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

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Respiratory Syncytial Virus Infection: Developing Antiviral Drugs for Prophylaxis and Treatment Guidance for Industry[1]

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I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment and prevention of disease caused by respiratory syncytial virus (RSV) infection.[2] Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and clinical trial designs for the development of drugs and biological products that support an indication for treatment and prevention of disease caused by RSV infection. This draft guidance is intended to serve as a focus for continued discussions among the Division of Antiviral Products (DAVP), pharmaceutical sponsors, the academic community, and the public.[3] This guidance focuses primarily on the development of drugs with antiviral mechanism for RSV-related illness in infants and young children (e.g., bronchiolitis) but also briefly discusses development for other populations. The sections of this guidance that discuss nonclinical development are intended to provide guidance regarding drug development for both prophylaxis and treatment.

This guidance does not address development of drugs that target the host response to RSV infection, vaccines, or blood-derived products. This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the

[1] This guidance has been prepared by the Division of Antiviral Products in the Center for Drug Evaluation and Research at the Food and Drug Administration.

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

[3] In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during the development of drugs for treatment and prevention of disease caused by RSV infection.

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

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

II. BACKGROUND

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

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

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

[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.

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

> *prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease*.

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

III. DEVELOPMENT PROGRAM

A. General Drug Development Considerations

Sponsors considering development of antiviral drugs for the treatment of RSV infection are encouraged to communicate with FDA through the pre-Investigational New Drug application (pre-IND) consultation program.[5] Pre-IND consultation with FDA is optional; although, it may 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.

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

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

1. Nonclinical Virology Development Considerations

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

a. Mechanism of Action

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

b. Antiviral activity in cell culture

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

c. Cytotoxicity and mitochondrial toxicity

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

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

d. Combination antiviral activity

The combination antiviral activity of approved drugs, such as approved anti-RSV drugs, that are likely to be used with an investigational drug should be evaluated early in drug development. Combination antiviral activity determinations with other investigational drugs should be conducted if the drugs may be used together in future trials or clinical practice. The combination antiviral activity assessments should include concentrations spanning each drug's EC_{50} value, when applicable, or relevant in vivo concentration. These studies should also include combination cytotoxicity assessments.

e. Activity in animal models

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

f. Resistance and cross-resistance

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

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

2. General Considerations for Phase 1 and Phase 2 Development

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

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

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

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

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

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

b. Phase 2 trials

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

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

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

a. Randomized, double-blind, placebo-controlled treatment trials in healthy adults experimentally infected with an acceptable RSV challenge strain. Subjects who are experimentally inoculated should have established infections before receiving the investigational drug. Many endpoints could be explored such as changes in RSV viral load, RSV-specific sign and symptom assessment scores, and mucus or tissue weights.

b. Randomized, double-blind, comparative treatment trials of immunocompromised and/or elderly adults with acute symptomatic RSV infection. Patients should have established infections before receiving the investigational drug. Many endpoints could be explored in phase 2 trials, such as changes in RSV viral load, changes in clinical symptom scores, duration of hospitalization, and other indicators of disease progression or resolution. A superiority trial comparing an investigational drug to ribavirin or an add-on superiority trial compared to a placebo added to a background of ribavirin could be considered for adult patients at institutions where ribavirin is considered part of the standard of care for acute RSV disease (e.g., immunosuppressed patients). Placebo-controlled trials may be appropriate for patients for whom no approved therapy exists and for whom ribavirin is not considered standard of care.

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

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

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

b. Randomized, double-blind, comparative trials of RSV prophylaxis in elderly and/or immunocompromised adults in centers, institutions, or regions in which widespread RSV disease activity has been documented. Sponsors should discuss endpoints with the Agency; one possibility is the incidence of laboratory-confirmed, symptomatic RSV infection.

c. Randomized, double-blind, placebo-controlled, comparative treatment trials of immunocompromised and/or elderly adults with acute symptomatic RSV infection. Trials could provide evidence of proof of concept that would support potential use for RSV prophylaxis. Patients should have established infection before receiving the investigational drug. Many endpoints could be explored in phase 2 trials, such as changes in RSV viral load, changes in RSV-specific sign and symptom assessment scores, duration of hospitalization, and other indicators of disease progression or resolution.

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

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

[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.

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

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

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

5. Efficacy Considerations

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

6. Safety Considerations

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

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

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

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

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

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

B. Phase 3 Efficacy Trial Considerations

1. Trial Design

a. Treatment of RSV LRTI

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

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

b. Prophylaxis for severe RSV LRTI

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

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

2. Trial Population

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

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

3. Entry Criteria

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

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

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

4. Randomization, Stratification, and Blinding

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

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

5. Other Populations

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

6. Use of Active Comparators

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

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

7. Efficacy Endpoints

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

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

a. Treatment

The primary efficacy endpoint should assess improvement in clinical signs and symptoms of RSV disease. RSV disease is typically short in duration (less than 2 weeks in most children), 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*.

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

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

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

Secondary and exploratory endpoints can include:

- Virologic assessments
- Prevention of hospitalization
- Prevention of disease progression, including prevention of intensive care unit admission
- Duration of supplemental oxygen use
- Duration of hospitalization
- Need for noninvasive positive-pressure ventilation or mechanical ventilation
- Duration of persistent symptoms such as wheezing and cough

Given that patients with RSV disease may be hospitalized and remain hospitalized for a variety 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/.

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

b. Prophylaxis

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

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

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

8. Trial Procedures and Timing of Assessments

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

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

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

9. Statistical Considerations

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

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

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

10. Accelerated Approval (Subpart H) Considerations

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

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

11. Risk-Benefit Considerations

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

C. Other Considerations

1. Relevant Nonclinical Safety Considerations

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

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

Drug development for biological products should employ a flexible and science-based approach. 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.

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

2. PK/PD Considerations

a. PK measurement

The ability to measure drug exposures in the physiological compartment relevant to prophylaxis or treatment of RSV is dependent on the route of administration and the mechanism of action. For example, plasma concentrations may be easily quantifiable for drugs delivered via the oral or parenteral routes, but may be less so for drugs that are inhaled or administered intranasally. Additionally, plasma concentrations are more likely to reflect the systemic immunomodulatory activity of prophylactic drugs, and local exposures may be more correlated with the antiviral activity of drugs intended for treatment of RSV infection. Thus, for drugs that are inhaled or delivered intranasally, drug concentrations in epithelial cells of the respiratory tract (estimated from nasal wash, sputum, and/or bronchoalveolar lavage) should be measured to evaluate the relationship of exposure and antiviral activity. Invasive procedures such as bronchoalveolar lavage should be reserved for adult patients because the procedures are not done electively in pediatrics.

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

b. PD measurement

The selection of robust and reproducible PD markers for antiviral activity against RSV is hindered by an incomplete understanding of RSV disease. At present, FDA recommends the use of changes in RSV virological measures and clinical symptoms related to RSV disease as response metrics in exposure-response evaluations. Sponsors should select response metrics based on biological plausibility, and relationships between selected response metrics and primary efficacy endpoints should be characterized. During protocol development, the selected metrics should be discussed and agreed upon with the Agency. Although information is limited, FDA encourages sponsors to relate dose/exposure-response observations from short-term measures to outcomes in phase 3 trials to inform dosing

The potential for clinical safety events to be exposure related should be assessed through exposure-response analyses. Characterization of the relationship between drug exposure and toxicity will help to delineate the upper limit of tolerable drug exposure and to estimate the likelihood of an adverse event within a given exposure range.

c. Modeling considerations

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

3. Clinical Virology Considerations

a. RSV diagnostic assays for screening and events

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

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

b. Resistance analysis

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

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

4. Regulatory Considerations

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

[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.

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