Expansion Cohorts: Use in First-in-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

March 2022
Procedural

Expansion Cohorts: Use in First-in-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics

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/guidance-compliance-regulatory-information/guidances-drugs

and/or

Office of Communication, 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/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

March 2022
Procedural

Contains Nonbinding Recommendations

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Expansion Cohorts: Use in First-in-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics 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

The purpose of this guidance is to provide advice to sponsors regarding the design and conduct of first-in-human (FIH) clinical trials intended to efficiently expedite the clinical development of oncology drugs, including biological products, through multiple expansion cohort trial designs.[2] These are trial designs that employ multiple, concurrently accruing subject cohorts, where individual cohorts assess different aspects of the safety, pharmacokinetics, and antitumor activity of the drug product.

This guidance provides FDA's current thinking regarding (1) characteristics of drug products best suited for consideration for development under a multiple expansion cohort trial; (2) information to include in investigational new drug applications (INDs) to support the use of individual cohorts; (3) when to interact with FDA on planning and conduct of multiple expansion cohort trials; and (4) safeguards to protect subjects enrolled in FIH expansion cohort trials.

This guidance does not address all issues relating to clinical trial design, statistical analysis, or the biomarker development process. Those topics are addressed in other guidances including the International Council for Harmonisation (ICH) guidances for industry *E9 Statistical Principles for Clinical Trials* (September 1998) and *E10 Choice of Control Group and Related Issues in*

[1] This guidance has been prepared by the Office of Oncologic Diseases in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

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

Clinical Trials (May 2001) as well as the guidance for industry and FDA staff *In Vitro Companion Diagnostic Devices* (August 2014).[3]

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA's guidance documents 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

Phase 1 clinical trials are designed to determine the metabolism and pharmacologic actions of an investigational drug in humans, the side effects associated with increasing doses, and, when conducted in patients rather than healthy subjects, to gain early evidence of effectiveness.[4] The primary rationale for conducting phase 1 studies is to obtain sufficient information about the drug's pharmacokinetic (PK) and pharmacologic effects to permit the design of subsequent well-controlled, scientifically valid phase 2 studies. The number of subjects included in phase 1 trials is anticipated to be 20 to 80 subjects.

FIH multiple expansion cohort trials are intended to expedite development by seamlessly proceeding from initial determination of a tolerated dose to assessments that are more typical of phase 2 trials (i.e., to estimate antitumor activity) within individual expansion cohorts. In general, these expansion cohorts will be initiated before the analysis of the metabolism and pharmacokinetics of the investigational drug and with limited safety assessment. Therefore, it is critical to ensure close and prompt monitoring for toxicity in expanded cohorts, given that such trials have enrolled between a few hundred to more than 1,000 subjects.[5, 6]

Because of the rapid enrollment and evolving nature of the information obtained in these trials, large numbers of subjects are exposed to drugs with unknown efficacy and minimally characterized toxicity profiles. To limit the number of subjects that could be exposed to unacceptable safety risks or an ineffective drug, sponsors should establish an infrastructure to streamline trial logistics, facilitate data collection (see section VII., Safety Considerations), and incorporate plans to rapidly assess emerging data in real time and to disseminate interim results to investigators, institutional review boards (IRBs), and regulators.

[3] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[4] 21 CFR 312.21(a)(1) and (2).

[5] See, for example, KEYNOTE-001 study design at https://clinicaltrials.gov/ct2/show/NCT01295827.

[6] See, for example, JAVELIN study design at https://clinicaltrials.gov/show/NCT01772004.

III. FIH MULTIPLE EXPANSION COHORT TRIAL DEFINITION AND POTENTIAL OPPORTUNITIES AND CHALLENGES

A. Definition

For the purpose of this guidance, an FIH multiple expansion cohort trial is an FIH trial with a single protocol with an initial dose-escalation phase followed by three or more additional subject cohorts with cohort-specific objectives. The objectives of these expansion cohorts can include assessment of antitumor activity in a disease-specific setting, assessment of a dose with acceptable safety in specific populations (e.g., pediatric or elderly subjects, subjects with organ impairment, subjects with specific tumor types), evaluation of alternative doses or schedules, establishment of dose and schedule for the investigational drug administered with another oncology drug, or evaluation of the predictive value of a potential biomarker. In general, comparison of activity between cohorts is not planned except when a prespecified randomization and analysis plan are part of the protocol design.

B. Potential Opportunities and Challenges

The principal advantage of conducting FIH multiple expansion cohort trials is efficiency in drug development by gaining earlier evidence on whether a drug may be effective across a range of diseases and populations.

FIH multiple expansion cohort trials pose several challenges and risks, including the following:

- The need to disseminate new safety information to investigators, IRBs, and regulators as soon as possible. FDA and investigators must be updated with new serious and unexpected safety information as soon as possible but no later than 15 calendar days after the sponsor determines that the information should be reported,[7,8,9] so that they can provide the necessary oversight for protection of human subjects and so that investigators can ensure that subjects can provide adequate informed consent.

- Exposing a large number of subjects across multiple, simultaneously accruing cohorts to potentially suboptimal or toxic doses of an investigational drug.

- Exposing more subjects to the potential risks of the investigational drug than required to achieve the cohort's objectives.

- Possible misinterpretation of preliminary trial results and unplanned analyses that can lead to delays in clinical development (e.g., selection of dosage regimens or biomarker-

[7] See, for example, 21 CFR 312.32(c)(1).

[8] 21 CFR 312.55. In turn, investigators must promptly notify an IRB of all unanticipated problems involving risks to human subject per 21 CFR 312.53(c)(vii), among other obligations.

[9] See 21 C.F.R. 312.50.

selected populations based on an apparent large effect that is a chance occurrence or reflects a response in a subpopulation that is not representative of the general population).

IV. DRUG PRODUCT AND SUBJECT CONSIDERATIONS

Given the potential for increased risks to subjects posed by these trial designs (see section III., FIH Multiple Expansion Cohort Trial Design Definition and Potential Opportunities and Challenges), clinical trials with FIH multiple expansion cohorts should be limited to investigational drug products for indications and subjects populations in which the potential risks are not unreasonable in the context of the disease for which the drug is being studied. The patient population should therefore be limited to subjects with serious oncologic diseases for which no satisfactory alternative therapies are available. Sponsors should provide a strong rationale for use of an expansion cohort trial. As drug product development progresses the drug product's potential to provide an advance over available therapy should continue to be examined as one measure of determining whether the potential benefits of using an expansion cohort continue to outweigh the potential for the increased risks to subjects.[10]

Drug product formulations containing drug substances with material attributes that allow for relatively straightforward bridging between early drug product formulations and marketing formulations (e.g., biopharmaceuticals classification system Class 1 designation, nonliposomal injections, immediate release oral drug products) may be more appropriate for multiple expansion cohort trials. For more complex drug products and drug substances, FDA encourages discussion early in the formulation and manufacturing development to address anticipated challenges in bridging between earlier formulations and the appropriateness for inclusion of the drug product in multiple expansion cohort trials.

Examples of characteristics of investigational drug products that are not suitable for study in clinical trials with multiple expansion cohorts because of increased risks of drug-related toxicity include those drug products with steep toxicity indices and large inter- and intra-patient variability (i.e., coefficient of variability greater than or equal to 100 percent) in pharmacokinetics unless there is adequate data to determine a recommended phase 2 dose.

V. CONSIDERATIONS BASED ON COHORT OBJECTIVES

Sponsors of FIH multiple expansion cohort trials should provide the scientific rationale for studying each proposed cohort. A sponsor should carefully design key elements for each cohort, including specific endpoints, eligibility, monitoring plan, and statistical considerations to justify the sample size in light of the available safety information and should include adjustments for Type I error when a prespecified randomization and analysis are part of the design and more than one comparison between cohorts is planned.[11] This information, as well as the information

[10] See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics* (May 2014).

[11] See the draft guidance for industry *Multiple Endpoints in Clinical Trials* (January 2017). When final, this guidance will represent the FDA's current thinking on this topic.

described in section VI., Statistical Considerations, should be included in all new FIH clinical trial protocols and subsequent protocol amendments adding one or more expansion cohorts.

A. Assessing Safety of Recommended Phase 2 Dose

Expansion cohorts can be intended to further evaluate safety beyond the initial dose-escalation portion of a trial. These studies should be supported by detailed information on available safety and PK data from the dose-escalation phase and a summary of safety data from other expansion cohorts, if available. In situations when there is a narrow therapeutic index and dose-limiting toxicities have been observed in the dose escalation phase that may be fatal or result in serious morbidity, FDA strongly recommends that expansion be delayed until sufficient data are available to determine the recommended phase 2 dose to help ensure subjects safety.

B. Evaluating Preliminary Antitumor Activity

Information to support expansion cohorts assessing disease-specific cohort antitumor activity should include the following:

- A scientific rationale for inclusion of each population within a cohort based on proposed mechanism of action of the drug, any antitumor activity data and data regarding acceptability of risks in the proposed population(s) considering the natural history and underlying comorbidities, as well as lack of satisfactory alternative therapy[12]

- A statistical analysis plan for the cohort that includes justification of the maximum sample size and stopping rules for lack of activity, to minimize the number of subjects exposed to an ineffective drug (e.g., generally limited to 40 subjects with solid tumors based on a Simon two-stage model[13] or 20 subjects with hematological malignancies when the rarity of the hematological malignancy may support initiation of efficacy trials based on smaller efficacy databases)

- Updated safety experience from the dose-escalation portion and other expansion cohorts, as available

In general, a sponsor intending to continue development of a drug for a new indication should submit a new IND to the appropriate review division to facilitate direct communication on the adequacy of the development program for that indication. If preliminary clinical evidence suggests a substantial improvement over available therapies on one or more clinically important efficacy endpoints in a patient population with an unmet medical need, the sponsor should ask to meet with FDA to discuss further development (see section VIII., Protocol Content). In the exceptional situation where data from an expansion cohort may provide primary support for a marketing application, the protocol should contain provisions ensuring adequate data quality, independent review of tumor-based endpoints, and justification of the selected dosage regimen as well as a prespecified statistical analysis plan.

[12] See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*.

[13] Simon, R, 1989, Optimal Two-Stage Designs for Phase II Clinical Trials, Control Clin Trials, 10(1): 1–10.

C. Evaluating Specific PK and Pharmacodynamic Aspects

Expansion cohorts designed to evaluate the effects of food intake, organ dysfunction, and concomitant medications on the exposure to the investigational drug should be designed with knowledge of the preliminary pharmacokinetics and safety profile observed in the safety and dose-finding phase of the phase 1 trial. Evaluation conducted in healthy subjects should be performed in separate clinical studies.

- **Food effects**
  - PK trials in cancer patients should refer to the recommendations in the draft guidance for industry *Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations* (February 2019)[14]
- **Organ dysfunction**
  - Expansion cohort(s) studying the effects of organ dysfunction on drug exposure should refer to the recommendations in the draft guidance for industry *Pharmacokinetics in Patients With Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing* (September 2020)[15] and the guidance for industry *Pharmacokinetics in Patients With Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling* (May 2003)
- **Drug interactions**
  - The dose and timing/sequence of all concomitant anticancer medications in the cohort should be well documented
  - Sponsors of drug interaction studies should refer to the recommendations in the guidance for industry *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme and Transporter-Mediated Drug Interactions* (January 2020)

D. Further Dose/Schedule Exploration

Sponsors of expansion cohort(s) intended to further assess the optimal dose/schedule of the investigational drug should consider the following:

- Randomization to two or more dosage regimens to increase the confidence that any differences between treatment arms are not due to chance alone
- Justification of sample size chosen to detect clinically important differences in safety and activity, if present

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

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

- Results of available safety, activity, and PK information to support the new proposed dosage(s)

- Results of exposure-response (safety and/or activity) modeling, if available, to justify new dosing regimens

E. Biomarker Development

If an in vitro diagnostic (IVD) will be used for patient management (e.g., selection) in a clinical trial, the requirements for an investigational device exemption at 21 CFR part 812 must be assessed by the sponsor and IRBs. FDA recommends that sponsors contact the appropriate IVD review center (Center for Devices and Radiological Health or Center for Biologics Evaluation and Research) or include such information in the IND early in the development program to obtain a risk assessment of the device and further guidance.[16] Additionally, sponsors should refer to FDA guidance regarding principles for codevelopment of an in vitro companion diagnostic device with a therapeutic product.[17]

Sponsors using expansion cohorts for evaluating biomarker-defined populations should justify the use of the biomarker and employ IVD assays that are adequately analytically validated to allow interpretation of the results. Use of IVDs with inadequate performance characteristics (e.g., specificity, sensitivity) may produce spurious results and/or delay the development of a potentially effective drug. Sponsors should establish procedures for tumor sample acquisition, handling, and the testing and analysis plans as early as possible in the biomarker development program. FDA may ask for submission of the IVD's analytical validation data to determine whether the clinical results will be interpretable. The clinical validity of the exploratory biomarker assay(s) should be further evaluated in confirmatory trial(s).[18]

F. Evaluating Drug Product Changes

The chemistry, manufacturing, and controls information submitted to support expansion cohort trials is expected to meet the level of detail appropriate for the stage of clinical development.[19]

---

[16] See the guidance for industry *Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination* (October 2019).

[17] See the draft guidance for industry and FDA staff *Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product* (July 2016). When final, this guidance will represent the FDA's current thinking on this topic.

[18] See the guidance for industry and FDA staff *In Vitro Companion Diagnostic Devices* (August 2014) and the draft guidance for industry and FDA staff *Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product*. When final, this guidance will represent the FDA's current thinking on this topic.

[19] See the guidances for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products* (November 1995) and *INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and Controls Information* (May 2003).

The sponsor should prominently identify in the cover letter of a protocol amendment any change that introduces into an ongoing trial a new formulation or presentation of a drug product or major manufacturing changes.[20] In such amendments, the sponsor should identify changes in drug product quality attributes that may require bridging to earlier clinical trial drug products that differ in their formulations, packaging configurations, manufacturing processes, and impurity profile to allow comparison of the clinical data across cohorts using different formulations.

Expansion cohorts intended to bridge new and older formulations should have clear objectives and analysis plans for assessing differences in safety and pharmacokinetics. When changes in presentation result in significant modifications to dose preparation, human factors studies may be requested.[21] Depending on the effect of the changes, FDA may recommend that studies of new drug product formulations be conducted under a new IND.

Given the challenges in bridging formulation, presentation, or drug product manufacturing changes, FDA urges sponsors to meet with the review division to ensure that such expansion cohort(s) are adequately designed to meet the intended objective of bridging clinical data across cohorts. FDA may recommend additional clinical trials to bridge safety and efficacy data in support of a marketing application if drug product changes (such as formulation changes, production scale-up, manufacturing site changes, and manufacturing process changes during clinical development) are not adequately bridged. Pooling of clinical data across different formulations, presentation, or drug product manufacturing processes may not be feasible in the absence of such bridging information.

G. Evaluating More Than One Therapeutic Drug

Expansion cohort trials evaluating an investigational drug administered with an approved drug or another investigational drug should be initiated only after the preliminary safety profile is characterized for each investigational drug as a single agent at the recommended phase 2 dose. The protocol for the expansion cohort trial should include the justification and scientific rationale for combining these drugs and a safety monitoring plan with attention to overlapping and potential synergistic toxicities.

For information regarding codevelopment of two investigational drugs, see the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination* (June 2013).

---

[20] See the ICH guidance for industry *Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process* (June 2005).

[21] See the draft guidance for industry and FDA staff *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development* (February 2016). When final, this guidance will represent the FDA's current thinking on this topic.

H. Evaluating PK, Tolerability, and Initial Evidence of Activity in the Pediatric Population

A sponsor should consider expansion cohorts for evaluating pediatric populations[22] if the drug has potential relevance for the treatment of one or more pediatric cancers based on the drug's mechanism of action, there is safety and dosing information in adults, and there is a lack of satisfactory alternative therapies for the pediatric population. Appropriate investigational drugs include targeted drugs where the cell surface receptor, fusion protein, amplified or mutated gene, or cell signaling pathway drug effects are known to be responsible for the development or progression of one or more pediatric cancers. Prospective inclusion of one or more pediatric cohorts in a multiple expansion cohort trial, as an alternative to separate pediatric dose-finding and activity-estimating protocols, provides an opportunity to shorten the timeline to begin pediatric development.

To ensure the prospect for direct clinical benefit from participation on a research study where there is a greater than minor increase over minimal risk, sponsors generally should enroll pediatric subjects in dose-finding and activity estimating cohorts only after a reasonably safe dose and preliminary activity have been established in adults. In exceptional circumstances, substantive nonclinical evidence of activity in tumor-derived cell lines or patient-derived xenografts alone may provide sufficient justification for enrollment of a pediatric cohort before the availability of full clinical data in adult subjects. In these situations, FDA recommends that sponsors consider staggered enrollment of older children or adolescents before younger children to minimize risk.

Information to support expansion cohorts for pediatric subjects should include detailed toxicity monitoring plans, plans for PK assessment, and, when appropriate, pharmacodynamic study objectives to guide further pediatric development. For targeted drugs, confirmation of the putative target's presence should be documented, and eligibility should be limited to pediatric subjects with relapsed or refractory disease for whom no satisfactory alternative therapy exists. Consideration of an orally administered drug's formulation, especially for younger children who may be unable to swallow capsules or tablets, may require development of an age-appropriate formulation for investigational use.[23]

In general, further development of the drug for one or more pediatric cancer-specific indications should be pursued as a separate protocol. Initial evaluation of a drug in the pediatric population as part of an expansion cohort should be included in the pediatric study plan.

---

[22] Section 505B(a)(1)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requires that all original new drug applications (NDAs) or biologics license applications (BLAs) for a new active ingredient that are submitted on or after August 18, 2020, must "submit with the application reports on the investigation described in paragraph (3) if the drug or biological product that is the subject of the application is- (i) intended for the treatment of an adult cancer; and (ii) directed at a molecular target that the [FDA] determines to be substantially relevant to the growth or progression of a pediatric cancer." Section 505B(a)(1) of the FD&C Act also requires NDAs and BLAs (or supplements to applications) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the requirement is waived or deferred.

[23] See FD&C Act section 505B(a)(2).

VI. STATISTICAL CONSIDERATIONS

The background information for each expansion cohort should contain its scientific rationale. Information supporting individual expansion cohorts should describe the prespecified stopping rules for that cohort, based on insufficient antitumor activity or unacceptable level of toxicity for that population. Finally, the analysis plan for each expansion cohort should contain adequate information justifying the planned sample size based on the cohort objectives. For those cohorts evaluating antitumor activity, the plans should specify the magnitude of antitumor activity that would warrant further evaluation of the drug, for example by specifying the precision and power considerations for detection of clinically meaningful antitumor activity. In general, in a nonrandomized cohort, assessment of antitumor activity is determined using a Simon two-stage design or other designs (e.g., Bayesian statistical design) to limit exposure of additional subjects to a potentially ineffective drug.[24]

The trial design for an individual cohort should ensure that the cohort's trial objectives can be met. For example, sponsors should consider the need for randomization within a cohort for comparison of activity between different dosing regimens. In a cohort with a randomized design, the sample size and the inference that can be made will be based on the prespecified null and alternative hypotheses to be tested, the level of significance, and the power of the test.

Sponsors should avoid comparisons between cohorts to which subjects were not randomly assigned.

VII. SAFETY CONSIDERATIONS

A. Safety Monitoring and Reporting Plans

The sponsor is required to ensure proper monitoring of the investigations and to ensure that the investigations are conducted in accordance with the general investigational plan and protocols contained in the IND, among other responsibilities.[25]

The sponsor should establish a systematic approach, including plans for activation of protocol amendments, to address serious safety issues and to ensure rapid communication of serious safety issues. This approach should be described in the protocol or its appendices.[267]

[24] Simon, R, 1989, Optimal Two-Stage Designs for Phase II Clinical Trials, Control Clin Trials, 10(1):1–10.

[25] 21 CFR 312.50. See also the guidance for industry *Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring* (August 2013).

[26] See 21 CFR 312.32; 21 CFR 312.23 (for information about safety reporting requirements and the information required in a protocol for an IND).

The IND should contain a proposed plan for submission of a cumulative summary of safety data and information, on a periodic basis that is more frequent than annual.[27] The plan should be discussed with the review division at the pre-IND meeting. The recommended frequency of the submissions will be dependent on specific program risks and the rapidity of subject accrual. New safety data that further identify, characterize, and provide insight on management of adverse reactions should be periodically assessed and submitted to the IND in support of modifications of one or more cohorts within the protocol.

The interval for submission of cumulative safety reports should be agreed upon with FDA. The most recent cumulative safety report should be referenced in support of protocol amendments proposing modifications of existing or new expansion cohorts. Given the complexity of these trials and potential increased risks to subjects, sponsors should select medical monitors who have training and experience in cancer treatment and clinical trial conduct.

B. Independent Data Monitoring Committee

An independent data monitoring committee (IDMC)[28] or other appropriate independent entity structured to assess safety in addition to efficacy should be established for all FIH multiple expansion cohort protocols, given that the complexity of these trials (with regard to different cohort objectives, trial populations, and dosages evaluated simultaneously) can lead to potential increased risks to subjects.

Responsibilities of the IDMC should include, but not be limited to, analysis of incoming expedited safety reports, review of cumulative summaries of all adverse events, and making recommendations to the IND sponsor regarding protocol modifications to reduce risks to subjects enrolled in the trial. The IDMC should be charged with the real-time review of all serious adverse events[29] and meet periodically to assess the totality of safety information in the development program. The IDMC should be responsible for performing prespecified and ad hoc assessments of safety and futility for each cohort, to recommend protocol modifications, or other actions including, but not limited to, the following:

- Changing the eligibility criteria if the risks of the intervention seem to be higher in a subgroup
- Altering the drug product dosage and/or schedule if the adverse events observed appear likely to be reduced by such changes
- Modifying monitoring plans for safety by the addition of more frequent or new types of assessments

[27] See also 21 CFR 312.33 (for information on requirements for submitting IND safety reports).

[28] See the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees* (March 2006).

[29] 21 CFR 312.32 (for information on IND safety reporting requirements related to serious adverse events).

- Identifying information needed to inform current and future trial subjects of newly identified risks via changes in the informed consent document and, in some cases, obtaining reconsent of current subjects to continued trial participation

In trials of limited sample size (no more than 90 subjects in the dose-finding portion and no more than 200 subjects across all dose-expansion cohorts), sponsors may wish to consider a safety assessment committee that is a group within the sponsor's organization alone or with external representation. If a safety assessment is performed within the sponsor's organization, a firewall should be established to ensure that the individuals performing those assessments are not otherwise involved in trial conduct or management to protect the integrity of the study.

C. IRB/Independent Ethics Committee

Under FDA's regulations, a clinical investigation generally may not be initiated until it has been reviewed and approved by an IRB/independent ethics committee, and it remains subject to continuing review by an IRB throughout the duration of the trial.[30] Consistent with the continuing review requirements,[31] the investigator should provide cumulative safety information provided by the IND sponsor to the IRB.

Because of the complexity of expansion cohorts as discussed in section V.A., Confirming Safety of Recommended Phase 2 Dose, in general, the sponsor should perform an assessment of safety more frequently than on an annual basis and, when such an assessment is done, must provide this information to the investigator (see section VII., Safety Considerations).[32] Sponsors are required to "keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use."[33]

The investigator is expected to convey new observations to the IRB at the time of continuing review, or sooner, if it is an unanticipated problem involving risk to human subjects or others.[34] The summary information conveyed to the IRB should include a description of the detailed plan for timely, periodic communication of trial progress, cumulative safety information, and other reports from the IDMC. This information is necessary to allow the IRB to evaluate the risks to subjects of the ongoing investigation, the risks to subjects of all protocol modifications (e.g., changes in dosing, addition of new cohorts), and the adequacy of the informed consent document.

[30] 21 CFR 56.103(a); 21 CFR 56.109(f).

[31] 21 CFR 56.109(f).

[32] 21 CFR 312.55(b).

[33] 21 CFR 312.55(b).

[34] See 21 CFR 312.66 and the guidance for clinical investigators, sponsors, and IRBs *Adverse Event Reporting to IRBs — Improving Human Subject Protection* (January 2009).

To facilitate IRB review of multicenter, FIH multiple expansion cohort trials, FDA recommends the use of a central IRB as permitted.[35] The central IRB should have adequate resources and appropriate expertise to review FIH multiple expansion cohort trials in a timely and thorough manner. When necessary, an IRB may invite individuals with competence in special areas (i.e., a consultant) to assist in the review of complex issues that require expertise beyond or in addition to that available on the IRB.[36]

Given the increased risks to subjects participating in FIH multiple expansion cohort trials, IRBs should consider convening additional meetings (i.e., ad hoc meetings of an existing IRB) to review the evolving new safety information, provided regulatory requirements such as the presence of a quorum can be met.[37] Alternatively, a separate, duly constituted specialty IRB can be established and specifically charged with meeting on short notice to review new information and/or modifications to FIH expansion cohort trials. Such an IRB would need to satisfy the same requirements of any IRB (i.e., 21 CFR part 56), but it could be designed to facilitate a quorum by keeping membership to a minimum (i.e., 21 CFR 56.107 requires that each IRB have at least five members) and being composed of experienced members who are capable of meeting and reviewing FIH multiple expansion cohort trial-related materials on short notice. Ad hoc meetings of an existing IRB or the establishment of a separate specialty IRB designed to facilitate the review of FIH multiple expansion cohort trials are acceptable approaches that, if appropriately constituted and operated, can satisfy the regulatory requirement for IRB oversight.

D. Informed Consent Document

Informed consent documents must be updated as new information is obtained during the trial that could affect a subjects decision to participate in or remain in the trial.[38] In general, FDA requests submission of the original and updated informed consent forms to the IND to permit an evaluation of whether subjects have the information to make informed decisions regarding participation in the trial.[39]

Updates to the informed consent document to reflect protocol modifications may be required.[40] In addition, many protocol amendments to FIH multiple expansion cohort trials are required to be submitted to the IND before they are implemented, unless immediate modifications are implemented for subjects safety (in which case, FDA must be subsequently notified).[41] The

[35] 21 CFR 56.114. See the guidance for industry *Using a Centralized IRB Review Process in Multicenter Clinical Trials* (March 2006).

[36] 21 CFR 56.107(f).

[37] 21 CFR 56.108(c).

[38] See 21 CFR 50.25(a) and 50.25(b)(5).

[39] See 21 CFR 312.23(a)(11).

[40] See 21 CFR 50.25(a).

[41] See 21 CFR 312.30(b).

updated informed consent document should be submitted in each IND amendment containing clinically important protocol modifications.

VIII. PROTOCOL CONTENT

FIH multiple expansion cohort protocols must contain all of the elements for clinical protocols;[42] however, sponsors should consider whether there is a need for a greater level of detail to allow FDA and others (investigators, IRBs) to ensure that the risks to subjects are not unreasonable and that the goals for each expansion cohort are clear and can be met. In addition, FDA requires most commercial INDs to be submitted in an electronic format (i.e., electronic common technical document) and highly encourages electronic submission for noncommercial INDs.[43]

FIH trials with multiple expansion cohorts can in some instances present challenges in subjects oversight caused by rapid enrollment of a large number of subjects exposed to the investigational drug. In general, safety information will be limited at the time of trial initiation, which may expose subjects to higher potential risks and may be unethical if the trial is not carefully planned to address the specific scientific objectives of each expansion cohort. Therefore, failure to provide sufficient detail, either in the initial protocol or in protocol amendments, on the goals and conduct of the clinical protocol in a well-defined population where the risks are not unreasonable can result in the trial being placed on clinical hold. In some cases, measures to stagger enrollment may be appropriate until adequate safety information is available to support exposure of a larger number of subjects.

A. Initial Protocol

The initial IND submission containing an FIH multiple expansion cohort protocol should contain all of the information described in sections V., VI., and VII.[44] Additionally, the protocol and IND should contain the following:

- Detailed and clearly identified table of contents and protocol section headers indicating the dosage regimen and dose modifications for each discrete cohort, to avoid medication errors when treatment plans differ by cohort (dose-escalation versus dose-expansion and between individual expansion cohorts, if applicable)

- A schema for the overall trial design

[42] 21 CFR 312.23(a)(6)(iii).

[43] See the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (February 2020). The guidance is not applicable to noncommercial INDs and INDs for devices that are regulated by CBER as biological products under section 351 of the Public Health Service Act and that also require the submission of an IND before the submission of a BLA. This guidance is considered binding under section 745A(a) of the FD&C Act.

[44] See also 21 CFR 312.23 for IND content and format requirements.

- A description of the plan for the data flow (data collection, analysis, and timing of data dissemination)

- A description of the plan for submission of interim safety and efficacy results to FDA, other groups responsible for monitoring subject safety (e.g., IRB, IDMC), and investigators, to ensure that the risks to subjects are mitigated

A cohort containing an FIH drug product or products regulated by the Center for Biologics Evaluation and Research (CBER) for which there is no existing IND in CBER cannot be conducted under a Center for Drug Evaluation and Research (CDER) IND. Similarly, a cohort containing an FIH drug product or products regulated by CDER for which there is no existing IND in CDER cannot be conducted under a CBER IND. The investigation of such drug products must proceed under a separate trial in an IND submitted to CBER or CDER, as appropriate.[45]

B. Protocol Amendments

Protocol amendments that substantively affect the safety or scope of the protocol should contain a clean version of the amended protocol, a copy of the protocol with tracked changes, and the following supportive information, if available:[46]

- A summary of the available adverse reaction profile observed by dose and schedule for subjects with adequate evaluation (i.e., subjects with at least one posttreatment adverse event or who have completed at least one treatment cycle with submission of safety information to the sponsor);

- New nonclinical toxicology or pharmacology data and clinical data as appropriate to support the protocol modification; and/or

- An updated informed consent document, as appropriate.

C. Communications and Interactions With FDA

For all communication with FDA, sponsors and FDA should consult the guidance for industry and review staff *Best Practices for Communication Between IND Sponsors and FDA During Drug Development* (December 2017).

- Sponsors should consider requesting a pre-IND meeting to discuss their plans to conduct an FIH multiple expansion cohort trial. When the original IND is submitted, the cover letter should prominently identify it as an FIH multiple expansion cohort trial.

[45] See 21 CFR § 312.140.

[46] See 21 CFR 312.30(d) and 312.31(b) for content and format requirements for protocol amendments and information amendments.

- The sponsor should also notify the regulatory project manager via secure email or telephone call 48 hours before submission of any protocol amendment that substantively affects the safety or scope of the protocol.

- Though an amended protocol may proceed upon submission to the IND and IRB approval, FDA strongly encourages sponsors to submit amendments for reasons other than those that affect the safety of subjects (e.g., change to analysis plan or addition of a new treatment arm) at least 30 days before initiation of subject enrollment under the amendment to allow FDA time to conduct a safety review. Amendments containing changes implemented immediately to ensure subject safety (e.g., closure of a cohort for unacceptable toxicity, modification of eligibility, monitoring to mitigate the risks of adverse reactions) should be submitted to the IND as soon as possible.

- Either FDA or sponsors may request a teleconference to discuss protocol amendments within 30 days of their submissions to the IND. If data from an expansion cohort or cohorts are intended to provide primary support a marketing application, the sponsor should request a formal meeting with FDA to obtain advice regarding the proposed cohort and the overall development plan.[47] The content and the format of marketing applications, including the content of the clinical study report, should be discussed with FDA in a formal meeting.[48]

[47] See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017). When final, this guidance will represent the FDA's current thinking on this topic

[48] For additional information, see 21 CFR 314.50, 21 CFR 601.2, and the ICH guidance for industry *E3 Structure and Content of Clinical Study Reports* (July 1996).