Epidermolysis Bullosa: Developing Drugs for Treatment of Cutaneous Manifestations

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Barbara Gould at 301-796-4224 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

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Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 with the development of drugs[2] for treatment or prevention of the serious cutaneous manifestations of the heterogeneous group of disorders collectively known as epidermolysis bullosa (EB).[3] There is an unmet medical need for EB patients due to the paucity of effective treatment options.

- This guidance focuses on drug development and trial design issues specific to the treatment of EB, including FDA's current thinking on endpoint considerations. There is not yet sufficient clinical trial precedent to guide definitive endpoint advice.

- FDA strongly encourages sponsors to meet with the appropriate review division in early planning stages for advice tailored to each drug development program.

  – General issues, such as the efficacy evidence needed to support approval for serious and life-threatening diseases or approaches to adaptive study design, are discussed in

[1] This guidance has been prepared by the Division of Dermatology and Dental Drug Products and by the Rare Diseases Program in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

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

guidances for industry,[4] as are general issues of statistical analysis and control selection.[5] FDA's flexible approach to drug development for rare diseases in general, including the important topic of safety assessment, is also described in the draft guidance for industry *Rare Diseases: Common Issues in Drug Development*.[6]

- The following guidances for industry provide recommendations for drug products intended for cellular and gene therapy:
  - Guidance for industry *Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products*
  - Guidance for industry *Gene Therapy Clinical Trials — Observing Subjects for Delayed Adverse Events*
  - Guidance for FDA reviewers and sponsors *Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)*
- Some advice in the guidance for industry *Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment* might be useful to developers of drugs for treatment of EB. However, the wound healing guidance is intended for acute burn wounds and chronic venous stasis, diabetic foot, and pressure ulcers. The distinct pathophysiology, natural history, and low prevalence of EB warrant distinct approaches.

- 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

EB encompasses a clinically and genetically heterogeneous group of rare inherited disorders characterized by mechanical fragility of epithelial tissues due to defective proteins integral to epithelial structure and function. Epithelial integrity is critical for protection and function of organs and tissues, and prevention of water loss and infection. Thus, the magnitude of disease burden and unmet medical need posed by EB cannot be overstated.

[4] See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* and the draft guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics* (when final, this guidance will represent the FDA's current thinking on this topic).

[5] See the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.

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

The classification of EB is evolving as new diagnostic techniques are developed.[7] EB has been traditionally divided into major subtypes based on the level within which blisters develop: intraepidermal (EB simplex), within (junctional EB) or beneath (dystrophic EB) the skin basement membrane zone, and mixed pattern (Kindler syndrome). More recent classification takes into account the mode of inheritance, phenotype, immunofluorescence antigen mapping findings, and gene defect. There is considerable variation in disease severity and natural history within each EB subtype because of modifying genetic and other factors.

III. CONSIDERATIONS FOR CLINICAL TRIAL DESIGN

A. Trial Population

- The trial population should have documentation of the clinical and laboratory evidence of the subtype(s) of EB that will form the basis of the proposed labeling claim (e.g., results of immunofluorescence antigen mapping or mutational analysis). Genetic testing, if performed, should also be documented; however, it should not be a requirement for study entry if mutational analysis is not relevant to the desired claim. Patients with adequate prior documented diagnosis generally need not have testing repeated.

  - The diagnostic method(s) used by a sponsor for the purposes of trial enrollment should be based on the characteristics of the specific development program, such as:

    - The investigational drug's mechanism of action, if known
    - The pathophysiology and natural history of the EB subtype(s) to be treated
    - The clinical trial endpoints and efficacy assessment tools

- Because EB subtypes differ in the extent and distribution of cutaneous wounds and the level of skin cleavage, results from an efficacy trial in EB simplex cannot be generalized to the more severe EB subtypes.

- Sponsors are encouraged to discuss the desired study EB population early with the FDA review division. The trial population should be representative of the phenotypic spectrum of interest, to the extent possible given the low prevalence of EB.

- Because the junctional and dystrophic forms of EB generally present clinically at birth, sponsors should also anticipate discussing with the review division any challenges and additional requirements for drug development in pediatric patients, especially with respect to trials in infancy and early childhood.[8]

[7] Fine JD, Bruckner-Tuderman L, Eady RA, Bauer EA, Bauer JW, Has C, Heagerty A, Hintner H, Hovnanian A, Jonkman MF, Leigh I, Marinkovich MP, Martinez AE, McGrath JA, Mellerio JE, Moss C, Murrell DF, Shimizu H, Uitto J, Woodley D, Zambruno G, 2014, Inherited Epidermolysis Bullosa: Updated Recommendations on Diagnosis and Classification, J Am Acad Dermatol, 70:1103–1126.

[8] See 21 CFR part 50, subpart D, Additional Safeguards for Children in Clinical Investigations.

B. Efficacy Endpoints

- Clinical trials should be designed to minimize bias with randomization whenever possible and include an appropriate control to show that the drug provides clinically meaningful improvement in at least one symptom or sign of EB. In appropriate cases, a single adequate and well-controlled trial with supporting evidence may suffice.[9] Examples of meaningful improvement might include significant relief from itching, pain, blister prevention, and wound healing, among others.

  - Before commencing clinical trials for EB, it is critically important to reach agreement with FDA about the primary efficacy endpoint(s) and the magnitude of change that will demonstrate clinically meaningful improvement, such as the degree of wound healing.

  - We encourage sponsors to propose endpoints for which there is (or will be before trial initiation) a validated and sufficiently sensitive assessment method.

  - Patient-reported outcome (PRO) instruments[10] and observer-reported outcome (ObsRO) instruments[11] play an important role in establishing effectiveness of EB treatment because they provide evidence of how patients feel or function in daily life. Sponsors should incorporate patient and caregiver perspectives in efficacy endpoint development.

    - FDA is not aware of PRO or ObsRO instruments shown to be adequate for regulatory use to assess improvement in EB, but sponsors are welcome to submit existing or modified PRO, ObsRO, and/or clinician-reported outcome instruments.

    - The guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* provides information about developing such instruments.

C. Special Considerations

Sponsors should consider development and validation of assessment tools and processes that minimize visits to study sites and maximize patient comfort, such as photographic/video documentation of wounds during routine dressing changes in the home, data collection via patient diaries, and telemedicine, among others.

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[9] See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* and the draft guidance for industry *Rare Diseases: Common Issues in Drug Development*.

[10] U.S. Food and Drug Administration and U.S. National Institutes of Health Biomarker Working Group, 2016, BEST (Biomarkers, EndpointS, and other Tools) Resource, Glossary Section Terms and Definitions under letter P, available at https://www.ncbi.nlm.nih.gov/books/NBK338448/#IX-P, accessed April 19, 2018.

[11] U.S. Food and Drug Administration and U.S. National Institutes of Health Biomarker Working Group, 2016, BEST (Biomarkers, EndpointS, and other Tools) Resource, Glossary Section Terms and Definitions under letter O, available at https://www.ncbi.nlm.nih.gov/books/NBK338448/#IX-O, accessed April 19, 2018.

In studies involving drug products intended for gene therapy, there should be assessments related to lentivirus vector-based risks and long-term follow-up.

1. Junctional and Dystrophic Subtypes

Trial recruitment and retention of patients with junctional and dystrophic subtypes of EB (characterized by extreme skin fragility) are challenging because trial procedures can exacerbate skin damage and increase the economic effect of intensive daily wound care. In addition, because of the low prevalence of these subtypes, these patients may be geographically remote from specialty centers. When designing clinical trials, sponsors are encouraged to prospectively consider:

- Damage to the skin and pain associated with travel.
- Identification of the essential aspects of skin care that must be standardized for trial interpretability versus those aspects that can remain patient or caregiver preference.
- Restriction of venipuncture and other procedures to those essential to efficacy evaluation, safety monitoring, and pharmacokinetic studies. For enrolled patients with extracutanous manifestations, trial procedures and sample collection should coincide with patient care procedures performed under sedation.

2. EB Simplex

Seasonal timing and geographic location of enrollment should address the disease-modifying influence of ambient temperature and physical activity.