
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DRAFT GUIDANCE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 Industry¹

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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This draft guidance is intended to serve as advice and as the starting point for discussions between FDA, pharmaceutical sponsors, the academic community, and the public.³ This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.

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36 *Clinical Trials and E10 Choice of Control Group and Related Issues in Clinical Trials* as well as
37 the guidance for industry and FDA staff *In Vitro Companion Diagnostic Devices*.⁴
38

39 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
40 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
41 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
42 the word *should* in Agency guidances means that something is suggested or recommended, but
43 not required.
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45
46 **II. BACKGROUND**
47

48 Phase 1 clinical trials are designed to determine the metabolism and pharmacologic actions of an
49 investigational drug in humans, the side effects associated with increasing doses, and, if possible,
50 to gain early evidence of effectiveness.⁵ The rationale for conducting phase 1 studies is to obtain
51 sufficient information about the drug’s pharmacokinetic (PK) and pharmacologic effects to
52 permit the design of subsequent well-controlled, scientifically valid safety and efficacy trials.
53 The total number of patients included in phase 1 studies is anticipated to be in the range of 20 to
54 80.
55

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

70 **III. FIH EXPANSION COHORT DEFINITION AND POTENTIAL**
71 **OPPORTUNITIES AND CHALLENGES**

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A. Definition of FIH Multiple Expansion Cohort Trials

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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.

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

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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.

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

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- 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.

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

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

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- 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.

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IV. DRUG PRODUCT AND PATIENT CONSIDERATIONS

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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

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

124
125 Drug product formulations containing drug substances with material attributes that allow for
126 relatively straightforward bridging between early drug product formulations and marketing
127 formulations (e.g., biopharmaceuticals classification system Class 1 designation, nonliposomal
128 injections, and immediate release oral drug products) may be more appropriate for multiple
129 expansion cohort trials.

130
131 Characteristics of investigational drugs that are not suitable for study in clinical trials with
132 multiple expansion cohorts because of increased risks of drug-related toxicity include steep
133 toxicity indices and large inter- and intra-patient variability (i.e., coefficient of variability
134 greater than or equal to 100 percent) in pharmacokinetics indicative of polymorphic enzyme
135 mediated drug clearance for small molecules.

136

137

V. CONSIDERATIONS BASED ON COHORT OBJECTIVES

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139
140 Sponsors of FIH multiple expansion cohort trials should provide the scientific rationale for
141 conducting each proposed cohort. To ensure that the objectives are met, a sponsor should
142 carefully design key elements for each cohort, including specific endpoints, eligibility,
143 monitoring plan, and statistical considerations to justify the sample size, in light of the available
144 safety information. This information, as well as the information described in section VI.,
145 Statistical Considerations, should be included in a new clinical protocol and subsequent protocol
146 amendments adding one or more expansion cohorts.

147

A. Confirming Safety of Recommended Phase 2 Dose

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149
150 Expansion cohorts intended to further evaluate safety beyond the initial dose-escalation portion
151 of a trial should be supported by detailed information on available safety and PK data from the
152 dose-escalation phase and a summary of safety data from other expansion cohorts, if available.
153 In situations where there is a narrow therapeutic index and dose-limiting toxicities may be fatal,
154 expansion may need to be delayed until the recommended phase 2 dose is identified.

155

B. Evaluating Preliminary Anti-Tumor Activity

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157
158 Expansion cohorts assessing disease-specific cohort anti-tumor activity should include the
159 following elements:

160

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

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- 161 • A scientific rationale for inclusion of each population within a cohort based on proposed
162 mechanism of action of drug and acceptability of risks in these proposed population(s)
163 considering the natural history, underlying comorbidities, and susceptibility for adverse
164 reactions due to tumor histology, as well as lack of satisfactory alternative therapy⁹
165
- 166 • A statistical analysis plan for the cohort that includes justification of the maximum
167 sample size and stopping rules for lack of activity, to minimize the number of patients
168 exposed to an ineffective drug (e.g., generally limited to 40 patients with solid tumors
169 based on a Simon 2-stage model¹⁰ or 20 patients with hematological malignancies) where
170 the rarity of the disease may support initiation of efficacy trials based on smaller efficacy
171 databases
172
- 173 • Updated safety experience from the dose-escalation portion and other expansion cohorts,
174 as available¹¹
175

176 In general, based on the results observed in a disease-specific expansion cohort, a sponsor
177 intending to continue development of a drug for that indication should submit a new IND to the
178 appropriate review division to facilitate direct communication on the adequacy of the
179 development program for that indication. If preliminary clinical evidence suggests a substantial
180 improvement over available therapies on a clinically significant endpoint(s) in a patient
181 population with a high unmet medical need, the sponsor should ask to meet with FDA to discuss
182 further development (see section VIII., Protocol Content). In the exceptional situation where
183 data from an expansion cohort may support a marketing application, the protocol should contain
184 provisions ensuring adequate data quality, independent review of tumor-based endpoints, and
185 optimal dose selection, as well as a prespecified plan ensuring statistical rigor.
186

C. Evaluating Specific PK and Pharmacodynamic Aspects

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188
189 Expansion cohorts designed to evaluate the effect of food intake, organ dysfunction, and
190 concomitant medications on the exposure to the investigational drug should be designed with
191 knowledge of the preliminary pharmacokinetics and safety profile observed in the safety and
192 dose-finding phase of the trial.
193

- 194 • **Food effects**
195
- 196 – PK trials in cancer patients should conform to the recommendations in the guidance
197 for industry *Food-Effect Bioavailability and Fed Bioequivalence Studies*
198
 - 199 – PK studies enrolling healthy subjects to assess food effects should be conducted as
200 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).

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- **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.

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244 early as possible in the biomarker development program. FDA may ask for submission of the
245 IVD's analytical validation data to determine whether the clinical results will be interpretable.
246 The clinical validity of the exploratory biomarker(s) should be further evaluated in confirmatory
247 trial(s).¹⁴

248
249 If an IVD will be used for patient management (e.g., selection) in a clinical trial, the
250 requirements for an investigational device exemption at 21 CFR part 812 must be assessed by the
251 sponsor and IRBs. FDA recommends that sponsors contact the appropriate IVD review center
252 (Center for Devices and Radiological Health or Center for Biologics Evaluation and Research)
253 early in the development program to obtain a risk assessment of the device and further
254 guidance.¹⁵

F. Evaluating Drug Product Changes

256
257
258 The chemistry, manufacturing, and controls information submitted to support expansion cohort
259 studies is expected to meet the level of detail appropriate for the stage of clinical
260 development.^{16,17}

261
262 The sponsor should prominently identify in the cover letter of a protocol amendment any change
263 that introduces into an ongoing trial a new formulation or presentation of a drug or major
264 manufacturing changes. In such amendments, the sponsor should identify changes in drug
265 product quality attributes that may require bridging to earlier clinical trial drug products that
266 differ in their formulations, packaging configurations, manufacturing processes, and impurity
267 profile to allow comparison of the clinical data across cohorts using different formulations.
268 Expansion cohorts intended to bridge new and older formulations should have clear objectives
269 and analysis plans for assessing differences in safety and pharmacokinetics. When changes in
270 presentation result in significant modifications to dose preparation, human factors studies may be
271 requested.¹⁸ Depending on the effect of the changes, FDA may recommend that studies of new
272 drug formulations be conducted under a new IND.

273
274 Given the challenges in bridging formulation, presentation, or drug product manufacturing
275 changes, FDA urges sponsors to meet with the review division to ensure that such expansion
276 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.

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277 cohorts. FDA may recommend additional clinical studies to bridge safety and efficacy data in
278 support of a marketing application if drug product changes, such as formulation changes,
279 production scale-up, manufacturing site changes, and manufacturing process changes during
280 clinical development, are not adequately bridged. In the absence of such bridging information, it
281 may not be scientifically valid to pool key clinical data and may significantly delay marketing
282 approval.

G. Evaluating More Than One Therapeutic Drug

286 Expansion cohort studies evaluating an investigational drug administered with an approved or
287 another investigational drug should be initiated only after the preliminary safety profile and
288 activity is characterized for each investigational drug as a single agent. The protocol for the
289 expansion cohort trial should include the justification and scientific rationale for combining these
290 drugs and a safety monitoring plan with attention to overlapping and potential synergistic
291 toxicities.

293 For information regarding codevelopment of two investigational drugs as a fixed-dose
294 combination drug product, see the guidance for industry *Codevelopment of Two or More New*
295 *Investigational Drugs for Use in Combination*.

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

300 Expansion cohorts evaluating pediatric populations should be strongly considered¹⁹ if the drug
301 has potential relevance for the treatment of one or more pediatric cancers based on the drug's
302 mechanism of action. Appropriate investigational drugs include targeted drugs where the cell
303 surface receptor, fusion protein, amplified or mutated gene, or cell signaling pathway drug
304 effects are known to be responsible for the development or progression of one or more pediatric
305 cancers. Prospective inclusion of one or more pediatric cohorts in a multiple expansion cohort
306 trial, as an alternative to separate pediatric dose-finding and activity-estimating protocols,
307 provides an opportunity to shorten the timeline to begin pediatric development. A description of
308 studies containing pediatric expansion cohorts could be included as part of an initial pediatric
309 study plan.

311 To ensure the prospect for direct clinical benefit from participation on a research study where
312 there is a greater than minor increase over minimal risk,²⁰ sponsors should enroll pediatric
313 patients in dose-finding and activity estimating cohorts after a reasonably safe dose and
314 preliminary activity have been established in adults. In exceptional circumstances, substantive
315 nonclinical evidence of activity in tumor-derived cell lines or patient-derived xenografts alone
316 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.

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

319
320 Information to support expansion cohorts for pediatric patients should include detailed toxicity
321 monitoring plans, plans for PK assessment, and, when appropriate, pharmacodynamic study
322 objectives to guide further pediatric development. For targeted drugs, confirmation of the
323 putative target's presence should be documented and eligibility should be limited to pediatric
324 patients with relapsed or refractory disease for whom no curative treatment exists.

325
326 Further development of the drug for one or more pediatric cancer-specific indications should be
327 pursued as a separate protocol.

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330 VI. STATISTICAL CONSIDERATIONS

331
332 The background information for each expansion cohort should contain the scientific rationale for
333 that individual cohort. Individual expansion cohorts should describe the prespecified stopping
334 rules for that cohort, based on insufficient anti-tumor activity or unacceptable level of toxicity
335 for that population. Finally, the analysis plan for each expansion cohort should contain adequate
336 information justifying the planned sample size based on the cohort objectives; for those cohorts
337 evaluating anti-tumor activity, the plans should specify the magnitude of anti-tumor activity that
338 would warrant further evaluation of the drug. In a nonrandomized cohort, assessment of anti-
339 tumor activity is generally determined using a Simon 2-stage design to limit exposure of
340 additional patients to an ineffective drug.²¹

341
342 The trial design for an individual cohort should ensure that the cohort's trial objectives can be
343 met. For example, sponsors should consider the need for randomization within a cohort for
344 comparison of activity between different dosing regimens. In a cohort with a randomized design,
345 the sample size and the inference that can be made will be based on the prespecified null and
346 alternative hypotheses to be tested, the level of significance, and the power of the test.
347 Comparisons between cohorts to which patients were not randomly assigned should be avoided.

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350 VII. SAFETY CONSIDERATIONS

351 A. Safety Monitoring and Reporting Plans

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353 The sponsor is required to ensure proper monitoring of the investigations and to ensure that the
354 investigations are conducted in accordance with the general investigational plan and protocols
355 contained in the IND.²²

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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*.

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

362
363 The IND should contain a proposed plan for submission of a cumulative summary of safety, on a
364 periodic basis that is more frequent than annually.²⁴ New safety data that further identify,
365 characterize, and provide insight on management of adverse reactions should be periodically
366 assessed and submitted to the IND in support of modifications of one or more cohorts within the
367 protocol.

368
369 The interval for submission of cumulative safety reports should be agreed upon with FDA. The
370 most recent cumulative safety report should be referenced in support of protocol amendments
371 proposing modifications of existing or new expansion cohorts. Given the complexity of these
372 trials and increased risks to patients, sponsors should select medical monitors who have training
373 and experience in cancer treatment and clinical trials conduct.

374

B. Independent Safety Assessment Committee

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376
377 An independent safety assessment committee (ISAC)²⁵ or an independent data monitoring
378 committee (IDMC)²⁶ structured to assess safety in addition to efficacy should be established for
379 all FIH multiple expansion cohort protocols, given that the complexity of these trials, with
380 regards to different cohort objectives, trial populations, and dosages evaluated simultaneously,
381 can lead to potential increased risks to patients. Responsibilities of the ISAC/IDMC should
382 include, but not be limited to, analysis of incoming expedited safety reports, development of
383 cumulative summaries of all adverse events, and making recommendations to the IND sponsor
384 regarding protocol modifications to reduce risks to patients enrolled in the trial. The ISAC/
385 IDMC should be charged with the real-time review of all serious adverse events²⁷ and meet
386 periodically to assess the totality of safety information in the development program.²⁸ The
387 ISAC/IDMC should have responsibility for performing prespecified and ad hoc assessments of
388 safety and futility for each cohort, to recommend protocol modifications or other actions,
389 including but not limited to:

390

- 391 • Changing the eligibility criteria if the risks of the intervention seem to be higher in a
392 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*.

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- 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 re-consent of current patients to continued trial participation

400

401 **C. Institutional Review Board /Independent Ethics Committee**

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403 A clinical trial may not be initiated until it has been reviewed and approved by an

404 IRB/independent ethics committee, and it remains subject to continuing review by an IRB

405 throughout the duration of the trial.²⁹ To meet the continuing review requirements,³⁰ the

406 investigator should provide cumulative safety information provided by the IND sponsor to the

407 IRB along with other information required by the IRB.

408

409 Because of the complexity of expansion cohorts as discussed in section V.A., Confirming Safety

410 of Recommended Phase 2 Dose, the sponsor is generally expected to perform an assessment of

411 safety more frequently than an annual basis and provide this information to the investigator (see

412 section VII., Safety Considerations). Sponsors are required to “keep each participating

413 investigator informed of new observations discovered by or reported to the sponsor on the drug,

414 particularly with respect to adverse effects and safe use.”³¹ The investigator is expected to

415 convey this information to the IRB at the time of continuing review, or sooner, if it is an

416 unanticipated problem involving risk to human subjects or others.³² This summary information

417 may include: a description of the detailed plan for timely, periodic communication of trial

418 progress; cumulative safety information; and other reports from the ISAC/IDMC. This

419 information is necessary to allow the IRB to evaluate the risks to patients of the ongoing

420 investigation, the risks to patients of all protocol modifications (e.g., changes in dosing and

421 addition of new cohorts), and the adequacy of the informed consent document.

422

423 To facilitate IRB review of multicenter, FIH multiple expansion cohort trials, FDA recommends

424 the use of a central IRB as permitted.^{33,34} The central IRB should have adequate resources and

425 appropriate expertise to review FIH multiple expansion cohort trials in a timely and thorough

426 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*.

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

429
430 Given the increased risks to patients participating in FIH multiple expansion cohort trials, IRBs
431 should consider convening additional meetings (i.e., ad hoc meetings of an existing IRB) to
432 review the evolving new safety information, provided regulatory requirements such as quorum
433 can be met.³⁶ Alternatively, a separate, duly constituted specialty IRB can be established and
434 specifically charged with meeting on short notice to review new information and/or
435 modifications to FIH expansion cohort trials. Such an IRB would need to satisfy the same
436 requirements of any IRB (i.e., 21 CFR part 56); however, it could be designed to facilitate
437 quorum by keeping membership to a minimum (i.e., 21 CFR 56.107 requires that each IRB have
438 at least five members) and being composed of experienced members who are capable of meeting
439 and reviewing FIH multiple expansion cohort trial-related materials on short notice. Ad hoc
440 meetings of an existing IRB or the establishment of a separate specialty IRB designed to
441 facilitate the review of FIH multiple expansion cohort trials are acceptable approaches that, if
442 appropriately constituted and operated, can satisfy the regulatory requirement for IRB oversight.
443

D. Informed Consent Document

444
445
446 Informed consent documents should be updated as new information is obtained during the trial
447 that may affect a patient's decision to participate in or remain in the trial. FDA may request
448 submission of the original and all updated informed consent forms to the IND to permit an
449 evaluation of whether patients have the information to make informed decisions regarding
450 participation in the trial.

451
452 In addition, the informed consent document should be updated to reflect all clinically important
453 protocol modifications. Amendments to FIH multiple expansion cohort trials should be
454 submitted to the IND before implemented, unless immediate modifications should be submitted
455 for patient safety. The updated consent document should be submitted in each IND amendment
456 containing clinically important protocol modifications.

457
458

VIII. PROTOCOL CONTENT

459
460
461 FIH multiple expansion cohort protocols should contain all of the elements for clinical
462 protocols;³⁷ however, sponsors should consider whether there is a need for a greater level of
463 detail to allow FDA and others (investigators, IRBs) to ensure that the risks to patients are not
464 unreasonable and that the goals for each expansion cohort are clear and can be met. In addition,
465 FDA expects that such INDs will be submitted in an electronic format (i.e., electronic common
466 technical document).

467

³⁵ 21 CFR 56.107(f).

³⁶ 21 CFR 56.108(c).

³⁷ 21 CFR 312.23(a)(6)(iii).

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468 This trial design presents challenges in patient oversight caused by rapid enrollment in a large
469 number of patients exposed to the investigational drug. Safety information may not be readily
470 available, which may expose patients to higher potential risks and may be unethical if the trial is
471 not carefully planned to adequately address the specific scientific objectives of each expansion
472 cohort. Therefore, failure to provide sufficient detail, either in the initial protocol or in protocol
473 amendments, on the goals and conduct of the clinical protocol in a well-defined population
474 where the risks may be acceptable can result in the trial being placed on clinical hold.
475

A. Initial Protocol

476
477
478 The initial IND submission containing an FIH multiple expansion cohort protocol should contain
479 all of the information described in sections V., VI., and VII.³⁸ Additionally, the protocol and
480 IND should contain:

- 481
482 • A detailed, clearly identified table of contents and protocol section headers indicating the
483 dosage regimen and dose modifications for each discrete cohort, to avoid medication
484 errors when treatment plans differ by cohort (dose-escalation versus dose-expansion and
485 between individual expansion cohorts, if applicable)
486
- 487 • A schema for the data flow (data collection, analysis, and dissemination in real time)
488
- 489 • A description of the plan for submission of interim safety and efficacy results to FDA,
490 other groups responsible for monitoring patient safety (e.g., IRB, ISAC, IDMC), and
491 investigators, to ensure that the risks to patients are mitigated
492

B. Protocol Amendments

493
494
495 Protocol amendments that substantively affect the safety or scope of the protocol should contain
496 a clean version of the amended protocol, a copy of the protocol with tracked changes, and the
497 following supportive information, if available:³⁹
498

- 499 • A summary of the available adverse reaction profile observed, by dose and schedule for
500 patients with adequate evaluation (i.e., patients that have completed at least one treatment
501 cycle with submission of safety information to the sponsor)
502
- 503 • New nonclinical toxicology or pharmacology data, and supportive clinical data as
504 appropriate to support the protocol modification
505
- 506 • An updated informed consent document
507
508

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.

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509 **IX. COMMUNICATIONS AND INTERACTIONS WITH FDA**

510

511 For all communication with FDA, sponsors and FDA should consult the guidance for industry
512 and review staff *Best Practices for Communication Between IND Sponsors and FDA During*
513 *Drug Development*.

514

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

518

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

522

523 • Though an amended protocol may proceed upon submission to the IND, FDA strongly
524 encourages sponsors to submit amendments at least 30 days before planned activation of
525 the amendment to allow FDA to conduct a safety review. Amendments containing
526 changes the sponsor considers necessary to ensure patient safety (e.g., closure of a cohort
527 for unacceptable toxicity, modification of eligibility, or monitoring to mitigate the risks
528 of adverse reactions) *should be implemented immediately and submitted as soon as*
529 *possible*.

530

531 • Either FDA or sponsors may request a teleconference to discuss protocol amendments
532 within 30 days of their submissions to the IND. Further development in specific patient
533 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.