Severely Debilitating or Life-Threatening Hematologic Diseases

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Outline

• Applicable guidelines
  – ICH M3
  – FDA guidance on rare diseases/enzyme replacement
  – ICH S9 and Q&A
  – FDA guidance on SDLTHD

• SDLTHD

• FDA reorganization

• ICH process and SDLT

• FDA Listening Session
Abbreviations

**DHOT**: Division of Hematology Oncology Toxicology

**DHP**: Division of Hematology Products

**HNSTD**: Highest non-severely toxic dose

**MCD**: multi-centric Castleman’s disease

**NOAEL**: no-observed adverse effect level

**OHOP**: Office of Hematology and Oncology Products

**OND**: Office of New Drugs

**SCD**: sickle cell disease

**SDLT**: severely debilitating and life-threatening

**SDLTHD**: severely debilitating and life-threatening hematologic disorder

**STD\(_{10}\)**: severely toxic dose in 10% of animals

**VOC**: veno-occlusive crisis
ICH M3

Pharmaceuticals under development for indications in life-threatening or serious diseases (e.g., advanced cancer, resistant HIV infection, and congenital enzyme deficiency diseases) without current effective therapy also warrant a case-by-case approach to both the toxicological evaluation and clinical development in order to optimise and expedite drug development. In these cases and for products using innovative therapeutic modalities (e.g., siRNA), as well as vaccine adjuvants, particular studies can be abbreviated, deferred, omitted, or added. Where ICH guidances for specific product areas exist, they should be consulted.
FDA Guidances

Rare Diseases: Common Issues in Drug Development Guidance for Industry  

Investigational Enzyme Replacement Therapy Products: Nonclinical Assessment Guidance for Industry

February 2019; FDA-2015-D-2818  
May 2015; FDA-2015-D-1246
FDA Guidance on Rare Diseases
Nonclinical Section

• Flexibility around nonclinical programs influenced by:
  – Pharmacological and chemical characteristics of the drug
  – Design and objectives of the proposed clinical trial
  – Anticipated risks to humans
  – Existing toxicology and human data

• Flexibility may include a toxicology study in a single species, less than chronic duration, or delayed submission of certain studies to a marketing application or to postmarketing

• Discusses utility of animal models of disease for safety testing

• Cites ICH M3, S6 and S9
FDA Guidance on Enzyme Replacement Products

- Guidance for lysosomal storage diseases or other diseases related to inborn errors of metabolism but not for the development of pancreatic enzyme products
- Factors to consider in a nonclinical development program
  - Proposed clinical indication and population (e.g., children included?)
  - Available nonclinical and clinical safety and pharmacology data
  - Relevant animal models
- Toxicology program depends on entry criteria; if the disease is expected to rapidly progress to death or substantive irreversible morbidity over 1 year, then the toxicology program may be abbreviated
- Cites ICH M3 and S6
ICH S9 and Q&A

ICH Harmonised Tripartite Guideline

Nonclinical Evaluation for Anticancer Pharmaceuticals

S9

Current Step 4 version
dated 29 October 2009
ICH S9 for Anticancer Pharmaceuticals

- Guidance covers advanced cancer and cancer patient populations with long expected survival
- Nonclinical program is not driven by specific life expectancy (e.g., 1 year or 5 years)
- One month toxicology studies usually sufficient to initiate clinical development; 3 month studies to support registrational trials; usually 2 species
- Safety pharmacology endpoints can be incorporated into general toxicology studies to support the principles of the 3Rs
- Submission of some studies deferred to the marketing application (e.g., reproduction toxicology)
PhRMA Proposal

Evaluation of Therapeutics for Advanced-Stage Heart Failure and Other Severely-Debilitating or Life-Threatening Diseases

JS Prescott¹, PA Andrews², RW Baker³, MS Bogdanffy⁴, FO Fields⁵, DA Keller⁶, DM Lapadula⁷, NM Mahoney⁸, DE Paul⁹, SJ Platz¹⁰, DM Reese¹¹, SA Stoch¹² and JJ DeGeorge¹

Clinical Pharmacol Therapeutics 2017: 102 (3); 219-227
PhRMA Proposal

• SDLT compared to oncology indications
• Provides examples of potential SDLT diseases’ e.g., severe congestive heart failure, advanced Parkinson’s
• A streamlined, clearly defined, standardized nonclinical development program is described only for oncology programs
• Recommends using ICH S9 for SDLT; the traditional 1 for 1 nonclinical to clinical dosing duration would not apply
• A recovery period, in needed, would only be conducted in one species to support late clinical development
• Genotoxicity would follow the recommendations in ICH M3
2010: DHP (in OHOP) was formed. DHP is responsible for the review of benign and malignant hematology applications.

- Different nonclinical review teams
- Agreements (FDA-Sponsors) already made and nonclinical studies ongoing
- DHOT staff assisting DHP learned about the diseases and their severity
- A period of transition: slowly moving to a streamlined approach. From ICH M3 to a hybrid of ICH M3/ICH S9 to less of M3 and more of S9 concepts
- 2020: Benign hematology moving out of oncology
The growing number of INDs for SDLT hematologic disorders led to...

• Development of an internal guidance (2016) to assist reviewers
  – Bring consistency in nonclinical recommendations
  – Focus on severely debilitating and life-threatening (SDLT) hematologic disorders regardless of prevalence or life expectancy
Life expectancy

• Short life expectancy (e.g. 1-2 yr) → serious; but

• Should not be the main criterion for taking a streamlined approach
  – Seriousness of the disease: in MCD, any episode can result in organ failure and death. In SCD, VOC can result in organ failure
  – Relevance/ importance of toxicology study results (independent of life expectancy):
    • How relevant is reproductive toxicity assessment when the subject won’t reach the age of puberty? Waive?
    • How critical is the results of fertility studies when the subject is bedridden? Waive? post-approval?
Severely Debilitating or Life-Threatening Hematologic Disorders: Nonclinical Development of Pharmaceuticals Guidance for Industry

March 2019
• Draft posted in June 2018
• Docket (FDA-2018-D-1328) was open for 60 days
• Comments were received and addressed
• Final guidance was posted in March 2019

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

Sec. 312.80 Purpose.

The purpose of this section is to establish procedures designed to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists. As stated 314.105(c) of this chapter, while the statutory standards of safety and effectiveness apply to all drugs, the many kinds of drugs that are subject to them, and the wide range of uses for those drugs, demand flexibility in applying the standards. The Food and Drug Administration (FDA) has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated. The procedure outlined in this section should be interpreted consistent with
(a) For purposes of this section, the term "life-threatening" means:
(1) Diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted; and
(2) Diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival.
(b) For purposes of this section, the term "severely debilitating" means diseases or conditions that cause major irreversible morbidity.
(c) Sponsors are encouraged to consult with FDA on the applicability of these procedures to specific products.

Sec. 312.85 Phase 4 studies.

Concurrent with marketing approval, FDA may seek agreement from the sponsor to conduct certain postmarketing (phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time.
Highlights of the guidance

• Guidance applies to
  – Hematologic diseases other than cancer (ICH S9 used for oncology indications)
    • Independent of disease incidence or prevalence
  – Drugs to treat the active disease, and
  – Drugs to prevent the recurrence of a life-threatening or debilitating event*
• No specified life-expectancy
  – E.g., in Castleman’s Disease any cytokine storm may be fatal, but patients may survive and live for many years
• Guidance modeled on ICH S9

* added to final guidance
Highlights of the guidance (Cont’d)

• One-month toxicology studies sufficient for initiation of FIH trials and for continuous administration in patients beyond 1 month

• Three-month toxicology studies are sufficient to support initiation of large-scale trials and for approval

• Fertility and PPND studies usually not needed
  – When needed (e.g. high cure rate with the use of investigational drug): can be conducted post-approval
Among the comments

• To better define SDLT
  – Initially had definition from 21 CFR 312.81; final guidance included additional factors:
    • Reduced life expectancy, organ damage or dysfunction, disability, need for hospitalization, risk of severe infection, or blood transfusion dependence.

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).
Examples of diseases

- Multicentric Castleman’s disease (MCD); hemophagocytic lymphohistiocytosis (HLH); hypereosinophilic syndrome; amyloidosis; cold agglutinin; aplastic anemia; paroxysmal nocturnal hemoglobinuria (PNH); sickle cell disease (SCD); beta-thalassemia major; hemophilia; thrombotic thrombocytopenic purpura; and warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis (WHIM) syndrome.

- Not an all-inclusive list
<table>
<thead>
<tr>
<th>Nonclinical studies or assessments</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacology: primary</td>
<td>With initial IND; continuing through development</td>
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<tr>
<td>Pharmacology: secondary</td>
<td>With initial IND</td>
</tr>
<tr>
<td>Safety pharmacology</td>
<td>With initial IND</td>
</tr>
<tr>
<td>Genetic toxicology</td>
<td>With initial IND; additional studies may be needed during drug development; the complete battery of studies not always necessary</td>
</tr>
<tr>
<td>General toxicology study: 1 month</td>
<td>With initial IND</td>
</tr>
<tr>
<td>General toxicology: 3 months</td>
<td>Before initiating a large-scale trial (e.g., phase 3)</td>
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<tr>
<td>ADME</td>
<td>In parallel with clinical development</td>
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<tr>
<td>Reproductive toxicology: EFD</td>
<td>With NDA/BLA</td>
</tr>
<tr>
<td>Reproductive toxicology: fertility and PPND (when needed)</td>
<td>With NDA/BLA or after approval</td>
</tr>
<tr>
<td>Carcinogenicity (when needed)</td>
<td>With NDA/BLA or after approval</td>
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</tbody>
</table>

*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.
# Nonclinical Recommendations

<table>
<thead>
<tr>
<th>Nonclinical evaluations</th>
<th>*Oncology (S9 and S9 Q/A)</th>
<th>*SDLTHD: regardless of prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacology; primary</td>
<td>With initial IND; continuing through development</td>
<td>With initial IND; continuing through development</td>
</tr>
<tr>
<td>Safety pharmacology</td>
<td>Assessment with initial IND <em>Stand-alone studies not necessary</em></td>
<td>Assessment with initial IND <em>Stand-alone studies not necessary</em></td>
</tr>
<tr>
<td>Genetic toxicology (small molecules)</td>
<td>With NDA</td>
<td>With initial IND; the complete battery not always necessary <em>Follow S9 for when testing may be abbreviated</em> <em>Follow M3 for timing</em></td>
</tr>
<tr>
<td>General toxicology study; 1 month</td>
<td>With initial IND <em>will allow continuous admin in patients beyond 1 month</em></td>
<td>With initial IND <em>will allow continuous admin in patients beyond 1 month</em></td>
</tr>
<tr>
<td>General toxicology; 3 months</td>
<td>Prior to initiation of a phase 3 trial</td>
<td>Prior to initiation of a phase 3 trial</td>
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<tr>
<td>Reproduction toxicology</td>
<td></td>
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<tr>
<td>EFD</td>
<td>With NDA/BLA <em>Generally not warranted</em></td>
<td>With NDA/BLA <em>When warranted</em></td>
</tr>
<tr>
<td>Fertility and PPND</td>
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</table>

* ADME (as applicable): In parallel with clinical development

* Carcinogenicity (when warranted): With NDA/BLA or post-approval

† Also see the Oncology guidance on reproductive toxicity testing

FIH dose selection

The start dose should be justified scientifically using all available nonclinical data (e.g., pharmacokinetics, pharmacodynamics, toxicity). The start dose should be chosen to minimize exposure to subtherapeutic doses.

**Small molecules**

- **Oncology:** $1/10^{th}$ STD10; $1/6^{th}$ HNSTD
- **SDLT hematologic disorders:** $1/10^{th}$ NOAEL?

  Why so low?
  - Traditionally used, with demonstrated safety
  - No one has evaluated other approaches (e.g. STD10/HNSTD)
Case 1: small molecule in PNH

Paroxysmal Nocturnal Hemoglobinuria (PNH)

• Rare and serious disease of the blood
• Hemolytic anemia, thrombosis (severe complications and death), impaired bone marrow function
• The median survival after diagnosis is ~10 years

SDLT regardless of prevalence or life expectancy

https://www.hopkinsmedicine.org/kimmel_cancer_center/types_cancer/paroxysmal_nocturnal_hemoglobinuria_PNH.html
Case 1 (cont’d): drug is a small molecule

- Sponsor proposed 4–week repeat dose toxicology: FDA agreed (will support continuous dosing in patients)
- No question on duration of chronic toxicology
- Question on Reproductive toxicity: FDA informed the sponsor “…the EFD studies can be submitted with the NDA”
- Question on carcinogenicity: FDA informed the sponsor “…carcinogenicity assessments may be conducted post-approval”
Case 2: AL Amyloidosis

• Hematologic disorder caused by clonal plasma cells that produce misfolded immunoglobulin light chains (AL). Deposition of misfolded protein (amyloid fibrils) causes progressive organ damage

• Results in: organ dysfunction that can include cardiac (e.g. failure), renal (e.g. failure), and hepatic dysfunction. Other symptoms; e.g. neuropathy, macroglossia (enlargement of the tongue → dyspnea, etc)

SDLT regardless of prevalence or life expectancy

https://www.mayoclinic.org/diseases-conditions/amyloidosis/symptoms-causes/syc-20353178

https://www.medicinenet.com/amyloidosis/article.htm
Case 2 (cont’d)
Drug: IgG1 mAb against amyloid A

• One month toxicology in monkeys: no drug-related findings
• 3-week tox in rodents (murine surrogate): animal model of disease (combined pharmacology/toxicity) - GLP

Further development

• No chronic toxicity study warranted:
  • no target in healthy monkeys (a study in healthy monkeys will not provide useful information);
  • too immunogenic in rodents to be able to maintain exposure beyond 3 weeks + death in animals (disease model) due to progression of disease
Case 3: Multicentric Castleman’s Disease (MCD)

• A group of heterogeneous inflammatory disorders affecting the lymph nodes

Symptoms:
• vascular leak;
• fluid collection in lungs and abdomen;
• multiple organ system dysfunction; organ failure (can result in death)

SDLT regardless of prevalence or life expectancy

✓ Castleman Disease Collaborative Network: http://www.cdcn.org/
✓ https://rarediseases.info.nih.gov/diseases/9644/multicentric-castlemans-disease
ICH Efforts

• Since publishing the draft (now final) guidance DHOT began seeing more requests to use the SDLTHD approach in drug development programs
• An FDA-only guidance, while useful, is not ideal due to the global nature of drug development
• Developing a guidance for the nonclinical safety evaluation of therapeutics for SDLT diseases discussed by ICH Assembly at June 2018 meeting in Kobe; not discussed since then
  – Next meeting Singapore 16-20 Nov
• “Pharmas want ICH to streamline toxicity requirements for severe diseases”; Stephen Hansen Associate Editor, BioCentury Aug 29, 2019
PhRMA Proposal Scope of ICH SDLT Guidance

Title: Evaluation of Therapeutics for Severely-Debilitating or Life Threatening Diseases or Conditions: Defining Scope to Enable Global Guidance Development

Man M. Liu1*, F. Owen Fields2*, Judith S. Prescott3*, Akintunde Bello4, Nancy Bower5, Salima Darakjy6, James Hartke7, Vivek Kadambi8, Daniel Lapadula9, Aubrey Stoch10, Mazin Derzi11

November 7th Listening Session

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
[Docket No. FDA–2019–N–3453]

Promoting Effective Drug Development Programs: Opportunities and Priorities for the Food and Drug Administration’s Office of New Drugs; Public Meeting; Request for Comments

AGENCY: Food and Drug Administration, HHS.
ACTION: Notice of public meeting; request for comments.

• FDA is soliciting feedback from stakeholders for actionable policy suggestions
• Among the topics for discussion are policy needs linked to shared therapeutic context (e.g., drugs intended to treat serious, life-threatening rare diseases)
• Interested in hearing specific suggestions for topics where further clarity in the Agency’s current thinking may be warranted
• How can OND promote effective drug development programs?
Summary

• Thinking evolved since 2010 reorganization:
  – Initiated with M3
  – Then a hybrid of S9 and M3
  – Then adopted more concepts from S9 for some indications
  – In general, current thinking is that the benefit/risk for SDLTHDs is similar to oncology indications

• DHOT generated an internal guidance for consistency in nonclinical recommendations of SDLTHDs

• FIH dose selection: STD10 and HNSTD approaches should be evaluated
Summary

• OHOP has adopted a streamlined approach for nonclinical development of pharmaceuticals to treat SDLTHDs
• The guidance is now available and should be followed
• Not sure if the indication falls under SDLTHD?
  – Pre-IND meeting may assist