Early-Phase IND Protocol Recommendations for Solid Tumors

Guidance for Industry

DRAFT GUIDANCE

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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)

November 2026
Clinical/Medical

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Guidance for Industry

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Early-Phase IND Protocol Recommendations for Solid Tumors Guidance for Industry[1]

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I. INTRODUCTION

This document is intended to provide recommendations to sponsors and clinical investigators developing early-phase trials, which include first-in-human (FIH) protocols or protocols for drugs and biologic products[2] with limited human experience, submitted under an Investigational New Drug Application (IND) to the appropriate disease-specific division located within the Center for Drug Evaluation and Research's Office of Oncologic Diseases (CDER/OOD)[3] and the Center for Biologics Evaluation and Research's Office of Clinical Evaluation (CBER/OCE)[4]. This guidance is specific to solid tumors and does not address protocols for investigational drugs intended to treat hematologic malignancies.

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

II. BACKGROUND

The Agency's primary objective in reviewing early-phase protocols is to ensure the safety and rights of human subjects participating in an investigation (21 CFR 312.22). This guidance provides recommendations for designing protocols that protect human subjects from

[1] This guidance has been prepared by the Oncology Center of Excellence (OCE), in collaboration with 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 purposes of this guidance, the term drug or drugs refers to drug products approved under section 505 of the Federal Food, Drug, and Cosmetic (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).

[3] See https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/information-sponsors-submissions-office-oncologic-diseases-ood.

[4] See https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/center-biologics-evaluation-and-research.

unreasonable and significant risk. These recommendations are based on common issues identified during the review of INDs at CDER/OOD and CBER/OCE. Each investigational drug and biological product is inherently different, and not all recommendations may be applicable to all protocols. Scientific and clinical judgment should be applied based on the specific characteristics of the investigational drug and disease setting to determine whether any of the following recommendations are appropriate or whether additional safety protections are needed. Therefore, FDA encourages sponsors to discuss unique disease settings and therapies with the Agency in a pre-IND meeting.

III. RECOMMENDATIONS FOR EARLY-PHASE TRIALS

A. Eligibility Criteria

Unnecessarily restrictive eligibility criteria may slow patient accrual, limit patient access to early-phase trials, and lead to trial results that have limited applicability in the patient population that will ultimately use the drug. Sponsors should reference FDA eligibility criteria guidances for trials enrolling patients with cancer for additional early-phase trial considerations to ensure patient safety and to ensure that access to clinical trials is not unnecessarily restricted. Many of these guidances are cited in this section.

1. Prior therapy[5]

- Eligibility criteria should include the requirement that patients have received available therapy(ies) that offer the potential for cure, or such available therapy be administered to all patients in the trial, where the investigational drug is added to such therapy (i.e., add-on trial).
- When conducting clinical trials in a non-curative setting, patients may be eligible for inclusion in trials, including early-phase trials, regardless of whether they have received available therapy in the non-curative setting.
- Sponsors must ensure the elements of informed consent, as required by 21 CFR 50.25, are addressed, including "a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject." The informed consent must clearly state whether other treatment options known to confer clinical benefit exist and must include discussion of reasonably foreseeable risks and any potential benefits associated with the administration of investigational drug. For disease settings in which there are available therapies that have demonstrated prolongation in survival (i.e., an overall survival benefit), these therapies should be explicitly stated in the informed consent document by name.

[5] See guidance for industry Cancer Clinical Trial Eligibility Criteria: Available Therapy in Non-Curative Settings (July 2022).

2. Age

- In general, protocols should not impose upper age limitations. If an upper age limitation is proposed, adequate justification should be provided.[6]
- For FIH or dose escalation protocols that investigate drugs primarily intended to treat adult cancers, restricting enrollment to adult patients is appropriate. Moreover, FDA encourages the timely inclusion of pediatric patients with solid tumors that have no curative options in early-phase trials when compelling nonclinical data or early adult clinical data indicate evidence of activity.
    - When an oncology drug offers a prospect of direct clinical benefit to pediatric patients, FDA recommends that sponsors prospectively plan for pediatric inclusion in select early-phase studies once adequate data on dosing and safety in adults are available to support safety and identification of the appropriate starting dosage(s) in the pediatric population.[7]
    - Absent development-specific safety concerns, given similarities in drug exposure between adolescents and adults (based on similar body weight and metabolic processes), adolescents may be enrolled concurrently with adult patients after some initial adult pharmacokinetics (PK) and toxicity data are obtained.
    - Sponsors should consult with the relevant FDA review division to determine the type and amount of adult data needed before enrolling pediatric patients.[8]
- For certain FIH or dose escalation protocols that investigate drugs primarily intended to treat pediatric cancers, substantive nonclinical evidence of activity may, on its own, provide sufficient justification for enrolling pediatric patients without prior experience in adults; this is appropriate only when the risks to pediatric patients can be adequately mitigated. In such cases, FDA recommends that sponsors consult with the relevant review division to discuss the planned study before the protocol is finalized.
- In select cases, staggered enrollment of older children or adolescents before younger children may be appropriate to minimize the risk to pediatric patients.

3. Brain metastases[9]

Thoughtful consideration should be given to the potential inclusion of patients with brain metastases in early-phase trials. Patients with brain metastases should be included in clinical trials in a way that contributes to a greater understanding of the efficacy and safety profile of the investigational drug while maintaining adequate patient safety. Clinical judgement should be exercised on whether it is appropriate to include patients with treated and stable metastases,

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[6] See guidance for industry Inclusion of Older Adults in Cancer Clinical Trials (March 2022).

[7] See draft guidance for industry, sponsors, and IRBs Ethical Considerations for Clinical Investigations of Medical Products Involving Children (September 2022). When final, this guidance will represent FDA's current thinking on this topic.

[8] See guidance for industry and IRBs Cancer Clinical Trial Eligibility Criteria: Minimum Age Considerations for Inclusion of Pediatric Patients (July 2020).

[9] See guidance for industry Cancer Clinical Trial Eligibility Criteria: Brain Metastases (July 2020).

active metastases, or leptomeningeal metastases in the trial. Important factors to influence the study protocol eligibility criteria regarding patients with brain metastasis include the mechanism of action of the drug, the targeted disease or patient population, the anticipated safety of the investigational drug, the availability of adequate safety data, and the ability to recruit trial participants from the patient population to meet the objectives of the clinical trial. Sponsors should also clearly outline requirements for the use of steroids, radiation and antiepileptic therapy, if any, in early-phase protocols if patients with brain metastases are included.

4. HIV, Hepatitis B, or Hepatitis C[10]

Thoughtful consideration should be given to the potential inclusion of patients infected with human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) in cancer clinical trials. Eligibility criteria that address requirements regarding relevant concurrent antiviral and other therapies (e.g., antibiotic prophylaxis) and degree of immunocompetence in patients with HIV, HBV, or HCV infections should be designed in a manner that is appropriate for a given cancer, investigational drug (for instance taking into account immunosuppressive potential, drug-drug interaction, etc.), and intended use population. Inclusion of these patients in early phase cancer clinical trials allows for evaluation of safe and effective use of the product across a broader patient population likely to use the drug in clinical practice.

5. Washout Periods[11]

Unless scientifically justified or necessary to achieve the goals of the clinical investigation, FDA generally does not recommend time-based wash-out and recovery periods. Eligibility after prior therapy/intervention should be based on recovery from clinically significant adverse events from the therapy or intervention preceding study enrollment.

6. Renal Function

- Use a contemporary, widely accepted and clinically applicable equation to estimate renal function and base inclusion criteria for renal function on the characteristics of the investigational drug (e.g., molecular weight, mechanism of elimination) such as:
    - For small molecules and antibody-drug conjugates (ADC), consider a creatinine clearance (CLcr) or estimated glomerular filtration rate (eGFR) of 60 mL/min or greater; however, lower values may be acceptable if the disease or population typically presents with renal insufficiency.
    - For biological products with a molecular weight greater than 69 kDa, consider a CLcr or eGFR of 30 mL/min or greater given that these larger molecules are less likely to undergo significant renal excretion.

[10] See guidance for industry Cancer Clinical Trial Eligibility Criteria: Patients with HIV, Hepatitis B Virus, or Hepatitis C Virus Infections (July 2020).

[11] See guidance for industry, IRBs, and Clinical Investigators Cancer Clinical Trial Eligibility Criteria: Washout Periods and Concomitant Medications (July 2026).

- Emerging pharmacokinetic and safety data may support lower cut-off values to facilitate enrollment in subsequent trials when an investigational drug is not considered nephrotoxic.
- Consider using a uniform method to estimate renal function to facilitate future pooled analyses across studies, such as population pharmacokinetic analyses.

7. QT Interval[12]

- Include QTc interval exclusion criteria that are appropriate for the study population and the investigational drug's potential for QT prolongation such as:
  - If there is a risk of QT prolongation, consider excluding concomitant medications with a risk of QT prolongation and patients with medical conditions that could increase the risk of QT prolongation.
  - For small molecules and ADCs, consider excluding patients with a QTc interval > 470 milliseconds. For small molecules with high potential for QTc prolongation based on observed data, including results from nonclinical studies or known drug class effects, consider excluding patients with QTc interval > 450 milliseconds. In protocol amendments or subsequent trials, the exclusion criterion may be modified if supported by available clinical data.
  - For biological products, with the exception of ADCs, consider excluding patients with QTc interval > 480 milliseconds given the lower risk of QTc interval prolongation.
- FDA does not recommend different QTc cutoffs based on sex, as available data show less differences in baseline QTc between sexes in patients with cancer than in healthy participants.[13]

8. Additional Considerations for Autologous Cell and Gene Therapy Products

For autologous cell and gene therapy (CGT) products, Sponsors should specify eligibility criteria to be confirmed at the time of lymphodepletion and product administration to account for potential changes in the patient's condition during the manufacturing period. Additionally, patients should not be eligible to begin lymphodepletion until it is known that the CGT product is available. Refer to FDA guidance *Considerations for the Development of CAR T Cell Products (January 2024)* for additional considerations.

[12] See guidance for industry E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (October 2005).

[13] Nan Zheng et al. QT assessments in oncology drug development and related labels.. J Clin Oncol 38, e14127-e14127(2020). DOI:10.1200/JCO.2020.38.15_suppl.e14127

9. Other Considerations

Sponsors should monitor the FDA guidance document website[14] for other cancer clinical trial eligibility guidances, such as Laboratory Values[15] and Performance Status[16], and for other FIH trial considerations to ensure patient safety. While Section III.A. highlights eligibility criteria specific to early-phase trials and common for solid tumors, it is not an exhaustive list. Other cancer clinical trial eligibility guidances may apply to your protocol.

B. Dose Escalation Trial Design

1. Study Objectives

- For a FIH trial, the primary objective(s) should be assessments of safety and tolerability.
- Other objectives can be secondary or exploratory and can include dose identification, pharmacokinetics, pharmacodynamics, immunogenicity (if applicable), biomarker analyses, dose-exposure-response relationships, food effect/drug-drug interactions (if applicable), and preliminary measures of activity (e.g., response rate).

2. Dose Escalation Methods and Procedures

a. Dose Escalation Design

- A rule-based or model-based design should be prespecified to guide the decisions regarding the dosage of the investigational agent in subsequent cohorts to ensure adequate control of the rate of excessive toxicity and the selection of a safe dose for further investigation.
- For dose escalation designs using decision criteria based on data from a single dose level (e.g., Bayesian Optimal Interval [BOIN] design), ensure that the upper boundary allowing a dose retention decision is specified and does not lead to an excessive observed toxicity rate.
- For dose escalation designs using decision rules based on data across all dose levels for which a decision table cannot be pre-tabulated (e.g., Bayesian Logistic Regression Model [BLRM]), a description of the data that support the assumptions for the model should be provided and simulation studies should be conducted to evaluate the operating characteristics of the design. The simulation studies should demonstrate a low probability of selecting a dose with excessive toxicity and a low percentage of patients exposed to an excessively toxic dose. The operating characteristics should be evaluated for robustness with different parameter settings which violate the model assumptions.

[14] See "Search for FDA Guidance Documents" on FDA's website

[15] See guidance for industry, IRBs, and clinical investigators Cancer Clinical Trial Eligibility Criteria: Laboratory Values (July 2026).

[16] See guidance for industry, IRBs, and clinical investigators Cancer Clinical Trial Eligibility Criteria: Performance Status (July 2026).

b. Accelerated Titration

For accelerated titration (e.g., single patient) dose-escalation cohorts:

- The acceptability of this approach depends on the safety margin proposed, the mechanism of action of the product and any known data on products of the same class, and the dose increments proposed between cohorts during titration.
- Single patient dose escalation cohorts may not be suitable for certain drugs depending on their mechanism of action. For example, because tumor burden differs between patients, a given dose that may be safe in one patient with lower tumor burden may cause considerable toxicities at the same dose in patients with higher tumor burden.
- When an accelerated titration approach is acceptable, switch to a dose escalation design with a larger cohort size (e.g., minimum 3 patients) following observation of any Grade 2 or higher adverse event regardless of attribution, unless clearly related to underlying disease or extraneous cause.

c. Intra-patient dose escalation (IPDE)

- IPDE should occur only if ≤ Grade 2 toxicity was observed during the previous treatment cycle.
- The decision to allow for IPDE should be made after considering the potential safety profile of the investigational drug, including cumulative drug toxicity. The maximal intra-patient dose escalation level should only be at the highest cleared dose level.
- IPDE may not be suitable for certain drugs depending on their mechanism of action. For example, because tumor burden differs between patients, a given dose that may be safe in one patient with lower tumor burden may cause considerable toxicities at the same dose in patients with higher tumor burden.

d. Dose Increments

- In general, the maximum dose increment for small molecules and ADCs should not exceed 100% and for biologics (with exception of ADCs) should not exceed half-log. Alternative proposals should have adequate justification.
- Dose increments of less than 100% (e.g., modified Fibonacci or 50%) for small molecules and ADCs, or less than half-log for biologics (with exception of ADCs and T-cell engagers [TCE]) may be warranted if the following situations occur:
    - If at least two ≥ Grade 2 treatment-emergent adverse events (TEAE) or one dose-limiting toxicity (DLT) are observed across the cohort with at least three patients enrolled.
    - If a single ≥ Grade 2 adverse event occurs in a single patient cohort. The protocol should be modified to require expansion of single patient cohorts (e.g., minimum 3 patients per cohort) for any ≥ Grade 2 adverse event, regardless of attribution.
- For TCE, dose increments should be limited to 100% or less for both step-up and full treatment doses if one or more incidences of ≥ Grade 2 cytokine release syndrome (CRS) during the DLT period and to 50% or less if two or more incidences of ≥ Grade 2 CRS or one or more DLT is observed during the DLT period. Optimize the step-up dosing regimen (e.g., step-up dose(s) and dosing schedule) that can minimize the risk of ≥ Grade 3 CRS.

e. Staggering Patient Enrollment

- For first-in-human trials, investigational drug(s) may have certain serious expected toxicities based on non-clinical studies, existing human data, or both on similar products. Depending on the expected toxicities and their severity, dosing several patients simultaneously may represent an unreasonable risk. To address this issue, sponsors may need to provide a plan to stagger administering the product to successive patients to limit the number of patients who might be exposed to risk within a cohort, followed by staggering between cohorts. The plan to stagger patients should include:
  - Justification showing that the interval is long enough to monitor for acute and subacute events
  - Consideration of the time course of adverse events that were observed in animal studies and in previous human experience with related products
  - Consideration of the expected duration of the drug's activity

f. Duration of dose delay prior to resumption of therapy

Any adverse event that requires the investigational drug to be held should return to Grade 1 or baseline within 14 days before resuming therapy at the current dose or a reduced dose. Delays longer than 14 days may be considered with justification (e.g., immunotherapies necessitating corticosteroid tapering).

3. Novel Combinations

When sponsors plan to combine one or more drugs in combination, consideration should be given early in drug development for how the contribution of effect of each drug(s) to the combination being studied will be demonstrated.[17]

C. Dose-Limiting Toxicity Criteria

All adverse events that occur or worsen after one treatment dose should be considered at least possibly related to the study drug regardless of investigator/sponsor/safety review committee causality assessment, excluding toxicities or death clearly related to disease progression or extraneous causes.

The DLT evaluation period (i.e., DLT window) should generally be at least one cycle (e.g., 21 or 28 days). For immunotherapy products, this DLT evaluation period may be reasonable for the purposes of patient enrollment into escalating dose cohorts. However, for certain cellular therapies with known toxicities that may occur after 28 days of patients' receiving the product, longer DLT observation period may be needed (e.g., 42 days). In addition, all patients should be monitored for approximately 90 days after treatment discontinuation, or longer based on the

[17] See draft guidance for industry Development of Cancer Drugs for Use in Novel Combination - Determining the Contribution of the Individual Drugs' Effects (July 2025). When final, this guidance will represent FDA's current thinking on this topic.

mechanism of action of the product, for late onset toxicities (e.g., delayed immune-related toxicities) that have been associated with immunotherapy products. Late onset toxicities after the DLT period should be considered when choosing doses to explore further.

The following DLT criteria are generally recommended for dose escalation. Sponsors may provide additional exceptions with a corresponding rationale for the safety of any alternative approach.

- Any death not clearly due to the underlying disease or extraneous causes
- Non-hematologic toxicity:
  - Grade 3 or higher
  - Any AST or ALT elevation > 8 times the upper limit of normal (ULN) regardless of duration or AST or ALT elevations 5 to 8 times the ULN that persist for greater than 2 weeks-all regardless of the presence or absence of liver metastases
  - Hy's law cases
- Hematologic toxicity
  - Absolute neutrophil count (ANC) < 0.5 x 10^9/L for more than 7 days in duration
  - Platelet count <50,000/mm^3 with clinically significant bleeding
  - Platelet count <25,000/mm^3 for more than 7 days in duration
  - Febrile neutropenia
- Any toxicity that results in a >14-day treatment delay

Exclusions when defining DLT should be justified and will be considered on a case-by-case basis. Sponsors may consider excluding:

- Grade 3 nausea/vomiting or diarrhea for less than 3 days
- Grade 3 fatigue for less than 7 days
- Grade 3 rash that improves to < Grade 3 with standard management within 7 days
- Grade 3 endocrinopathies that are well controlled with supplemental medication
- Grade 3 or Grade 4 electrolyte abnormality that:
  - lasts less than 3 days,
  - is not clinically complicated (e.g., asymptomatic G3+ electrolyte, abnormality),
  - does not require hospitalization, and
  - resolves spontaneously or responds to conventional medical interventions.
- Grade 3 amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis and does not require hospitalization

For CAR T and other immune effector cell products, additional DLT criteria apply (e.g., CRS and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS).[18]

[18] See guidance for industry Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products (January 2024).

D. Early-Phase Studies with Dose Expansion Cohorts[19]

- To minimize the number of subjects exposed to a potentially ineffective drug or drug associated with substantial toxicity, the statistical analysis plan for expansion cohorts in early-phase studies or protocols should include a justification of the maximum sample size. It should also include stopping rules based on observation of excessive toxicity or lack of activity.
    - For randomized cohorts used for dose optimization, the sample size should still be sufficient to characterize different dosages.[20]
    - Safety stopping rules should be included for the study overall and for expansion cohorts.
    - An adaptive design (e.g., Simon two-stage design) may be considered to initiate efficacy cohorts using smaller initial sample size.
- Protocols with dose expansion cohorts (e.g., backfill cohorts, expansion cohorts in specific tumor types, protocols with Phase 1b or Phase 2 elements) should include dose modification guidelines and other information that is relevant to maintaining patient safety. In cases where there is insufficient information to ensure the safety of patients enrolling into these cohorts at the time of IND submission, sponsors should consider restricting their early-phase IND protocol to include only dose escalation, with consideration for adding expansion cohorts as an amendment when more information is available.
- As development proceeds and activity or safety signals are identified in a specific tumor, sponsors should consider submitting protocols to a new IND to the division responsible for reviewing that solid tumor indication.[21] This is preferred over expanding disease specific cohorts under the existing IND.
    - For example, an early-phase study may include exploratory cohorts across various tumor types. If activity and safety signals are identified in a specific tumor type during the trial, the sponsor should submit a new IND to the appropriate review division rather than expanding that cohort beyond 40 patients under the early-phase IND.
    - See additional information on Dose Optimization in Section III.F.

E. Considerations for Assessment of Activity in Early-Phase Trials

Assessments of activity are typically included in early-phase trials for oncology therapeutics. The following should be considered:

- Single-arm trials do not adequately characterize endpoints, such as overall survival or progression-free survival. Because of variability in the natural history of many forms of cancer, a randomized study is generally necessary to evaluate time-to-event endpoints. Evaluating these endpoints for exploratory or hypothesis-generating purposes in early-phase

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

[20] See guidance for industry Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases (August 2024) and Oncology Dosing Tool Kit on FDA's website.

[21] See "Submissions to the Office of Oncological Diseases (OOD)" on FDA's website.

studies is reasonable; however, because early-phase trials are usually non-randomized, the study results on time-to-event efficacy endpoints should be interpreted with caution.

- Sponsors should meet with the appropriate FDA review division as early as possible if they intend to use data from early-phase trials and dose expansion cohorts to provide substantial evidence of effectiveness to support a future marketing approval application.

F. Determination of Recommended Phase 2 Dose (RP2D) and Dose Optimization

- Any late toxicity will need to be considered in the determination of the RP2D (e.g., up to 90 days for immunotherapy) and schedule to be taken forward into the expansion phase of the study.
- Adequate dose exploration of multiple dose levels should be conducted and the RP2D should not be based only on a maximum tolerated dose, but instead on the totality of the PK, safety, and efficacy information. Refer to Project Optimus[22] Tool Kit and guidances for more information to select an optimized dosage.

G. Individual Patient Treatment Considerations

1. Patient Stopping Rules

In addition to trial stopping rules, protocols should include patient stopping rules based on observed toxicity. For early-phase dose escalation trials, patients should generally discontinue therapy when they experience a DLT. Sponsors may consider continuing patients on therapy at reduced doses (e.g., lower than the dose at which the DLT occurred) with a strong rationale for doing so.

2. Treatment Beyond Radiographic Progression

The protocol may allow patients to continue taking the investigational drug after radiographic progression if they are deriving clinical benefit.

- When alternative treatment options exist, patients should be re-consented using a written informed consent document that details all alternative FDA-approved therapies, participation in alternative clinical trials, and potential clinical benefit that the patient may be foregoing in order to continue receiving the investigational drug. This written informed consent may be a separate informed consent document or a separate section in the main informed consent document and should be signed at the time of progressive disease, prior to continuing treatment.
- Sponsors should include criteria to ensure that patients are not exposed to unreasonable risks. Criteria to continue therapy could include, but are not limited to:
  - Absence of symptoms and signs that may indicate clinically significant progression of disease
  - No decline in performance status
  - Absence of symptomatic rapid disease progression, threat to vital organs or critical anatomical sites (e.g., CNS metastasis, respiratory failure due to tumor compression,

[22] See "Project Optimus" on FDA's website.

symptomatic pleural effusion, peritoneal effusion or ascites that leads to or requires frequent drainage, spinal cord compression) requiring urgent medical intervention
    - Treatment must be tolerated (e.g., patient is experiencing no or only mild [Grade 1] toxicities or patient is not experiencing chronic or persistent moderate [Grade 2] toxicities.)

3. Safety Monitoring

- Protocols should include safety monitoring plans (e.g., a schedule of events for physical exams, vital signs, laboratory assessments) and risk mitigation strategies for known or expected serious toxicities.
- In FIH studies with risks that include acute toxicities that could result in respiratory or hemodynamic compromise, inpatient monitoring may be warranted for the initial patients to receive the investigational product(s). In these cases, sponsors should provide a plan to monitor patients and a duration of monitoring with accompanying rationale on justification of the proposed duration. After initial safety data is generated, it may be reasonable to administer subsequent doses in an outpatient setting with appropriate safety monitoring. Protocols can be amended based on emerging safety data.
- Cell and gene therapy products require additional product-specific safety monitoring (e.g., vector shedding, integration site analysis).[23]
- Certain products may require additional safety considerations (e.g., intra-tumorally administered therapies).
- For radiolabeled products, patients should be followed for at least 5 years after the last dose, or until death in cases where life expectancy is typically expected to be less than 5 years, to monitor for late-onset radiation-associated toxicities including secondary malignancies and renal failure. Refer to FDA guidance on *Oncology Therapeutic Radiopharmaceutical Dose Optimization During Clinical Development*[24] for additional information.
- For gene therapy products, long-term follow-up of up to 15 years may be required.[25]
- The protocol should contain pre-specified subject and trial stopping rules that are based on the observation of unacceptable toxicity such as treatment-related death or Grade 4 toxicity not clearly related to the underlying disease or extraneous causes.

H. Companion Diagnostic Device Considerations

If selection of patients based on a biomarker assessment is essential for the safe and effective use of the drug, the development and validation of an in vitro companion diagnostic device (CDx)

[23] See guidance for industry Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (June 2015).

[24] See draft guidance for industry Oncology Therapeutic Radiopharmaceuticals: Dosage Optimization During Clinical Development (August 2025). When final, this guidance will represent FDA's current thinking on this topic.

[25] See guidance for industry Long Term Follow-up After Administration of Human Gene Therapy Products (January 2020).

may ultimately be needed. Consultation with the Center for Devices and Radiologic Health (CDRH) early in clinical development is recommended if a CDx needs to be developed.[26]

I. Administration Relative to Food[27]

The recommended approach for early-phase trials is typically a modified fasted condition (such as taking on an empty stomach, defined as at least 1 hour before and 2 hours after a meal). This approach avoids confounding dose-finding assessments while maintaining patient safety and tolerability. Alternative food intake instructions may be supported with adequate justifications, such as anticipated gastrointestinal intolerability. If the investigational drug is to be administered with food, protocols should provide adequate PK and safety justification and detailed meal composition. In subsequent trials, food administration requirements may be modified based on emerging pharmacokinetic and safety data, including results from preliminary or dedicated food effect studies.

J. Sampling and Analysis Plans

1. Pharmacokinetic

Protocols should include pharmacokinetic (PK) sampling plans that adequately characterize the PK profile of the investigational drug and support dosage selection for subsequent trials. The sampling plan should clearly specify which analyte or analytes will be measured.

For early-phase trials, FDA recommends including intensive PK sampling following the first dose and at steady state or after multiple doses. Additionally, it is recommended to include sparse sampling throughout the study to support population pharmacokinetic modeling and exposure-response analyses. The sampling plan should include samples around the anticipated time of the maximum concentration, if applicable and extend sufficiently to characterize the elimination phase, with the duration informed by the anticipated elimination half-life based on nonclinical data or data from related compounds. In subsequent trials, PK sampling frequency and timing may be adjusted based on emerging pharmacokinetic and safety data.

Protocols should include a comprehensive PK analysis plan that describes the analytical approaches to be used. The analysis plan may include non-compartmental and population pharmacokinetic modeling to characterize PK variability across the patient population and identify covariates that may influence drug exposure, as well as exposure-response analyses to evaluate relationships between drug exposure and both activity and safety outcomes.

[26] See guidance for industry and FDA staff Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program (May 20250) and guidance for industry and FDA staff In Vitro Companion Diagnostic Devices (August 2014).

[27] See guidance for industry Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations (May 2026).

For virus or bacteria-based gene therapy and oncolytic products, FDA recommends a vector shedding study to assess the potential for transmission to untreated individuals be included in the early-phase product development plans.[28]

2. ECG Monitoring

For small molecules, ADCs, and some biological products, FDA recommends including ECG monitoring plans. For early-phase trials, the recommended sampling frequency includes monitoring pre-dose and around anticipated time to maximum concentration following the first dose and at steady state or after multiple doses, as well as clinically indicated monitoring throughout the trial. Triplicate ECGs can support QT-concentration analysis. In subsequent studies, the frequency may be adjusted based on emerging pharmacokinetic and safety data.

3. Immunogenicity[29]

For biological products, include immunogenicity sampling plans to assess immune responses against the investigational product, such as the development of anti-drug antibodies (ADAs). FDA recommends collecting immunogenicity samples pre-dose to minimize drug interference with immunogenicity assays, as circulating drug can affect the sensitivity and accuracy of ADA detection. For early-phase trials, the recommended sampling frequency includes collection at each cycle for at least the first three cycles, followed by sampling every other cycle for three to four cycles, then every four cycles thereafter. Consider collecting additional samples at the end of treatment and at safety follow-up visits, if feasible, and an earlier timepoint for products with a short elimination half-life to capture potential early onset of immunogenicity response. In subsequent trials, immunogenicity sampling frequency may be adjusted based on emerging pharmacokinetic and safety data.

It is recommended that the immunogenicity analysis plan include an assessment of the impact of ADAs and neutralizing antibodies (NAbs) on safety, efficacy, pharmacokinetics, and pharmacodynamics and describe the use of screening and confirmatory assays for ADA detection.

4. Other Considerations

While Section III.J highlights recommendations for PK, ECG monitoring, and immunogenicity plans that are specific to early-phase trials and common for solid tumors, it is not an exhaustive list. Other sampling and analysis plans, such as pharmacogenomics and biomarker plans, may apply to certain protocols.

[28] See guidance for industry Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products (August 2015).

[29] See guidance for industry Immunogenicity Assessment for Therapeutic Protein Products (August 2014).