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

Guidance for Industry

DRAFT GUIDANCE

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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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1 **Optimizing the Dosage of Human Prescription Drugs and Biological**
2 **Products for the Treatment of Oncologic Diseases**
3 **Guidance for Industry¹**
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7 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
8 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
9 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
10 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
11 for this guidance as listed on the title page.
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15 **I. INTRODUCTION**

16 This guidance is intended to assist sponsors in identifying the optimal dosage(s)² for human
17 prescription drugs³ or biological products for the treatment of oncologic diseases during clinical
18 development and prior to submitting an application for approval for a new indication and usage.

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

22 Additional information on related topics can be found in:

- 23 • Draft guidance for industry *Population Pharmacokinetics* (July 2019).⁵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

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

29 In general, FDA's guidance documents do not establish legally enforceable responsibilities.
30 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.

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

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35 **II. BACKGROUND**

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

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

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

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

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

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

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81 **III. DOSE OPTIMIZATION RECOMMENDATIONS**

82 Dosages selected for administration in a clinical trial(s) should be adequately supported by data
83 appropriate to the stage of development for each indication and usage. Relevant nonclinical⁷ and
84 clinical data, as well as the dose- and exposure-response relationships for safety and efficacy
85 should be evaluated to select a dosage(s) for clinical trial(s). An approach where a dosage is
86 chosen for a trial without adequate justification or consideration of relevant data may not be
87 acceptable because FDA may determine that patients are exposed to unreasonable and significant
88 risk, or there is insufficient information to determine risk, or the design of the trial is deficient to
89 meet its stated objectives.⁸

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

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

100 **A. Collection and Interpretation of Clinical Pharmacokinetic, Pharmacodynamic, and** 101 **Pharmacogenomic Data**

- 102 • Dose-finding trials should include PK sampling and an analysis plan such that PK
103 data are of sufficient quality and quantity to allow an adequate characterization of the
104 PK (e.g., linearity, absorption, elimination) of an oncology drug following the
105 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.

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- 106 • The PK sampling and analysis plan should also be sufficient to support population PK
107 and dose- and exposure-response analyses for safety and efficacy.¹⁰
- 108 • Following the completion of the dose-finding trial(s), population PK⁹ and exposure-
109 response¹⁰ analyses, data should be evaluated along with the anti-tumor activity,
110 safety, and tolerability data to select dosage(s) for further evaluation.
- 111 • For oral drugs, the effect of food on PK and safety should be evaluated early in drug
112 development to support the relative administration of the dosage(s) selected for
113 evaluation in a registration trial(s) with food.¹¹
- 114 • Clinical trials should enroll an appropriately broad population^{12,13,14,15,16} to allow
115 assessment of the dosage(s) across relevant subpopulations.
- 116 • Population PK data should be evaluated to identify specific populations (e.g., defined
117 based on weight, age, sex, race and ethnicity, or organ impairment) in which the PK
118 demonstrate clinically meaningful differences in exposure.
- 119 • Relevant covariates should be incorporated into the exposure-response analyses to
120 identify potential differences in safety or effectiveness for relevant subpopulations.¹⁰
- 121 • When appropriately justified, simulated exposure metrics may be used to conduct
122 exposure-response analyses to evaluate alternative dosages, if applicable, in the
123 relevant subpopulations. Alternative dosages for relevant subpopulations should be
124 incorporated into a registration trial(s) when feasible and appropriate.
- 125 • A sampling and analysis plan for PD and pharmacogenetic data^{17,18} should be
126 considered if appropriate.
- 127 • 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).

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128 **B. Trial Designs to Compare Multiple Dosages**

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

162 **C. Safety and Tolerability**

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

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- 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.
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- 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.
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- 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.
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- 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
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- 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

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- 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.
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- 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).
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- 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

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- 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.

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

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