Severely Debilitating or Life-Threatening Hematologic Disorders: Nonclinical Development of Pharmaceuticals

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Pharmacology/Toxicology

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Severely Debilitating or Life-Threatening Hematologic Disorders: Nonclinical Development of Pharmaceuticals 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 assist sponsors in the design of nonclinical studies for the development of pharmaceuticals used to treat patients with severely debilitating or life-threatening hematologic disorders (SDLTHDs).[2] This guidance is intended to facilitate the development of pharmaceuticals used to treat patients with SDLTHDs while still protecting patients' safety and avoiding unnecessary use of animals, in accordance with the 3R (reduce/ refine/ replace) principles.

This guidance discusses a streamlined nonclinical program for development of pharmaceuticals intended for the treatment of patients with SDLTHDs as compared to programs for pharmaceuticals to treat patients with less severe diseases. This guidance is intended to assist sponsors in the development of pharmaceuticals for treating SDLTHDs other than cancer and is intended to be used in conjunction with existing guidance documents.

This guidance does not address radiopharmaceuticals, vaccines, cellular and gene therapy products, and blood products. This guidance does not discuss nonclinical studies in support of a trial in healthy subjects, which is at times proposed for initial clinical programs, or anticancer pharmaceuticals intended to treat hematologic malignancies. These topics are discussed in the ICH guidances for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* and *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals*, respectively.[3]

[1] This guidance has been prepared by the Division of Hematology Oncology Toxicology in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, the term *pharmaceuticals* refers to small molecules, therapeutic proteins, antibodies, and related products such as conjugated products.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA drugs guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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

II. BACKGROUND

The SDLTHDs include conditions in which life expectancy is short or quality of life is greatly diminished despite available therapies. The Agency has defined life-threatening and severely debilitating diseases in regulations .[4] *Life threatening* means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the endpoint of clinical trial analysis is survival.[5] *Severely debilitating* means diseases or conditions that cause major irreversible morbidity.[6] Some examples of SDLTHDs are hemophagocytic lymphohistiocytosis, cold agglutinin, severe aplastic anemia, paroxysmal nocturnal hemoglobinuria, and severe idiopathic thrombocytopenic purpura.

Guidances for industry for anticancer therapies and therapies for rare diseases can apply to SDLTHDs;[7] however, these guidances do not specifically facilitate the nonclinical development of pharmaceuticals for treatment of SDLTHDs. The draft guidance for industry *Rare Diseases: Common Issues for Drug Development*, which includes nonseverely debilitating or life-threatening conditions, is not specific to SDLTHDs.

III. NONCLINICAL EVALUATIONS

A. Pharmacology

Before initiating clinical trials, the sponsor should conduct in vitro and/or in vivo proof-of-concept studies to investigate the mode of action and effects of the pharmaceutical in relation to its intended therapeutic effect. Pharmacology studies can also provide information on species selection for toxicology studies, particularly for biological products. The sponsor should also evaluate potential secondary pharmacological characteristics of the pharmaceutical based on general screening approaches, as applicable.

[4] See 21 CFR 312.81.

[5] 21 CFR 312.81.

[6] 21 CFR 312.81.

[7] See ICH S9 and the draft guidance for industry *Rare Diseases: Common Issues in Drug Development*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

B. Safety Pharmacology

An assessment of the potential effect of the pharmaceutical on vital organ functions (including central nervous, cardiovascular, and respiratory systems) should be available before the sponsor initiates clinical trials. Conducting stand-alone safety pharmacology studies is not necessary. As feasible, the sponsor can integrate these parameters into general toxicology studies in at least one species. In cases where specific concerns have been identified that could put patients at significant additional risk, sponsors should consider appropriate safety pharmacology studies described in the ICH guidances for industry *S7A Safety Pharmacology Studies for Human Pharmaceuticals* and *S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals*.

C. General Toxicology

The planned dose of the pharmaceutical and the proposed safety monitoring plan for the initial clinical trials should be supported by nonclinical data similar to that available for anticancer pharmaceuticals.[8] In general, studies of 1-month durations are sufficient for initiation of first-in-human (FIH) trials and for continuous administration in patients beyond 1 month. In general, studies of 3-month durations are sufficient to support phase 3 trials and marketing applications. The sponsor should initiate the 3-month repeat-dose studies when a phase 2 trial starts or as soon as feasible when a pharmaceutical is designated as a breakthrough therapy.[9] The sponsor should choose the design of nonclinical studies to approximate the various dosing schedules that might be utilized in initial clinical trials. The frequency of administration in animals can be adjusted based on available data such as toxicities and pharmacokinetic data (half-life, receptor saturation, etc.).

For small molecules, toxicology studies are generally conducted in two species (rodent and nonrodent). For biopharmaceuticals, a single pharmacologically relevant species is generally acceptable for toxicology studies. When an animal model of the disease is considered more relevant in determining toxicities associated with the pharmaceutical, the sponsor can consider a combined pharmacology and toxicology study, and a separate toxicology study in healthy animals may not be warranted. The duration of studies conducted in an agreed-upon animal model of disease should be the same as those that would be done in healthy animals to support clinical development. A sponsor should discuss with the Division of Hematology Oncology Toxicology the inclusion of additional endpoints (e.g., markers of the disease) in studies using disease-relevant models.

The sponsor should provide an assessment of the potential to recover from toxicity to understand whether serious adverse effects are reversible. A study that includes a terminal nondosing period is called for in toxicology studies supporting FIH trials. Recovery in 3-month studies is not specifically warranted unless there is a compelling concern from nonclinical or clinical studies

[8] See ICH S9.

[9] See the FDA Fact Sheet: Breakthrough Therapies web page available at https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FDASIA/ucm329491.htm.

that recovery animals could address. The Agency does not consider demonstration of complete recovery to be essential.

D. Genotoxicity

The sponsor should provide an assessment of genotoxicity for small molecule pharmaceuticals before initiating an FIH study; however, the complete battery is not always necessary. See Table 1 in section IV. Timing of Nonclinical Studies and ICH M3(R2) for timing of the study result submissions. See the ICH guidance for industry *S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use* for genotoxicity testing and data interpretation. See ICH S9 for when genotoxicity testing may be abbreviated.

In general, the Agency considers an assay for gene mutation to be sufficient to support single-dose clinical trials.[10] The sponsor should complete an additional genotoxicity assay before initiating a multidose clinical trial. The sponsor should complete a battery of tests for genotoxicity before initiating phase 2 trials. Under certain circumstances, the genotoxicity testing may be abbreviated. For instance, when two assays are positive, a third assay might not be warranted.[11] Sponsors of biopharmaceuticals should follow the principles outlined in the ICH guidances for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* and *S6(R1) Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*.

E. Reproductive Toxicology

The recommendations for reproductive toxicity evaluation for anticancer pharmaceuticals in ICH S9 as well as recommendations for reproductive toxicology studies and labeling in the draft guidance for industry *Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations* [12] (*Oncology Pharmaceuticals* draft guidance) are relevant for SDLTHDs. Embryo-fetal development (EFD) toxicity risk assessment of pharmaceuticals used to treat patients with SDLTHD should be available when the marketing application is submitted, but the Agency does not consider these studies essential to support clinical trials. Additionally, the Agency does not consider these studies essential for the purpose of marketing applications for pharmaceuticals that are genotoxic and target rapidly dividing cells (e.g., crypt cells, bone marrow) in general toxicity studies or under certain other conditions (e.g., use in males only). The *Oncology Pharmaceuticals* draft guidance describes scenarios for which an EFD study is not warranted.

A study of fertility and early embryonic development and a study to assess pre- and postnatal development (PPND) may be warranted, but these studies, when needed, could be conducted after approval. The *Oncology Pharmaceuticals* draft guidance describes when the fertility and PPND studies are not warranted. For instance, when results of general toxicology studies

[10] See ICH M3(R2).

[11] See ICH S9.

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

indicate adverse fertility effects, a separate fertility study is typically not warranted, and when a pharmaceutical is teratogenic in EFD studies, a PPND study is generally not warranted.

F. Carcinogenicity

ICH S6(R1) and the ICH guidance for industry *S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals* address the need for a carcinogenicity study or assessment. Animal carcinogenicity studies, when warranted, can be deferred to after approval when the clinical development is short and carcinogenicity studies would delay pharmaceutical approval.[13]

G. Immunotoxicity

For most pharmaceuticals used to treat patients with SDLTHDs, the Agency considers the design components of the general toxicology studies to be sufficient to evaluate immunotoxic potential in support of clinical trials and marketing. For immunomodulatory pharmaceuticals or pharmaceuticals activating the immune system, a sponsor should consider additional endpoints (such as immunophenotyping by flow cytometry) in the toxicology or proof-of-concept study design.

H. Photosafety Testing

The sponsor should conduct an initial assessment of phototoxic potential before phase 1, based on photochemical properties of the pharmaceutical and information on other pharmaceuticals in the same class. If assessment of these data indicates a potential risk, the sponsor should take appropriate protective measures during outpatient trials. If the photosafety risk cannot be evaluated adequately using nonclinical data or clinical experience, the sponsor should provide a photosafety assessment consistent with the principles described in ICH M3(R2) and the ICH guidance for industry *S10 Photosafety Evaluation of Pharmaceuticals* before marketing the pharmaceutical.[14]

I. Pharmacokinetics

The evaluation of limited pharmacokinetic parameters (e.g., peak plasma/serum level, area under the curve, half-life) in the general toxicology studies can facilitate many aspects of a phase 1 clinical trial, such as dose selection, schedule of administration, and dose escalation. Pharmacokinetic endpoints should also be included in other toxicology studies as applicable, such as 3-month toxicology, reproductive toxicology, and carcinogenicity studies. Further information on absorption, distribution, metabolism, and excretion (ADME) of the drug in animals can normally be generated in parallel with clinical development when applicable. The ADME studies can be abbreviated for biological products (e.g., evaluation of metabolism is generally not warranted).

[13] See the guidance for industry *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act.*

[14] See ICH S9.

IV. TIMING OF NONCLINICAL STUDIES

Table 1 below indicates the recommended timing for submission of the results of nonclinical studies to the Agency, when applicable. The sponsor can provide study results earlier than the timings listed, and is encouraged to do so, when a cause for concern exists. For example, results of secondary pharmacology studies may be provided when phase 1 clinical data indicate unexpected severe toxicities. Another example is early submission of metabolism data for small molecules to allow better characterization of toxicities associated with human metabolites; this information may assist sponsors in selecting species for toxicology studies and in better designing a toxicology study, particularly for reproductive and carcinogenicity studies.

Table 1: Timing for Submission of Nonclinical Studies

Nonclinical studies	Timing
Pharmacology: primary	With initial IND;* continuing through development
Pharmacology: secondary	With NDA/BLA*
Safety pharmacology	With initial IND
Genetic toxicology	With initial IND; the complete battery of studies not always necessary
General toxicology study: 1 month	With initial IND
General toxicology: 3 months	Before initiating a phase 3 trial *Initiate the study when a phase 2 trial starts or as soon as feasible when a pharmaceutical is designated as a breakthrough therapy*
ADME*	In parallel with clinical development
Reproductive toxicology: EFD*	With NDA/BLA
Reproductive toxicology: fertility and PPND* (when needed)	With NDA/BLA or after approval
Carcinogenicity (when needed)	With NDA/BLA or after approval

* IND – investigational new drug application; NDA – new drug application; BLA – biologics license application; ADME – absorption, distribution, metabolism, and excretion; EFD – embryo-fetal development; PPND – pre- and postnatal development.

V. FIRST-IN-HUMAN DOSE AND DOSE ESCALATION

The starting dose should be justified scientifically using all available nonclinical data (e.g., pharmacokinetics, pharmacodynamics, toxicity). The sponsor should choose the starting dose to minimize exposure to subtherapeutic doses. Dosing in patients should initiate at or near a

pharmacologically relevant dose up to a no observed adverse effect level (NOAEL) determined in toxicology studies, when toxicities were observed in animals and a NOAEL was identified.

The highest dose or exposure tested in the nonclinical studies usually does not limit the dose escalation or highest dose investigated in a clinical trial in patients with SDLTHDs if the nonclinical studies include toxic doses and toxicities are monitorable in patients. The steepness of the dose-toxicity curve can assist in planning the dose-escalation scheme in clinical trials.

VI. OTHER STUDIES

A. Combination of Pharmaceuticals

Concepts described in ICH S9 apply to combination therapies. Pharmaceuticals planned for use in combination therapies should be well studied individually in toxicology studies. The sponsor should provide data to support a rationale for the combination before starting the clinical trial. In general, for the Agency, toxicology studies investigating the safety of combinations of pharmaceuticals intended to treat patients with SDLTHDs are not warranted.[15]

B. Nonclinical Studies to Support Trials in Pediatric Populations

For the Agency, juvenile animal studies are not warranted to initiate clinical trials in pediatric populations for SDLTHDs if clinical data in adults are available.

[15] See ICH S9 for additional information.