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

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Lee Pai-Scherf at 301-796-3400 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

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)

August 2018
Procedural

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Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 staff 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 cancer drugs, including biological products, through multiple expansion cohort trial designs.[2] These are trial designs that employ multiple, concurrently accruing patient cohorts, where individual cohorts assess different aspects of the safety, pharmacokinetics, and anti-tumor activity of the drug. 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 application (IND) submissions to support the use of individual cohorts; (3) when to interact with FDA on planning and conduct of multiple expansion cohort studies; and (4) safeguards to protect patients enrolled in FIH expansion cohort studies.

This draft guidance is intended to serve as advice and as the starting point for discussions between FDA, pharmaceutical sponsors, the academic community, and the public.[3] This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 Conference on Harmonisation guidances for industry *E9 Statistical Principles for*

[1] This guidance has been prepared by the Office of Hematology and Oncology Drug Products 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.

[3] In addition to consulting guidances, sponsors are encouraged to contact the appropriate review division to discuss specific issues that arise during the development of cancer drugs.

Clinical Trials and *E10 Choice of Control Group and Related Issues in Clinical Trials* as well as the guidance for industry and FDA staff *In Vitro Companion Diagnostic Devices*.[4]

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

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, if possible, to gain early evidence of effectiveness.[5] The 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 safety and efficacy trials. The total number of patients included in phase 1 studies is anticipated to be in the range of 20 to 80.

FIH multiple expansion cohort trials are intended to expedite development by seamlessly proceeding from initial determination of a potentially effective dose to individual cohorts that have trial objectives typical of phase 2 trials (i.e., to estimate anti-tumor activity). These cohorts may be initiated before the analysis of the metabolism and pharmacokinetics of the investigational drug and with limited safety assessment. Such trials have enrolled between a few hundred to more than a thousand patients.[6,7] Because of the rapid enrollment and evolving nature of the information obtained in these trials, large numbers of patients are exposed to drugs with unknown efficacy and minimally characterized toxicity profiles. To mitigate such risks and to protect patients, it is imperative that sponsors establish an infrastructure to streamline trial logistics, facilitate data collection, and incorporate plans to rapidly assess emerging data in real time and to disseminate interim results to investigators, institutional review boards (IRBs), and regulators.

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

[6] KEYNOTE-001 study design at https://clinicaltrials.gov/ct2/show/NCT01295827.

[7] JAVELIN study design at https://clinicaltrials.gov/show/NCT01772004.

III. FIH EXPANSION COHORT DEFINITION AND POTENTIAL OPPORTUNITIES AND CHALLENGES

A. Definition of FIH Multiple Expansion Cohort Trials

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 that also contains three or more additional patient cohorts with cohort-specific objectives. The objectives of these expansion cohorts can include assessment of anti-tumor activity in a disease-specific setting, assessment of a reasonably safe dose in specific populations (e.g., pediatric or elderly patients or patients with organ impairment), 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 where a prespecified randomization and analysis plan are part of the protocol design.

B. Potential Opportunities and Challenges Posed by FIH Multiple Expansion Cohort Trials

The principal advantage of conducting FIH multiple expansion cohort trials is efficiency in drug development, with the goal of making highly effective drugs widely available to the public as quickly as possible.

FIH multiple expansion cohort studies pose several challenges and risks, including:

- Challenges in disseminating new safety information to investigators, IRBs, and regulators in a timely manner. It is critical that investigators, IRBs, and regulators are updated with new safety information so that they can provide the necessary oversight for protection of human subjects and so that investigators can ensure that patients can provide adequate informed consent.

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

- Exposing more patients than required to achieve the cohort's objectives.

- Inefficient drug development based on *possibly missed interpretation* of preliminary trial results and unplanned analyses that can lead to delays in proper clinical development. For example, selection of dosage regimens or biomarker-selected populations based on unplanned between-cohort comparisons.

IV. DRUG PRODUCT AND PATIENT CONSIDERATIONS

Given the potential for increased risks to patients posed by this trial design (see section III., FIH Expansion Cohort Definition and Potential Opportunities and Challenges), clinical trials with FIH multiple expansion cohorts should be limited to investigational drugs for indications and

patient populations in which the potential benefits justify the increased risks. To ensure that potential benefits outweigh the risks to patients, the patient population should be limited to patients with serious diseases for which no curative therapies are available. Sponsors should provide a robust rationale for use of an expansion cohort trial. As drug product development progresses, FDA expects that the investigational drug has the potential to meet the criteria for breakthrough therapy designation to support continuation of the expedited clinical development program,[8] such that the potential benefits of enrollment in these complex clinical protocols continue to outweigh the potential for the increased risks to patients.

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, and immediate release oral drug products) may be more appropriate for multiple expansion cohort trials.

Characteristics of investigational drugs that are not suitable for study in clinical trials with multiple expansion cohorts because of increased risks of drug-related toxicity include steep toxicity indices and large inter- and intra-patient variability (i.e., co-efficient of variability greater than or equal to 100 percent) in pharmacokinetics indicative of polymorphic enzyme mediated drug clearance for small molecules.

V. CONSIDERATIONS BASED ON COHORT OBJECTIVES

Sponsors of FIH multiple expansion cohort trials should provide the scientific rationale for conducting each proposed cohort. To ensure that the objectives are met, 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. This information, as well as the information described in section VI., Statistical Considerations, should be included in a new clinical protocol and subsequent protocol amendments adding one or more expansion cohorts.

A. Confirming Safety of Recommended Phase 2 Dose

Expansion cohorts intended to further evaluate safety beyond the initial dose-escalation portion of a trial 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 where there is a narrow therapeutic index and dose-limiting toxicities may be fatal, expansion may need to be delayed until the recommended phase 2 dose is identified.

B. Evaluating Preliminary Anti-Tumor Activity

Expansion cohorts assessing disease-specific cohort anti-tumor activity should include the following elements:

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

- A scientific rationale for inclusion of each population within a cohort based on proposed mechanism of action of drug and acceptability of risks in these proposed population(s) considering the natural history, underlying comorbidities, and susceptibility for adverse reactions due to tumor histology, as well as lack of satisfactory alternative therapy[9]

- 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 patients exposed to an ineffective drug (e.g., generally limited to 40 patients with solid tumors based on a Simon 2-stage model[10] or 20 patients with hematological malignancies) where the rarity of the disease 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[11]

In general, based on the results observed in a disease-specific expansion cohort, a sponsor intending to continue development of a drug for that 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 a clinically significant endpoint(s) in a patient population with a high 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 support a marketing application, the protocol should contain provisions ensuring adequate data quality, independent review of tumor-based endpoints, and optimal dose selection, as well as a prespecified plan ensuring statistical rigor.

C. Evaluating Specific PK and Pharmacodynamic Aspects

Expansion cohorts designed to evaluate the effect 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 trial.

- **Food effects**

  – PK trials in cancer patients should conform to the recommendations in the guidance for industry *Food-Effect Bioavailability and Fed Bioequivalence Studies*

  – PK studies enrolling healthy subjects to assess food effects should be conducted as separate clinical studies

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

[10] Simon, R, 1989, Optimal Two-Stage Designs for Phase II Clinical Trials, Controlled Clinical Trials, Vol. 10, Issue 1, March, 1–10.

[11] 21 CFR 312.30(b).

- **Organ dysfunction**

  – Expansion cohort(s) studying organ dysfunction should conform to the recommendations in the draft guidance for industry *Pharmacokinetics in Patients With Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling*[12] and the guidance for industry *Pharmacokinetics in Patients With Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*

- **Drug interactions**

  – The dose and timing/sequence of the concomitant medications used in the cohort should be well-documented

  – Drug interaction studies should conform to the recommendations in the draft guidance for industry *Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications*[13]

D. Further Dose/Schedule Exploration

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

- 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

- 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

Expansion cohorts evaluating biomarker-defined populations should employ in vitro diagnostic (IVD) assays that are analytically validated and should justify the use of the biomarker. 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

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

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

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(s) should be further evaluated in confirmatory trial(s).[14]

If an 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) early in the development program to obtain a risk assessment of the device and further guidance.[15]

F. Evaluating Drug Product Changes

The chemistry, manufacturing, and controls information submitted to support expansion cohort studies is expected to meet the level of detail appropriate for the stage of clinical development.[16,17]

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 or major manufacturing changes. 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.[18] Depending on the effect of the changes, FDA may recommend that studies of new drug 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

[14] See the guidance for industry and FDA staff *In Vitro Companion Diagnostic Devices*.

[15] See the draft guidance for industry *Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination*. When final, this guidance will represent the FDA's current thinking on this topic.

[16] See the guidance for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products.*

[17] See the guidance for industry *INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and Controls Information*.

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

cohorts. FDA may recommend additional clinical studies 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. In the absence of such bridging information, it may not be scientifically valid to pool key clinical data and may significantly delay marketing approval.

G. Evaluating More Than One Therapeutic Drug

Expansion cohort studies evaluating an investigational drug administered with an approved or another investigational drug should be initiated only after the preliminary safety profile and activity is characterized for each investigational drug as a single agent. 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 as a fixed-dose combination drug product, see the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination*.

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

Expansion cohorts evaluating pediatric populations should be strongly considered[19] if the drug has potential relevance for the treatment of one or more pediatric cancers based on the drug's mechanism of action. 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. A description of studies containing pediatric expansion cohorts could be included as part of an initial pediatric study plan.

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,[20] sponsors should enroll pediatric patients in dose-finding and activity estimating cohorts 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

[19] Section 505B(a)(1)(B) of the FD&C Act requires that all original NDAs or 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 Secretary determines to be substantially relevant to the growth or progression of a pediatric cancer."

[20] 21 CFR 50.52.

full clinical data in adults. In these situations, sponsors should consider staged enrollment of older children or adolescents before younger children.

Information to support expansion cohorts for pediatric patients 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 patients with relapsed or refractory disease for whom no curative treatment exists.

Further development of the drug for one or more pediatric cancer-specific indications should be pursued as a separate protocol.

VI. STATISTICAL CONSIDERATIONS

The background information for each expansion cohort should contain the scientific rationale for that individual cohort. Individual expansion cohorts should describe the prespecified stopping rules for that cohort, based on insufficient anti-tumor 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 anti-tumor activity, the plans should specify the magnitude of anti-tumor activity that would warrant further evaluation of the drug. In a nonrandomized cohort, assessment of anti-tumor activity is generally determined using a Simon 2-stage design to limit exposure of additional patients to an ineffective drug.[21]

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. Comparisons between cohorts to which patients were not randomly assigned should be avoided.

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.[22]

[21] Simon, R, 1989, Optimal Two-Stage Designs for Phase II Clinical Trials, Controlled Clinical Trials, Vol. 10, Issue 1, March, 1–10.

[22] 21 CFR 312.50. See the guidance for industry *Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring.*

The sponsor should establish a systematic approach that ensures rapid communication of serious safety issues, including plans for activation of protocol amendments to address serious safety issues, to clinical investigators and regulatory authorities under IND safety reporting regulations.[23]

The IND should contain a proposed plan for submission of a cumulative summary of safety, on a periodic basis that is more frequent than annually.[24] 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 increased risks to patients, sponsors should select medical monitors who have training and experience in cancer treatment and clinical trials conduct.

B. Independent Safety Assessment Committee

An independent safety assessment committee (ISAC)[25] or an independent data monitoring committee (IDMC)[26] 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 regards to different cohort objectives, trial populations, and dosages evaluated simultaneously, can lead to potential increased risks to patients. Responsibilities of the ISAC/IDMC should include, but not be limited to, analysis of incoming expedited safety reports, development of cumulative summaries of all adverse events, and making recommendations to the IND sponsor regarding protocol modifications to reduce risks to patients enrolled in the trial. The ISAC/IDMC should be charged with the real-time review of all serious adverse events[27] and meet periodically to assess the totality of safety information in the development program.[28] The ISAC/IDMC should have responsibility 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:

- Changing the eligibility criteria if the risks of the intervention seem to be higher in a subgroup

[23] 21 CFR 312.32.

[24] 21 CFR 312.33.

[25] See the draft guidance for industry *Safety Assessment for IND Safety Reporting*. When final, this guidance will represent the FDA's current thinking on this topic.

[26] See the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees*.

[27] 21 CFR 312.32.

[28] See the draft guidance for industry *Safety Assessment for IND Safety Reporting*.

- Altering the drug product dosage and/or schedule if the adverse events observed appear likely to be reduced by such changes

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

C. Institutional Review Board /Independent Ethics Committee

A clinical trial 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.[29] To meet the continuing review requirements,[30] the investigator should provide cumulative safety information provided by the IND sponsor to the IRB along with other information required by the IRB.

Because of the complexity of expansion cohorts as discussed in section V.A., Confirming Safety of Recommended Phase 2 Dose, the sponsor is generally expected to perform an assessment of safety more frequently than an annual basis and provide this information to the investigator (see section VII., Safety Considerations). 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."[31] The investigator is expected to convey this information to the IRB at the time of continuing review, or sooner, if it is an unanticipated problem involving risk to human subjects or others.[32] This summary information may include: a description of the detailed plan for timely, periodic communication of trial progress; cumulative safety information; and other reports from the ISAC/IDMC. This information is necessary to allow the IRB to evaluate the risks to patients of the ongoing investigation, the risks to patients of all protocol modifications (e.g., changes in dosing and addition of new cohorts), and the adequacy of the informed consent document.

To facilitate IRB review of multicenter, FIH multiple expansion cohort trials, FDA recommends the use of a central IRB as permitted.[33,34] 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

[29] 21 CFR 56.103(a).

[30] 21 CFR 56.109(f).

[31] 21 CFR 312.55(b).

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

[33] 21 CFR 56.114.

[34] See the guidance for industry *Using a Centralized IRB Review Process in Multicenter Clinical Trials*.

consultant) to assist in the review of complex issues that require expertise beyond or in addition to that available on the IRB.[35]

Given the increased risks to patients 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 quorum can be met.[36] 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); however, it could be designed to facilitate 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 should be updated as new information is obtained during the trial that may affect a patient's decision to participate in or remain in the trial. FDA may request submission of the original and all updated informed consent forms to the IND to permit an evaluation of whether patients have the information to make informed decisions regarding participation in the trial.

In addition, the informed consent document should be updated to reflect all clinically important protocol modifications. Amendments to FIH multiple expansion cohort trials should be submitted to the IND before implemented, unless immediate modifications should be submitted for patient safety. The updated consent document should be submitted in each IND amendment containing clinically important protocol modifications.

VIII. PROTOCOL CONTENT

FIH multiple expansion cohort protocols should contain all of the elements for clinical protocols;[37] 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 patients are not unreasonable and that the goals for each expansion cohort are clear and can be met. In addition, FDA expects that such INDs will be submitted in an electronic format (i.e., electronic common technical document).

[35] 21 CFR 56.107(f).

[36] 21 CFR 56.108(c).

[37] 21 CFR 312.23(a)(6)(iii).

This trial design presents challenges in patient oversight caused by rapid enrollment in a large number of patients exposed to the investigational drug. Safety information may not be readily available, which may expose patients to higher potential risks and may be unethical if the trial is not carefully planned to adequately 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 may be acceptable can result in the trial being placed on clinical hold.

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.[38] Additionally, the protocol and IND should contain:

- A detailed, 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 data flow (data collection, analysis, and dissemination in real time)

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

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:[39]

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

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

- An updated informed consent document

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

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

IX. 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.*

- Sponsors should request 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.

- 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, FDA strongly encourages sponsors to submit amendments at least 30 days before planned activation of the amendment to allow FDA to conduct a safety review. Amendments containing changes the sponsor considers necessary to ensure patient safety (e.g., closure of a cohort for unacceptable toxicity, modification of eligibility, or monitoring to mitigate the risks of adverse reactions) *should be implemented immediately and submitted 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. Further development in specific patient populations should be discussed with FDA in a formal meeting.[40]

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