Guidance for Industry

SEVERELY DEBILITATING OR LIFE-THREATENING HEMATOLOGIC DISORDERS

Nonclinical Development of Pharmaceuticals

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

Guidance for Industry

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

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

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Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
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Contains Nonbinding Recommendations

Severely Debilitating or Life-Threatening Hematologic Disorders: Nonclinical Development of Pharmaceuticals Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to 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 streamline the development of pharmaceuticals used to treat patients with SDLTHDs, other than cancer, while still protecting patients' safety and avoiding unnecessary use of animals, in accordance with the 3R (reduce, refine, replace) principles. This guidance applies to pharmaceuticals used both to treat the active disease and to prevent the recurrence of a life-threatening or debilitating event.

This guidance does not address radiopharmaceuticals, vaccines, cellular and gene therapy products, or blood products. This guidance provides recommendations for nonclinical studies in support of trials in patients only. For nonclinical studies in support of studies in healthy volunteers, consult the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010).[3] This guidance is not for anticancer pharmaceuticals intended to treat hematologic malignancies. For oncology indications, consult the ICH guidances for industry *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals* (March 2010) and *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals Questions and Answers* (June 2018).

The draft guidances for industry titled *Rare Diseases: Early Drug Development and the Role of Pre-IND Meetings* (October 2018) and *Rare Diseases: Common Issues in Drug Development* (August 2015) do not specifically facilitate the nonclinical development of pharmaceuticals for

[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 that are regulated by CDER.

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

treatment of SDLTHDs. Because SDLTHDs are not all rare diseases, they can fall outside the scope of the draft guidances for rare diseases. The present document provides consistent guidance for all nononcology SDLTHDs, independent of disease incidence or prevalence.

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

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] The following factors are examples that could be considered, alone or combined and in no specific order, to determine whether a hematologic disorder is severely debilitating or life-threatening (SDLT): reduced life expectancy, organ damage or dysfunction, disability, need for hospitalization, risk of severe infection, or blood transfusion dependence. Other factors may be considered and should be discussed with the Agency. A hematologic disorder may be considered SDLT, despite available therapies, depending on how the patient population is defined (e.g., refractory), the effectiveness of available therapies, and whether available therapies include medications or procedures associated with undesired health outcomes (e.g., complications associated with organ transplant).

Some examples of SDLTHDs are multicentric Castleman's disease; hemophagocytic lymphohistiocytosis; hypereosinophilic syndrome; amyloidosis; cold agglutinin; aplastic anemia; paroxysmal nocturnal hemoglobinuria; sickle cell disease; beta-thalassemia major; hemophilia; thrombotic thrombocytopenic purpura; and warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis (WHIM) syndrome. The sponsor should discuss with the review division whether the indication is considered an SDLTHD.

FDA supports the principles of the 3Rs, to reduce, refine, and replace animal use when appropriate. Although this guidance provides recommendations for nonclinical studies, sponsors can consult with the Agency if they wish to propose nonanimal testing methods or strategies not

[4] See 21 CFR 312.81.

[5] 21 CFR 312.81.

[6] 21 CFR 312.81.

described in this guidance. The Agency will consider if such an alternative method or strategy could be used instead of an animal study.

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 biotechnology-derived products. The sponsor should also evaluate potential secondary pharmacological characteristics of the pharmaceutical based on general screening approaches, as applicable. The sponsor should provide data from secondary pharmacology assessments, as applicable, with the initial investigational new drug (IND) application to assist in the safety evaluation.

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 initiation of clinical trials. Detailed clinical observations following dosing and appropriate electrocardiographic measurements in nonrodents are generally considered sufficient. Conducting stand-alone safety pharmacology studies is not necessary. In cases where specific concerns have been identified that could put patients at significant additional risk, the sponsor should consider appropriate safety pharmacology studies described in the ICH guidances for industry *S7A Safety Pharmacology Studies for Human Pharmaceuticals* (July 2001) and *S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals* (October 2005). In the absence of a specific risk, such studies will not be called for to support clinical trials or for marketing.

C. General Toxicology

The sponsor should ensure that the planned dose of the pharmaceutical and the proposed safety-monitoring plan for the initial clinical trials are supported by nonclinical data. In general, animal toxicology studies of 1 month's duration are sufficient for initiation of first-in-human (FIH) trials and for continuous administration in patients beyond 1 month. Toxicology studies of shorter than 1 month's duration may be acceptable in support of clinical trials that are shorter than 1 month. In general, studies of 3 months' duration are sufficient to support initiation of large-scale trials (e.g., phase 3) and marketing applications. When the investigational pharmaceutical extends survival or lessens the severity or the frequency of a debilitating event, toxicology studies of 6 to 9 months' duration are generally not warranted. The Agency still considers the results of 3-month toxicology studies sufficient and that the data generated in patients are most meaningful and relevant to inform the safety of patients.

The sponsor should choose the design of nonclinical studies to accommodate different dosing schedules that might be utilized in initial clinical trials. It is not expected that the exact clinical schedule always will be followed in the toxicology study, but the information provided from the toxicity studies should be sufficient to support the clinical dose and schedule and to identify potential toxicity. For example, one factor the sponsor can consider is the half-life in the test species and the projected (or known) half-life in humans. Other factors could include exposure assessment, toxicity profile, saturation of receptors, etc. Identification of a no observed adverse effect level (NOAEL) in general toxicology studies is not always necessary; for example, when the initial clinical trial is in patients and the FIH dose may not be based on a NOAEL (see section V, FIH Dose and Dose Escalation).

For small molecules, toxicology studies are generally conducted in two species (rodent and nonrodent). For biotechnology-derived pharmaceuticals, the principles of the ICH guidance for industry *S6 (R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (June 2011) apply in that a single pharmacologically relevant species may be acceptable for toxicology studies. Safety assessment in an animal model of the disease in lieu of (or in addition to) a toxicology study in healthy animals is acceptable when justified. The duration of studies conducted in an animal model of disease should be the same as those that would be done in healthy animals, unless a decrease in life span relating to the disease makes studies of standard duration not possible. Also, a study in an animal model of the disease could be of short duration when the toxicology data from an animal disease model would be significantly confounded by the disease state.

For general toxicology studies used to support clinical development, the sponsor should provide a scientific assessment for the potential to recover from toxicity, but recovery groups do not need to be automatically included in all general toxicology studies. The sponsor can obtain this information by understanding that the particular effect observed is generally reversible or nonreversible or by including a recovery group in at least one study and one dose level, to be justified by the sponsor.

1. Studies to Support Change in Clinical Schedule

When considering a change in the clinical schedule, the sponsor should conduct an evaluation of the existing clinical data to justify such change. If the clinical data alone are inadequate to support the change in schedule, the sponsor should consider results of toxicology studies previously conducted and any additional relevant factors (such as toxicities, half-life, duration of pharmacodynamic effects, receptor saturation) to determine the need for additional toxicity studies. In cases for which the available information does not support a change in clinical schedules, an additional toxicology study of up to 1 month's duration in a single species is usually sufficient to support the new clinical schedule.

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. These

concepts are discussed in ICH M3(R2), ICH S9, and ICH S9 Questions and Answers guidance documents and further described below.

An assay for gene mutation is generally sufficient to support single-dose clinical trials. To support multidose clinical trials, the sponsor should complete an additional assessment capable of detecting chromosomal damage in a mammalian system. The sponsor should also conduct a complete battery of tests for genotoxicity (as described in the ICH guidance for industry *S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use* (June 2012)) before initiating multidose phase 2 trials. The complete battery of genotoxicity studies is not necessary when there is clear indication of mutagenicity. For example, when the bacterial mutation (Ames) test is clearly positive, then additional genotoxicity testing is generally not warranted. When the bacterial mutation assay is negative, but an in vitro chromosome damage test result (such as chromosome aberration, micronucleus or mouse lymphoma tk+/- assay) is positive, the sponsor should consider in vivo genotoxicity testing.

Genotoxicity studies are generally not called for with the initial IND when the investigational drug will be administered to patients only after available therapies that include genotoxic drugs. In such a case, the sponsor can submit results of genotoxicity studies with the marketing application.

The sponsor of biopharmaceuticals should follow the principles outlined in the ICH guidances for industry *S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (November 1997) and *S6(R1) Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (May 2012).

E. Reproductive Toxicology

The recommendations for reproductive toxicity evaluation for anticancer pharmaceuticals in the draft guidance for industry *Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations* (September 2017)[7] (*Oncology Pharmaceuticals* draft guidance) are relevant for SDLTHDs and are described below. The *Oncology Pharmaceuticals* draft guidance takes into consideration recommendations in relevant guidance documents, such as those in ICH S9, the ICH guidance for industry *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals Questions and Answers*, and ICH S6 (R1).

Embryo-fetal development (EFD) toxicity risk assessment of pharmaceuticals used to treat patients with SDLTHD should be available when the marketing application is submitted; the Agency does not consider these studies essential to support clinical trials. A weight-of-evidence approach showing potential for reproductive toxicity may eliminate the need to conduct a dedicated EFD study. The *Oncology Pharmaceuticals* draft guidance describes scenarios for which an EFD study is not warranted based on the patient population or the type of pharmaceuticals (e.g., use in postmenopausal women only or for drugs that are genotoxic and target rapidly dividing cells); these scenarios are applicable to SDLTHDs as well.

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

Fertility and early embryonic development and pre- and postnatal development (PPND) studies are usually not warranted for treatment of patients with SDLTHD. In cases in which there is a well-understood high cure rate associated with the use of the investigational pharmaceutical or the investigational pharmaceutical results in substantial reduction in the occurrence of life-threatening or debilitating events, fertility and PPND studies may be needed on a case-by-case basis. If the Agency considers these studies important, the results of such studies could be submitted after approval.

The *Oncology Pharmaceuticals* draft guidance describes scenarios that are applicable to SDLTHDs and for which a fertility or PPND study is not warranted. For instance, a stand-alone fertility study is not warranted if, based on the totality of data (e.g., knowledge of the target biology and/or results of general toxicology studies), the sponsor identifies potential fertility risk or when the pharmaceutical will be used in postmenopausal women only. PPND studies are not needed for pharmaceuticals that cause malformations or result in high embryo-fetal death.

F. Carcinogenicity

ICH S6(R1) and the ICH guidance for industry *S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals* (March 1996) 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 product approval.[8]

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 pharmaceuticals activating the immune system, the 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 with the use of 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* (January 2015) before marketing the pharmaceutical.

[8] See the guidance for industry *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (April 2011).

I. Pharmacokinetics

The evaluation of limited pharmacokinetic parameters (e.g., peak plasma/serum level, area under the curve (AUC), 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. The sponsor should include pharmacokinetic endpoints 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).

IV. TIMING OF NONCLINICAL STUDIES

Table 1 indicates the recommended timing for submission of the results of nonclinical studies to the Agency, when applicable.

Table 1. Timing for Submission of Nonclinical Studies[*]

Nonclinical studies or assessments	Timing
Pharmacology: primary	With initial IND; continuing through development
Pharmacology: secondary	With initial IND
Safety pharmacology	With initial IND
Genetic toxicology	With initial IND; additional studies may be needed during drug development; the complete battery of studies not always necessary
General toxicology study: 1 month	With initial IND
General toxicology: 3 months	Before initiating a large-scale trial (e.g., phase 3)
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. FIH DOSE AND DOSE ESCALATION

The goal of selecting the start dose is to identify a dose that is expected to have pharmacologic effects and is reasonably safe. The sponsor should scientifically justify the starting dose using all

available nonclinical data (e.g., pharmacokinetics, pharmacodynamics, toxicity). When the first-in-human (FIH) study is conducted in patients, the FIH dose may be based on the severely toxic dose in 10% of rodents (STD_{10}), the highest nonseverely toxic dose in nonrodents, the NOAEL in either species, or other approaches as relevant and justified. For most systemically administered small molecules, interspecies scaling of the animal doses to an equivalent human dose is usually based on normalization to body surface area. For both small molecules and biopharmaceuticals, interspecies scaling based on body weight, AUC, or other exposure parameters might be appropriate.

For biopharmaceuticals with immune agonistic properties, the sponsor should consider selecting the start dose using a minimally anticipated biologic effect level.

In general, the highest dose or exposure tested in the nonclinical studies does not limit the dose escalation or highest dose investigated in a clinical trial in patients with SDLTHD. When a steep dose- or exposure-response curve for severe toxicity is observed in nonclinical toxicology studies, or when no preceding marker of severe toxicity is available, smaller than usual dose increments (fractional increments rather than dose doubling) should be considered.

VI. OTHER STUDIES

A. Combination of Pharmaceuticals

The sponsor should provide a rationale to support the combination, which can include in vitro or in vivo pharmacology data or a literature assessment.

In general, toxicology studies investigating the safety of combinations of pharmaceuticals intended to treat patients with SDLTHDs are not warranted. Instead, pharmaceuticals planned for use in combination therapies should be well studied individually in toxicology studies. “Well-studied individually” means a toxicological evaluation sufficient to support clinical studies of the individual pharmaceutical alone.

If there is no or very limited human safety data for one of the combination components, the sponsor should consider a nonclinical pharmacology study of the combination, containing limited safety endpoints (such as mortality, clinical signs, and body weight). This would be in addition to the toxicology studies with the single agents. If sufficient clinical data (e.g., a completed phase 1 or a monotherapy phase within phase 1) are available with the individual pharmaceuticals, additional nonclinical studies may not be warranted.

If there is no or very limited human safety data for one of the combination components, and yet the pharmaceutical is pharmacologically inactive in animal species, safety assessment of the combination can be based on relevant in vitro tests and/or mechanistic understanding of target biology.

If the available clinical and nonclinical data are insufficient to establish a safe starting dose of the combination, a dedicated toxicology study may be needed with the combination to establish a safe starting dose in humans.

B. Nonclinical Studies to Support Studies in Pediatric Populations

Juvenile animal toxicology studies are not warranted to initiate clinical trials in pediatric populations for SDLTHDs when clinical data in adults are available. In this case, juvenile toxicology studies are not warranted concurrent with a pediatric study or to support product approval; data obtained in adult and pediatric patients will be more relevant for safety assessment and labeling. On a case-by-case basis, juvenile toxicology studies may be warranted to address specific targeted questions that could not be answered through the adult or pediatric clinical study or existing nonclinical data.