
Respiratory Syncytial Virus Infection: Developing Antiviral Drugs for Prophylaxis and Treatment Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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

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

**October 2017
Clinical/Antimicrobial**

Respiratory Syncytial Virus Infection: Developing Antiviral Drugs for Prophylaxis and Treatment Guidance for Industry

Additional copies are available from:

*Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002*

*Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>*

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

**October 2017
Clinical/Antimicrobial**

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND	2
III.	DEVELOPMENT PROGRAM.....	3
A.	General Drug Development Considerations	3
	<i>1. Nonclinical Virology Development Considerations</i>	<i>4</i>
	a. Mechanism of Action	4
	b. Antiviral activity in cell culture.....	4
	c. Cytotoxicity and mitochondrial toxicity	4
	d. Combination antiviral activity	5
	e. Activity in animal models.....	5
	f. Resistance and cross-resistance.....	5
	<i>2. General Considerations for Phase 1 and Phase 2 Development</i>	<i>5</i>
	a. Phase 1a/First-in-human trials	6
	b. Phase 2 trials.....	6
	c. Data needed to proceed to phase 3	9
	<i>3. Dose Selection</i>	<i>9</i>
	<i>4. Drug Development Population.....</i>	<i>9</i>
	<i>5. Efficacy Considerations</i>	<i>10</i>
	<i>6. Safety Considerations.....</i>	<i>10</i>
B.	Phase 3 Efficacy Trial Considerations.....	11
	<i>1. Trial Design.....</i>	<i>11</i>
	a. Treatment of RSV LRTI.....	11
	b. Prophylaxis for severe RSV LRTI	12
	<i>2. Trial Population</i>	<i>12</i>
	<i>3. Entry Criteria</i>	<i>12</i>
	<i>4. Randomization, Stratification, and Blinding</i>	<i>13</i>
	<i>5. Other Populations</i>	<i>13</i>
	<i>6. Use of Active Comparators</i>	<i>14</i>
	<i>7. Efficacy Endpoints.....</i>	<i>14</i>
	a. Treatment.....	14
	b. Prophylaxis.....	16
	<i>8. Trial Procedures and Timing of Assessments</i>	<i>16</i>
	<i>9. Statistical Considerations.....</i>	<i>17</i>
	<i>10. Accelerated Approval (Subpart H) Considerations</i>	<i>17</i>
	<i>11. Risk-Benefit Considerations</i>	<i>18</i>
C.	Other Considerations	18
	<i>1. Relevant Nonclinical Safety Considerations</i>	<i>18</i>
	<i>2. PK/PD Considerations.....</i>	<i>19</i>
	a. PK measurement.....	19
	b. PD measurement.....	19
	c. Modeling considerations.....	20
	<i>3. Clinical Virology Considerations.....</i>	<i>20</i>
	a. RSV diagnostic assays for screening and events	20
	b. Resistance analysis	20
	<i>4. Regulatory Considerations.....</i>	<i>21</i>

REFERENCES..... 22

Contains Nonbinding Recommendations

Draft — Not for Implementation

33 ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of*
34 *Control Group and Related Issues in Clinical Trials*, respectively.⁴

35
36 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
37 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
38 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
39 the word *should* in Agency guidances means that something is suggested or recommended, but
40 not required.

41

42

II. BACKGROUND

44

45 RSV has two subtypes, RSV A and RSV B, that may circulate concurrently, and both have been
46 associated with disease. RSV infections range from asymptomatic to severe and life-threatening
47 lower respiratory tract infection (LRTI). LRTI in infants and young children most commonly
48 presents as bronchiolitis, which is characterized by increased mucus production, bronchospasm,
49 and acute inflammation, edema, and necrosis of epithelial cells lining small airways
50 (Viswanathan, King, et al. 2003). Other manifestations of LRTI in all age groups include
51 pneumonia, as well as exacerbations of chronic lung disease such as asthma and chronic
52 obstructive pulmonary disease. All types of RSV LRTI are associated with a spectrum of illness
53 ranging from mild cough and wheezing to fulminant respiratory failure. Populations at high risk
54 for more severe disease include term infants younger than 6 months of age, preterm infants, older
55 adults, patients with chronic lung or cardiac disease, and immunocompromised patients,
56 particularly those who have undergone hematopoietic stem cell transplantation (HSCT).

57

58 Currently, there are no established definitions for disease severity in pediatric patients with RSV
59 bronchiolitis. Therefore, the following definitions are used for the purpose of this guidance.
60 Severe RSV bronchiolitis is characterized by signs and symptoms of LRTI (e.g., tachypnea,
61 nasal flaring, and hypoxemia) with obvious respiratory distress, accompanied by poor feeding.
62 Moderate RSV bronchiolitis is defined as symptomatic respiratory illness without overt
63 respiratory distress, which often requires additional caregiver activities (e.g., frequent nasal
64 suctioning, repositioning, changes to feeding schedule) to sustain normal daily activities.
65 Moderate disease is more likely to result in a visit to a health care provider than mild disease,
66 which is defined as symptomatic respiratory illness with limited disruption of daily activities
67 (e.g., feeding, sleeping).

68

69 One challenge in the development of drugs for treatment and prophylaxis of RSV disease in
70 pediatric patients is a lack of full understanding of the pathogenesis of RSV infection. The role
71 of RSV cytotoxicity versus that of the host immune response in RSV disease remains uncertain.
72 Therefore, optimal approaches for treatment and prophylaxis of RSV disease have not been
73 established.

74

⁴ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA
Drugs guidance web page at
<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

Contains Nonbinding Recommendations

Draft — Not for Implementation

75 Currently, two drugs are FDA approved for prevention or treatment of RSV LRTI in pediatric
76 patients: palivizumab for prophylaxis and aerosolized ribavirin for treatment. In 1996,
77 palivizumab (a monoclonal antibody that targets the RSV F protein) was approved for the
78 following indication:

79
80 *prevention of serious lower respiratory tract disease caused by RSV in children at high risk*
81 *of RSV disease.*
82

83 Palivizumab was initially approval based on the results of a double-blind placebo controlled
84 study of 1,502 patients 24 months of age or younger with bronchopulmonary dysplasia (BPD) or
85 infants with premature birth (35 weeks or less gestation) who were 6 months of age or younger at
86 study entry. In this study, reductions of RSV hospitalization were observed for both of these
87 high-risk groups. Among patients with BPD, 7.9% (39/496) of palivizumab patients were
88 hospitalized compared to 12.8% (34/266) of placebo patients. Among premature infants without
89 BPD, 1.8% (19/234) of palivizumab-treated pediatric patients were hospitalized compared to
90 8.1% (9/506) of pediatric patients who received placebo. The use of palivizumab in the United
91 States is largely guided by a clinical practice guideline published by the American Academy of
92 Pediatrics (AAP) in 2014 and the AAP's 2014 guidance for palivizumab prophylaxis (Ralston,
93 Lieberthal, et al. 2014; AAP Committee on Infectious Diseases and Bronchiolitis Guidelines
94 Committee 2014). In 1985, FDA approved aerosolized ribavirin for treatment of hospitalized
95 infants and young children with severe LRTIs caused by RSV. The approval was based on two
96 small placebo-controlled studies in nonmechanically ventilated infants; the results of which were
97 subsequently published (Hall, McBride, et al. 1983; Taber, Knight, et al. 1983). On day 3 of
98 treatment, both studies showed statistically significant differences in mean symptom scores.
99 However, a subsequent meta-analysis by Randolph and Wang (1996) cited many methodological
100 errors in the studies that had supported aerosolized ribavirin's clinical benefits, and the authors
101 concluded that treatment with aerosolized ribavirin failed to impart any clinically significant
102 benefits. At present, health care providers' perceptions of limited clinical benefits, in addition to
103 concerns for mutagenicity, carcinogenicity, and teratogenicity with ribavirin, has resulted in
104 infrequent use of ribavirin for the treatment of RSV-associated illness. Currently, ribavirin is
105 used mainly when the outcome of an RSV LRTI could be fatal, such as in RSV infections in
106 bone marrow transplant patients.

107
108

III. DEVELOPMENT PROGRAM

109

A. General Drug Development Considerations

110
111

112
113 Sponsors considering development of antiviral drugs for the treatment of RSV infection are
114 encouraged to communicate with FDA through the pre-Investigational New Drug application
115 (pre-IND) consultation program.⁵ Pre-IND consultation with FDA is optional; although, it may
116 be particularly helpful for sponsors with limited experience in the IND process or to obtain FDA

⁵ See the FDA web page Getting Started with the Division of Antiviral Products Pre-IND Process at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/ucm077546.htm>.

Contains Nonbinding Recommendations

Draft — Not for Implementation

117 advice in the development of drug products with unique considerations based on mechanistic
118 action or novel treatment approaches or the use of novel biomarkers.

119
120 The following sections address nonclinical virology, phase 1 and 2 trials, target population, and
121 overall efficacy and safety considerations.

122 123 *1. Nonclinical Virology Development Considerations*

124
125 The antiviral activity of an investigational drug should be determined using a cell culture model
126 of infection before submission of an initial investigational new drug application (IND).
127 Additional recommendations for antiviral drug development can be found in the guidance for
128 industry *Antiviral Product Development — Conducting and Submitting Virology Studies to the*
129 *Agency*.

130 131 *a. Mechanism of Action*

132
133 Ideally, sponsors should determine the mechanism by which a drug inhibits RSV. Mechanism of
134 action investigations should include an assessment of the drug's specificity for the target and
135 should employ appropriate controls, such as uninfected cells, cells infected with viruses other
136 than RSV, and/or cells infected with drug-resistant RSV variants. Biochemical or subcellular
137 quantitative assays supporting the mechanism of action should report the 50 and 90 percent
138 inhibitory concentrations (IC₅₀ and IC₉₀ values).

139 140 *b. Antiviral activity in cell culture*

141
142 The antiviral activity of a new drug should be characterized using a cell culture model of RSV
143 infection to demonstrate activity and identify a target concentration for the initial clinical trials.
144 Antiviral activity studies should include assessments against a broad range of RSV A and RSV B
145 laboratory and clinical isolates, preferably representing multiple RSV seasons and different
146 geographic regions. The effective concentrations at which virus replication is inhibited by 50
147 and 90 percent (EC₅₀ and EC₉₀ values) should be determined using a quantitative assay. Also,
148 the sponsor should determine the effect of serum and mucosal proteins on antiviral activity and
149 calculate a protein binding-adjusted EC₅₀ value. Sponsors developing monoclonal antibodies
150 should evaluate the potential for antibody dependent enhancement of infection.

151 152 *c. Cytotoxicity and mitochondrial toxicity*

153
154 The cytotoxicity evaluation should make use of the same cells and culture conditions (e.g., drug
155 exposure durations) used for determining antiviral activity. A 50 percent cytotoxic concentration
156 (CC₅₀) and a therapeutic index (i.e., CC₅₀/EC₅₀) should be calculated. Sponsors may need to use
157 different assay methodologies to evaluate cytotoxicity (Smee, Hurst, et al. 2017) and should note
158 that cytotoxic effects that reduce viral replication may not manifest as cell death. Therefore,
159 assessments of cellular metabolism (e.g., transcription levels of cellular genes) may provide
160 more relevant measures of toxicity. The cytotoxicity evaluation should use multiple RSV-
161 susceptible human cell lines and primary cells cultured under proliferating and nonproliferating
162 conditions. Some investigational drugs (e.g., nucleos(t)ide analog inhibitors) should also be

Contains Nonbinding Recommendations

Draft — Not for Implementation

163 evaluated for inhibitory activity against host DNA polymerases, mitochondrial DNA
164 polymerases, and RNA polymerases, as well as for mitochondrial toxicity (Marroquin, Hynes, et
165 al. 2007; Arnold, Sharma, et al. 2012). Sponsors should note that these biochemical and cell-
166 based toxicity evaluations should not be considered substitutes for animal toxicity studies.

167
168 d. Combination antiviral activity

169
170 The combination antiviral activity of approved drugs, such as approved anti-RSV drugs, that are
171 likely to be used with an investigational drug should be evaluated early in drug development.
172 Combination antiviral activity determinations with other investigational drugs should be
173 conducted if the drugs may be used together in future trials or clinical practice. The combination
174 antiviral activity assessments should include concentrations spanning each drug's EC₅₀ value,
175 when applicable, or relevant in vivo concentration. These studies should also include
176 combination cytotoxicity assessments.

177
178 e. Activity in animal models

179
180 Demonstrating anti-RSV activity using animal models of infection could be useful for
181 characterizing potential clinical use (e.g., prophylaxis or treatment, identifying the potential
182 therapeutic window) and for providing additional proof-of-concept data to support clinical
183 development. Sponsors can discuss with the DAVP the selection and use of animal models of
184 RSV infection before conducting studies.

185
186 f. Resistance and cross-resistance

187
188 Resistance studies are useful for identifying resistance pathways, determining genetic barriers to
189 resistance, assessing cross-resistance with other antiviral drugs, and providing additional data to
190 support the proposed mechanism of action. RSV variants that are resistant to an investigational
191 drug should be selected using a cell culture or animal model of infection and then genotypically
192 and phenotypically characterized. The effect of each selected amino acid substitution on
193 antiviral activity should be assessed individually and in combination using an RSV reverse
194 genetics system when feasible.

195
196 Resistance studies should include an evaluation of potential cross-resistance with approved
197 drugs. In addition, cross-resistance between investigational drugs should be completed for drug
198 combinations that may be used in clinical trials. The evaluation should include: (1) assessments
199 of the antiviral activity of the investigational drug against mutant viruses that are resistant to
200 other drugs and (2) assessments of the antiviral activities of other drugs against mutant viruses
201 that are resistant to the investigational drug. Evaluating cross-resistance is particularly important
202 for drugs belonging to the same class (e.g., nucleoside analog inhibitors) or targeting the same
203 viral protein or protein complex (e.g., fusion protein).

204
205 2. *General Considerations for Phase 1 and Phase 2 Development*

206
207 The primary objective of early clinical trials should be to establish pharmacokinetics, safety, and
208 antiviral activity and to provide sufficient data for study design and dose selection for phase 3

Contains Nonbinding Recommendations

Draft — Not for Implementation

209 trials. For most viral infections, efficacy of an antiviral drug is evaluated initially in adults and
210 extrapolated to the pediatric population if the pathophysiology of the disease is similar in adults
211 and pediatric patients. Then, generally, pharmacokinetics, safety, and antiviral activity of the
212 drug are evaluated in a smaller pediatric study. However, the pathophysiology of RSV disease is
213 thought to differ significantly between adult and pediatric patients. One of the key physiological
214 and anatomical differences between the respiratory tracts of infants and older children or adults
215 is that infants have smaller airways, which appear to be more susceptible to compromise from
216 inflammation caused by RSV infection. Therefore, extrapolation of efficacy data from adults to
217 pediatric patients is not possible for bronchiolitis and may not be possible for other types of RSV
218 LRTI in young children. Thus, sponsors should conduct fully powered clinical studies
219 evaluating efficacy and safety of an antiviral drug for treatment of RSV infection in pediatric
220 patients.

221
222 Before initiating pediatric studies, safety should be demonstrated in adult clinical trials and in
223 juvenile animal toxicology studies, as discussed in section III.C.1., Relevant Nonclinical Safety
224 Considerations. In addition, transition to pediatric studies depends on adequate demonstration of
225 proof of concept because, for any clinical investigation involving more than minimal risk, a
226 potential benefit for pediatric patients must exist (21 CFR 50.52). The types of trials to be
227 considered may differ for treatment and prophylaxis indications. In some cases, studies
228 demonstrating in vivo antiviral activity in well-characterized animal model or models of RSV
229 infection can also support initiation of pediatric clinical studies.

230
231 The following subsections provide general recommendations and examples for potential phase 1
232 and phase 2 trial designs for investigational drugs for RSV disease treatment or prophylaxis.

a. Phase 1a/First-in-human trials

233
234
235
236 Phase 1 trials should be conducted to assess safety and pharmacokinetics of the investigational
237 drug. In general, FDA recommends single- and/or multiple-ascending-dose trials in healthy
238 adult subjects to assess safety and pharmacokinetics for the first-in-human trials. Combined with
239 nonclinical virology data, these trials support dose selection for phase 2 trials.

b. Phase 2 trials

240
241
242
243 The primary objectives of phase 2 trials should be characterization of the safety profile and
244 demonstration of proof of concept in adults and children. Phase 2 trials should also identify the
245 optimal dose and treatment duration of the investigational drug with regard to pharmacokinetics,
246 safety, and antiviral activity. Below are three potential study designs for phase 2 trials in adults
247 and in children:

248
249 (1) Phase 2 RSV treatment trials in adults. Currently, it is not known whether demonstration
250 of antiviral (anti-RSV) activity in adults predicts efficacy in treatment of RSV LRTI in
251 infants and young children. However, obtaining evidence for proof of concept in adults
252 with symptomatic RSV infection supports the prospect of clinical benefit in infants and
253 young children. Therefore, FDA recommends evaluating both antiviral activity (using

Contains Nonbinding Recommendations

Draft — Not for Implementation

254 virological measurements) and clinical signs and symptoms in adults in early phase trials.
255 Possible trial design options for proof-of-concept clinical trials include:

- 256
- 257 a. Randomized, double-blind, placebo-controlled treatment trials in healthy adults
258 experimentally infected with an acceptable RSV challenge strain. Subjects who are
259 experimentally inoculated should have established infections before receiving the
260 investigational drug. Many endpoints could be explored such as changes in RSV
261 viral load, RSV-specific sign and symptom assessment scores, and mucus or tissue
262 weights.
 - 263
 - 264 b. Randomized, double-blind, comparative treatment trials of immunocompromised
265 and/or elderly adults with acute symptomatic RSV infection. Patients should have
266 established infections before receiving the investigational drug. Many endpoints
267 could be explored in phase 2 trials, such as changes in RSV viral load, changes in
268 clinical symptom scores, duration of hospitalization, and other indicators of disease
269 progression or resolution. A superiority trial comparing an investigational drug to
270 ribavirin or an add-on superiority trial compared to a placebo added to a background
271 of ribavirin could be considered for adult patients at institutions where ribavirin is
272 considered part of the standard of care for acute RSV disease (e.g.,
273 immunosuppressed patients). Placebo-controlled trials may be appropriate for
274 patients for whom no approved therapy exists and for whom ribavirin is not
275 considered standard of care.
 - 276

277 Each of these trial designs has advantages and disadvantages. Although challenge trials
278 are simpler to conduct, demonstrating clinical benefit may be more difficult because
279 disease is mild and generally limited to the upper respiratory tract. Therefore, these trials
280 may only be useful to demonstrate antiviral activity. Randomized controlled trials of
281 naturally infected patients are logistically more complicated than challenge trials; the
282 former are more likely to enroll patients with clinically significant illness and lower
283 respiratory tract disease and are therefore more likely to be able to demonstrate a clinical
284 treatment benefit. Ultimately, data from both types of trials may be used together to
285 support further development for adult and pediatric indications.

- 286
- 287 (2) Phase 2 RSV prophylaxis trials in adults. Historically, development of prophylactic
288 drugs for RSV disease focused on passive immunoprophylaxis, defined as the prevention
289 of disease by the administration of antibodies. The scientific basis for
290 immunoprophylaxis of RSV disease is based on observational studies of RSV infection in
291 infants, which revealed a correlation between circulating maternal anti-RSV antibody
292 levels and decreased severity of disease (Englund 1994). Development of new drugs for
293 RSV prophylaxis may need proof-of-concept trials in adults before pediatric studies.
294 Examples of proof-of-concept trials in adults include the following:

- 295
- 296 a. Randomized, double-blind, placebo-controlled RSV challenge trials in healthy adults
297 who have received the investigational drug before inoculation with an acceptable
298 RSV challenge strain. Sponsors should discuss endpoints with the Agency; one
299 possibility is prevention of symptomatic laboratory-confirmed RSV infection.

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 300
301 b. Randomized, double-blind, comparative trials of RSV prophylaxis in elderly and/or
302 immunocompromised adults in centers, institutions, or regions in which widespread
303 RSV disease activity has been documented. Sponsors should discuss endpoints with
304 the Agency; one possibility is the incidence of laboratory-confirmed, symptomatic
305 RSV infection.
306
307 c. Randomized, double-blind, placebo-controlled, comparative treatment trials of
308 immunocompromised and/or elderly adults with acute symptomatic RSV infection.
309 Trials could provide evidence of proof of concept that would support potential use for
310 RSV prophylaxis. Patients should have established infection before receiving the
311 investigational drug. Many endpoints could be explored in phase 2 trials, such as
312 changes in RSV viral load, changes in RSV-specific sign and symptom assessment
313 scores, duration of hospitalization, and other indicators of disease progression or
314 resolution.

- 315
316 (3) Phase 2 pediatric studies for treatment and prophylaxis. After proof of concept and
317 safety in adults have been demonstrated, pediatric patients can be enrolled. Generally,
318 the initial pediatric study should be small, but could be expanded after safety is
319 demonstrated in the initial cohort. The pediatric study design should be similar to adult
320 trial design (i.e., randomized, double-blind, placebo-controlled, dose-ranging trials), but
321 different endpoints may be appropriate for the pediatric population because the disease
322 course may be different (e.g., wheezing is prominent in children but not in adults).
323

324 To identify a potentially safe and effective dose to be confirmed in phase 3 for the intended
325 population, robust dose-ranging trials should be considered in phase 2 before initiation of phase
326 3 trials. The initial dose selection in pediatrics should be based on
327 pharmacokinetic(PK)/pharmacodynamic (PD) data (if available), safety data from adult phase 1
328 and phase 2 trials, antiviral activity data from cell culture and animal models, and the safety data
329 from nonclinical juvenile animal toxicology studies. PD data can include, as described in
330 III.A.2.b.(1)(b), changes in RSV viral load, and improvement in signs or symptoms. Additional
331 clinical pharmacology evaluations may be needed to assess appropriate dose adjustments for
332 specific populations, including for patients with hepatic or renal impairment or patients taking
333 concomitant medications.⁶
334

⁶ For information on specific populations and drug-drug interactions, see the guidance for industry *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling* and the draft guidances for industry *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling* and *Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*. When final, these guidances will represent the FDA’s current thinking on these topics.

Contains Nonbinding Recommendations

Draft — Not for Implementation

c. Data needed to proceed to phase 3

For an end-of-phase 2 meeting, data from phase 2 trials, including all pharmacokinetic, safety, proof of concept, and antiviral activity data, should be available to support progression to phase 3. Data from all regimens under study in the drug development program should be used to select appropriate drug regimens and patient populations for study in phase 3.

3. *Dose Selection*

The following recommendations on dose selection are not definitive and may vary between drug development programs depending on the characteristics of an individual drug as well as the proposed indication and patient population. Additional consideration may be given to other drug development plans or clinical trial designs as warranted. FDA encourages sponsors to engage in discussions on dose selection with the DAVP as early as possible.

The dose selected for phase 3 trials should be based on the exposure-response relationships established in phase 2 studies in pediatrics. Different dosing strategies based on patient factors (e.g., body weight) may be appropriate to achieve target exposures, and prospective dose adjustment based on such factors should be considered in phase 3. The safety and efficacy of the selected dose or doses should be further evaluated and confirmed in phase 3 trials.

For some drugs, more than one route of administration can be considered; however, different dosing, safety, and efficacy issues may arise with different routes of administration. For example, an oral form may be desirable for moderate RSV disease whereas an intravenous formulation may be more desirable for seriously ill patients who may not be able to take oral formulations. For inhalational routes, determining appropriate initial dosing for clinical trials can be challenging. Using appropriate safety precautions and monitoring, sponsors should evaluate the safety of drugs delivered by inhalational routes initially in adults without and then with preexisting pulmonary disease because individuals with pulmonary disease may be at high risk for adverse reactions caused by inhalational drugs.

4. *Drug Development Population*

Phase 3 clinical development programs for pediatric treatment and prophylaxis indications should focus initially on patient groups at risk for severe illness because the risk-benefit considerations are likely most favorable for these groups. Based on the epidemiology of RSV disease, the population at most significant risk includes infants and children younger than 24 months of age. The risk of severe RSV LRTI is highest in infants younger than 6 months of age, infants born prematurely who are younger than 1 year of age, and infants and children younger than 24 months of age with either cyanotic congenital heart disease (CHD) or chronic lung disease of prematurity (CLD).

In addition to the pediatric population, RSV LRTI can also be severe in elderly patients, and RSV drugs (for treatment and prophylaxis) could potentially be evaluated in this population. Additional high-risk populations to consider for RSV clinical trials include immunocompromised

Contains Nonbinding Recommendations

Draft — Not for Implementation

380 patients (e.g., hematopoietic stem cell or lung transplant recipients) and patients with chronic
381 lung disease such as cystic fibrosis.

382
383 Protocols with a range of both Northern and Southern Hemisphere clinical investigational sites
384 may increase efficiency of drug development by allowing data collection during different RSV
385 seasons. When sponsors rely on foreign clinical trial data — whether from multinational trials
386 that include the United States or from trials conducted entirely outside the United States — to
387 support the marketing approval of candidate drugs, sponsors should supplement the foreign data
388 with information about circulating RSV strains, patterns of clinical illness, trial population
389 demographics, standards of medical care, and the use of other medical interventions in the
390 countries where the trials were conducted. Sponsors should evaluate the relevance of foreign
391 data under applicable FDA regulations considering trial conduct standards, trial population
392 demographics, availability of sites for regulatory inspection, and applicability of disease
393 manifestations and the standard medical care compared to that in the United States. Sponsors
394 also can consult the guidance for industry and FDA staff *FDA Acceptance of Foreign Clinical*
395 *Studies Not Conducted Under an IND Frequently Asked Questions*.

396 397 5. *Efficacy Considerations*

398
399 In general, treatment and prophylaxis indications should each be supported by two adequate and
400 well-controlled trials. However, sometimes a single persuasive trial may be sufficient for each
401 indication depending on other supportive evidence. In general, two trials that differ in design
402 parameters and populations are more useful than two identically designed trials or a single large
403 trial. For example, one treatment trial in adults and one treatment study in children may be
404 considered sufficient to support a treatment indication in adults and children. In addition, one
405 prophylaxis trial and one treatment trial may also be sufficient for consideration of an initial
406 marketing application for both indications in some populations.

407 408 6. *Safety Considerations*

409
410 At least 100 adults should be exposed to the drug (at exposures similar to or higher than that
411 expected with the proposed pediatric dosage regimen) in clinical trials before initiating pediatric
412 studies. However, depending on the nonclinical pharmacology and toxicology findings and the
413 preliminary pharmacokinetic and safety profile of the drug observed in adults, additional data in
414 adults may be needed before initiation of pediatric studies. The initial evaluation in pediatric
415 patients should be small to characterize pharmacokinetics and to provide preliminary safety data.
416 If no safety or tolerability issues are identified in the initial cohort, then sponsors can expand the
417 evaluations.

418
419 A robust safety database from adequately blinded, well-controlled clinical trials in appropriate
420 populations is important because of the wide variety of affected populations with a range of
421 comorbidities that could interact with both disease and treatment. The size of the safety database
422 needed for a new drug application depends on the risk-benefit profile of the drug, the proposed
423 indication or indications, and the weight of evidence from nonclinical toxicology studies. For
424 both treatment and prophylaxis trials, the safety population should consist of patients who are
425 exposed to the proposed or higher level dose for the proposed duration of therapy. For treatment

Contains Nonbinding Recommendations

Draft — Not for Implementation

426 of severe RSV disease (e.g., bronchiolitis in pediatric patients, RSV pneumonia in adults), 300 to
427 500 patients are recommended; while for prophylaxis indications or for treatment of mild to
428 moderate RSV disease, a minimum of 1,500 patients are recommended for an adequate safety
429 assessment.

430
431 Immunogenicity is a potential concern with any therapeutic biological product, and early clinical
432 trials with these products should evaluate the potential effects on pharmacokinetics, safety, and
433 efficacy (see the guidance for industry *Immunogenicity Assessment for Therapeutic Protein*
434 *Products*).

435
436 Sponsors should provide adequate rationale for proposing specific populations for evaluation of
437 drugs for RSV prophylaxis. If the risk-benefit assessment of the investigational drug is
438 favorable, evaluation of the drug for RSV prophylaxis in lower risk patients may be appropriate.
439

440 Trials that have vulnerable populations enrolled, such as infants and young children, will likely
441 need a data monitoring committee.
442

B. Phase 3 Efficacy Trial Considerations

1. Trial Design

a. Treatment of RSV LRTI

443
444
445
446
447
448
449 In the absence of a generally accepted standard-of-care antiviral treatment for acute bronchiolitis
450 in infants and children, a randomized, double-blind, placebo-controlled trial in infants may be
451 appropriate to demonstrate efficacy of the drug. In this case, the investigational drug could be
452 added to the current standard-of-care treatment (currently supportive care) compared to standard-
453 of-care therapy plus placebo. In circumstances where aerosolized ribavirin is considered the
454 standard of care for RSV bronchiolitis, the investigational drug can be evaluated as an add-on
455 therapy to aerosolized ribavirin and compared to aerosolized ribavirin and placebo in a
456 superiority trial. Noninferiority trials comparing the investigational drug to ribavirin are not
457 feasible because the registrational ribavirin trials used endpoints that are no longer clinically
458 relevant and do not allow for calculation of a noninferiority margin (Hall, McBride, et al. 1983;
459 Taber, Knight, et al. 1983). Depending on the findings of clinical trials in phase 2, additional
460 dose finding may be needed in phase 3 to optimize the dosing regimen. The design of proposed
461 clinical trials should also depend on the drug formulation and the route of administration.
462

463 After safe and effective anti-RSV drugs become available for treatment of RSV LRTI, placebo-
464 controlled trials may no longer be appropriate (e.g., trials evaluating serious or life-threatening
465 infection), and trials should include an active control arm using a superiority or noninferiority
466 design. If a noninferiority design is proposed, justification for the noninferiority margin should
467 be submitted to the DAVP for review and concurrence.
468

Contains Nonbinding Recommendations

Draft — Not for Implementation

469 b. Prophylaxis for severe RSV LRTI
470

471 Several factors influence the design of RSV prophylaxis trials, including the type of drug (e.g.,
472 monoclonal antibody, small molecule), its PK and PD properties, and its therapeutic target as
473 well as the safety profile of the drug or drug class.
474

475 Use of an active-controlled versus placebo-controlled trial design depends on the population
476 being studied. Randomized, double-blind trials comparing the investigational drug to an
477 approved prophylactic drug may be appropriate for populations for which RSV prophylaxis is
478 considered the current standard of care. Such trials could evaluate superiority to the active
479 comparator; noninferiority trials can also be considered if a noninferiority margin is determined
480 and adequately justified (see III.B.6., Use of Active Comparators). Placebo-controlled
481 superiority trials may be appropriate for populations for which RSV prophylaxis is not approved
482 or considered the current standard of care.
483

484 2. *Trial Population*
485

486 For treatment indications, sponsors should justify the pediatric patient populations evaluated in
487 the initial pediatric studies. Sponsors should take multiple considerations into account, including
488 the likelihood of demonstrating clinical benefit in specific populations and safety issues with the
489 drug, which could have a focused use initially in patients who have severe illness or are at risk of
490 severe LRTI disease.
491

492 For RSV prophylaxis indications in pediatric patients, initial pivotal studies should be conducted
493 in those patients at increased risk for developing moderate-to-severe RSV LRTI (i.e., infants and
494 children younger than 24 months of age). For prophylaxis trials, enriching the population of
495 patients at risk for severe RSV disease, such as premature infants who are in their first year of
496 life or infants with CHD or CLD in the first two years of life, may help to better define the
497 efficacy of the drug. Sponsors could also consider enriching the population by studying ethnic or
498 racial groups more prone to severe illness (Bockova, O'Brien, et al. 2002).
499

500 3. *Entry Criteria*
501

502 For treatment trials, patients should be enrolled based on the presentation of symptoms consistent
503 with RSV LRTI. Signs and symptoms defining LRTI should be specified in the inclusion criteria
504 of the clinical protocol. Diagnostic assays, such as rapid antigen tests, can be used at the time of
505 subject screening to limit enrollment to individuals most likely to be infected, thereby enriching
506 the patient population. However, the potentially limited sensitivities of some diagnostic assays
507 (e.g., rapid antigen tests) may inadvertently exclude some patients with RSV infection from
508 enrollment thereby increasing the number of prospective patients to be screened and introducing
509 a bias in enrollment (i.e., the trial population might reflect those patients who are infected with
510 strains for which the screening assay is sensitive rather than representing patients with clinically
511 significant infections). In any case, RSV infections should be confirmed by a central laboratory
512 using a sensitive assay (e.g., real-time reverse transcription polymerase chain reaction (RT-
513 PCR)).
514

Contains Nonbinding Recommendations

Draft — Not for Implementation

515 Because RSV coinfections with other respiratory viruses may be common and because the
516 contribution of viral coinfection to symptom resolution is not known, coinfections should be
517 documented and sensitivity analyses should be performed to evaluate treatment efficacy in
518 patients with and without viral coinfections. In cases where the investigational RSV antiviral
519 drug has a broad spectrum of antiviral activity (including, for example, against other
520 paramyxoviruses such as metapneumovirus), sensitivity analyses are even more important.
521 Alternatively, stratification by the presence or absence of other respiratory virus coinfection
522 could be considered. In general, unlike influenza, RSV LRTI is not associated with a
523 concomitant or secondary bacterial respiratory tract infection. Therefore, FDA recommends the
524 exclusion of patients with potential concomitant bacterial respiratory tract infections requiring
525 treatment with antibacterial drugs.

526
527 For prophylaxis trials in infants and young children, all patients should have at least one risk
528 factor for severe RSV infection, such as prematurity, young chronological age at the onset of
529 RSV season, or a comorbid disease, as previously discussed. Patients with a history of
530 hypersensitivity to immunoglobulin preparations should be excluded from immunoprophylaxis
531 trials. Patients who receive another RSV prophylactic drug during the same RSV season should
532 also be excluded.

533 534 4. *Randomization, Stratification, and Blinding*

535
536 Clinical trials for prophylaxis and treatment indications should be randomized, double blind, and
537 controlled. Given the subjectivity of endpoints and the potential for variability in the course of
538 RSV disease, double blinding of treatment group assignment is important to reduce bias. In
539 cases where blinding is not considered feasible (e.g., use of an injectable placebo control in
540 pediatric studies of an injectable investigational formulation), additional measures should be
541 taken to minimize bias and ensure integrity of randomization.

542
543 Stratification factors to consider include known risk factors for moderate-to-severe RSV LRTI,
544 such as gestational and chronological age, comorbid conditions (e.g., CHD or CLD), and
545 geographic region. For treatment indications, stratification factors to consider include prior
546 prophylaxis with palivizumab in the same RSV season, severity of RSV disease, and coinfection
547 with other respiratory viruses.

548 549 5. *Other Populations*

550
551 Although the majority of severe RSV infections occur in young infants, several other populations
552 are at risk for severe RSV disease. HSCT patients of any age can have severe life-threatening
553 disease with RSV, and this population has a substantial need for RSV drugs. Depending on the
554 state of stem cell engraftment, HSCT patients may benefit from treatment of RSV infections
555 confined to the upper respiratory tract to reduce progression to the lower respiratory tract. The
556 severity of RSV disease may be dependent on the degree of immune suppression, with some
557 patients being at higher risk because of the nature of their transplants and the need for a high
558 degree of immune suppression. Other populations at risk for severe RSV disease include
559 patients with cystic fibrosis and older adults, especially those residing in long-term care
560 facilities.

Contains Nonbinding Recommendations

Draft — Not for Implementation

561

562

6. Use of Active Comparators

563

564 In randomized, controlled treatment trials in which a placebo is not considered appropriate,
565 active-controlled trials in which the comparator is an FDA-approved drug or considered the
566 standard of care for the indication may be appropriate (e.g., ribavirin for treatment of RSV LRTI
567 in bone marrow transplant patients). If a noninferiority trial design is considered, then a
568 noninferiority margin should be proposed, justified, and discussed with the DAVP because a
569 noninferiority trial may not always be considered appropriate.⁷ See section III.B.1.a., Treatment
570 of RSV LRTI, for further discussion about appropriate comparators.

571

572 An active control should be used in prophylaxis trials that include pediatric patients for whom
573 RSV prophylaxis is currently recommended. Placebo-controlled trials may be appropriate for
574 populations for which RSV prophylaxis is not recommended per local standard of care. Active-
575 controlled trials can be designed as superiority or noninferiority trials. Prevention of
576 hospitalization was used as the primary endpoint to support approval of palivizumab. A
577 noninferiority margin can be determined for prophylaxis studies in which palivizumab is the
578 comparator for the endpoint of hospitalization (or another agreed upon similar endpoint
579 demonstrated to be robust in a clinical trial) based on the treatment difference between
580 palivizumab and placebo for the same or similar population. Sponsors should discuss
581 construction of an appropriate noninferiority margin with the DAVP.

582

7. Efficacy Endpoints

583

584
585 Currently, efficacy endpoints have not been definitively established for clinical trials of RSV
586 treatment or prophylaxis; sponsors should work closely with the DAVP to identify reliable and
587 robust endpoints for treatment and prophylaxis of RSV disease of varying severity. For
588 treatment of RSV disease, a surrogate marker that reasonably predicts clinical response has not
589 been identified. Changes in RSV viral load may be informative for dose-ranging phase 2 PK/PD
590 analysis, but at this time, primary endpoints in phase 3 trials should be clinical outcome
591 measures. In addition, virologic surrogates are not expected to offer an advantage over clinical
592 endpoints because changes in both occur over the same time course.

593

594 Exploration of multiple secondary endpoints, including clinical and virological endpoints, is
595 strongly advised in phase 2 trials to show consistency of effect with the primary endpoint and to
596 inform selection of endpoints for pivotal phase 3 trials. Protocol submissions should include and
597 discuss prospectively the rationale for both primary and secondary endpoints.

598

a. Treatment

599

600

601 The primary efficacy endpoint should assess improvement in clinical signs and symptoms of
602 RSV disease. RSV disease is typically short in duration (less than 2 weeks in most children),
603 which allows for assessment of a primary clinical endpoint in a reasonable time frame in a

⁷ See the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness*.

Contains Nonbinding Recommendations

Draft — Not for Implementation

604 clinical trial setting, obviating the need for a surrogate measure of efficacy (El Saleeby, Bush, et
605 al. 2011; DeVincenzo, Whitley, et al. 2014).

606
607 The primary endpoint for treatment of RSV bronchiolitis could be time to a clinically
608 meaningful, defined level of improvement. Another option for the primary endpoint could be the
609 degree of improvement/resolution of signs and symptoms using a multipoint scale at a
610 prespecified time point. Instruments for sign and symptom measurement should be developed
611 and standardized to reliably and reproducibly measure signs and symptoms of RSV disease.
612 Relevant elements could include signs such as tachypnea, hypoxia, and chest wall retractions as
613 well as symptoms such as cough, wheezing, lethargy, and poor feeding. Some signs, such as
614 fever, tachypnea, and accessory muscle use, may resolve more quickly whereas other symptoms,
615 such as wheezing and cough, may persist and could be assessed separately as coprimary or
616 secondary endpoints. Sponsors should provide adequate justification for proposed endpoints and
617 the instruments used for sign and symptom assessment.

618
619 Patient-reported outcome (PRO) tools could be considered to assess symptoms in adults and
620 children who can reliably self-report. For patient populations that are unable to self-report (e.g.,
621 infants, young children, cognitively impaired), an observer-reported outcome (ObsRO) tool
622 could potentially be used to assess observable RSV-related signs, events, and behaviors.
623 Because no validated sign and symptom scoring system for RSV disease exists at this time,
624 sponsors should propose and provide justification for a standardized or well-studied instrument
625 for sign and symptom measurement and consult with FDA to develop well-defined and reliable
626 instruments. For further details regarding PRO and ObsRO development, refer to the guidance
627 for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to*
628 *Support Labeling Claims*. Although not a regulatory requirement, the Drug Development Tools
629 Qualification Programs provide FDA consultation and advice on tools such as PRO and ObsRO
630 instruments that, once qualified, will be publicly available for use in multiple drug development
631 programs over time.⁸

632
633 Secondary and exploratory endpoints can include:

- 634
- 635 • Virologic assessments
 - 636 • Prevention of hospitalization
 - 637 • Prevention of disease progression, including prevention of intensive care unit admission
 - 638 • Duration of supplemental oxygen use
 - 639 • Duration of hospitalization
 - 640 • Need for noninvasive positive-pressure ventilation or mechanical ventilation
 - 641 • Duration of persistent symptoms such as wheezing and cough
- 642

643 Given that patients with RSV disease may be hospitalized and remain hospitalized for a variety
644 of reasons (e.g., respiratory compromise, the inability to take oral hydration or nutrition),

⁸ See the FDA web page Drug Development Tools Qualification Programs at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/>.

Contains Nonbinding Recommendations

Draft — Not for Implementation

645 interpretation of endpoints such as prevention of hospitalization or duration of hospitalization
646 may not always be straightforward.

647

648 b. Prophylaxis

649

650 In pediatric studies, the primary endpoint for prophylaxis studies should be the occurrence of
651 laboratory-confirmed RSV LRTI. In the past, prevention of RSV-related hospitalization was
652 used for approval of RSV immunoprophylactic drugs in pediatric patients; however, the utility of
653 prevention of RSV-related hospitalization as a primary endpoint has diminished as outpatient
654 management of RSV has improved and as patients with more serious RSV disease are managed
655 more often in the outpatient setting.

656

657 There has been considerable interest in the use of RSV prophylactic drugs to prevent wheezing
658 or asthma later in childhood. Assessment of long-term outcomes on symptoms such as wheezing
659 is not required for FDA marketing approval, but clinical trials could be designed to evaluate a
660 drug's effect on wheezing or the development of asthma. Sponsors should be aware that the
661 more meaningful endpoint is prevention of asthma rather than reduction of long-term wheezing;
662 however, the Agency acknowledges that the studies evaluating prevention of asthma are longer
663 in duration and more difficult to conduct. Sponsors that plan to seek an indication for prevention
664 of long-term wheezing should discuss their plans with the Agency, because there may be unique
665 considerations with respect to trial design and endpoints that are beyond the scope of this
666 guidance.

667

668 In adult trials, possible endpoints for prophylaxis could include prevention of all symptomatic
669 respiratory infections, RSV LRTI (pneumonia), or progression of RSV upper respiratory tract
670 infection to LRTI.

671

672 8. *Trial Procedures and Timing of Assessments*

673

674 For treatment trials, intensive clinical assessments are important in the period shortly after
675 treatment initiation because the typical self-limited disease course in otherwise healthy children
676 may limit the ability to detect treatment effects at later time points. Clinical assessments should
677 be made at least three times daily. Virologic assessments should be performed by a central
678 laboratory using clinical samples obtained at presentation and at prespecified intervals
679 throughout the clinical course. These assessments should include quantitative RSV RT-PCR and
680 quantitative RSV culture. Clinical assessments can include serial measurement of respiratory
681 rate, oxygen saturation, work of breathing, and ability to maintain hydration through oral intake.

682

683 In prophylaxis trials, all patients who develop RSV bronchiolitis or pneumonia (i.e., prophylaxis
684 failures) should undergo virologic assessments performed by a central laboratory to confirm
685 RSV infection. These assessments should include quantitative RSV RT-PCR and quantitative
686 RSV culture. Because of the possibility of coinfection, diagnostic tests that detect multiple
687 respiratory viruses should be performed. Performance characteristics and descriptions of the
688 virologic assays should be provided in clinical trial protocols. Currently, an international
689 standard is not available for quantification of RSV RNA. Sponsors should include a readily
690 available reference for interstudy comparisons in their assays.

Contains Nonbinding Recommendations

Draft — Not for Implementation

691
692 Treatment trials should include at least 21 days of follow-up to detect symptom recurrence after
693 initial improvement, late-onset adverse events, or emergence of a resistant virus. Follow-up for
694 prophylaxis trials should continue for five half-lives of the drug to assess late-onset safety
695 events. Length of follow-up for treatment or prophylaxis studies may need to be longer
696 depending on the population (e.g., immunocompromised patients with prolonged viral shedding).
697

698 9. *Statistical Considerations*

699
700 Sponsors should provide a protocol with a statistical analysis plan for review and concurrence
701 before initiating patient enrollment. For treatment trials, the primary efficacy analyses should
702 focus on the population with laboratory-confirmed RSV infections, a baseline characteristic,
703 even if RSV infection is not confirmed until after baseline data are collected. Given the
704 likelihood that treatment decisions in clinical practice would be made before confirmation of
705 diagnosis, analyses of safety data should be based on all randomized patients. For prophylaxis
706 trials, the primary efficacy analysis should include all patients who are randomized and receive
707 at least one dose of assigned treatment during the trial.
708

709 In noninferiority trials, the choice of a noninferiority margin for statistical hypotheses should be
710 discussed and agreed upon with the DAVP before study initiation. Sponsors should determine a
711 reliable control treatment effect (M1) based on historical evidence of the quantitative
712 contribution of the active control. This contribution should be determined in trials evaluating a
713 similar population with similar length of follow-up as the proposed trial. In addition, the
714 noninferiority margin should be smaller than the M1 to preserve a clinically important effect
715 compared to an active control. For noninferiority testing, sponsors should employ two-sided, 95
716 percent confidence intervals adjusted for multiple comparisons or other appropriate testing
717 procedures. For additional information regarding noninferiority studies, see ICH E10 and the
718 guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness*.
719

720 Sponsors should provide adequate details regarding the design, hypothesis, primary and
721 secondary analyses, control of family-wise type I error rate, and any assumptions for the
722 proposed sample size. If sponsors consider more than one primary endpoint, sponsors should
723 adjust the sample size at the planning stage to ensure sufficient power. FDA recommends a
724 stratified analysis when a trial is to be conducted in a heterogeneous population in which specific
725 characteristics might affect the magnitude of the treatment effect. Such specific characteristics
726 or factors should be prespecified and considered for stratified randomization. In these short-term
727 trials, sponsors should avoid censoring patients in the intent-to-treat infected population.
728 Missing data should be controlled and minimized, and the sponsor should have an explicit and
729 adequate plan to address issues relating to missing data.
730

731 10. *Accelerated Approval (Subpart H) Considerations*

732
733 Currently, no reasonably predictive surrogate endpoints are known for RSV disease in infants
734 and young children, and accelerated approval of RSV drugs is not a feasible drug development
735 pathway. In addition, it is not clear that surrogate endpoints would be useful in accelerating drug

Contains Nonbinding Recommendations

Draft — Not for Implementation

736 development because improvements in clinical symptoms can occur over the same time course
737 as changes in virologic measurements.

738

739 *11. Risk-Benefit Considerations*

740

741 RSV infection can result in a wide spectrum of illness in infants and young children from
742 asymptomatic infection to RSV bronchiolitis and pneumonia. Therefore, risk-benefit
743 considerations are extremely important for the development of RSV drugs for infants and young
744 children. Because RSV drug development will likely focus on studies in pediatric patients (21
745 CFR part 50, subpart D), risk-benefit assessments should be done for all drugs that are to be
746 tested. Depending on the patient population targeted (e.g., hospitalized patients with severe RSV
747 disease versus those with milder RSV disease), different degrees of risk may be reasonable.
748 However, any RSV drug targeting the entire infant population from birth to 12 months of age (or
749 up to 2 years of age in children with CLD or CHD) to prevent progression of RSV disease should
750 have a low risk profile to justify widespread use of the drug in children.

751

752 **C. Other Considerations**

753

754 *1. Relevant Nonclinical Safety Considerations*

755

756 General recommendations for supportive, nonclinical safety studies, including for the design and
757 timing, are addressed in other FDA and ICH guidances for industry. Small molecule drug
758 development is discussed in the ICH guidances for industry *M3(R2) Nonclinical Safety Studies*
759 *for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* and
760 *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing*
761 *Authorization for Pharmaceuticals: Questions and Answers (R2)*. Recommendations for
762 biologically derived drugs are discussed in the ICH guidance for industry *S6(R1) Preclinical*
763 *Safety Evaluation of Biotechnology-Derived Pharmaceuticals*. Nonclinical considerations
764 specific to RSV drug development are discussed in this guidance.

765

766 In general, for small molecule drug development, FDA prefers that sponsors study the safety of
767 new pharmaceuticals initially in adult clinical trials. Nonclinical studies in two species of adult
768 animals (rodent and nonrodent) are commonly conducted to support the first-in-human trials in
769 healthy adults.⁹ If the small molecule pharmaceutical indication is intended primarily for a
770 pediatric population, FDA recommends that sponsors conduct juvenile animal toxicology studies
771 before initiation of pediatric studies to support the safety of the drug in the pediatric population.
772 Depending on the proposed duration of the exposure in the pediatric population, long-term
773 testing starting in juvenile animal toxicology studies may also be needed.

774

775 Drug development for biological products should employ a flexible and science-based approach.
776 If the biological product indication is intended primarily for a pediatric population, sponsors

⁹ The FDA encourages sponsors to consult the FDA when considering a non-animal testing method believed to be suitable, adequate, validated, and feasible. The FDA will consider if the alternative method could be assessed for equivalency to an animal test method.

Contains Nonbinding Recommendations

Draft — Not for Implementation

777 should consider feasibility and potential utility of a nonclinical safety evaluation in a juvenile
778 animal toxicology study.

779

780 2. *PK/PD Considerations*

781

782 a. PK measurement

783

784 The ability to measure drug exposures in the physiological compartment relevant to prophylaxis
785 or treatment of RSV is dependent on the route of administration and the mechanism of action.

786 For example, plasma concentrations may be easily quantifiable for drugs delivered via the oral or
787 parenteral routes, but may be less so for drugs that are inhaled or administered intranasally.

788 Additionally, plasma concentrations are more likely to reflect the systemic immunomodulatory
789 activity of prophylactic drugs, and local exposures may be more correlated with the antiviral

790 activity of drugs intended for treatment of RSV infection. Thus, for drugs that are inhaled or
791 delivered intranasally, drug concentrations in epithelial cells of the respiratory tract (estimated

792 from nasal wash, sputum, and/or bronchoalveolar lavage) should be measured to evaluate the
793 relationship of exposure and antiviral activity. Invasive procedures such as bronchoalveolar

794 lavage should be reserved for adult patients because the procedures are not done electively in
795 pediatrics.

796

797 Regardless of the route of administration, plasma drug concentrations should be collected
798 because the concentrations should be considered during safety assessments. FDA recognizes
799 that the collection of PK samples may be limited by the patient population under evaluation (e.g.,
800 pediatric patients); therefore, sample collection timelines should be designed to be maximally
801 informative.

802

803 b. PD measurement

804

805 The selection of robust and reproducible PD markers for antiviral activity against RSV is
806 hindered by an incomplete understanding of RSV disease. At present, FDA recommends the use

807 of changes in RSV virological measures and clinical symptoms related to RSV disease as

808 response metrics in exposure-response evaluations. Sponsors should select response metrics

809 based on biological plausibility, and relationships between selected response metrics and primary

810 efficacy endpoints should be characterized. During protocol development, the selected metrics

811 should be discussed and agreed upon with the Agency. Although information is limited, FDA

812 encourages sponsors to relate dose/exposure-response observations from short-term measures to

813 outcomes in phase 3 trials to inform dosing

814

815 The potential for clinical safety events to be exposure related should be assessed through

816 exposure-response analyses. Characterization of the relationship between drug exposure and

817 toxicity will help to delineate the upper limit of tolerable drug exposure and to estimate the

818 likelihood of an adverse event within a given exposure range.

819

Contains Nonbinding Recommendations

Draft — Not for Implementation

820 c. Modeling considerations

821
822 Sponsors should explore exposure-response relationships for efficacy and safety as early as
823 possible during clinical development (e.g., following adult phase 2 trial or trials).
824 Physiologically based pharmacokinetic analyses and/or population PK/PD analysis can be
825 utilized. Modeling should incorporate nonclinical antiviral activity, animal PK, safety, and PD
826 data as appropriate, as well as data from adult phase 1 and phase 2 trials, and physiological
827 difference between adults and infants to establish the initial dose to be evaluated in the first
828 infant study. This model should be refined on an ongoing basis as additional data become
829 available. It is not clear whether a model derived from adult and nonclinical data will be directly
830 applicable to the infant data. However, this model should be a starting point for continuous
831 model development. Sponsors should incorporate efficacy and safety data from placebo-
832 controlled arms into exposure-response models to allow for a clinically meaningful interpretation
833 of the safety and efficacy of the investigational drug. Sponsors should assess the influence of
834 demographic and baseline factors on models as appropriate. As with any drug development
835 program, knowledge of the exposure-response relationships for efficacy and safety will facilitate
836 dose selection in the primary patient population as well as for specific populations in which dose
837 adjustments may be needed.

838

839 3. *Clinical Virology Considerations*

840

841 a. RSV diagnostic assays for screening and events

842

843 Diagnosis of RSV infection should be confirmed by a central laboratory using an assay or assays
844 that are sensitive and specific for RSV A and RSV B. Performance data for the central
845 laboratory assay evaluating the geographically and temporally distinct isolates should be
846 submitted to the FDA for review. In addition, FDA recommends collecting any diagnostic
847 laboratory results from local clinical sites participating in trials, including identification of the
848 assay used.

849

850 Some RSV antiviral drugs might inhibit RSV diagnostic assays; for example, certain anti-RSV
851 monoclonal antibodies have been shown to compete with the antibodies used in specific
852 diagnostic assays, thereby reducing assay sensitivity (Deming, Patel, et al. 2013). Sponsors
853 should determine the effect of investigational drugs on the sensitivities of commercially available
854 diagnostic assays, particularly those used in clinical trials. These evaluations should be
855 performed using drug concentrations consistent with drug use.

856

857 b. Resistance analysis

858

859 Patients might fail RSV prophylaxis or treatment because of infection with a virus that is
860 resistant to the investigational drug. Resistant viruses may be transmitted (e.g., a patient is
861 infected with a virus that harbors polymorphisms that affect drug susceptibility) or selected (i.e.,
862 a resistant virus is selected within a patient after replicating in the presence of the drug).
863 Baseline and postfailure isolates from patients failing treatment should be genotypically
864 characterized and compared to determine if a drug-resistant virus is present and, if so, if the
865 resistant virus was present at baseline or selected within the patient. If genotypic analysis of

Contains Nonbinding Recommendations

Draft — Not for Implementation

866 RSV isolates identifies the emergence of a virus expressing novel substitutions not previously
867 analyzed during nonclinical resistance studies, the virus expressing those substitutions should be
868 phenotypically characterized. Sponsors should contact the DAVP to obtain the current format
869 for submission of resistance data. Sponsors proposing to use next generation sequencing should
870 consult with the DAVP early in the process.

871

872 4. *Regulatory Considerations*

873

874 Under the Pediatric Research Equity Act (Public Law 108-155) as amended by the Food and
875 Drug Administration Reauthorization Act (Public Law 115-52), sponsors must submit an initial
876 pediatric study plan (iPSP) to FDA no later than 60 days after the end-of-phase 2 meeting or at
877 such time as may be agreed upon between FDA and the sponsor.¹⁰ However, sponsors are
878 encouraged to begin discussions of their pediatric formulations and clinical development plans
879 early in drug development. The timing and content of the submission of an iPSP are described in
880 detail in the draft guidance for industry *Pediatric Study Plans: Content of and Process for*
881 *Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans*. As noted in
882 the guidance, the iPSP should include the entire pediatric age range.

883

884

¹⁰ See section 505B(e)(2)(A)(ii) of the Federal Food, Drug, and Cosmetic Act (Public Law 75-717), as amended by section 506 of the Food and Drug Administration Safety and Innovation Act (Public Law 112-144) and the Food and Drug Administration Reauthorization Act (Public Law 115-52), and the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans*. When final, this guidance will represent FDA's current thinking on this topic.

Contains Nonbinding Recommendations

Draft — Not for Implementation

REFERENCES

- 885
886
887 American Academy of Pediatrics, Committee on Infectious Diseases and Bronchiolitis
888 Guidelines Committee, 2014, Updated Guidance for Palivizumab Prophylaxis Among Infants
889 and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus
890 Infection, *Pediatrics*, 134(2):415–420.
891
892 Arnold JJ, Sharma SD, Feng JY, Ray AS, Smidansky ED, Kireeva ML, Cho A, Perry J, Vela JE,
893 Park Y, Xu Y, Tian Y, Babusis D, Barauskus O, Peterson BR, Gnatt A, Kashlev M, Zhong W,
894 and Cameron CE, 2012, Sensitivity of Mitochondrial Transcription and Resistance of RNA
895 Polymerase II Dependent Nuclear Transcription to Antiviral Ribonucleosides, *PLoS Pathog*,
896 8(11):e1003030.
897
898 Bockova J, O'Brien KL, Oski J, Croll J, Reid R, Weatherholtz RC, Santosham M, and Karron
899 RA, 2002, Respiratory Syncytial Virus Infection in Navajo and White Mountain Apache
900 Children, *Pediatrics*, 110(2 Pt 1):e20.
901
902 Deming DJ, Patel N, McCarthy MP, Mishra L, Shapiro AM, and Suzich JA, 2013, Potential for
903 Palivizumab Interference With Commercially Available Antibody-Antigen Based Respiratory
904 Syncytial Virus Diagnostic Assays, *Pediatr Infect Dis J*, 32(10):1144–1146.
905
906 DeVincenzo JP, Whitley RJ, Mackman RL, Scaglioni-Weinlich C, Harrison L, Farrell E,
907 McBride S, Lambkin-Williams R, Jordan R, Xin Y, Ramanathan S, O'Riordan T, Lewis SA, Li
908 X, Toback SL, Lin SL, and Chien JW, 2014, Oral GS-5806 Activity in a Respiratory Syncytial
909 Virus Challenge Study, *N Engl J Med*, 371(8):711–722.
910
911 El Saleeby CM, Bush AJ, Harrison LM, Aitken JA, and Devincenzo JP, 2011, Respiratory
912 Syncytial Virus Load, Viral Dynamics, and Disease Severity in Previously Healthy Naturally
913 Infected Children, *J Infect Dis*, 204(7):996–1002.
914
915 Englund J, 1994, Passive Protection Against Respiratory Syncytial Virus Disease in Infants: The
916 Role of Maternal Antibody, *Pediatr Infect Dis J*, 13:449–453.
917
918 Hall CB, McBride JT, Walsh EE, Bell DM, Gala CL, Hildreth S, Ten Eyck LG, and Hall WJ,
919 1983, Aerosolized Ribavirin Treatment of Infants With Respiratory Syncytial Virus Infection. A
920 Randomized Double-Blind Study, *N Engl J Med*, 308(24):1443–1447.
921
922 Marroquin LD, Hynes J, Dykens JA, Jamieson JD and Will Y, 2007, Circumventing the Crabtree
923 Effect: Replacing Media Glucose With Galactose Increases Susceptibility of HepG2 Cells to
924 Mitochondrial Toxicants, *Toxicol Sci*, 97(2):539–547.
925
926 Ralston SL, Lieberthal AS, Meissner HC, Alverson BK, et al., 2014, Clinical Practice Guideline:
927 The Diagnosis, Management, and Prevention of Bronchiolitis, *Pediatrics*, 134(5): e1474–e1502.
928
929 Randolph AG and Wang EL, 1996, Ribavirin for Respiratory Syncytial Virus Lower Respiratory
930 Tract Infection, *Arch of Pediatr Adolesc Med*, 150(9):942–947.

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 931
932 Smee DF, Hurst BL, Evans WJ, Clyde N, Wright S, Peterson C, Jung KH, Day CW, 2017,
933 Evaluation of Cell Viability Dyes in Antiviral Assays with RNA Viruses That Exhibit Different
934 Cytopathogenic Properties, *J Virol Methods*, 246:51–57.
935
936 Taber LH, Knight V, Gilbert BE, McClung HW, Wilson SZ, Norton HJ, Thurson JM, Gordon
937 WH, Atmar RL, and Schlaudt WR, 1983, Ribavirin Aerosol Treatment of Bronchiolitis
938 Associated With Respiratory Syncytial Virus Infection in Infants, *Pediatrics*, 72(5):613–618.
939
940 Viswanathan M, King V, Bordley C, et al., 2003, Management of Bronchiolitis in Infants and
941 Children, Evidence Report/Technology Assessment No. 69: U.S. Dept of Health and Human
942 Services, Agency for Healthcare Research and Quality.