Attention Deficit Hyperactivity Disorder: Developing Stimulant Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

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

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I. INTRODUCTION AND BACKGROUND

This guidance is intended to provide general framework recommendations to sponsors developing stimulant drugs for treatment of attention deficit hyperactivity disorder (ADHD) in pediatric and adult patients. This guidance does not address development programs for nonstimulant drugs.

ADHD is a common neurobehavioral disorder with onset in childhood. It is characterized by a pattern of developmentally inappropriate and maladaptive inattentiveness, impulsivity, and hyperactivity, resulting in impairment in family, social, academic, and occupational functioning. Stimulant drugs (e.g., methylphenidate, amphetamine) are the most commonly prescribed medications for treatment of ADHD.

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II. GENERAL CONSIDERATIONS

The principles outlined below apply to drug development programs for methylphenidate and amphetamine products developed and submitted under the 505(b)(2) application pathway (hereafter referred to as *505(b)(2) products*) (section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)) as well as for novel (i.e., new molecular entity (NME)) stimulant drugs.

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

A. Clinical Pharmacology

In general, central nervous system stimulant drugs demonstrate a strong concentration-response relationship for efficacy and safety (Kimko et al. 2012; Li et al. 2017). Therefore, sponsors can develop formulations using the same active moiety with the objective of creating drug product-specific release features intended to affect the shape of the pharmacokinetic (PK) profile and the onset or duration of effect. Various clinical and clinical pharmacology trials may be of value in the clinical development program based on the characteristics of the active moiety, formulation features, and clinical experience.

The PK and pharmacodynamic (PD) features of a drug product, including the following, should be characterized in early-phase development in the target pediatric and adult patient populations:

- The sponsor should characterize the relationship between blood concentrations of the drug product and cardiac parameters (e.g., heart rate, blood pressure) over time.

- The sponsor should use dose-response or exposure-response modeling and simulation to inform the dose regimen selection for the adequate and well-controlled trials intended to support a marketing indication.

B. Trial Design

Sponsors developing stimulant drug products for treatment of ADHD should consider the following for trial design:

- Because ADHD is a disorder that begins in childhood, a new drug application (NDA) for any drug intended to treat ADHD should include data from adequate and well-controlled studies in pediatric patients (see sections III., Methylphenidate and Amphetamine 505(b)(2) Development Programs, and IV., New Molecular Entity).

- In general, the pathophysiology, disease characteristics, and treatment outcomes in ADHD are sufficiently similar between pediatric and adult patients such that, with two positive pediatric studies, an adult indication can be supported by a single trial in adult patients.

- An NDA for a stimulant drug product should include data that are adequate to assess the safety and effectiveness of the drug for pediatric patients 4 years of age and older. The relevant pediatric age groups are 4 to 5 years of age, 6 to 12 years of age, and 13 to 17 years of age. FDA recommends one study in adolescent patients (13 to 17 years of age) and one study in younger pediatric patients (4 to 12 years of age) to provide substantial evidence of effectiveness, as long as the following apply:

  – The duration of drug product effect is less than 12 hours

  – The shape of the PK profile is similar across age groups

  - No safety concerns exist that preclude studying specific pediatric age groups (see sections III., Methylphenidate and Amphetamine 505(b)(2) Development Programs, and IV., New Molecular Entity)

- For drug products with a long duration of effect (i.e., greater than 12 hours) and thus a greater potential to lead to important adverse events (e.g., significant effect on growth), or for new molecular entities about which little is known, safety data from pediatric patients 6 years of age and older may be necessary before the sponsor initiates studies in pediatric patients 4 to 5 years of age. FDA encourages sponsors to discuss the details and timing of their development programs with the Agency early, particularly for the studies in pediatric patients 4 to 5 years of age and, preferably, before initiating studies in pediatric patients 6 to 12 years of age.

- For drug products with a long duration of effect or with PK profiles that are not similar in different age groups, FDA encourages sponsors to discuss their development strategies with the Agency.

- The investigator should confirm the diagnosis of ADHD using a structured or semi-structured clinical interview (e.g., Kiddie Schedule for Affective Disorders and Schizophrenia, Diagnostic Interview Schedule for Children).

- The sponsor should evaluate safety and effectiveness in randomized, double-blind, placebo-controlled, parallel-group design trials. At least one randomized, fixed-dose trial examining more than one dose should be conducted. Patients should be randomized to drug or placebo, without open-label titration or dose-optimization before randomization that may obscure important safety findings.

- Potentially acceptable primary efficacy measures include the ADHD Rating Scale; the Conners Comprehensive Behavior Rating Scales; Permanent Product Measure of Performance; and the Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale. Sponsors should use a scale or version of a scale that has been appropriately validated for the age range of the patients in a given clinical trial. FDA may consider other endpoints acceptable following review by the Division of Psychiatry Products and the Clinical Outcome Assessments staff. For clinical studies with pediatric patients, the primary endpoint should be assessed in a laboratory classroom setting by a trained clinician rater. For clinical trials with adult patients, sponsors can consider using a simulated workplace environment in lieu of a laboratory classroom.

- Adverse events of special interest in stimulant drug trials include changes in vital signs, insomnia, decreased appetite, weight loss, irritability or mood changes, and psychosis. Pulse, blood pressure, and weight should be evaluated at every clinic visit. Sleep, appetite, mood, and psychotic symptoms should be assessed using specific questioning rather than relying on patients to volunteer symptoms and problems spontaneously.

C. Pregnancy

Women of reproductive potential are sometimes prescribed treatment for ADHD. Therefore, sponsors should consider inclusion of pregnant women in clinical trials when scientifically and ethically justified. If a sponsor excludes pregnant women from trial enrollment, the sponsor should provide a scientific justification.[2] In addition, FDA may also require postmarketing safety data collection pursuant to section 505(o)(3) of the FD&C Act. Sponsors should use existing stimulant drug pregnancy registries (e.g., National Pregnancy Registry for Psychiatric Medications) or establish their own registries.

III. METHYLPHENIDATE AND AMPHETAMINE 505(b)(2) DEVELOPMENT PROGRAMS

Methylphenidate and amphetamine drug products are available in multiple formulations with a variety of dosage forms and durations of effect. The safety profiles of these products are well characterized and their PD effects are tightly linked to their PK profiles. Thus, FDA believes it is reasonable to rely on safety information from a listed drug to develop new methylphenidate or amphetamine product via the 505(b)(2) application pathway and, in certain cases, it may be reasonable to rely on the efficacy information. For instance, if a 505(b)(2) applicant can establish a bridge to the relied-upon listed drug by demonstrating either bioequivalence or comparative bioavailability of the proposed drug product with the listed drug, additional clinical trials may not be necessary to support approval of the 505(b)(2) application. The sponsor should consult the FDA's drug product-specific guidances regarding trial design and data analysis for bioequivalence evaluations.[3]

Sponsors should consider the following when developing methylphenidate and amphetamine products via the 505(b)(2) application pathway:

- The listed drug(s) should be selected to reflect the active moiety or moieties of the new 505(b)(2) product. A relative bioavailability study should be conducted in adult patients to bridge the new product to each selected listed drug. In general, cross-trial bridging is not recommended.

- For drug products that are not bioequivalent to a listed drug, the sponsor should explore the following PK and PD characteristics of the drug product in the clinical development program:

[2] See the draft guidance for industry *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials* (April 2018). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[3] We note that product-specific guidances are typically used in the context of generic drug development, but the bioequivalence principles discussed in those guidances are equally applicable to sponsors of 505(b)(2) products seeking to establish bioequivalence. For the most recent version of a product-specific guidance, check the web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

  - The shape of PK profiles for drug products with complicated release features (e.g., a combination of immediate-release and extended-release components in the formulation) should be characterized in the relevant pediatric age groups and in adults to ensure consistent drug release and performance in patients of different ages.

  - For pediatric patients, the sponsor should evaluate the onset and duration of the clinical effect in an adequate and well-controlled trial conducted in a laboratory classroom setting. For adult patients, the sponsor can use a simulated workplace setting.

- A standalone PK study in each relevant pediatric age group may not be needed if a population PK model based on data available in adults can be used to simulate anticipated PK profiles in pediatric patients. The sponsor should discuss the modeling strategy with the Agency. The sponsor should use results of simulations to guide dose selection in clinical trials and inform the timing of assessments of adverse events. Confirmatory sparse PK data can be collected at designated time windows in efficacy and safety studies.

- For some clinical development programs of a methylphenidate or amphetamine 505(b)(2) product, the findings of safety and effectiveness in younger pediatric patients (4 to 12 years of age) can be extrapolated to support the use of the drug product in adolescent and adult patients. FDA strongly encourages the sponsor to discuss the development strategy with the Agency during the pre-investigational new drug application stage. Some of the factors that should be considered to allow the extrapolation include the following:

  - The 505(b)(2) product is given in the morning and has a duration of effect of 12 hours or less.

  - The shape of the PK profile of the active moiety or moieties of the 505(b)(2) product is similar in younger pediatric, adolescent, and adult patients.

  - The approved patient population of the listed drug includes younger pediatric, adolescent, and adult patients. The dose for each patient population is clearly defined.

  - Adequate bridging through a relative bioavailability study should be established between the 505(b)(2) product and the listed drug, such that the dose of the 505(b)(2) product in each patient population can be reliably derived.

- Sponsors should include pediatric patients 4 and 5 years of age in clinical studies. Although it is reasonable to extrapolate effectiveness from older pediatric patients to pediatric patients 4 to 5 years of age, clinical study data are necessary to compare the safety profile in this population to what is known about the listed drug.

- For a 505(b)(2) product (e.g., a methylphenidate product, amphetamine product) that targets a treatment duration greater than 12 hours or is not intended to be given in the morning, a study focused on safety, tolerability, and pharmacokinetics in the target

patient populations may be necessary before an evaluation of safety and effectiveness can proceed. FDA recommends specific assessments for concentrations around dinner time and sleep time in the target populations. In the relevant pediatric and adult clinical studies, assessment of both frequency and severity of insomnia, loss of appetite, body weight, and neurological/psychiatric adverse events is critical. Sponsors should perform evaluations of long-term (e.g., 12 months) growth change in pediatric patients 4 years of age and older.

IV. NEW MOLECULAR ENTITY

Unlike 505(b)(2) products, the safety, effectiveness, and PK-PD relationship for NMEs are unknown and must be evaluated in the development program (i.e., the pharmacologic properties alone are not sufficient evidence of effectiveness and safety). Although a sponsor cannot rely on information from other stimulant drug products for the evidence of effectiveness and safety, knowledge of the class and the indication can help to inform the drug development program.

- A demonstration of safety and effectiveness of stimulant drugs for the treatment of ADHD in 4- to 5-year-old pediatric patients would require at least one adequate and well-controlled clinical study in this population (21 CFR 314.126); this study should be a randomized, double-blind, placebo-controlled, parallel group study. A placebo control is necessary to provide interpretable results. The timing of such a study would depend largely on what is known about the safety of the particular investigational drug. FDA encourages sponsors to discuss the details and timing of the 4- to 5-year-old pediatric patient portion of the drug development programs early, preferably before initiating studies in 6- to 12-year-old pediatric patients.

- A sponsor should include the following safety assessments (in addition to those listed in section II., General Considerations) in the drug development program:

  - Thorough QT study or alternative agreed upon by the QT Interdisciplinary Review Team

  - Human abuse potential study

  - Long-term safety, including assessment of growth using replicated and standardized measurements of weight (using a calibrated scale) and height (using a stadiometer), for at least 1 year in prepubertal patients

REFERENCES

Kimko H, Gibiansky E, Gibiansky L, Starr HL, Berwaerts J, Massarella J, and Wiegand F, 2012, Population Pharmacodynamic Modeling of Various Extended-Release Formulations of Methylphenidate in Children with Attention Deficit Hyperactivity Disorder Via Meta-Analysis, J Pharmacokinet Pharmacodyn, 39(2):161–176.

Li L, Wang Y, Uppoor RS, Mehta MU, Farchione T, Mathis MV, and Zhu H, 2017, Exposure-Response Analyses of Blood Pressure and Heart Rate Changes for Methylphenidate in Healthy Adults, J Pharmacokinet Pharmacodyn, 44(3):245–262.