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

Guidance for Industry

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[1]

This guidance represents 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 office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist sponsors in identifying an optimized 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 of 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 (November 1994)* when identifying an optimized dosage(s).[4]

Additional information on related topics can be found in:

- Guidance for industry *Population Pharmacokinetics* (February 2022).
- Guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications* (April 2003).

[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, an optimized dosage is a dosage that can maximize the benefit/risk profile or provide the desired therapeutic effect while minimizing toxicity. 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.

[3] For the purposes of this guidance, references to *drug* or *drugs* include both human drug products and biological products regulated by CDER and CBER, unless otherwise specified.

[4] See ICH guideline for industry *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.

This guidance does not specifically provide recommendations addressing dosage optimization for radiopharmaceuticals, cellular and gene therapy products, oncolytic viruses, microbiota, or cancer vaccines. However, some of the recommendations outlined may be applicable to these therapeutic modalities.

This guidance also does not specifically address pediatric drug development, for which there are unique considerations; however, some of the recommendations outlined may be applicable to dosage optimization for pediatric patients.

This guidance also does not address selection of the starting dose for first-in-human trials.

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

II. BACKGROUND

Dose-finding trials (i.e., trials that include dose-escalation and dose-expansion portions with the primary objective of selecting the recommended phase II dosage) for oncology drugs have historically been designed to determine the maximum tolerated dose (MTD). This paradigm was developed for cytotoxic chemotherapies based on their observed steep dose-response relationships, their limited drug target specificity, and the willingness of patients and providers to accept substantial toxicity due to the lack of effective alternatives for this serious, life-threatening disease. The MTD was identified by evaluating stepwise, 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). Sponsors typically administered the MTD, or a dose close to the MTD, in subsequent clinical trials.

Most modern oncology drugs, such as kinase inhibitors and antibodies, are designed to interact with a molecular pathway critical to an oncologic disease(s) (i.e., targeted therapies). These drugs often demonstrate different dose-response relationships with wider therapeutic indices compared to cytotoxic chemotherapy, such that doses below the MTD may have similar activity to the MTD with fewer toxicities or the MTD may never be reached. Patients may receive these targeted therapies for much longer periods (i.e., many months or years), potentially leading to persistent symptomatic toxicities, which can be challenging to tolerate over time. Nevertheless, the dosage administered in a registration trial(s) (i.e., the trial or study designed to evaluate safety and efficacy and support a marketing application) for these drugs is often the MTD or the maximum administered dose from the dose-finding trial if the MTD is not defined. This paradigm can result in a recommended dosage in labeling that may be unnecessarily high, and is poorly or not adequately tolerated, adversely impacts functioning and quality-of-life, and moreover, affects a patient's ability to remain on the drug and thereby derive maximal clinical benefit. Additionally, patients who experience adverse reactions may have difficulty tolerating

subsequent treatments, especially if the treatments are associated with similar toxicities. In some cases, adverse reactions may negatively impact overall survival.

Dose-finding trials designed to determine the MTD may not adequately consider other data, such as low-grade symptomatic toxicities (i.e., grade 1-2), dosage modifications, drug activity, pharmacokinetics, pharmacodynamics, and dose- and exposure-response relationships, to select a dosage(s) for subsequent trials. Dose-finding trials that adequately evaluate a range of dosage(s) and select the dosages to be further investigated based on all available clinical data, and a preliminary understanding of dose- and exposure-response (such as for safety, tolerability, and activity), represent a more informed approach to identify dosage(s) to be further evaluated in subsequent trials.

Despite therapeutic progress, most advanced cancers remain incurable, and patients continue to have high unmet medical needs 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 optimized dosage(s) can be aligned with the goal of expediting clinical development.[5]

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. DOSAGE OPTIMIZATION RECOMMENDATIONS

Dosages selected for administration in a clinical trial(s) should be adequately supported by data appropriate to the stage of development. Relevant nonclinical[6] and clinical data (such as PK, PD, safety, tolerability, dosage convenience, and activity), as well as the dose- and exposure-response relationships 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 all 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 and may place a protocol on clinical hold.[7]

Sponsors, including those pursuing development of a drug under an FDA expedited program (e.g., breakthrough therapy designation), should plan their development programs such that

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

[6] 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, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

[7] See 21 CFR 312.42

identification of an optimized dosage(s) can occur prior to or concurrently with the establishment of the drug's safety and efficacy. Sponsors should note that development of a drug under an FDA expedited program is not a sufficient justification to avoid identifying an optimized dosage(s) prior to submitting a marketing application.

FDA recognizes that the best approach to determining the optimized dosage(s) for a specific drug development program depends upon a variety of factors including but not limited to the drug class, proposed indicated patient population, and prior knowledge about the drug that is pertinent to dosing. Sponsors are therefore strongly encouraged to discuss their plans for dosage optimization with FDA during formal meetings, including early in clinical development.[8,9] The briefing document should include a brief summary of available relevant data used to select the proposed dosage(s); the oncology dosing tool kit is an available resource to summarize the relevant data[10]. Sponsors may also consider the Model-Informed Drug Development (MIDD) paired meeting program,[11] if appropriate.

FDA recommends the following regarding collection of relevant data and trial design to identify optimized dosages:

A. Clinical Pharmacokinetics, Pharmacodynamics, and Pharmacogenomics

- A PK sampling and analysis plan should be included in each protocol.
  - The PK sampling and analysis plan for dose-finding trials should be sufficient to adequately characterize the PK (e.g., linearity, absorption, distribution, elimination) following the first dose and at steady-state (or after administration of multiple or repeated doses if steady-state will not be reached) for each dosage evaluated in the trial.
  - The PK sampling and analysis plan for all clinical trials should be sufficient to support population PK[12] and dose- and exposure-response[13] analyses for safety, activity, and efficacy.

[8] See draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023). When final, this guidance will represent the FDA's current thinking on this topic.

[9] See PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027 available at https://www.fda.gov/media/151712/download?attachment.

[10] Additional information on the Oncology Dosing Tool Kit is available here https://www.fda.gov/about-fda/oncology-center-excellence/oncology-dosing-tool-kit.

[11] Additional information on the MIDD paired meeting program is available here https://www.fda.gov/drugs/development-resources/model-informed-drug-development-paired-meeting-program.

[12] See guidance for industry *Population Pharmacokinetics* (February 2022).

[13] See guidance for industry *Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications* (April 2003).

- A sampling and analysis plan for PD and pharmacogenomics data (including drug metabolizing enzyme or transporter gene variation, germline or somatic tumor gene variation, or target protein expression)[14] should be considered when appropriate.

- Population PK analyses should be initiated early and updated as additional data become available to identify specific populations (e.g., defined based on weight, age, sex, race and ethnicity, organ impairment, genetic factors) in which the PK demonstrate clinically meaningful differences in exposure.

- Evaluation of dose- and exposure-response relationships should be initiated early and updated as additional data become available. The metrics for evaluating safety (such as laboratory data and adverse events) and activity (such as tumor-assessment based endpoints[15] or other biomarkers) should be appropriate for the stage of development, drug, and disease setting. Relevant covariates should be examined in these analyses to identify potential clinically meaningful differences for relevant subpopulations.[16]

- PK, PD, population PK[17] and dose-response and exposure-response[18] analyses, should be considered along with other data, such as safety, tolerability, dosage convenience, and activity, to select dosage(s) for each clinical trial. Semi-mechanistic or mechanistic modeling approaches may be used to support selection of the dosage(s) to be evaluated in clinical trials.

- Dosing strategies, such as a priming dose and intra-patient dose escalation/de-escalation, should be explored in dose-finding trials when appropriate.

- If an intrinsic factor(s) is particularly relevant in a given indication, (such as genetic variation[19], organ impairment[20]) the impact on PK, PD, safety, and activity should be evaluated early in drug development using dedicated studies and/or quantitative approaches. If alternative dosages for relevant subpopulations are identified, these

[14] See guidances for industry *Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling* (January 2013), *E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories* (April 2008), and *E18 Genomic Sampling and Management of Genomic Data* (March 2018).

[15] See guidance for industry *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (December 2018).

[16] See footnote 13.

[17] See footnote 12.

[18] See footnote 13.

[19] See footnote 12.

[20] See guidances for industry *Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing* (March 2024) and *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling* (May 2003).

alternative dosages should be incorporated into a pivotal trial(s) when feasible and appropriate.

- 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 pivotal trial(s) with regard to food when applicable.[21]

- The potential for drug interactions with concomitant medications relevant to the intended population(s) should be evaluated early in development to support the administration of the dosage(s) selected for evaluation in a pivotal trial(s) with these concomitant medications.

B. Trial Designs to Compare Multiple Dosages

- Multiple dosages should be compared in a trial(s) that is designed to assess antitumor activity, safety, and tolerability to support the proposed recommended dosage(s) listed in a marketing application.

  - Data from products in similar classes or with the same mechanism of action can also be used, when appropriate, to support the dosages for further evaluation, if relevant.

  - Model-informed or model-based approaches can be helpful to identify and select the dosage(s) to be compared.

  - It may be useful to evaluate additional dose-level cohorts or add more patients to existing dose-level cohorts (i.e., backfill cohorts) in the dose-finding trial for dosages which are being considered for further development. This would provide additional clinical data to allow for further assessment of safety and activity prior to initiating a trial to compare multiple dosages.

- A recommended trial design to compare multiple dosages is a randomized, parallel dose-response trial.[22]

  - Randomization (rather than enrolling patients to non-randomized dosage cohorts) promotes comparability of patients receiving each dosage, minimizing bias in estimation of dose- and exposure-response relationships. Stratified randomization may be useful to improve comparability.

  - Blinding patients and investigators to dosage arm assignment may be considered as there could be bias that higher dosages are associated with greater activity.

[21] See guidance for industry *Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations* (June 2022).

[22] See Footnote 4.

- The trial should be sized to allow for sufficient assessment of safety and antitumor activity 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 using Type I error rates which would be used in registrational trials.

- Relevant measures of activity may include tumor assessment-based endpoints (e.g., overall response rate: ORR, progression-free survival: PFS), and other tissue, blood, or imaging-based endpoints.

- An adaptive design to stop enrollment of patients to one or more dosage arms of a clinical trial following an interim assessment of activity and/or safety could be considered.

- If crossover is permitted, the analysis plan should pre-specify how safety and activity will be assessed to account for crossover.

- Multiple dosages may also 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

- When selecting dosages for further evaluation or as the recommended dosage, safety and tolerability should be compared across the multiple dosages, including: duration of exposure; proportion of patients who are able to receive all planned doses; percentage of patients that require dosage interruptions, dose reductions, and drug discontinuations for adverse reactions; time to the first dosage modification; length of the dosage interruptions(s); percentage of patients with serious adverse reactions (including fatal adverse reactions), and percentage of patients with certain toxicities of interest for the product.

- Trial stopping rules for excessive toxicity should be pre-specified. The acceptable percentages and type of toxicities will depend on the stage of development, drug, and disease setting, among other factors. The protocol should clearly state what actions will be taken in specific situations, for example, if the percentages of dosage modifications, serious adverse reactions, fatal adverse reactions, or certain toxicities of interest are too high for one or more of the dosages. Such actions can include pausing the trial to review

these events, closing one or more of the dosage arms, adding one or more dosage arms, and/or discontinuing the trial.

- Persistent symptomatic adverse reactions, including those that may be reported as less severe (e.g., Grade 1-2 diarrhea), may significantly affect a patient's ability to remain on the drug for extended periods. The frequency and impact (i.e., frequency of drug discontinuation, duration of interruption or percentage dose reductions) 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 (i.e., cytokine release syndrome) which may lessen in severity or not occur with subsequent administration. Evaluation of an alternative dosing strategy, such as titration, to improve tolerability could be considered.

- Patient-reported outcomes (PRO) can provide a systematic and quantitative assessment of expected symptomatic side effects and their impact on function. Inclusion of PROs should be considered to enhance the assessment of tolerability in dose-finding trials, as well as subsequent 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).[23]

- Engaging with patients and other key stakeholders, such as advocacy groups in a given disease area, can provide valuable input on important considerations regarding safety, tolerability, and dosage convenience (e.g., schedule, pill burden) when selecting an optimized dosage(s).

D. Drug Formulation

- Various dose strengths should be planned 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

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

concurrent therapies, among other factors. Relevant nonclinical and clinical data along with established dose- and exposure-response relationships should be considered when selecting the proposed dosage(s) to be evaluated for each subsequent indication and usage.

- Quantitative approaches, such as mechanistic and semi-mechanistic modeling, could be used to support the dosage(s) selected for evaluation for a subsequent indication and usage.

- If sufficient relevant data are not available to support the proposed dosage(s) for a new combination or indication and usage, additional dose-finding should be conducted.