FDA Briefing Document

Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)

June 16, 2023

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office.

We have brought the following issues to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package will not include issues relevant to any final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee.

The subcommittee will discuss considerations related to dosage optimization of new drug and biological products for pediatric patients with cancer. Dosage optimization is an integral aspect of oncology drug development and is important to maximizing the safety, efficacy, and tolerability of new drugs and biological products for pediatric cancers. Unique considerations associated with dosage selection and optimization for pediatric patients with cancer include variability in pharmacokinetic (PK) and pharmacodynamic parameters (PD) by age and size, the need for age-appropriate formulations, potential for toxicities associated with long-term use, and the rarity of pediatric cancers. Representatives from the European Medicines Agency (EMA), the pediatric oncology investigator community, and the pharmaceutical industry have also been invited to present.

FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Memorandum

Date: May 24, 2023

To: Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC) Members, Consultants, and Guests

From: Martha Donoghue, MD
Associate Director for Pediatric Oncology and Rare Cancers,
Oncology Center of Excellence, Office of the Commissioner, FDA

Subject: FDA Background Package for the June 16, 2023, Meeting

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Thank you for agreeing to participate in the upcoming Pediatric Oncology Subcommittee of the ODAC meeting. The Subcommittee will discuss considerations related to dosage optimization of new drug and biological products for pediatric patients with cancer. Dosage optimization is an integral aspect of oncology drug development and is important to maximizing the safety, efficacy and tolerability of new drugs and biological products for pediatric cancers. Unique considerations associated with dosage selection and optimization in for pediatric patients with cancer include variability in pharmacokinetic (PK) and pharmacodynamic (PD) parameters by age and size, the need for age-appropriate formulations, potential for toxicities associated with long-term use, and the rarity of pediatric cancers.

In this meeting, the Subcommittee will discuss the clinical importance of dosage optimization of targeted therapies (e.g., kinase inhibitors, monoclonal antibodies, antibody-drug conjugates, and cell-based therapies) and the unique considerations and challenges associated with dosage optimization in pediatric patients with cancer. The Subcommittee will also discuss the timing of dosage optimization and strategies to facilitate efficient dosage optimization of these therapies in pediatric patients with cancer.

As always, we appreciate your time and commitment and look forward to an informative meeting on June 16, 2023.

Dosage optimization of new drug and biological products for pediatric patients with cancer

In oncology, dose-finding trials have historically been designed with the primary objectives of selecting the maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D) and making a preliminary assessment of antitumor activity at the RP2D. The MTD has typically been identified by evaluating increasing doses in a small number of patients at each dose level for short periods of time until a prespecified rate of severe or life-threatening dose-limiting toxicities (DLTs) is observed. Subsequent trials have generally evaluated the drug at the RP2D, which is often equivalent to the MTD or a dosage close to the MTD, without further efforts to optimize the dosage. This traditional dose-finding paradigm often does not adequately consider other information, such as low-grade symptomatic toxicities, the need for dosage modifications, activity, dose- and exposure- response relationships, and relevant specific populations (defined by age, organ impairment, concomitant medications or concurrent illnesses) when selecting dosages to be evaluated in subsequent trials.

This MTD-based paradigm was implemented for cytotoxic chemotherapies based on their observed steep dose-response relationships, limited drug target specificity, the desire to develop oncology drugs as quickly as possible to make them available to patients with limited treatment options, and the willingness of patients and providers to accept substantial toxicity to treat their cancer. This practice can result in suboptimal characterization of dosages prior to initiation of trials intended to support marketing applications. In some cases, doses or schedules have been modified to improve safety or tolerability after approval[1]. Dosage optimization should generally occur prior to approval in order to avoid exposing a large number of patients to a dosage that does not confer the best balance between clinical benefit and risk of toxicity.

Most targeted therapies (e.g., kinase inhibitors, monoclonal antibodies, and antibody-drug conjugates) exert an antitumor effect by interacting with a molecular pathway unique to certain cancers. The dose-response relationships for these targeted therapies can differ from that of cytotoxic chemotherapy, such that doses below the MTD may have similar efficacy with less toxicity. In some cases, the MTD may never be reached and serious toxicities may occur only after several months of treatment. Furthermore, patients may receive targeted therapies for much longer periods of time compared to cytotoxic chemotherapy, which can place them at risk for lower grade but chronic symptomatic toxicities. Such toxicities can adversely impact quality of life and limit a patient's ability to remain on the drug and derive the maximum potential benefit from treatment.

In 2021, the FDA Oncology Center for Excellence launched Project Optimus, an initiative to reform the dosage optimization and dosage selection paradigm in oncology drug development. [2] Project Optimus works with multiple stakeholders including drug companies, academia, professional societies, international regulatory authorities, and patients to advance an oncology

1 Shah M, Rahman A, Theoret MR, Pazdur R. The Drug-Dosing Conundrum in Oncology - When Less Is More. N Engl J Med. 2021 Oct 14;385(16):1445-1447. doi: 10.1056/NEJMp2109826. Epub 2021 Oct 9. PMID: 34623789.
2 https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus

dosing paradigm centered around identification of an optimized dosage(s) that provides the desired therapeutic effect while also minimizing toxicity.

The January 2023 FDA draft Guidance for Industry, *Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases* provides FDA's current thinking on approaches to identifying an optimized dosage(s) for human drugs and biological products for the treatment of oncologic diseases during clinical development and prior to submitting an application for approval.[3] This guidance document provides recommendations regarding the collection and interpretation of clinical PK, PD, and pharmacogenomic data; trial designs to compare multiple dosages in order to aid dosage selection; methods to assess safety and tolerability; drug formulation considerations relevant to dosing; and approaches to dosage selection for subsequent indications and usages of a previously approved drug. FDA recommends that this guidance be considered during clinical development to guide identification of the optimal dosage(s) of oncology products, along with the International Conference on Harmonisation (ICH) E4 guidance on *Dose-Response Information to Support Drug Registration,* and the FDA Guidances for Industry, *Population Pharmacokinetics* and *Exposure-Response Relationships – Study Design, Data Analysis and Regulatory Applications*.[4,5,6]

Drug development in pediatric patients with cancer often occurs after there is considerable experience with the drug in adult patients with cancer. Thus, data from adults is routinely used to help identify the dosages to be evaluated in pediatric trials. The starting dose in pediatric dose finding trials is often selected as 80% of the recommended dose in adults, adjusted for body weight or body surface area. The starting dose in pediatrics that is equal to that of the adult RP2D, adjusted for body weight or body surface area may also be selected, especially when the adult MTD exceeds the RP2D. In pediatric oncology trials, incremental dose increases are usually relatively small (with dose increases often in the 25-30% range) and a limited number of dose levels are typically explored since the pediatric RP2D is generally similar to the adult RP2D.[7] One published review of pediatric dose-finding trials of targeted therapies reported that the pediatric RP2D ranged between 90% to 130% of the adult RP2D for 13 (69%) of the 19 trials reviewed; the majority of differences between the adult and pediatric RP2Ds occurred in trials of targeted therapies in which DLTs were not observed and the MTD could not be determined.[8]

The September 2022 FDA Draft Guidance for Industry entitled *General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products* provides recommendations regarding clinical pharmacology information that can support selection of optimized recommended dosages for pediatric patients. The guidance also describes how

3 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/optimizing-dosage-human-prescription-drugs-and-biological-products-treatment-oncologic-diseases
4 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e4-dose-response-information-support-drug-registration
5 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/population-pharmacokinetics.
6 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/exposure-response-relationships-study-design-data-analysis-and-regulatory-applications
7 Smith M, Bernstein M, Bleyer WA, Borsi JD, Ho P, Lewis IJ, et al. Conduct of phase I trials in children with cancer. J Clin Oncol. 1998;16(3):966–978.
8 Doussau A, Geoerger B, Jiménez I, Paoletti X. Innovations for phase I dose-finding designs in pediatric oncology clinical trials. Contemp Clin Trials. 2016 Mar;47:217-27. doi: 10.1016/j.cct.2016.01.009. Epub 2016 Jan 26. PMID: 26825023; PMCID: PMC4818190.

quantitative approaches can leverage an understanding of the disease in adults and pediatrics and of the dose- or exposure-response relationships to help design pediatric trials.[9] In this guidance, FDA recommends that sponsors collect and analyze PK and, whenever possible, PD data, in pediatric trials to evaluate the relationship between the two (i.e., the PK-PD or exposure-response relationships). This information can also lead to a better understanding of whether the PK-PD relationships of the drug in pediatrics are similar to those observed in adults and can help derive rational dosing strategies in pediatrics. In addition, exposure-response information can support pediatric dosage selection, dosage optimization and formulation development. When applicable, similarity in exposure-response relationships on a clinically relevant biomarker or an appropriate clinical endpoint can also contribute to an assessment of the appropriateness of efficacy extrapolation from adults to pediatric patients. The guidance also emphasizes that modeling and simulation approaches can help reduce the uncertainty about dosing regimen in pediatric populations. Model-informed drug development (MIDD), including population PK (popPK) and physiologically based PK (PBPK) approaches, have been applied in regulatory applications for pediatric drug development.[10] In addition, the ICH E11A Pediatric Extrapolation guidance provides recommendations on extrapolation approaches and potential study designs, depending on a continuum of the level of evidence/prior knowledge and confidence level in similarity of disease and response to treatment between adults and pediatrics.[11]

Although the goals and fundamental principles of dosage optimization outlined in the FDA Guidance *Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases* apply to drugs being developed for adult and pediatric oncologic diseases, there are unique considerations associated with dosage selection and optimization in pediatric patients with cancer. Such considerations include variability in PK and PD parameters by age and size, the need for age-appropriate formulations, potential for toxicities associated with long-term use in children across stages of development, and the rarity of pediatric cancers. Additionally, there is increasing awareness and interest in studying new drugs and biological products in combination with either established treatment regimens (i.e., standard of care) or other novel therapies to address potential drug resistance mechanisms and maximize the potential for meaningful antitumor activity. Taken together, these considerations increase the complexity associated with identifying the optimized dosage(s) of drugs and biological products for pediatric patients with cancer. Therefore, well-considered, tailored approaches to dosage optimization are needed to achieve the goals and benefits of an optimized dosage while maintaining feasibility and promoting efficient pediatric cancer drug development. Such approaches can leverage information obtained in adults (when available), employ thoughtful dose-finding trial designs to maximize the information that can be obtained from smaller numbers of patients, and utilize modern clinical pharmacology approaches such as MIDD. Early, collaborative interactions with regulatory authorities such as the FDA and EMA are also recommended to develop a comprehensive dosage optimization plan to help achieve this goal.

9 https://www fda.gov/regulatory-information/search-fda-guidance-documents/general-clinical-pharmacology-considerations-pediatric-studies-drugs-including-biological-products

10 Bi, Y, J Liu, L Li, J Yu, A Bhattaram, M Bewernitz, R Li, C Liu, J Earp, L Ma, L Zhuang, Y Yang, X Zhang, H Zhu, and Y Wang, 2019, Role of Model-Informed Drug Development in Pediatric Drug Development, Regulatory Evaluation, and Labeling, J Clin Pharmacol, 59(S1):S104-S111.

11 https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-guideline-e11a-pediatric-extrapolation-step-2b_en.pdf

Draft Points of Consideration Related to Dosage Optimization of New Drug and Biological Products for Pediatric Patients with Cancer

1. Discuss the clinical importance of identifying an optimized dosage of targeted drugs and biological products for pediatric patients with cancer.

2. Discuss the unique considerations associated with dosage selection and optimization in pediatric oncology and potential challenges to identifying an optimized dosages for new drugs and biological products for pediatric cancers. Discuss potential strategies to address these challenges.

3. For drugs and biological products being developed in both adult and pediatric patients with cancer, consider how the timing of dosage selection in adults impacts the timing of trial initiation and dosage optimization in pediatric patients with cancer.

4. Discuss the considerations for dosage optimization in pediatric oncology clinical trials investigating novel combination therapies (two or more previously unapproved drugs or two drugs not previously studied in pediatric patients with cancer).

APPENDICES

APPENDIX-1

Draft Guidance: Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases Guidance for Industry

Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases

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 Mirat Shah at 301-796-8547 or Stacy Shord at 301-796-6261.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases

Guidance for Industry

Additional copies are available from:
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U.S. Department of Health and Human Services
Food and Drug Administration
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Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases
Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist sponsors in identifying the optimal dosage(s)[2] for human prescription drugs[3] or biological products for the treatment of oncologic diseases during clinical development and prior to submitting an application for approval for a new indication and usage.

This guidance should be considered along with the International Conference on Harmonisation (ICH) E4 guidance on *Dose-Response Information to Support Drug Registration* when identifying the optimal dosage(s).[4]

Additional information on related topics can be found in:

- Draft guidance for industry *Population Pharmacokinetics* (July 2019).[5]
- Guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications* (April 2003).

This guidance does not address selection of the starting dosage for first-in-human trials nor does it address dosage optimization for radiopharmaceuticals, cellular and gene therapy products, microbiota, or cancer vaccines.

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

[1] This guidance has been prepared by the Oncology Center of Excellence (OCE), the Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.
[2] For the purpose of this guidance, dosage refers to the dose and schedule (i.e., the recommended interval between doses and duration of treatment) and dose refers to the quantity of the drug. Optimal dosage is the dosage that can maximize the benefit/risk profile or provide the desired therapeutic effect while minimizing toxicity.
[3] For the purposes of this guidance, references to drugs include drugs approved under section 505 of the FD&C Act (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262).
[4] See guideline for industry *ICH Topic E4 Dose Response Information to Support Drug Registration* (November 1994). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www fda.gov/RegulatoryInformation/Guidances/default htm.
[5] When final, this guidance will represent the FDA's current thinking on this topic.

as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

Dose-finding trials (e.g., trials that include dose-escalation and dose-expansion portions with the primary objective of selecting the recommended phase II dose) for oncology drugs have historically been designed to determine the maximum tolerated dose (MTD). This paradigm was developed for cytotoxic chemotherapy drugs based on their observed steep dose-response, their limited drug target specificity, and the willingness of patients and providers to accept substantial toxicity to treat a serious, life-threatening disease. The MTD was identified by evaluating stepwise, increasing doses in a small number of patients at each dose for short periods of time until a prespecified rate of severe or life-threatening dose-limiting toxicities (DLTs) was observed. Sponsors typically administered the MTD, or a dosage close to the MTD, in subsequent clinical trials without further efforts to optimize the dosage.

Most modern oncology drugs, such as kinase inhibitors and monoclonal antibodies, are designed to interact with a molecular pathway unique to an oncologic disease(s) (i.e., targeted therapies). These targeted therapies demonstrate different dose-response relationships compared to cytotoxic chemotherapy, such that doses below the MTD may have similar efficacy to the MTD but with fewer toxicities. Additionally, the MTD may never be reached in certain situations. Compared to, for example, cytotoxic chemotherapies, patients may receive targeted therapies for much longer periods, potentially leading to lower grade but persistent symptomatic toxicities, which can be more challenging to tolerate over time. Nevertheless, the dosage administered in a registration trial(s) (i.e., the trial or substudy designed to evaluate safety and effectiveness and support a marketing application) for these targeted therapies is often the MTD or the highest dosage administered in the dose-escalating trial if the MTD is not defined. This paradigm can result in a recommended dosage that is poorly tolerated, adversely impacts functioning and quality-of-life, and moreover, affects a patient's ability to remain on a drug and thereby derive maximal clinical benefit. Additionally, patients who experience adverse reactions from one treatment may have difficulty tolerating future treatments, especially if there are overlapping toxicities.

The traditional MTD paradigm often does not adequately evaluate other data, such as low-grade symptomatic toxicities (i.e., grade 1-2), dosage modifications, drug activity, dose- and exposure-response relationships, and relevant specific populations (defined by age, organ impairment, concomitant medications or concurrent illnesses). Dose-finding trials that investigate a range of dosage(s) and select the dosages to be further investigated based on clinical data and an understanding of dose- and exposure-response, represent a more informed approach to identify the optimal dosage(s).

Despite therapeutic progress, most advanced cancers remain incurable, and patients continue to have high unmet medical need for effective and tolerable therapies. Rapid access to safe and efficacious therapies remains critical. Some oncology development programs follow a seamless approach, characterized by rapid transitions between initial dose-finding trials and registration trial(s) to expedite development. With sufficient planning, identifying an optimal dosage(s) can

be aligned with the goal of expediting clinical development, and strategies to optimize the dosage can be merged into a seamless development program.[6]

Dosage optimization prior to approval is recommended because delaying until after approval may result in large numbers of patients being exposed to a poorly tolerated dosage or one without maximal clinical benefit. Furthermore, conducting clinical trials to compare multiple dosages may be challenging to complete once a drug is approved for a given indication.

III. DOSE OPTIMIZATION RECOMMENDATIONS

Dosages selected for administration in a clinical trial(s) should be adequately supported by data appropriate to the stage of development for each indication and usage. Relevant nonclinical[7] and clinical data, as well as the dose- and exposure-response relationships for safety and efficacy should be evaluated to select a dosage(s) for clinical trial(s). An approach where a dosage is chosen for a trial without adequate justification or consideration of relevant data may not be acceptable because FDA may determine that patients are exposed to unreasonable and significant risk, or there is insufficient information to determine risk, or the design of the trial is deficient to meet its stated objectives.[8]

Sponsors, including sponsors pursuing development of a drug under an FDA expedited program (e.g., breakthrough therapy designation), should plan their development programs such that identification of the optimal dosage(s) can occur prior to or concurrently with the establishment of the drug's safety and effectiveness. Sponsors should note that development of a drug under an FDA expedited program (e.g., breakthrough therapy designation) is not a sufficient justification to avoid identifying an optimal dosage(s) prior to submitting a marketing application. FDA is available to discuss strategies to determine the optimal dosage(s), and sponsors are strongly encouraged to discuss their plans for dosage optimization with FDA at relevant milestone meetings.

FDA recommends the following to identify the optimal dosage(s):

A. Collection and Interpretation of Clinical Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Data

- Dose-finding trials should include PK sampling and an analysis plan such that PK data are of sufficient quality and quantity to allow an adequate characterization of the PK (e.g., linearity, absorption, elimination) of an oncology drug following the administration of multiple dosages.[9]

[7] See guidance for industry *Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics* (March 2022).

[7] We support the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if it they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

[8] See 312.42(b).

[9] See draft guidance for industry *Population Pharmacokinetics* (July 2019). When final, this guidance will represent the FDA's current thinking on this topic.

- The PK sampling and analysis plan should also be sufficient to support population PK and dose- and exposure-response analyses for safety and efficacy.[10]
- Following the completion of the dose-finding trial(s), population PK[9] and exposure-response[10] analyses, data should be evaluated along with the anti-tumor activity, safety, and tolerability data to select dosage(s) for further evaluation.
- For oral drugs, the effect of food on PK and safety should be evaluated early in drug development to support the relative administration of the dosage(s) selected for evaluation in a registration trial(s) with food.[11]
- Clinical trials should enroll an appropriately broad population[12,13,14,15,16] to allow assessment of the dosage(s) across relevant subpopulations.
- Population PK data should be evaluated to identify specific populations (e.g., defined based on weight, age, sex, race and ethnicity, or organ impairment) in which the PK demonstrate clinically meaningful differences in exposure.
- Relevant covariates should be incorporated into the exposure-response analyses to identify potential differences in safety or effectiveness for relevant subpopulations.[10]
- When appropriately justified, simulated exposure metrics may be used to conduct exposure-response analyses to evaluate alternative dosages, if applicable, in the relevant subpopulations. Alternative dosages for relevant subpopulations should be incorporated into a registration trial(s) when feasible and appropriate.
- A sampling and analysis plan for PD and pharmacogenetic data[17,18] should be considered if appropriate.
- The proposed sampling and analysis plan(s) should be submitted to FDA for review.

[10] See guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications* (April 2003).
[11] See draft guidance for industry *Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations* (February 2019). When final, this guidance will represent the FDA's current thinking on this topic.
[12] See guidance for industry and FDA staff *Collection of Race and Ethnicity Data in Clinical Trial* (October 2016).
[13] See guidance for industry *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020).
[14] See draft guidance for industry *Cancer Clinical Trial Eligibility Criteria: Available Therapy in Non-Curative Settings* (June 2021). When final, this guidance will represent the FDA's current thinking on this topic.
[15] See guidance for industry *Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies* (July 2020).
[16] See draft guidance for industry *Diversity Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials (April 2022).* When final, this guidance will represent the FDA's current thinking on this topic.
[17] See guidance for industry *Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling* (January 2013).
[18] See guidance for industry *E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories* (April 2008).

B. Trial Designs to Compare Multiple Dosages

- Multiple dosages should be compared in a clinical trial(s) designed to assess activity, safety, and tolerability to decrease uncertainty with identifying an optimal dosage(s) in a marketing application.
    - These dosages should be selected based on the relevant nonclinical and clinical data that provide a preliminary understanding of dose- and exposure-response relationships for activity, safety, and tolerability.
    - Prior to initiating a trial directly comparing multiple dosages, it may be reasonable to add more patients to dose-level cohorts in a dose-finding trial which are being considered for further development. This would allow for further assessment of activity and safety.
- A recommended trial design to compare these dosages is a randomized, parallel dose-response trial.
    - Randomization when feasible (rather than enrolling patients to non-randomized dosage cohorts) ensures similarity of patients receiving each dosage and interpretability of dose- and exposure-response relationships.
    - The trial should be sized to allow for sufficient assessment of activity, safety, and tolerability for each dosage. The trial does not need to be powered to demonstrate statistical superiority of a dosage or statistical non-inferiority among the dosages.
    - An adaptive design to stop enrollment of patients to one or more dosage arms of a clinical trial following an interim assessment of efficacy and/or safety could be considered.
- Multiple dosages may be compared prior to a registration trial(s) or as part of a registration trial(s) by adding an additional dosage arm(s).
    - When a registration trial contains multiple dosages and a control arm and is designed to establish superior efficacy of one of the dosages compared to the control arm, the trial design should provide strong control of Type I error. The analysis plan should specify a multiple-testing procedure which accounts for testing multiple treatments versus a control as well as any interim assessments after which an inferior arm is dropped.
- If safety and efficacy data from multiple dosages will be used to support a marketing application, this approach should be discussed with FDA early in clinical development.

C. Safety and Tolerability

- The duration of exposure; the proportion of patients who are able to receive all planned doses; the percentage of patients that require dosage interruptions, dose reductions, and drug discontinuations for adverse reactions; and the percentage of patients with serious adverse reactions (including fatal adverse reactions), should be compared across the multiple dosages.

- Safety monitoring rules should be pre-specified for trial designs that include dosages associated with a high percentage of dosage modifications or serious adverse reactions. The protocol should clearly state what action will be taken if the percentage of dosage modifications or serious adverse reactions is too high. Such actions may include pausing the trial so the safety monitoring committee can review these events, changing the starting dosage for future patients, and/or discontinuing the trial.

- Specific adverse reactions, including those that are symptomatic and may be reported as less severe (e.g., Grade 1-2 diarrhea), may still significantly affect a patient's ability to remain on the drug for extended periods. The frequency and impact (i.e., the frequency of drug discontinuation, or paused/reduced dose) of such reactions should be carefully assessed and considered in selecting the dosage(s) for subsequent clinical trials.

- Some oncology drugs may be associated with early-onset, serious, or life-threatening toxicities which may lessen in severity or not occur with subsequent administration. Evaluation of an alternative dosing strategy, such as stepwise dosing (i.e., titration), to improve tolerability could be considered.

- Patient-reported outcomes (PRO) can provide a systematic and quantitative assessment of expected symptomatic adverse events and their impact on function. Inclusion of PROs should be considered to enhance the assessment of tolerability in early phase dosage finding trials. Recommendations for PRO instrument selection and assessment frequency can be found in the draft Guidance for Industry, *Core Patient-Reported Outcomes in Cancer Clinical Trials* (June 2021).[19]

- Engaging with patients and other key stakeholders, such as advocacy groups in a given disease area, will provide valuable input on important safety and tolerability considerations when selecting the optimal dosage(s).

D. Drug Formulation

- Various dose strengths should be available to allow multiple dosages to be evaluated in clinical trials. Perceived difficulty in manufacturing multiple dose strengths is an insufficient rationale for not comparing multiple dosages in clinical trials.

- For oral use, the appropriateness of the size and number of tablets or capsules required for an individual dose should be considered when selecting the final dosage form and strength(s).

- For parenteral use, the appropriateness of the final concentration and volume to be administered should be considered when selecting the final dosage form and strength(s).

E. Subsequent Indications and Usages

- Different dosages may be needed in different disease settings or oncologic diseases based on potential differences in tumor biology, patient population, treatment setting, and concurrent therapies (for combination regimens), among other factors. Applicable nonclinical and clinical data should be considered to support the proposed

[19] When final, this guidance will represent the FDA's current thinking on this topic.

dosage to be evaluated in a registration trial(s) to support a subsequent indication and usage.

- Strong rationale for choice of dosage should be provided before initiating a registration trial(s) to support a subsequent indication and usage, especially for oncologic diseases not adequately represented in completed dose-finding trials or for new combination regimens. If sufficient rationale for choice of dosage cannot be provided, additional dose-finding should be conducted.

APPENDIX-2

Guideline for Industry: Dose-Response Information to Support Drug Registration

Guideline for Industry

Dose-Response Information to Support Drug Registration

ICH-E4

November 1994

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GUIDELINE FOR INDUSTRY[1]

DOSE-RESPONSE INFORMATION TO SUPPORT DRUG REGISTRATION

I. INTRODUCTION

A. Purpose of Dose-Response Information

Knowledge of the relationships among dose, drug concentration drug concentration in blood, and clinical response (effectiveness and undesirable effects) is important for the safe and effective use of drugs in individual patients. This information can help identify an appropriate starting dose, the best way to adjust dosage to the needs of a particular patient, and a dose beyond which increases would be unlikely to provide added benefit or would produce unacceptable side effects. Dose-concentration, concentration- and/or dose-response information is used to prepare dosage and administration instructions in product labeling. In addition, knowledge of dose-response may provide an economical approach to global drug development, by enabling multiple regulatory agencies to make approval decisions from a common

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[1]This guideline was developed within the Expert Working Group (Efficacy) of the International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, March 10, 1994. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and the USA. This guideline was published in the Federal Register on November 9, 1994 (59 FR 55972) and is applicable to both drug and biological products. In the past, guidelines have generally been issued under § 10.90(b) [21 CFR 10.90(b)], which provides for the use of guidelines to state procedures or standards of general applicability that are not legal requirements but that are acceptable to FDA. The agency is now in the process of revising §10.90(b). Therefore, this guideline is not being issued under the authority of §10.90(b), and it does not create or confer any rights, privileges or benefits for or on any person, nor does it operate to bind FDA in any way. For additional copies of this guideline contact the Executive Secretariat Staff, HFD-8, Center for Drug Evaluation and Research, 7500 Standish Place, Rockville, MD, 20855, 301-594-1012. An electronic version of this guideline is also available via Internet by connecting to the CDER FTP server (CDVS2.CDER.FDA.GOV) using the FTP protocol.

database.

Historically, drugs have often been initially marketed at what were later recognized as excessive doses (i.e., doses well onto the plateau of the dose-response curve for the desired effect), sometimes with adverse consequences (e.g., hypokalemia and other metabolic disturbances with thiazide-type diuretics in hypertension). This situation has been improved by attempts to find the smallest dose with a discernible useful effect or a maximum dose beyond which no further beneficial effect is seen, but practical study designs do not exist to allow for precise determination of these doses. Further, expanding knowledge indicates that the concepts of minimum effective dose and maximum useful dose do not adequately account for individual differences and do not allow a comparison, at various doses, of both beneficial and undesirable effects. Any given dose provides a mixture of desirable and undesirable effects, with no single dose necessarily optimal for all patients.

B. Use of Dose-Response Information in Choosing Doses

What is most helpful in choosing the starting dose of a drug is knowing the shape and location of the population (group) average dose-response curve for both desirable and undesirable effects. Selection of dose is best based on that information, together with a judgment about the relative importance of desirable and undesirable effects. For example, a relatively high starting dose (on or near the plateau of the effectiveness dose-response curve) might be recommended for a drug with a large demonstrated separation between its useful and undesirable dose ranges or where a rapidly evolving disease process demands rapid effective intervention. A high starting dose, however, might be a poor choice for a drug with a small demonstrated separation between its useful and undesirable dose ranges. In these cases, the recommended starting dose might best be a low dose exhibiting a clinically important effect in even a fraction of the patient population, with the intent to titrate the dose upwards as long as the drug is well tolerated. Choice of a starting dose might also be affected by potential intersubject variability in pharmacodynamic response to a given blood concentration level, or by anticipated intersubject pharmacokinetic differences, such as could arise from nonlinear kinetics, metabolic polymorphism, or a high potential for pharmacokinetic drug-drug interactions. In these cases, a lower starting dose would protect patients who obtain higher blood concentrations. It is entirely possible that different physicians and even different regulatory authorities, looking at the same data, would make different choices as to the appropriate starting doses, dose-titration steps, and maximum recommended dose, based on different perceptions of risk/benefit

relationships. Valid dose response data allow the use of such judgment.

In adjusting the dose in an individual patient after observing the response to an initial dose, what would be most helpful is knowledge of the shape of individual dose-response curves, which is usually not the same as the population (group) average dose-response curve. Study designs that allow estimation of individual dose-response curves could therefore be useful in guiding titration, although experience with such designs and their analysis is very limited.

In utilizing dose-response information, it is important to identify, to the extent possible, factors that lead to differences in pharmacokinetics of drugs among individuals, including demographic factors (e.g., age, gender, race), other diseases (e.g., renal or hepatic failure), diet, concurrent therapies, or individual characteristics (e.g., weight, body habitus, other drugs, metabolic differences).

C. Uses of Concentration-Response Data

Where a drug can be safely and effectively given only with blood concentration monitoring, the value of concentration-response information is obvious. In other cases, an established concentration-response relationship is often not needed, but may be useful: (1) For ascertaining the magnitude of the clinical consequences of pharmacokinetic differences, such as those due to drug-disease (e.g., renal failure) or drug-drug interactions; or (2) for assessing the effects of the altered pharmacokinetics of new dosage forms (e.g., controlled release formulation) or new dosage regimens without need for additional clinical trial data, where such assessment is permitted by regional regulations. Prospective randomized concentration-response studies are obviously critical to defining concentration monitoring therapeutic "windows," but are also useful when pharmacokinetic variability among patients is great; in that case, a concentration-response relationship may in principle be discerned in a prospective study with a smaller number of subjects than could the dose-response relationship in a standard dose-response study. Note that collection of concentration-response information does not imply that therapeutic blood level monitoring will be needed to administer the drug properly. Concentration-response relationships can be translated into dose-response information. Concentration-response information can also allow selection of doses (based on the range of concentrations they will achieve) most likely to lead to a satisfactory response. Alternatively, if the relationships between concentration and observed effects (e.g., an undesirable or desirable pharmacologic effect) are defined, the drug can be titrated according to patient response without the need for further

blood level monitoring.

D. Problems With Titration Designs

A study design widely used to demonstrate effectiveness utilizes dose titration to some effectiveness or safety endpoint. Such titration designs, without careful analysis, are usually not informative about dose-response relationships. In many studies, there is a tendency to spontaneous improvement over time that is not easily distinguishable from an increased response to higher doses or cumulative drug exposure. This leads to a tendency to choose, as a recommended dose, the highest dose used in such studies that was reasonably well tolerated. Historically, this approach has often led to a dose that was well in excess of what was really necessary, resulting in increased undesirable effects, e.g., to high-dose diuretics used for hypertension. In some cases, notably where an early answer is essential, the titration-to-highest-tolerable-dose approach is acceptable, because it often requires a minimum number of patients. For example, the first marketing of zidovudine (AZT) for treatment of people with acquired immune deficiency syndrome (AIDS) was based on studies at a high dose; later studies showed that lower doses were as effective and far better tolerated. The urgent need for the first effective anti-HIV (human immunodeficiency virus) treatment made the absence of dose-response information at the time of approval reasonable (with the condition that more data were to be obtained after marketing), but in less urgent cases this approach is discouraged.

E. Interactions Between Dose-Response and Time

The choice of the size of an individual dose is often intertwined with the frequency of dosing. In general, when the dose interval is long compared to the half-life of the drug, attention should be directed to the pharmacodynamic basis for the chosen dosing interval. For example, there might be a comparison of the long dose interval regimen with the same dose in a more divided regimen, looking, where this is feasible, for persistence of desired effect throughout the dose interval and for adverse effects associated with blood level peaks. Within a single dose interval, the dose-response relationships at peak and trough blood levels may differ and the relationship could depend on the dose interval chosen.

Dose-response studies should take time into account in a variety of other ways. The study period at a given dose should be long enough for the full effect to be realized, whether delay is the result of pharmacokinetic or pharmacodynamic factors. The dose-response may also be different for

morning versus evening dosing. Similarly, the dose-response relationship during early dosing may not be the same as in the subsequent maintenance dosing period. Responses could also be related to cumulative dose, rather than daily dose, to duration of exposure (e.g., tachyphylaxis, tolerance, or hysteresis) or to the relationships of dosing to meals.

II. OBTAINING DOSE-RESPONSE INFORMATION

A. Dose-Response Assessment Should Be an Integral Part of Drug Development

Assessment of dose-response should be an integral component of drug development with studies designed to assess dose-response an inherent part of establishing the safety and effectiveness of the drug. If development of dose-response information is built into the development process it can usually be accomplished with no loss of time and minimal extra effort compared to development plans that ignore dose-response.

B. Studies in Life-Threatening Diseases

In particular therapeutic areas, different therapeutic and investigational behaviors have evolved; these affect the kinds of studies typically carried out. Parallel dose-response study designs with placebo, or placebo-controlled titration study designs (very effective designs, typically used in studies of angina, depression, hypertension, etc.) would not be acceptable in the study of some conditions, such as life-threatening infections or potentially curable tumors, at least if there were effective treatments known. Moreover, because in those therapeutic areas considerable toxicity could be accepted, relatively high doses of drugs are usually chosen to achieve the greatest possible beneficial effect rapidly. This approach may lead to recommended doses that deprive some patients of the potential benefit of a drug by inducing toxicity that leads to cessation of therapy. On the other hand, use of low, possibly subeffective, doses, or of titration to desired effect may be unacceptable, as an initial failure in these cases may represent an opportunity for cure forever lost.

Nonetheless, even for life-threatening diseases, drug developers should always be weighing the gains and disadvantages of varying regimens and considering how best to choose dose, dose-interval and dose-escalation steps. Even in indications involving life-threatening diseases, the highest tolerated dose, or the dose with the largest effect on a surrogate marker will not always be the optimal dose. Where only a

single dose is studied, blood concentration data, which will almost always show considerable individual variability due to pharmacokinetic differences, may retrospectively give clues to possible concentration-response relationships.

Use of just a single dose has been typical of large-scale intervention studies (e.g., post-myocardial infarction studies) because of the large sample sizes needed. In planning an intervention study, the potential advantages of studying more than a single dose should be considered. In some cases, it may be possible to simplify the study by collecting less information on each patient, allowing study of a larger population treated with several doses without significant increase in costs.

C. Regulatory Considerations When Dose-Response Data Are Imperfect

Even well-laid plans are not invariably successful. An otherwise well-designed dose-response study may have utilized doses that were too high, or too close together, so that all appear equivalent (albeit superior to placebo). In that case, there is the possibility that the lowest dose studied is still greater than needed to exert the drug's maximum effect. Nonetheless, an acceptable balance of observed undesired effects and beneficial effects and beneficial effects might make marketing at one of the doses studied reasonable. This decision would be easiest, of course, if the drug had special value, but even if it did not, in light of the studies that partly defined the proper dose range, further dose-finding might be pursued in the postmarketing period. Similarly, although seeking dose response data should be a goal of every development program, approval based on data from studies using a fixed single dose or a defined dose range (but without valid dose response information) might be appropriate where benefit from a new therapy in treating or preventing a serious disease is clear.

D. Examining the Entire Database for Dose-Response Information

In addition to seeking dose-response information from studies specifically designed to provide it, the entire database should be examined intensively for possible dose-response effects. The limitations imposed by certain study design features should, of course, be appreciated. For example, many studies titrate the dose upward for safety reasons. As most side effects of drugs occur early and may disappear with continued treatment, this can result in a spuriously higher rate of undesirable effects at the lower doses. Similarly, in studies where patients are titrated to a desired response, those patients relatively unresponsive to the drug are more likely to receive the higher dose, giving an apparent, but misleading,

inverted "U-shaped" dose-response curve. Despite such limitations, clinical data from all sources should be analyzed for dose-related effects using multivariate multivariate or other approaches, even if the analyses can yield principally hypotheses, not definitive conclusions. For example, an inverse relation of effect to weight or creatinine clearance could reflect a dose-related covariate relationship. If pharmacokinetic screening (obtaining a small number of steady-state blood concentration measurements in most Phase 2 and Phase 3 study patients) is carried out, or if other approaches to obtaining drug concentrations during trials are used, a relation of effects (desirable or undesirable) to blood concentrations may be discerned. The relationship may by itself be a persuasive description of concentration-response or may suggest further study.

III. STUDY DESIGNS FOR ASSESSING DOSE RESPONSE

A. General

The choice of study design and study population in dose-response trials will depend on the phase of development, the therapeutic indication under investigation, and the severity of the disease in the patient population of interest. For example, the lack of appropriate salvage therapy for life-threatening or serious conditions with irreversible outcomes may ethically preclude conduct of studies at doses below the maximum tolerated dose. A homogeneous patient population will generally allow achievement of study objectives with small numbers of subjects given each treatment. On the other hand, larger, more diverse populations allow detection of potentially important covariate effects.

In general, useful dose-response information is best obtained from trials specifically designed to compare several doses. A comparison of results from two or more controlled trials with single fixed doses might sometimes be informative, e.g., if control groups were similar, although even in that case, the many across-study differences that occur in separate trials usually make this approach unsatisfactory. It is also possible in some cases to derive, retrospectively, blood concentration-response relationships from the variable concentrations attained in a fixed-dose trial. While these analyses are potentially confounded by disease severity or other patient factors, the information can be useful and can guide subsequent studies. Conducting dose-response studies at an early stage of clinical development may reduce the number of failed Phase 3 trials, speeding the drug development process and conserving development resources.

Pharmacokinetic information can be used to choose doses that ensure adequate spread of attained concentration-response values and diminish or eliminate overlap between attained concentrations in dose-response trials. For drugs with high pharmacokinetic variability, a greater spread of doses could be chosen. Alternatively, the dosing groups could be individualized by adjusting for pharmacokinetic covariates (e.g., correction for weight, lean body mass, or renal function) or a concentration-controlled study could be carried out.

As a practical matter, valid dose-response data can be obtained more readily when the response is measured by a continuous or categorical variable, is relatively rapidly obtained after therapy is started, and is rapidly dissipated after therapy is stopped (e.g., blood pressure, analgesia, bronchodilation). In this case, a wider range of study designs can be used and relatively small, simple studies can give useful information. Placebo-controlled individual subject titration designs typical of many early drug development studies, for example, properly conducted and analyzed (quantitative analysis that models and estimates the population and individual dose-response relationships), can give guidance for more definitive parallel, fixed-dose, dose-response studies or may be definitive on their own.

In contrast, when the study endpoint or adverse effect is delayed, persistent, or irreversible (e.g., stroke or heart prevention, asthma prophylaxis, arthritis treatments with late onset response, survival in cancer, treatment of depression), titration and simultaneous assessment of response is usually not possible, and the parallel dose-response study is usually needed. The parallel dose-response study also offers protection against missing an effective dose because of an inverted "U-shaped" (umbrella or bell-shaped) dose-response curve, where higher doses are less effective than lower doses, a response that can occur, for example, with mixed agonist-antagonists.
Trials intended to evaluate dose- or concentration-response should be well-controlled, using randomization and blinding (unless blinding is unnecessary or impossible) to assure comparability of treatment groups and to minimize potential patient, investigator, and analyst bias, and should be of adequate size.

It is important to choose as wide a range of doses as is compatible with practicality and patient safety to discern clinically meaningful differences. This is especially important where there are no pharmacologic or plausible surrogate endpoints to give initial guidance as to dose.

B. Specific Trial Designs

A number of specific study designs can be used to assess dose-response. The same approaches can also be used to measure concentration-response relationships. Although not intended to be an exhaustive list, the following approaches have been shown to be useful ways of deriving valid dose-response information. Some designs outlined in this guidance are better established than others, but all are worthy of consideration. These designs can be applied to the study of established clinical endpoints or surrogate endpoints.

1. Parallel Dose-Response

Randomization to several fixed-dose groups (the randomized parallel dose-response study) is simple in concept and is a design that has had extensive use and considerable success. The fixed dose is the final or maintenance dose; patients may be placed immediately on that dose or titrated gradually (in a scheduled "forced" titration) to it if that seems safer. In either case, the final dose should be maintained for a time adequate to allow the dose-response comparison. Although including a placebo group in dose-response studies is desirable, it is not theoretically necessary in all cases; a positive slope, even without a placebo group, provides evidence of a drug effect. To measure the absolute size of the drug effect, however, a placebo or comparator with very limited effect on the endpoint of interest is usually needed. Moreover, because a difference between drug groups and placebo unequivocally shows effectiveness, inclusion of a placebo group can salvage, in part, a study that used doses that were all too high and, therefore, showed no dose-response slope, by showing that all doses were superior to placebo. In principle, being able to detect a statistically significant difference in pair-wise comparisons between doses is not necessary if a statistically significant trend (upward slope) across doses can be established using all the data. It should be demonstrated, however, that the lowest dose(s) tested, if it is to be recommended, has a statistically significant and clinically meaningful effect.

The parallel dose-response study gives group mean (population-average) dose-response, not the distribution or shape of individual dose-response curves.

It is all too common to discover, at the end of a parallel dose-response study, that all doses were too high (on the plateau of the dose-response curve), or that doses did not go high enough. A formally planned interim analysis (or other multi-stage design)

might detect such a problem and allow study of the proper dose range.

As with any placebo-controlled trial, it may also be useful to include one or more doses of an active drug control. Inclusion of both placebo and active control groups allows assessment of "assay sensitivity," permitting a distinction between an ineffective drug and an "ineffective" (null, no test) study. Comparison of dose-response curves for test and control drugs, not yet a common design, may also represent a more valid and informative comparative effectiveness/safety study than comparison of single doses of the two agents.

The factorial trial is a special case of the parallel dose-response study to be considered when combination therapy is being evaluated. It is particularly useful when both agents are intended to affect the same response variable (a diuretic and another anti-hypertensive, for example), or when one drug is intended to mitigate the side effects of the other. These studies can show effectiveness (a contribution of each component of the combination) and, in addition, provide dosing information for the drugs used alone and together.

A factorial trial employs a parallel fixed-dose design with a range of doses of each separate drug and some or all combinations of these doses. The sample size need not be large enough to distinguish single cells from each other in pair-wise comparisons because all of the data can be used to derive dose-response relationships for the single agents and combinations, i.e., a dose-response surface. These trials, therefore, can be of moderate size. The doses and combinations that could be approved for marketing might not be limited to the actual doses studied but might include doses and combinations in between those studied. There may be some exceptions to the ability to rely entirely on the response surface analysis in choosing dose(s). At the low end of the dose range, if the doses used are lower than the recognized effective doses of the single agents, it would ordinarily be important to have adequate evidence that these can be distinguished from placebo in a pair-wise comparison. One way to do this in the factorial study is to have the lowest dose combination and placebo groups be somewhat larger than other groups; another is to have a separate study of the low-dose combination. Also, at the high end of the dose range, it may be necessary to confirm the contribution of each component to the overall effect.

2. Cross-over Dose-Response

A randomized multiple cross-over study of different doses can be successful if drug effect develops rapidly and patients return to baseline conditions quickly after cessation of therapy, if responses are not irreversible (cure, death), and if patients have reasonably stable disease. This design suffers, however, from the potential problems of all cross-over studies: It can have analytic problems if there are many treatment withdrawals; it can be quite long in duration for an individual patient; and there is often uncertainty about carry-over effects (longer treatment periods may minimize this problem), baseline comparability after the first period, and period-by-treatment interactions. The length of the trial can be reduced by approaches that do not require all patients to receive each dose, such as balanced incomplete block designs.

The advantages of the design are that each individual receives several different doses so that the distribution of individual dose-response curves may be estimated, as well as the population average curve, and that, compared to a parallel design, fewer patients may be needed. Also, in contrast to titration designs, dose and time are not confounded and carry-over effects are better assessed.

3. Forced Titration

A forced titration study, where all patients move through series of rising doses, is similar in concept and limitations to a randomized multiple cross-over dose-response study, except that assignment to dose levels is ordered, not random. If most patients complete all doses, and if the study is controlled with a parallel placebo group, the forced titration study allows a series of comparisons of an entire randomized group given several doses of drug with a concurrent placebo, just as the parallel fixed-dose trial does. A critical disadvantage is that, by itself, this study design cannot distinguish response to increased dose from response to increased time on drug therapy or a cumulative drug dosage effect. It is therefore an unsatisfactory design when response is delayed, unless treatment at each dose is prolonged. Even where the time until development of effect is known to be short (from other data), this design gives poor information on adverse effects, many of which have time-dependent characteristics. A tendency toward spontaneous improvement, a very common circumstance,

will be revealed by the placebo group, but is nonetheless a problem for this design, as over time, the higher doses may find little room to show an increased effect. This design can give a reasonable first approximation of both population-average dose response and the distribution of individual dose-response relationships if the cumulative (time-dependent) drug effect is minimal and the number of treatment withdrawals is not excessive. Compared to a parallel dose-response study, this design may use fewer patients, and by extending the study duration, can be used to investigate a wide range of doses, again making it a reasonable first study. With a concurrent placebo group this design can provide clear evidence of effectiveness, and may be especially valuable in helping choose doses for a parallel dose-response study.

4. Optional Titration (Placebo-Controlled Titration to Endpoint)

In this design, patients are titrated until they reach a well-characterized favorable or unfavorable response, defined by dosing rules expressed in the protocol. This approach is most applicable to conditions where the response is reasonably prompt and is not an irreversible event, such as stroke or death. A crude analysis of such studies, e.g., comparing the effects in the subgroups of patients titrated to various dosages, often gives a misleading inverted "U-shaped" curve, as only poor responders are titrated to the highest dose. However, more sophisticated statistical analytical approaches that correct for this occurrence, by modeling and estimating the population and individual dose-response relationships, appear to allow calculation of valid dose-response information. Experience in deriving valid dose-response information in this fashion is still limited. It is important, in this design, to maintain a concurrent placebo group to correct for spontaneous changes, investigator expectations, etc. Like other designs that use several doses in the same patient, this design may use fewer patients than a parallel fixed-dose study of similar statistical power and can provide both population average and individual dose-response information. The design does, however, risk confounding of time and dose effects and would be expected to have particular problems in finding dose-response relationships for adverse effects. Like the forced titration design, it can be used to study a wide dose range and, with a concurrent placebo group, can provide clear evidence of effectiveness. It too may be especially valuable as an early study to identify doses for a definitive parallel study.

IV. GUIDANCE AND ADVICE

1. Dose response data are desirable for almost all new chemical entities entering the market. These data should be derived from study designs that are sound and scientifically based; a variety of different designs can give valid information. The studies should be well-controlled, using accepted approaches to minimize bias. In addition to carrying out formal dose-response studies, sponsors should examine the entire database for possible dose-response information.

2. The information obtained through targeted studies and analyses of the entire database should be used by the sponsor to:

    a. Identify a reasonable starting dose, ideally with specific adjustments (or a firm basis for believing none is needed) for patient size, gender, age, concomitant illness, and concomitant therapy, reflecting an integration of what is known about pharmacokinetic and pharmacodynamic variability. Depending on circumstances (the disease, the drug's toxicity), the starting dose may range from a low dose with some useful effect to a dose that is at or near the full-effect dose.

    b. Identify reasonable, response-guided titration steps, and the interval at which they should be taken, again with appropriate adjustments for patient characteristics. These steps would be based either on the shape of the typical individual's dose-effect dose-effect curves (for both desirable and undesirable effects), if individual dose-response data were available, or if not, on the shape of the population (group)-average dose-response, and the time needed to detect a change in these effects. It should be noted that methodology for finding the population (group)-average dose-response, at present, is better established than is methodology for finding individual dose-response relationships.

    c. Identify a dose, or a response (desirable or undesirable), beyond which titration should not ordinarily be attempted because of a lack of further benefit or an unacceptable increase in undesirable effects.

3. It is prudent to carry out dose-ranging or concentration-response studies early in development as well as in later stages in order to avoid failed Phase 3 studies or accumulation of a database that consists largely of exposures at ineffective or excessive doses. The endpoints of studies

may vary at different stages of drug development. For example, in studying a drug for heart failure, a pharmacodynamic endpoint might be used early (e.g., cardiac output, pulmonary capillary wedge pressure), an intermediate endpoint might be used later (e.g., exercise tolerance, symptoms) and a mortality or irreversible morbidity endpoint might be the final assessment (survival, new infarction). It should be anticipated that the dose response for these endpoints may be different. Of course, the choice of endpoints that must be studied for marketing approval will depend on the specific situation.

4. A widely used, successful, and acceptable design, but not the only study design for obtaining population average dose-response data, is the randomized parallel, dose-response study with three or more dosage levels, one of which may be zero (placebo). From such a trial, if dose levels are well chosen, the relationship of drug dosage, or drug concentration, to clinical beneficial or undesirable effects can be defined.

   Several dose levels are needed, at least two in addition to placebo, but in general, study of more than the minimum number of doses is desirable. A single dose level of drug versus placebo allows a test of the null hypothesis of no difference between drug and placebo, but cannot define the dose-response relationship. Similarly, although a linear relationship can be derived from the response to two active doses (without placebo), this approximation is usually not sufficiently informative. Study designs usually should emphasize elucidation of the dose-response function, not individual pair-wise comparisons. If a particular point on the curve, e.g., whether a certain low dose is useful, becomes an issue, it should be studied separately.

5. Dose-response data for both beneficial and undesirable effects may provide information that allows approval of a range of doses that encompass an appropriate benefit-to-risk ratio. A well-controlled dose-response study is also a study that can serve as primary evidence of effectiveness.

6. Regulatory agencies and drug developers should be open to new approaches and to the concept of reasoned and well-documented exploratory data analysis of existing or future databases in search of dose-response data. Agencies should also be open to the use of various statistical and pharmacometric techniques such as Bayesian and population methods, modeling, and pharmacokinetic- pharmacodynamic approaches. However, these approaches should not subvert the requirement for dose-response data from prospective, randomized, multi-dose-level clinical trials. Post-hoc exploratory data analysis in

search of dose-response information from databases generated to meet other objectives will often generate new hypotheses, but will only occasionally provide definitive assessment of dose-response relationships.

A variety of data analytical techniques, including increased use of retrospective population-type analyses, and novel designs (e.g., sequential designs) may help define the dose-response relationship. For example, fixed-dose designs can be reanalyzed as a continuum of dose levels if doses are refigured on a milligram per kilogram (mg/kg) basis, or adjusted for renal function, lean body mass, etc. Similarly, blood levels taken during a dose-response study may allow estimates of concentration-response relationships. Adjustment of drug exposure levels might be made on the basis of reliable information on drug-taking compliance. In all of these cases, one should always be conscious of confounding, i.e., the presence of a factor that alters both the refigured dose and response or that alters both blood level and response, compliance and response, etc.

7. Dose-response data should be explored for possible differences in subsets based on demographic characteristics, such as age, gender, or race. To do this, it is important to know whether there are pharmacokinetic differences among these groups, e.g., due to metabolic differences, differences in body habitus, or composition, etc.

8. Approval decisions are based on a consideration of the totality of information on a drug. Although dose-response information should be available, depending on the kind and degree of effectiveness shown, imperfections in the database may be acceptable with the expectation that further studies will be carried out after approval. Thus, informative dose-response data, like information on responses in special populations, on long-term use, on potential drug-drug and drug-disease interactions, is expected, but might, in the face of a major therapeutic benefit or urgent need, or very low levels of observed toxicity, become a deferred requirement.

V. REFERENCE

Federal Register. Vol. 59, No. 216, Wednesday, November 9, 1994, pages 55972-55976.

APPENDIX-3

Draft Guidance: General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products Guidance for Industry

General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products 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 90 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 CDER_OCP_GPT@fda.hhs.gov

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

September 2022
Clinical Pharmacology
Revision 1

General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products Guidance for Industry

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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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General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance assists sponsors of investigational new drug applications (INDs) and applicants of new drug applications (NDAs) under section 505 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), biologics license applications (BLAs) under section 351(a) of the Public Health Service Act (PHS Act), and supplements to such applications who are planning to conduct clinical studies in pediatric populations.[2,3,4] In addition, this guidance assists clinical investigators in the design and planning of, and Institutional Review Boards (IRBs) in the assessment of, clinical studies in pediatric populations.

Effectiveness, safety, or dose-finding studies in pediatric populations involve gathering clinical pharmacology information, such as information regarding a product's pharmacokinetics and pharmacodynamics, to inform dose selection and individualization. This guidance addresses general clinical pharmacology considerations for conducting studies so that the dosing and safety

[1] This guidance has been prepared by the Pediatric Working Group of the Office of Clinical Pharmacology in conjunction with the Pediatric Subcommittee of the Medical Policy Coordinating Committee in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, the term *sponsor* refers to both sponsors and applicants.

[3] For purposes of this guidance, references to *drugs* includes drugs approved under section 505 of the FD&C Act (21 U.S.C. 355) and biological products licensed under 351(a) of the PHS Act (42 U.S.C. 262(a)) that are regulated as drugs. Hereafter, the term *drug* will be used to refer to all such products.

[4] This guidance is applicable to BLAs submitted under section 351(a) of the PHS Act. For the Agency's thinking regarding clinical pharmacology considerations for BLAs submitted under section 351(k), see the FDA guidance entitled *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product* (December 2016). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm. Additionally, for information about the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act) in the context of biosimilar applications, see the FDA guidance entitled *Questions and Answers on Biosimilar Development and the BPCI Act (Revision 2)* (September 2021).

information for drugs in pediatric populations can be sufficiently characterized, leading to well-designed trials to evaluate effectiveness.

In general, this guidance focuses on the clinical pharmacology information (e.g., exposure-response, pharmacokinetics, and pharmacodynamics) that supports findings of effectiveness and safety and helps identify appropriate doses in pediatric populations. This guidance also describes how quantitative approaches (i.e., pharmacometrics) can use disease and exposure-response knowledge from relevant prior clinical studies to help design and evaluate future pediatric studies.

This guidance does not describe: (1) the standards for the approval of drugs in the pediatric population; (2) the determination that the course of a disease is the same in adults and pediatric populations; or (3) the clinical pharmacology studies for the development of vaccine therapies, blood products, or other products not regulated by the Center for Drug Evaluation and Research.

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 guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

Over the past several decades, the FDA has tackled the problem of inadequate testing of drugs in pediatric patients and inadequate pediatric use information in drug labeling. The Food and Drug Administration Modernization Act of 1997 (FDAMA) addressed the need for improved information about the use of drugs in the pediatric population by establishing incentives for conducting pediatric studies on drugs for which exclusivity or patent protection exists.[5] Congress subsequently passed the Best Pharmaceuticals for Children Act (BPCA)[6] in 2002 and the Pediatric Research Equity Act (PREA) in 2003.[7] Both BPCA and PREA were reauthorized in 2007.[8] In 2010, the Biologics Price Competition and Innovation Act extended certain provisions of the BPCA to biological products.[9] In 2012, BPCA and PREA were made permanent under Title V of the FDA Safety and Innovation Act (FDASIA).[10]

[5] Public Law No. 105-115, 111 Stat. 2296 (November 21, 1997).

[6] Public Law No. 107-109, 115 Stat. 1408 (January 4, 2002).

[7] Public Law No. 108-155, 117 Stat. 1936 (December 3, 2003).

[8] Food and Drug Administration Amendments Act of 2007 (FDAAA), Public Law No. 110-85, 121 Stat. 823 (September 27, 2007).

[9] See section 351(m) of the PHS Act (42 U.S.C. 262(m)).

[10] Public Law No. 11 2-144, 126 Stat. 993 (July 9, 2012).

Under BPCA, sponsors of certain applications and supplements filed under section 505 of the FD&C Act and under section 351(a) of the PHS Act can obtain an additional six months of exclusivity if, in accordance with the requirements of the statute, the sponsor submits information responding to a Written Request from the Secretary relating to the use of a drug in the pediatric population.[11]

Under PREA, sponsors of certain applications and supplements filed under section 505 of the FD&C Act or section 351(a) of the Public Health Service Act are required to submit pediatric assessments, unless they receive an applicable waiver or deferral of this requirement.[12,13] If applicable, sponsors must submit a request for a deferral or waiver as part of an initial pediatric study plan (iPSP)[14] (see section V of this guidance).

The FD&C Act requires a description of pediatric study data in labeling arising from study data submitted in response to a Written Request under BPCA and/or data from studies required under PREA, whether the findings are positive, negative, or inconclusive.[15] The PREA requirements are triggered by the submission of an application or supplement for a drug under section 505 of the FD&C Act or section 351 of the PHS Act for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.[16] If a full or partial waiver is granted under PREA because there is evidence that the drug would be ineffective or unsafe in some or all pediatric populations, the information must be included in the product's labeling.[17]

This guidance addresses the clinical pharmacology considerations of any planned pediatric study, whether or not it is conducted pursuant to BPCA or PREA.[18]

III. CLINICAL PHARMACOLOGY CONSIDERATIONS

Clinical pharmacology studies in the pediatric population should be conducted in individuals with the disease which the drug is intended to treat, or in rare instances, in those who are at risk of this disease. Identifying the appropriate pediatric population to study should take into

[11] Section 505A of the FD&C Act, 21 U.S.C. 355a.

[12] Section 505B of the FD&C Act, 21 U.S.C. 355c.

[13] For more information, see the FDA draft guidance entitled *How to Comply with the Pediatric Research Equity Act* (September 2005). When final, this guidance will represent the Agency's current thinking on this topic.

[14] Section 505B(e)(2)(B) of the FD&C Act, 21 U.S.C. 355c(e)(2)(B).

[15] Section 505A(j) of the FD&C Act, 21 U.S.C. 355a(j); Section 505B(g)(2) of the FD&C Act, 21 U.S.C. 355c(g)(2).

[16] Section 505B(a)(1) of the FD&C Act, 21 U.S.C. 355c(a)(1).

[17] Section 505B(a)(5)(D) of the FD&C Act, 21 U.S.C. 355c(a)(5)(D).

[18] For more information, please see the FDA guidance entitled *General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products* (July 2022).

consideration: 1) the disease; 2) the profile of the drug under study; 3) scientific and ethical justifications; and 4) developmental changes in the pediatric population.

Sponsors should address the entire pediatric age range (birth to <17 years of age[19]) in their iPSP (waivers and deferrals of the requirements under PREA may be appropriate for specific age ranges). The pharmacokinetics of a drug is typically evaluated over the entire pediatric age range in which the agent will be used. See the FDA guidance entitled *E11 Clinical Investigation of Medicinal Products in the Pediatric Population* (December 2000) for more information. The Center for Drug Evaluation and Research generally divides the pediatric population into the following groups:[20]

- Neonates: Birth up to 1 month[21,22]
- Infants: 1 month up to 2 years
- Children: 2 years up to 12 years
- Adolescents: 12 years up to younger than 17 years

If other categorizations such as physiologic categories based upon systems ontogeny or disease pathophysiology are used, they should be supported with scientific and developmental data. These categories should not be arbitrarily applied for trial enrollment but can help ensure adequate inclusion of participants across the pediatric age range.

The measurement or prediction of a drug's pharmacokinetics (exposure) and pharmacodynamics (response) is essential to the clinical pharmacology assessment. It is important to describe the exposure-response relationship of a drug in the pediatric population when possible to enhance the understanding of effective dose ranges or support the ability to extrapolate information from older pediatric participants. A pediatric drug development program should consider the time course of development of the drug metabolizing enzymes, drug excretory systems, transporters and drug target/receptors relevant (if known) to the drug being studied. This can be addressed by characterizing the pharmacokinetics and/or pharmacodynamics of the drug across the appropriate pediatric age range.

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[19] See 21 CFR 201.57(c)(9)(iv).

[20] In 1994, the FDA revised its regulations to include more complete information about the use of a drug in pediatric populations. See the final rule on Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection in the Labeling, 59 FR 64240, 64241-42, (December 13, 1994). Pediatric age groups are described in the preamble to that final rule. Although the Agency has since further revised those labeling requirements (see the final rule on Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 FR 3922 (January 24, 2006)), the Agency's general thinking regarding these pediatric subpopulations has remained the same.

[21] In this guidance, as in the FDA guidance entitled *E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population* (April 2018), the neonatal period is defined for the term and post-term newborn as the day of birth plus 27 days, and for the preterm newborn, as the day of birth, through the expected date of delivery plus 27 days.

[22] For more information, please see the FDA guidance entitled *General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products* (July 2022).

A. Pharmacokinetics

Pharmacokinetic (PK) measures, such as area under the curve (AUC) and maximum concentration (C_{max}), and parameters such as clearance (CL), half-life, and volume of distribution, reflect the absorption (A), distribution (D), and excretion (E) of a drug from the body. Drugs can be eliminated in the unchanged (parent) form or undergo metabolism (M) to one or more active and inactive metabolites. This overall set of processes is often referred to as ADME, which ultimately determines the systemic exposure to a drug and its metabolites after drug administration. This systemic exposure, reflected as drug or metabolite concentrations or both, is generally correlated with both beneficial and adverse drug effects. All drugs show inter- and intra-individual variability in PK measures and parameters.

In the pediatric population, growth and developmental changes in the factors that influence ADME can lead to changes in PK parameters which can lead to changes in drug response/adverse effects. Specifically, the ontogeny of drug metabolizing enzymes, transporters, and receptors should be taken into account when planning and analyzing data from pediatric PK studies.

The methodological issues in designing pediatric PK studies have been reviewed previously.[23] Special areas of importance in planning pediatric PK studies are discussed in the following paragraphs.

1. Absorption

Developmental changes in the pediatric population that can affect absorption include effects on gastric acidity, rates of gastric and intestinal emptying, surface area of the absorption site, gastrointestinal drug-metabolizing enzyme systems, gastrointestinal permeability, biliary function, and transporter expression. Similarly, developmental changes in skin, muscle, and fat, including changes in water content and degree of vascularization, can affect absorption patterns of drugs delivered by intramuscular, subcutaneous, or percutaneous absorption.[24] See section V.D for a discussion on the effect of the formulation on drug absorption.

2. Distribution

Distribution of a drug can be affected by changes in body composition, such as changes in total body water and adipose tissue, which are not necessarily proportional to changes in total body weight. Plasma protein binding and tissue-binding changes arising from changes in body composition with growth and development can also influence distribution. Differences between the pediatric and adult populations in blood flow to an organ, such as the brain, can also affect the distribution of a drug in the body.

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[23] Burckart, GJ, KE Estes, R Leong, Y Mulugeta, V Tandon, J Wang, DR Abernethy, and PR Jadhav, 2012, Methodological Issues in the Design of Pediatric Pharmacokinetic Studies, Pharm Med, 26:13-22.

[24] Hong, L and S Rosenbaum, 2014, Developmental Pharmacokinetics in Pediatric Populations, J Pediatr Pharmacol Ther, 19(4):262-276.

3. Metabolism

Drug metabolism commonly occurs in the liver, but can also occur in the blood, gastrointestinal wall, kidney, lung, and skin. Developmental changes in metabolizing capacity can affect both bioavailability and elimination, depending on the degree to which intestinal and hepatic metabolic processes are involved.[25] Developmental changes in drug metabolism are well recognized, and information on the ontogeny of drug metabolism in newborns, infants, and children is now included in modeling approaches to predicting drug elimination in these groups. Both the rates of metabolite formation and the principal metabolic pathway can be different in the pediatric population compared to adults and within the pediatric population. In vitro studies performed early in drug development can be useful in identifying the metabolic pathways for a drug. See the FDA guidance entitled *In Vitro Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020) for more information.

4. Excretion

Drug excretion by the kidney is the net result of glomerular filtration, tubular secretion, and tubular reabsorption. Because these processes mature at different rates in the pediatric population, age can affect the systemic exposure of drugs when renal excretion is a dominant pathway of elimination. The maturation of other excretory pathways, including biliary and pulmonary routes of excretion, is also important.

5. Protein Binding

Protein binding to a drug or its metabolites can change with age and concomitant illness. In certain circumstances, an understanding of protein binding is important to interpret the data from a blood level measurement and to determine appropriate dose adjustments.[26] In vitro plasma protein binding studies can determine the extent of binding of the parent and the major active metabolite(s) and identify specific binding proteins, such as albumin and alpha-1 acid glycoprotein.

6. Clearance

Clearance of drugs as a function of age and body weight is generally a valuable parameter for determining the dose in the pediatric population, and drug clearance has provided a valuable tool in the assessment of pediatric clinical pharmacology studies. Scaling of drug clearance from one age group to another is a commonly used approach.

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[25] Leeder, JS, 2004, Translating Pharmacogenetics and Pharmacogenomics into Drug Development for Clinical Pediatrics and Beyond, Drug Disc Today, 9(13):567-573.

[26] Kearns, GL, SM Abdel-Rahman, SW Alander, DL Blowey, JS Leeder, and RE Kauffman, 2003, Developmental Pharmacology - Drug Disposition, Action, and Therapy in Infants and Children, NEJM, 349;12:1157-1167.

B. Pharmacodynamics

Sponsors should collect and analyze PK and, whenever possible, pharmacodynamic (PD) data in pediatric studies to determine how the two are linked (i.e., the PK-PD or exposure-response relationship). PD data can include the effect of the drug on biomarkers or clinical endpoints for both effectiveness and safety. These measurements can allow a better understanding of whether the PK-PD relationships of the drug in pediatrics are similar to those observed in adults and can help derive rational dosing strategies in pediatrics.

If the clinical endpoint cannot be measured directly because the effect is delayed or infrequent, then the selection of an appropriate biomarker to substitute for the clinical effectiveness or toxicity endpoint is essential. Endpoint selection is a critical part of pediatric study design.[27]

C. Pharmacogenomics

Documentation that genetic differences can impact drug exposure and response is increasing,[28] but the relationship between genomic profiles and developmentally regulated gene expression has not been extensively studied in pediatric populations. Genotype-phenotype relationships observed in adults are not always representative of those observed in pediatric populations, particularly neonates and infants.[29] Nevertheless, if drug exposure and/or response is dependent on a well-known pharmacogenomic biomarker (e.g., cytochrome P4502D6), collecting and analyzing pharmacogenetic samples in a pediatric clinical pharmacology study could provide additional information for the interpretation of the PK and PD results. See the FDA guidance entitled *Clinical Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020) for more information.

IV. ETHICAL CONSIDERATIONS

FDA-regulated clinical investigations are governed, in part, by IRB regulations in 21 CFR Part 56 and the human subject protection regulations in 21 CFR Part 50. The requirements in 21 CFR Part 50, subpart D, Additional Safeguards for Children in Clinical Investigations, apply to FDA-regulated clinical pharmacology studies that enroll pediatric participants. If the proposed intervention or procedure does not offer a prospect of direct clinical benefit to the individual child, these safeguards restrict the allowable risk to which a pediatric participant can be exposed in a clinical investigation to minimal risk (21 CFR 50.51) or no more than a minor increase over

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[27] Green, DJ, JM Burnham, P Schuette, XI Liu, BM Maas, L Yao, SK McCune, J Chen, JN van den Anker, and GJ Burckart, 2018, Primary Endpoints in Pediatric Efficacy Trials Submitted to the US FDA, J Clin Pharmacol 58(7):885-890.

[28] Food and Drug Administration: Table of Pharmacogenomic Biomarkers in Drug Labeling (June 2021)), available at: https://www fda.gov/media/124784/download (Accessed December 21, 2021).

[29] Green, DJ, P Mummaneni, IW Kim, JM Oh, M Pacanowski, and GJ Burckart, 2016, Pharmacogenomic Information in FDA-Approved Drug Labels: Application to Pediatric Patients, Clin Pharmacol Ther, 99(6):622-632.

minimal risk (21 CFR 50.53) unless the protocol is referred to the FDA by the IRB and allowed to proceed under 21 CFR 50.54 (see further description below).

Clinical pharmacology studies generally do not provide a direct clinical benefit to individual pediatric participants and must therefore present minimal risk (21 CFR 50.51) or no more than a minor increase over minimal risk (21 CFR 50.53) in order to be approved by an IRB under 21 CFR Part 50, subpart D. However, if a clinical pharmacology study offers the prospect of direct benefit to the participant, such as by ensuring that serum levels of a drug remain within the therapeutic range, then the study potentially could be approvable by an IRB under 21 CFR 50.52.

Before initiation of the clinical trial, an IRB must determine that the proposed trial is in compliance with the requirements of 21 CFR 50, subpart D.[30] However, if FDA has concerns that the rights and safety of pediatric participants may not be adequately protected, such concerns could present sufficient grounds for the FDA to impose a clinical hold because the investigation could present an unreasonable and significant risk of illness or injury to the pediatric participants (21 CFR 312.42(b)).

The assessment of a clinical pharmacology protocol under 21 CFR part 50, subpart D depends on whether the investigational drug is being administered: (1) solely for the purposes of obtaining PK data; or (2) in such a way that it offers the pediatric participant a prospect of direct clinical benefit. The two scenarios are discussed further in the case studies below.

Regardless of the scenario, administration of an investigational drug would generally be considered to represent more than minimal risk and thus would not meet the requirements for approval by an IRB under 21 CFR 50.51 (clinical investigations not involving greater than minimal risk). For IRB approval under 21 CFR 50.53, the pediatric participants must have a disorder or condition that is the focus of the clinical investigation, the investigational drug must present experiences to those subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations, and the clinical investigation must be likely to yield generalizable knowledge about the disease or condition that is of vital importance for the understanding or amelioration of that disorder or condition. For IRB approval of a clinical investigation under 21 CFR 50.52, the pediatric participants must have a prospect of direct clinical benefit from administration of the investigational product, the risk to the pediatric participants must be justified by the anticipated benefit, and the relation of the anticipated benefit to the risk must be at least as favorable to the pediatric participants as that presented by available alternative approaches. Accordingly, healthy pediatric participants (i.e., without a disorder or condition which is the focus of the research) cannot be enrolled in FDA-regulated clinical pharmacology studies unless the Commissioner determines, after consultation with a panel of experts in pertinent disciplines and opportunity for public review and comment, that the conditions in 21 CFR 50.54 are met.[31] That regulation applies to clinical investigations that are not approvable under 21 CFR 50.51, 50.52, or 50.53 but

[30] See 21 CFR 56.109(h) and 21 CFR 56.111(c).

[31] See the FDA guidance entitled *Process for Handling Referrals to FDA Under 21 CFR 50.54 - Additional Safeguards for Children in Clinical Investigations* (December 2006).

that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

A. Case 1: IRB Review of a Clinical Pharmacology Study Involving Pediatric Participants Under 21 CFR 50.53

When the investigational drug is being administered to a pediatric participant with the disease or condition for which the drug is being developed, but the intent of the study is solely for the purpose of obtaining PK data, the risk(s) presented by the investigational drug, the route of administration, and the PK sampling schedule must represent no more than a minor increase over minimal risk (21 CFR 50.53(a)) in order to be approvable by the IRB. Pediatric participants may be exposed to no more than a minor increase over minimal risk if, among other criteria, the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of that disorder or condition (21 CFR 50.53(c)). Thus, for a clinical investigation to be approved by an IRB under this category, the enrolled pediatric participant must have a disorder or condition that meets these requirements. The FDA interprets "condition" to include being at risk for the disease (disorder) based on, for example, epidemiologic, genetic, and other factors.

Furthermore, sufficient empirical data regarding the risks of the proposed interventions or procedures should be available to ascertain that the risks are no more than a minor increase over minimal risk (21 CFR 50.53(a)). If available, adult data (including dose-response information) should be considered for this purpose. When there are not enough human data to adequately characterize the risk, then the intervention or procedure generally would not be considered to present no more than a minor increase over minimal risk because the risks of the intervention or procedure would not be known with sufficient accuracy.

The risks of any blood and/or fluid sampling procedures also must represent no more than a minor increase over minimal risk (21 CFR 50.53(a)). The limited venipunctures to obtain specimens for PK analyses would generally be considered either minimal risk or a minor increase over minimal risk, and therefore could be approvable by the IRB even without the prospect of direct benefit (see 21 CFR 50.51(a) and 50.53(a)). This approach to the analysis of clinical trials is often called a *component analysis of risk*, whereby to determine the overall acceptability of the clinical investigation, the risks and anticipated direct clinical benefits of the interventions included in a protocol are analyzed individually as well as collectively.[32,33,34]

An example of a clinical pharmacology study that generally would fall under 21 CFR 50.53 is the pharmacokinetics of the oral administration of a *single dose* of an over-the-counter cough and cold product. To be enrolled in such a study, a child would either be symptomatic from an upper

[32] See the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Research Involving Children: Report and Recommendations of the Commission for the Protection of Human Subjects of Biomedical and Behavioral Research*, (43 FR 2084, 2086), January 13, 1978.

[33] See Preamble to the Final Rule, Additional Safeguards for Children in Clinical Investigations of Food and Drug Administration-Regulated Products, (78 FR12937, 12937-12950), February 26, 2013.

[34] See the FDA guidance entitled *Acute Bacterial Otitis Media: Developing Drugs for Treatment* (October 2012).

respiratory infection (URI) or be at risk for a future URI based on the presence of criteria such as the frequency of past infections, number of people living in the home, or exposure to others in a preschool or school setting. As stated above, the associated blood draws to collect PK samples would generally be considered to be minimal risk (21 CFR 50.51(a)) or no more than a minor increase over minimal risk (21 CFR 50.53(a)) and a single oral dose of the over-the-counter cough and cold product would generally be considered as no more than a minor increase over minimal risk (21 CFR 50.53(a)), thus allowing the study to proceed under 21 CFR 50.53.

If administration of a single dose of an investigational drug exceeds a minor increase over minimal risk (or there are insufficient data available to make that determination), the clinical pharmacology study either would be required to meet the requirements in 21 CFR 50.52 (as discussed below) or would require referral for review under 21 CFR 50.54 (assuming that the other requirements of that regulation were met).

B. Case 2: IRB Review of a Clinical Pharmacology Study Involving Pediatric Participants Under 21 CFR 50.52

The administration of an investigational drug with more than a minor increase over minimal risk could be approved by an IRB if the level of risk exposure is justified by a sufficient prospect of direct clinical benefit to the participants (21 CFR 50.52(a)). For example, dose-monitoring studies that ensure serum levels of an investigational drug remain within a therapeutic range generally would fall under 21 CFR 50.52 when the investigational drug presents the prospect of direct benefit to the enrolled pediatric participants and the investigational drug is administered under the protocol using a dosing regimen (including duration) that offers a sufficient prospect of direct clinical benefit to justify the risks (21 CFR 50.52(a)).

Multiple-dose PK-PD studies can be designed to offer a prospect of direct benefit, but the dose and duration of exposure to the investigational product should be sufficient to result in potential changes in the clinical manifestations of the condition or in disease-specific biomarkers that reflect a clinical benefit. For example, the duration of the PK-PD study could be extended, or perhaps combined as the lead-in phase to an efficacy trial, to provide a suitable duration of drug exposure that offers a sufficient prospect of direct clinical benefit to justify the risks.[35]

C. Ethical Justification for Pediatric Pharmacology Studies

Adequate information from clinical pharmacology studies to support pediatric dosing is critical to the development of ethically sound confirmatory trials. Inadequate pediatric dosing may lead

[35] Roth-Cline, M and RM Nelson, 2015, Ethical Considerations in Conducting Pediatric and Neonatal Research in Clinical Pharmacology, Curr Pharm Design, 21:5619-5635.

to failed pediatric clinical trials.[36] The FDA considers the public health need for adequate pediatric dosing in its assessment of the ethical propriety of proposed studies.[37,38]

V. THE PEDIATRIC STUDY PLAN DESIGN AND POINTS TO CONSIDER

A sponsor who is planning to submit a marketing application (or supplement to an application) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration is required to submit an iPSP[39] unless the drug is for an indication for which orphan designation has been granted.[40] In addition, a sponsor who is planning to submit, on or after August 20, 2020, an original application for a new active ingredient that is subject to the molecularly targeted cancer drug provision of PREA (i.e., the drug that is the subject of the application is intended for the treatment of an adult cancer and is directed at a molecular target that the FDA determines to be substantially relevant to the growth or progression of a pediatric cancer) is also required to submit an iPSP,[41] regardless of whether the drug is for an indication for which orphan designation has been granted.[42] By statute, a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a new active ingredient for purposes of PREA.[43]

The submission of the iPSP is intended to encourage sponsors to consider pediatric studies early in product development and, when appropriate, begin planning for these studies. The FDA guidance entitled *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* (July 2020) discusses the content of and process for submitting initial and amended PSPs and states that Section 10.1 (Pediatric Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Studies) should include:

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[36] Benjamin, DK, Jr, PB Smith, P Jadhav, JV Gobburu, MD Murphy, V Hasselblad, C Baker-Smith, RM Califf, and JS Li, 2008, Pediatric Antihypertensive Trial Failures: Analysis of End Points and Dose Range, Hypertension, 51(4):834-840.

[37] See the FDA guidance entitled *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (March 2018).

[38] This issue is also discussed in the American Academy of Pediatrics Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations. See Shaddy, R and SC Denne, 2010, Clinical Report-Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations, Pediatrics,125(4):850-860.

[39] See section 505B(e)(1) of the FD&C Act; 21 U.S.C. 355c(e)(1); and section 505B(a)(1)(A) of the FD&C Act; 21 U.S.C. 355c(a)(1)(A).

[40] See section 505B(k)(1) of the FD&C Act; 21 U.S.C. 355c(k)(1).

[41] See section 505B(e)(1) of the FD&C Act; 21 U.S.C. 355c(e)(1); and section 505B(a)(1)(B) of the FD&C Act; 21 U.S.C. 355c(a)(1)(B).

[42] See section 505B(k)(2) of the FD&C Act; 21 U.S.C. 355c(k)(2).

[43] See section 505B(l) of the FD&C Act; 21 U.S.C. 355c(l).

- The type of study/study design
- The objectives of the study
- The age group and population in which the study will be conducted
- The pediatric formulation(s) to be used in the study
- The dose ranges to be used in the PK studies
- The endpoints and justification (PK parameters; PD parameters)
- The existing or planned modeling and simulation to support dose selection and/or study design, data analysis, and interpretation for planned pediatric studies
- Any planned pharmacogenomic analyses
- A justification for the sample size

When designing pediatric clinical studies, sponsors should be mindful that modeling and simulation and pharmacologic considerations are often critical for the successful completion of a study. Modeling and simulation (e.g., PK, PD, and trial simulations) should use all of the information available and be an integral part of all pediatric development programs followed by verification using results from pediatric clinical studies. The following sections are critically important when developing the clinical pharmacology components of a pediatric study plan.

A. Approaches to Pediatric Studies

There are several recognized approaches to providing substantial evidence to support the safe and effective use of drugs in pediatric populations.[44] In some cases, previous data in adults and other pediatric indications can be leveraged to provide this substantial evidence. This concept is often referred to as pediatric extrapolation.

Pediatric extrapolation of efficacy is defined as an approach to providing evidence in support of effectiveness of drugs in the pediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric and reference (adult or other pediatric) populations.[45] Determination of the extent of pediatric extrapolation is predicated on the understanding of the disease and drug effect in the reference (adult or other pediatric) population and their similarity to the target pediatric

[44] For more information, see the FDA draft guidance entitled *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent the Agency's current thinking on this topic.

[45] See the FDA guidance entitled *E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population* (April 2018). See also 21 CFR 314.55(a).

population. The data necessary to support efficacy when pediatric extrapolation is considered will depend upon the existing data and the gaps in knowledge that should be addressed.[46] Examples of potential approaches based on the availability and confidence in existing data are discussed in sections 1 through 3 below.

While it is helpful and provides additional evidence to support extrapolation, formally establishing and documenting similarity in exposure-response in adults and target pediatric population is not a requirement in order to consider some degree of extrapolation. Exposure-response assessments are, however being conducted more frequently in both adult and pediatric patients. Knowledge of exposure-response, when available, can play a critical role in informing the assessment of drug effect similarity between adults and pediatric patients and the acceptability of an exposure-matching approach. In addition, exposure-response information can serve a crucial role in supporting pediatric dose selection, dose optimization and formulation development. When applicable, similarity in exposure-response relationships on a clinically relevant biomarker or an appropriate clinical endpoint can contribute to an assessment of the appropriateness of efficacy extrapolation from adults to pediatric patients.

Additionally, the extent of the required pediatric safety data can take into consideration prior experience with similar drugs in pediatric populations and the seriousness of the adverse events in adults or in pediatric populations. Usually, additional safety data in the indicated pediatric indication will be needed. See the FDA guidance entitled *E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population* (April 2018) for more information. The potential for pediatric patients to have a significantly different incidence, severity, and types of adverse events compared to adults should always be considered.[47,48]

1. PK, Safety, and Efficacy Approach

If the disease or disease progression is unique to pediatric patients or its progression and/or response to intervention is undefined or dissimilar to that in adults, then the pediatric development program should use a PK, safety, and efficacy approach. The objectives of the studies in the pediatric program would be to characterize the PK and exposure-response relationships to help optimize pediatric dosing strategies and to provide evidence of effectiveness and safety. A population PK analysis can be conducted using PK data from the efficacy study to confirm PK estimates in the age subgroups.

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[46] See the FDA guidance entitled *E11 Clinical Investigation of Medicinal Products in the Pediatric Population* (December 2000) for more information.

[47] Liu XI, P Schuette, GJ Burckart, DJ Green, J La, JM Burnham, N Rakhmanina, A Robb, SM Huang, and JN van den Anker, 2019, A Comparison of Pediatric and Adult Safety Studies for Antipsychotic and Antidepressant Drugs Submitted to the US FDA, J Pediatrics, doi: 10.1016/j.jpeds.2018.12.033.

[48] Momper JD, Y Chang, M Jackson, P Schuette, S Seo, I Younis, DR Abernethy, L Yao, EV Capparelli, and GJ Burckart, 2015, Adverse Event Detection and Labeling in Pediatric Drug Development: Antiretroviral Drugs, Ther Inn Reg Sci, 49(2):302-309.

2. PK, Safety, and PD/Efficacy Approach

This approach should be considered when the disease and intervention are believed to behave similarly in pediatrics and adults, but the exposure-response relationship in pediatrics is either inadequately documented or assumed to not be sufficiently similar to adults. A clinically relevant PD biomarker may be appropriate for purposes of evaluating the evidence of effectiveness and to select pediatric doses. In the absence of a clinically relevant PD biomarker, clinical measures (e.g., symptoms, signs, outcomes) may be appropriate. The number, type, and size of pediatric studies to support a pediatric program depends on the residual uncertainty associated with understanding of similarity of the disease and drug effect.

For the two approaches described above, response data in pediatric studies should be collected and analyzed. Response or PD data can include biomarkers or clinical endpoints for both safety and effectiveness. The specific endpoints, including those for an exposure-response evaluation, for each drug should be discussed with the Agency. Appropriate endpoint selection and enrichment strategies for the pediatric population in a trial are important. Of note, endpoints that are unique to pediatric participants have been previously associated with failed pediatric trials and should be carefully considered.[49]

3. PK and Safety Approach

The PK and safety approach should be considered when there is evidence that adults and pediatrics share a sufficiently similar disease course and response to intervention to allow for exposure matching to establish efficacy.

A PK study should be performed to identify the pediatric dose that will provide an exposure similar to that found to be effective in adults. The antibacterial therapeutic area is a good example of this approach, where the organism is expected to respond to similar systemic concentrations in adults and pediatrics. In this example, the study should focus on identifying the doses in the pediatric setting that would result in exposures similar to those attained in adults. The criteria for determining exposure matching should be prospectively agreed upon with the Agency before initiating these studies.[50]

Before conducting a PK study in any of these approaches, simulations should be performed to identify initial dosing regimens. Clinical trial simulations may be performed to determine a trial design, sample size, and the appropriateness of an endpoint for the pediatric study. Refining models with available data can help verify assumptions made during the design of the study.

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[49] Green DJ, J Burnham, P Schuette, XI Liu, BM Maas, L Yao, SK McCune, J Chen, JN van den Anker, and GJ Burckart, 2018, Primary Endpoints in Pediatric Efficacy Trials Submitted to the US FDA, J Clin Pharmacol, 58(7):885-890.

[50] Mulugeta, Y, JS Barrett, R Nelson, AT Eshete, A Mushtaq, L Yao, N Glasgow, AE Mulberg, D Gonzalez, D Green, J Florian, K Krudys, S Seo, I Kim, D Chilukuri, and GJ Burckart, 2016, Exposure Matching for Extrapolation of Efficacy in Pediatric Drug Development, J Clin Pharmacol, 56(11):1326-1334.

B. Alternative Approaches to Conventional PK Studies

A dedicated PK study with intensive PK sampling may not be necessary in every age group. For example, prior experience with dosing in adolescent participants has demonstrated that knowledge of adult dosing and appropriate dose scaling can be sufficient for some drugs with adequate justification. When a dedicated PK study is not considered essential or cannot be conducted, it may be appropriate to use sparse PK sampling in the safety and/or efficacy studies to confirm dose predictions. Modeling and simulation can also be used, when appropriate, to help to fill these gaps in knowledge. See the FDA guidance entitled *Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials* (March 2019) for more information.

Other approaches beyond the use of conventional PK studies with intensive blood sampling may be appropriate in pediatric participants to obtain useful drug exposure information, including:

- Sparse PK sampling with the use of modeling and simulation
- Opportunistic approaches that use excess blood collected for laboratory studies[51]
- Use of alternative specimens:
    - Urine and saliva collection are noninvasive. However, the interpretation of drug analyses of either source is complicated and requires careful consideration before use.
    - Likewise, tissue or cerebrospinal fluid collected for clinical purposes present both an opportunity and a challenge for the appropriate interpretation of these results in understanding the pharmacokinetics of the drug.

Modeling and simulation can help reduce the uncertainty about drug dosing in pediatric populations. Model-informed drug development has been applied in regulatory applications for pediatric drug development.[52] Population PK approaches are commonly used, and physiologically based PK (PBPK) approaches are increasingly applied in pediatric drug development. In addition, quantitative systems pharmacology (QSP) models can help

[51] For more information, see the FDA guidance entitled *General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products* (July 2022).

[52] Bi, Y, J Liu, L Li, J Yu, A Bhattaram, M Bewernitz, R Li, C Liu, J Earp, L Ma, L Zhuang, Y Yang, X Zhang, H Zhu, and Y Wang, 2019, Role of Model-Informed Drug Development in Pediatric Drug Development, Regulatory Evaluation, and Labeling, J Clin Pharmacol, 59(S1):S104-S111.

incorporate disease processes.[53,54] As science and technology continue to advance, in silico and other alternative modeling study methods can provide preliminary data to inform the design and conduct of PK-PD studies for investigational drugs in pediatric populations. For example, the development of a PBPK in silico model that integrates drug-dependent parameters (e.g., physicochemical properties, hepatic intrinsic clearance, affinities to metabolic enzymes, transporters, and proteins) and system- and age-dependent parameters (e.g., blood flow rate, protein contents, tissue and organ size and composition, and enzyme and transporter abundances and activities) is one possible approach.

Various modeling approaches have been used in pediatric drug development programs for a variety of purposes, including:

- Planning for a first-in-pediatric PK study
- Optimizing the study design
- Verifying the model in specific age groups
- Recommending starting doses
- Informing enzyme ontogeny using a benchmark drug
- Facilitating covariate analysis for the effects of organ dysfunction or drug interactions in pediatric participants[55]

The model selected should incorporate in vivo PK-PD data obtained in other groups of pediatric and adult participants as well as human volunteer studies, as appropriate. To account for growth across the pediatric population for modeling purposes, refer to standardized growth charts. The Centers for Disease Control and Prevention (CDC) growth charts provide a preliminary assessment of the weight ranges that can be anticipated within specific age groups.[56] For example, weights can vary 2.5- to 3-fold in healthy children between the 10th percentile at 2 years and 90th percentile at age 6 (10.6 kg to 25.3 kg for males) and between the 10th percentile at

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[53] Momper, JD, GJ Burckart, and P Jadhav, 2013, Applications of Population Pharmacokinetics for Pediatric Drug Development, Pediatric Drug Development: Concepts and Applications, AE Mulberg, D Murphy and LL Mathis, Chichester, UK, John Wiley & Sons Ltd.

[54] Wang, J, AN Edginton, D Avant, and GJ Burckart, 2015, Predicting Neonatal Pharmacokinetics From Prior Data Using Population Pharmacokinetic Modeling, J Clin Pharmacol, 55(10):1175-1183.

[55] Leong, R, MLT Vieira, P Zhao, Y Mulugeta, CS Lee, SM Huang, and GJ Burckart, 2012, Regulatory Experience With Physiologically Based Pharmacokinetic Modeling for Pediatric Drug Trials, Clin Pharmacol Ther, 91(5):926-931.

[56] Centers for Disease Control and Prevention, National Center for Health Statistics, 2000 CDC Growth Charts for the United States: Methods and Development (May 2002), available at: http://www.cdc.gov/nchs/data/series/sr_11/sr11_246.pdf (Accessed September 17th, 2019).

6 years and the 90th percentile at 12 years (17.7 kg to 54 kg in males). Caution should be taken in the use of standardized growth charts as they do not always represent the target pediatric patient population.

C. Pediatric Dose Selection

Selecting a dose(s) and an age range should consider the overall benefit/risk profile of the drug. When possible, a range of doses should be studied in the pediatric population.

Factors for consideration in dose selection include:

- The similarity of the disease and exposure-response in pediatric and adult groups
- The relative bioavailability of the new formulation compared to the previous formulations
- The age and developmental stage of the pediatric population
- Any pharmacogenomic characteristics of the drug
- The toxicity of the drug
- Any PK data from other pediatric populations

Because there can be limited information on the safety of the dose to be administered to a neonate or infant, the dose range used in initial studies requires careful consideration.[57] When developmental maturation and body size changes impact dosing, modeling and simulation can help define an initial pediatric dosing in order to adequately minimize the risk for specific age groups. Initial doses within a pediatric age group are typically normalized to body size (e.g., mg/kg), but developmental maturation can be an additional critical factor to be considered in establishing initial doses in some age groups. In some pediatric participants such as adolescents, body weight or surface area-based dosing are not always necessary. In some cases, final dosing recommendations can include tiered dosing based on weight bands.

There are situations in which interpolation or scaling can reduce the uncertainty regarding initial pediatric dosing. PK or PD information in certain pediatric age groups can be gained by interpolating or bridging from existing data in adults, pediatric participants in other age groups, or both. However, bridging of data to younger pediatric age groups, particularly neonates, should be done cautiously and confirmed. Significant developmental differences that can exist between young pediatric age groups and older pediatric age groups or adults are associated with considerable differences in metabolism and drug disposition. This difference can lead to an altered dose-exposure relationship and therefore the dose-response relationships.

[57] For more information, see the FDA guidance entitled *General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products* (July 2022).

When initial PK studies are not feasible (see section IV), an adaptive design to selecting a dose can be practical for the pediatric clinical studies. Adaptive designs should be prospectively determined. See the FDA guidance entitled *E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population* (April 2018) for more information.

When separate efficacy studies in pediatrics are not conducted (i.e., for the *PK and safety only* approach described in section V.A above), in general, PK studies in the pediatric population should determine how the dosage regimen should be adjusted to achieve the same level of systemic exposure in adults. Differences in intersubject variability in these PK measures and/or parameters between age groups or between pediatric and adult populations should be interpreted with regard to their impact on dosing, safety, and/or efficacy. In these instances, the sponsor should pre-specify the criteria by which exposure matching is acceptable. For example, one approach is to select the appropriate dosing strategy through simulations which result in pediatric exposures within the 5th to 95th percentile shown to be safe and effective in adults.

Estimating the exposure-response relationship across a range of body-size doses (dose/kg or dose/m^2) can be important. For the *PK and PD/efficacy* approaches discussed in section V.A2 above, investigating a range of doses and exposures allows for an assessment of those relationships and the development of rational dosing instructions. The sponsor should also consider determining the variability in achieved systemic exposures in the pediatric population in the context of the exposure-response relationships for pharmacodynamics or efficacy.

When PK-PD data are available, the dose range should account for observed differences in response between adults and the pediatric population, both in terms of exposure and response. For example, there is evidence that pediatric populations are on average less sensitive to antihypertensive drugs than the adult population.[58] Therefore, pediatric studies could include exposures greater than the highest drug exposure associated with the approved adult dose, provided that prior data about the exposure-response relationship and safety information justify such an exposure. Studies of distinctly different ranges of exposure are desirable to provide sufficient information for the calculation of an optimal dose.

D. Pediatric Dosage Formulation

Pediatric formulations that permit accurate dosing and enhance adherence (e.g., palatability) are an important part of pediatric drug development.[59] See the FDA guidance entitled *E11 Clinical*

[58] Benjamin, DK, Jr, PB Smith, P Jadhav, JV Gobburu, MD Murphy, V Hasselblad, C Baker-Smith, RM Califf, and JS Li, 2008, Pediatric Antihypertensive Trial Failures: Analysis of End Points and Dose Range, Hypertension, 51(4):834-840.

[59] Refer to the FDA draft guidance entitled *Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments* (July 2018) for information on the use of liquids and/or soft foods for drug administration. When final, this guidance will represent the Agency's current thinking on this topic. In addition, refer to the following FDA guidances for more information on assessing the bioavailability and effect of food on a new formulation: *Assessing the Effects of Food on Drugs in INDs and NDAs - Clinical Pharmacology Considerations* (June 2022) and *Bioavailability Studies Submitted in NDAs or INDs - General Considerations* (April 2022).

Investigation of Medicinal Products in the Pediatric Population (December 2000) for more information. If there is a pediatric indication, an age-appropriate dosage formulation must be made available for pediatric patients in all relevant age groups.[60] One way to fulfill this requirement, when the adult formulation is not acceptable for the planned pediatric age range, is to develop and test a pediatric formulation and seek approval for that formulation. To the extent practicable, sponsors should include information in the iPSP regarding planned excipients that will be contained in a pediatric formulation.

The bioavailability of any formulation used in pediatric studies should be characterized in relation to the adult formulation. In some circumstances, a relative bioavailability study comparing the age-appropriate formulation to the approved drug may be required.[61] These studies are generally performed in adults due to ethical reasons. Potential drug-food or vehicle interactions should be considered, such as those that have been reported with apple juice.[62]

E. Sample Size

1. Number of Pediatric Participants

Prior knowledge of the disease, exposure, and response from adult and other relevant pediatric data, such as that related to variability, can be used to derive a sample size for ensuring precise parameter estimation. The sponsor should account for all potential sources of variability, including inter-subject and intra-subject variability as well as differences between the adult and pediatric populations when making the final selection of the sample size for each age group.

The distinct age groups to be studied should be chosen based upon what is known about potential changes in drug response with age, the development of the drug-metabolizing enzymes and excretory mechanisms, as well as safety considerations. Pediatric studies in all age groups should be initiated as early as possible in drug development. The sequential study of age cohorts, starting with the oldest pediatric age group, may be appropriate when there is a clear rationale for doing so. If the drug is intended to be used in newborn infants, the iPSP should specify how premature infants will be considered in the study population.

Because the selected age groups (strata) will be drug product-specific, the sponsor should discuss the stratification plan, the distribution of the number of pediatric participants within each stratum, and the appropriateness of these strata with the Agency.[63] Justification should be provided for the sample size selected. For example, one approach would be to prospectively

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[60] See section 505B(a)(2) of the FD&C Act, 21 U.S.C. 355c(a)(2).

[61] 21 CFR 320.21.

[62] Abdel-Rahman, SM, MD Reed, TG Wells, and GL Kearns, 2007, Considerations in the Rational Design and Conduct of Phase I/II Pediatric Clinical Trials: Avoiding the Problems and Pitfalls, Clin Pharmacol Ther, 81(4):483-494.

[63] McMahon, AW, K Watt, J Wang, D Green, R Tiwari, and GJ Burckart, 2016, Stratification, Hyopthesis Testing, and Clinical Trial Simulation in Pediatric Drug Development, Ther Inn Regu Sci, doi: 10.1177/2168479016651661.

target a 95 percent confidence interval within 60 percent and 140 percent of the geometric mean estimates of clearance and volume of distribution for the drug in each pediatric stratum with at least 80 percent power. Noncompartmental analysis (NCA) based on rich PK sampling, population PK modeling analysis based on sparse PK sampling, or other scientifically justified methods can be applied as appropriate to achieve this precision standard.[64]

Conceivably, certain disease states might not allow for the recruitment of an adequate number of participants to meet the above standard, and as such, practical considerations should be taken into account in determining the sample size.

2. Number of Samples Per Participant

In addition to the number of participants, the number of blood samples collected in the clinical pharmacology study to estimate PK measures and parameters for each individual in the study should be carefully considered. The amount of blood or number of samples possible is very limited in some pediatric participants such as neonates (for more on collection of blood or plasma samples, see section F below). Clinical trial simulations and optimal sampling strategies are recommended to justify the proposed sampling scheme.

F. Sample Collection

The volume and frequency of blood sampling are often of concern in pediatric studies. Blood samples can be obtained by direct venipuncture, through the use of an indwelling intravascular catheter, or when appropriate, by capillary sampling. Because repeated venipuncture can cause discomfort and bruising at the puncture site, an indwelling intravascular catheter should be used when possible. The volume and frequency of blood sampling may be minimized by using micro-volume drug assays, dried blood spots, and sparse-sampling techniques. See the FDA guidance entitled *Bioanalytical Method Validation* (May 2018) for more information. These types of assays and analysis are especially relevant when studying neonates.[65] Modern assay techniques allow small sample volumes to be used to determine drug concentrations, but data quality can be affected if the sample volume is insufficient to allow for reanalysis when necessary. Blood samples for analysis should be collected from the circulating blood volume and not from reservoir dead space created by catheters or other devices. Sampling technique is critical when using the available pediatric indwelling intravenous catheters. The time of sample collection, proper sample transportation and storage, and sample handling techniques should be documented. The collection of fluids such as cerebral spinal fluid (CSF) or bronchial fluids can be beneficial when samples are being obtained for clinical purposes. Noninvasive sampling procedures, such as urine and saliva collection, may be sufficient if correlated with outcomes or if the correlation with blood, serum or plasma levels has been documented.

[64] Wang, Y, PR Jadhav, M Lala, and JV Gobburu, 2012, Clarification on Precision Criteria to Derive Sample Size When Designing Pediatric Pharmacokinetic Studies, J Clin Pharmacol, 52:1601-1606.

[65] Long, D, G Koren, and A James, 1987, Ethics of Drug Studies in Infants: How Many Samples are Required for Accurate Estimation of Pharmacokinetic Parameters in Neonates?, J Pediatrics, 111(6Pt1):918-921.

Samples for DNA should be collected when appropriate, as discussed in section III of this guidance. See also the FDA guidance entitled *Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling* (January 2013) for more information.

G. Covariates and Phenotype Data

Growth and developmental changes in the pediatric population create substantial changes in the ADME characteristics of a drug. PK measures and parameters for a drug should be described as a function of age and be related to some measure of body size, such as height, weight, or body surface area (BSA). The maturational changes in systems affecting ADME, such as membrane transporters and metabolizing enzymes, should be considered when choosing age groups and doses to study in the pediatric population (see section III).

The sponsor should, at a minimum, obtain the following covariates for each pediatric participant:

- Age
- Body weight
- Height
- Calculated BMI
- Gestational age
- Post-menstrual and postnatal age for neonates[66]
- Race and ethnicity
- Sex
- Laboratory tests reflecting the function of organs responsible for drug elimination
- Concomitant and recent drug therapy

The impact of the disease state and obesity upon drug disposition and response should be considered.[67] Sponsors are encouraged to collect DNA samples in pediatric PK studies under the circumstances described in section III, along with appropriate phenotype information to optimize the interpretation of pharmacogenomics findings. For example, when genotype information is obtained for a cytochrome P450 enzyme, the sponsor should investigate the influence of genetic mutations on pharmacokinetics, pharmacodynamics, and/or dose-response to determine whether genetically defined subsets of patients need special dosing considerations.

The sponsor should examine the relationship between the covariates and the pharmacokinetics of the drug of interest. The contribution of weight or BSA and age to PK variability should be assessed. Examples of practices for assessing the effect of age on pediatric pharmacokinetics could include:

[66] See the FDA guidance entitled *General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products* (July 2022) for more information.

[67] Vaughns JD, LS Conklin, Y Long, P Zheng, F Faruque, D Green, J van den Anker, and GJ Burckart, 2018, Obesity and Pediatric Drug Development, J Clin Pharmacol, doi:10.1002/jcph.1054.

- Identifying the accurate relationship between a drug's pharmacokinetics and body weight or BSA using allometric scaling

- Analyzing the residuals versus age, after accounting for body weight or the BSA effect on CL, followed by a more formal analysis exploiting the physiological understanding underlying CL, if appropriate. Testing for other biologically relevant predictive factors for determining the pharmacokinetics of a drug in pediatrics can be important. The covariate analysis may be performed on pooled data sets to allow for comparisons between adults and/or different pediatric subgroups.

1. Immunogenicity

The pharmacokinetics of a drug such as therapeutic proteins can be affected by immunogenicity to the drug. Immunogenicity to the administered product can negatively impact the safety and/or efficacy of the drug. Therefore, assessing the immunogenicity of the relevant drugs and determining its impact on pharmacokinetics, safety, and efficacy are critical components of drug development and post-marketing surveillance. See the following FDA guidances for more information:

- *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014)

- *Immunogenicity Testing of Therapeutic Protein Products - Developing and Validating Assays for Anti-Drug Antibody Detection* (January 2019)

In general, it is not appropriate to apply findings of the immunogenicity potential of a drug from adult populations to pediatric populations; therefore, evaluation of the immunogenicity potential of a drug should be conducted in pediatric trials regardless of the knowledge gained from adult trials.

2. Renal Function

For drugs that are renally cleared, exposures can be impacted by both the maturation of kidney function and renal impairment due to kidney disease. For this reason, pediatric patients with impaired renal function should be recruited for clinical study when it is possible and ethically justifiable to do so. One commonly used equation for the estimation of renal function is the bedside Schwartz equation;[68] however, in general any widely accepted measurement method (where necessary) or equation for the estimation of renal function in pediatric PK studies is acceptable[69] and should be described in the protocol and labeling when relevant dose

[68] Schwartz, GJ, A Munoz, MF Schneider, RH Mak, F Kaskel, BA Warady, and SL Furth, 2009, New Equations to Estimate GFR in Children with CKD, J Amer Soc Nephrol 20(3):629-637.

[69] Muhari-Stark E and GJ Burckart, 2018, Glomerular Filtration Rate Estimation Formulas for Pediatric and Neonatal Use, J Pediatr Pharmacol Ther, 23(6):424–431.

adjustments are derived. Sponsors should be aware of the laboratory methods used for the measurement of creatinine, as this can influence which equation is useful.

Data from adults are generally used to complement the information obtained in pediatrics to characterize the relationship between renal function and pharmacokinetics. Modeling and simulation approaches should be applied to derive dosing recommendations for the entire pediatric age range in which the product will be used.[70] Generally, for children over the age of 2 years, where kidney function maturation is considered complete, the need for dose adjustment should be evaluated and derived based on information evaluated in adults. For children less than 2 years of age, the additional impact of renal function ontogeny should be considered.[71] Quantitative approaches such as PBPK analysis can also be explored to address dosing needs in these situations. Of note, the application of modeling is limited by current understanding of ontogeny and is particularly challenging in neonates. However, modeling approaches should use all of the clinical information available.

H. Drug-Drug Interactions

In general, evaluations of drug-drug interactions (DDIs) are performed in adults. In some cases, however, the potential or magnitude of a DDI in pediatrics can differ from that observed in adults. Such differences in DDIs in pediatrics compared to adults can potentially be attributed to the ontogeny of metabolizing enzymes and transporters as well as differences in intragastric pH, gastric emptying, intestinal motility, or protein binding. Differences in diet, concomitant medications, drug formulation, and dosing regimen could also contribute to differences in DDIs between adults and pediatrics.[72]

Considering potential ethical concerns for standalone DDI studies in pediatrics, quantitative approaches such as PBPK analyses should be explored to address pediatric DDIs during drug development when differences in DDI are expected. Refer to the following FDA guidances for more information:

- *Clinical Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020)

- *Physiologically Based Pharmacokinetic Analyses — Format and Content* (September 2018)

[70] For information on studying trial participants with impaired renal function, see the FDA draft guidance entitled *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing* (September 2020) for general concepts of study design. When final, this guidance will represent FDA's current thinking on the topic.

[71] Zhang Y, N Mehta, E Muhari-Stark, GJ Burckart, J van den Anker, L Yao, and J Wang, 2019, Pediatric Renal Ontogeny and Applications in Drug Development, J Clin Pharmacol, 59(S1):S9-S20.

[72] Salerno, SN, GJ Burckart, SM Huang, and D Gonzalez, 2019, Pediatric Drug-Drug Interaction Studies: Barriers and Opportunities, Clin Pharmacol Ther 105(5):1067-1070.

Planning for DDI evaluations should be included as a section of the iPSP under Pediatric Pharmacokinetic Studies and should address the impact of DDIs on drug dosing in specific age groups. See the FDA guidance entitled *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* (July 2020) for more information.

I. Sample Analysis

An accurate, precise, sensitive, specific, and reproducible analytical method to quantify the drug and metabolites in the biological fluids of interest is essential. See the FDA guidance entitled *Bioanalytical Method Validation* (May 2018) for more information. The sponsor should choose a method that is readily adaptable and uses only minimum sample volumes.

J. Data Analysis

The development of PK models should occur throughout the pediatric development program. All prior knowledge, including adult data, should be used to develop initial models which can be adapted as new data become available in pediatric subgroups. There are several basic approaches for performing PK analysis in pediatrics. Population PK and noncompartmental PK approaches are two of the most commonly used; however, novel approaches may be acceptable as justified by the sponsor.

1. Population Analysis

A common approach for analyzing data from pediatric clinical pharmacology studies is the population approach to PK analysis. Population PK accommodates rich (intensive) and infrequent (sparse) sampling of blood, serum, or plasma from a larger population than in a compartmental or noncompartmental analysis PK approach to determine the PK parameters. Sparse sampling is generally considered more acceptable for pediatric studies because the total volume of blood sampled in an individual can be minimized. Sampling can even be performed concurrently with clinically necessary blood or urine sampling (e.g., opportunistic PK studies). Because relatively large numbers of pediatric participants are studied, and samples can be collected at various times of the day and repeated over time in a given participant, estimates of both population and individual means, as well as estimates of intra- and inter-subject variability, can be obtained if the population PK study is properly designed. See the FDA guidance entitled *Population Pharmacokinetics* (February 2022) for more information.

Exposure-response analyses predominantly employ a population analysis approach. Individual analysis is generally not recommended unless responses from a wide range of doses from each participant are available. Modeling of data across all study participants typically provides the best opportunity to describe the exposure-response relationship. See the FDA guidance entitled *Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications* for more information (May 2003).

2. Noncompartmental Analysis

If consistent with relevant ethical considerations (see Section IV: Ethical Considerations), it may be possible to utilize intensive PK sampling with relatively frequent blood and urine sample collection, when administering either single or multiple doses of a drug to a relatively small group of study participants. Samples are collected over specified time intervals chosen on the basis of absorption and disposition half-lives, and subsequently assayed for either total or unbound concentrations of drug and relevant metabolites. Noncompartmental analysis is a general approach to establish PK statistics and parameters such as AUC, C_{max}, CL, volume of distribution, and half-life, which are descriptive of the concentration of drug or metabolite over time. Data are usually expressed as the means of the relevant measure or parameter and inter-individual variances. In this approach, including a sufficient number of study participants to give a precise estimate of the mean is essential, as discussed in section V.E. If drug administration and sampling are repeated in a participant in the PK study, some understanding of intra-individual variability in PK parameters can be obtained.

K. Clinical Study Report

The clinical study report should follow the FDA guidance entitled *E3 Structure and Content of Clinical Study Reports* (January 2013) for the general content and the format of the pediatric clinical study report. The evaluation of exposure-response relationships and the population PK analyses should be included as stipulated in the following FDA guidances:

- *Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications* (May 2003)

- *Population Pharmacokinetics* (February 2022)

When submitting PK information, the sponsor should submit data that illustrate the relationship between the relevant PK parameters (e.g., CL unadjusted and adjusted for body size in the manner described in section VI.G) and important covariates (e.g., age, renal function) in addition to the results of noncompartmental analysis.

L. Data Submission

The preferred submission standard for clinical data is the Clinical Data Interchanges Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) standard. Please see the FDA Data Standards Advisory Board[73] and the CDER Study Data Standards web sites for more information.[74] The sponsor should also submit PK and exposure-response data used for modeling and simulation in an SAS.XPT-compatible format.

[73] See the FDA Data Standards Advisory Board, available at: https://www fda.gov/industry/fda-resources-data-standards.

[74] See the FDA Study Data Standards for Submission to CDER, available at: https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber.