposals
430 for pre-exposure prophylaxis should be described and discussed in advance on a case-by-
431 case basis.

432 433 3. *Route of Administration* 434

435 The route of administration should reflect the indication being sought and the anticipated
436 clinical scenario, such as mass casualty. For example, if a large number of people were
437 exposed to anthrax, an oral dosage form would be preferred over an injectable for
438 postexposure prophylaxis. It may be important to study multiple routes.

439 440 4. *Dosing Regimen* 441

442 The determination of the dosing regimen relies on sufficient PK and PD data or other
443 relevant product information in animals and/or humans. The goals are to (a) determine a
444 regimen in animals that is safe and effective for the indication studied; (b) determine the
445 corresponding exposure in animals that is yielded by that dosing regimen; and (c)
446 calculate a dosing regimen in humans that will give an equivalent exposure to that seen in
447 the animal. This will enable initial extrapolation from a dosing regimen found to be
448 efficacious in the animal model to one expected to produce a similar benefit in humans,
449 assuming similar exposure–response relationships. Different dosing regimens in animals
450 and humans may be needed to provide equivalent exposure to the product and thus should
451 be discussed with the Agency. However, for vaccines, the goal should be to develop
452 regimens that are safe and that provide an adequate protective immune response. For
453 vaccines, these goals are typically achieved without extrapolation based on PK or relative
454 PD, as the full human dose should be used in the dosing strategy when feasible. A shorter
455 dosing interval between inoculations can be incorporated into the nonclinical study
456 design as compared to the proposed clinical dosing interval. The dosing interval that is
457 selected for the nonclinical toxicity study should maximize the immune response.¹²
458

459 In summary, the indication being sought drives the study design. The desired outcomes of the
460 study (i.e., product’s effect) should be determined early and carefully factored into the study
461 design to ensure that the study meets both scientific and regulatory objectives.

462 463 **G. Available Safety Information** 464

465 The body of available human safety data, including data from the product’s evaluation and use in
466 other indications, is a critical component of any product’s development plan and influences the
467 risk/benefit considerations. FDA may ask for additional human safety trials to complete the

¹² See WHO Technical Report Series, No. 927, 2005, Annex 1, WHO guidelines on nonclinical evaluation of vaccines, World Health Organization, available at http://www.who.int/biologicals/publications/trs/areas/vaccines/nonclinical_evaluation/en/.

468 safety profile of the product. Healthy human volunteers should be enlisted when there is no
469 known significant risk in the administration of the product. If the risk is significant, study in a
470 patient population with a similar disease should be considered if a population can be identified
471 for which the risk/benefit balance of the study is appropriate. Sponsors should propose selection
472 and justification of the appropriate study population in advance for FDA review and feedback.
473

474 The size of the required clinical safety database depends on many factors. Existing safety data
475 would generally be satisfactory for products that are already marketed for another indication
476 and known to have an acceptable safety profile in the populations that would receive the product
477 for the new indication. When the new indication requires a longer duration of use or higher
478 dose, additional safety data must be obtained (21 CFR 314.50(d)(5)(v)). The type of indication
479 being sought is another factor. For example, a product that will be used as prophylaxis in large
480 numbers of people should have a larger safety database than a product developed for treatment of
481 patients who are symptomatic with a disease of known high mortality. In prophylaxis scenarios,
482 it is likely that some proportion of humans will receive the product without having been exposed
483 to the threat agent. An adequate safety database is needed to reduce the risk of serious harm in a
484 healthy population.

485
486 The timing and design of clinical safety studies should be coordinated with exploration of the
487 efficacious dose and regimen in animals to plan adequate studies to characterize the safety of the
488 intended human dose, formulation, route of administration, and duration of use.
489 Preclinical safety information should guide the choice of additional safety assessments of interest
490 in the human safety studies. This is particularly useful for products with no prior human safety
491 data, or when the anticipated human dosing regimen has not been previously studied or
492 approved.

493
494 FDA may request that products with significant toxicity show greater evidence of efficacy. For
495 example, the use of an extremely nephrotoxic product, whose administration would likely lead to
496 the requirement for chronic dialysis, could potentially be justified if animal models showed very
497 robust evidence of effectiveness in a disease with significant mortality and no approved
498 treatments.

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IV. ESSENTIAL DATA ELEMENTS OF AN ANIMAL MODEL

The essential data elements for the development and evaluation of animal models are listed in the table below. These elements serve as a guide. They may be modified or revised as new scientific information relevant to the condition under study becomes available. Early and frequent interactions between the sponsor and FDA are critical for feedback on proposals and appropriate discussion of uncertainties and the risk/benefit balance.

Table: Essential Data Elements of an Animal Model

Data Elements	Animal(s)	Human
A. Characteristics of the CBRN Agent that Influence the Disease or Condition		
1. The challenge agent		
2. Pathogenic determinants		
3. Route of exposure		
4. Quantification of exposure		
B. Host Susceptibility and Response to Etiologic Agent		
C. Natural History of Disease: Pathophysiologic Comparability		
1. Time to onset of disease/condition		
2. Time course of progression of disease/condition		
3. Manifestations (signs and symptoms)		
D. Trigger for Intervention		
E. Characterization of the Medical Intervention		
1. Product class		
2. Mechanism of action		
3. In vitro activity		
4. Activity in disease/condition of similar pathophysiology		
5. PK in unaffected animals/humans		
6. PK/PD in affected animals/humans		
7. PK interactions with medical products likely to be used concomitantly		
8. Synergy or antagonism of medical products likely to be used in combination		
F. Design Considerations for Efficacy Studies		
1. Endpoints		
2. Timing of intervention		
3. Route of administration		
4. Dosing regimen		
G. Available Safety Information		

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ATTACHMENT: ACRONYMS AND ABBREVIATIONS

511		
512		
513	ADME	Absorption, distribution, metabolism, and excretion
514		
515	BSL	Biosafety Level
516		
517	CBER	Center for Biologics Evaluation and Research
518		
519	CBRN	Chemical, Biological, Radiological, or Nuclear
520		
521	CDER	Center for Drug Evaluation and Research
522		
523	FDA	Food and Drug Administration
524		
525	GLP	Good Laboratory Practices
526		
527	IV	Intravenous
528		
529	NHP	Nonhuman Primate
530		
531	PD	Pharmacodynamics
532		
533	PK	Pharmacokinetics
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535	SPA	Special Protocol Assessment

Contains Nonbinding Recommendations

Draft — Not for Implementation

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REFERENCES

21 CFR, Part 58. Good Laboratory Practice for Nonclinical Laboratory Studies (accessible at <http://www.nal.usda.gov/awic/legislat/21cfr97.htm>).

42 CFR, Parts 72 and 73. “Possession, Use and Transfer of Select Agents and Toxins,” (CDC) *Federal Register* 70 (March 18, 2005): 13293 – 13325. (accessible at http://www.cdc.gov/od/sap/final_rule.htm)

FDA, “New Drug and Biological Drug Products; Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical and Feasible,” *Federal Register* 67 (31 May 2002): 37988-37998.

FDA, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, guidance for industry, *Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling*.

FDA, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, guidance for industry, *Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies in Vitro*.

FDA, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, guidance for industry, *Special Protocol Assessment*.

FDA, Center for Drug Evaluation and Research, draft guidance for industry, *Smallpox (Variola) Infection: Developing Drugs for Treatment or Prevention*.

Leffel, E.K. and Pih, L.M. (2006), Anthrax. In Swearingen, J.R. (Ed.). *Biodefense: Research Methodology and Animal Models*. (pp. 77-93). Boca Raton, FL: CRC Press.

USDA Animal Welfare Act, Public Law 89-544, as amended, 7 U.S.C. 2131 *et seq.* (accessible at <http://www.nal.usda.gov/awic/legislat/awa.htm>).

U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Institute of Health, *Biosafety in Microbiological and Biomedical Laboratories (BMBL)*, 5th Edition, (Washington, DC: U.S. Government Printing Office, 2007): (accessible at <http://www.cdc.gov/od/ohs/biosfty/bmb15/bmb15toc.htm>).

WHO guidelines on nonclinical evaluation of vaccines, Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 927, Annex 1) (accessible at http://www.who.int/biologicals/publications/trs/areas/vaccines/nonclinical_evaluation/en/).