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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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)
January 2023
Clinical/Medical

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

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

Office of Communications, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
https://www.fda.gov/BiologicBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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)
January 2023
Clinical/Medical

TABLE OF CONTENTS

Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases Guidance for Industry[1]

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.