
Epidermolysis Bullosa: Developing Drugs for Treatment of Cutaneous Manifestations Guidance for Industry

**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)**

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Epidermolysis Bullosa: Developing Drugs for Treatment of Cutaneous Manifestations Guidance for Industry¹

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 with the development of drugs² for treatment or prevention of the serious cutaneous manifestations of the heterogeneous group of disorders collectively known as epidermolysis bullosa (EB).³ The paucity of effective treatment options for EB represents an important unmet medical need.

This guidance focuses on drug development and trial design issues specific to the treatment of EB, including FDA's current thinking on trial endpoints. There is not yet sufficient clinical trial experience to establish definitive endpoints.

FDA strongly encourages sponsors to meet with the appropriate review division in early planning stages for information 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 guidances for

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* (May 2014). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

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industry,⁴ as are general issues of statistical analysis and control selection.⁵ In appropriate cases, a single adequate and well-controlled trial with confirmatory evidence may suffice for such conditions. 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* (February 2019).⁶

The following guidances for industry provide recommendations for products intended for cellular and gene therapies:

- Guidance for industry *Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products* (June 2015)
- Guidance for industry *Gene Therapy Clinical Trials — Observing Subjects for Delayed Adverse Events* (November 2006)
- 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)* (April 2008)

Some recommendations in the guidance for industry *Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment* (June 2006) 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 may justify and even 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 as a result of absent, reduced quantity of, or defective proteins integral to epithelial structure and function. Epithelial integrity is

⁴ See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998) and the draft guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics* (September 2018) (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/regulatory-information/search-fda-guidance-documents>.

⁵ See the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* (September 1998) and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001), respectively.

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

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critical for protection and function of organs and tissues and prevention of water loss and infection. In EB, defective epithelial integrity in the skin leads to chronic and relapsing wounds that predispose patients to repeated infections and may result in unwanted fibrosis and deformities as well as cutaneous carcinogenesis. Skin lesions are associated with itching and pain, the latter aggravated during dressing changes. These complications and symptoms represent a major disease burden for patients.

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. For some trials, mutational analysis may be important, and such data will need to be collected; however, it should not be a requirement for trial entry if this testing is not relevant to the desired claim. In general, patients with adequate prior documented diagnosis do not need to have testing repeated.
 - As investigational products for cutaneous manifestations of EB can be directed at palliative treatment or be disease-modifying, 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 following examples:
 - The investigational drug's mechanism of action, if known. For example, a clinical trial for a product intended for palliation of EB wounds may not warrant extensive diagnostic work-up. For a disease-modifying product (e.g., a gene therapy) a more extensive diagnostic workup is usually necessary.
 - The pathophysiology and natural history of the EB subtype(s) to be treated. For a disease-modifying product designed to treat a specific subtype, it may be important to include mutational analysis.

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.

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- The clinical trial endpoints and efficacy assessment tools. These should be relevant to the claims on the desired target population
- 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.
- FDA encourages sponsors to discuss the desired trial population early with the 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 anticipate discussing with the review division the challenges of studying these EB subtypes in the newborn and in early infancy. Sponsors also need to meet additional requirements for drug development in pediatric patients.⁸

B. Efficacy Endpoints

- Sponsors should design clinical trials on EB to minimize bias using randomization to treatment and an appropriate control with blinded assessment of outcomes. As EB is a rare disease, intrasubject randomization in early development to minimize sample size can be considered for topical drug product trials. The trial endpoints can include effects on patients' signs or symptoms such as itching, pain, blister prevention, wound healing, etc.
 - Before initiating clinical trials for EB, it is important for sponsors to discuss with the review division the choice of the primary efficacy endpoint(s), including whether the endpoint will be an effect on a continuous scale or on specified effect sizes (such as complete healing or a specified minimum degree of healing), as well as the time point for efficacy evaluation.
 - We encourage sponsors to propose endpoints for which there is (or will be before trial initiation) a validated and sufficiently sensitive assessment method to be used in EB clinical trials intended for regulatory review.
 - Patient-reported outcome (PRO) instruments⁹ and observer-reported outcome (ObsRO) instruments¹⁰ play an important role in establishing effectiveness of EB

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

⁹ 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.

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 O, available at <https://www.ncbi.nlm.nih.gov/books/NBK338448/#IX-O>, accessed April 19, 2018.

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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 that have undergone evaluation for adequacy as measures to specifically assess cutaneous manifestations in the heterogeneous group of EB conditions in support of regulatory use. Sponsors can submit existing or modified PRO, ObsRO, and/or clinician-reported outcome instruments for discussion and review.
- The guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009) provides information about developing such instruments.

C. Special Considerations

Sponsors should consider development and validation of assessment tools and also consider processes that minimize visits to trial sites and maximize patient comfort, including assessment tools that may be more conveniently deployed — such as assessments performed at home visits. For example, sponsors can implement the following operational elements to achieve the above objectives:

- Electronic informed consent
- Telemedicine interactions with the assistance of mobile nurses as needed and their deployments for sample collection at patients' homes
- Photographic or video documentation of wounds during routine dressing changes in the home and at specified study visits for wound observation endpoint data, via standardized digital photographic images from photo capture and validated assessment of the images. The sponsor should discuss proposals for validation with FDA and reach agreement in advance of validation efforts
- Validation and use of electronic PRO instruments
- Data collection via electronic diaries

In trials involving drug products intended for gene therapy, there should be assessments related to specific vector-based risks and long-term follow-up, especially for lentiviral vectors.

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 cost of intensive daily wound care to the patient. In addition,

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because of the low prevalence of these subtypes, such patients may not live near specialty centers. When designing clinical trials, FDA encourages sponsors to consider the following:

- The importance of minimizing travel, which can lead to skin damage and pain
- 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 extracutaneous manifestations, trial procedures and sample collection should coincide with patient care procedures performed under sedation

2. EB Simplex

For sponsors developing drugs to treat EB simplex, seasonal timing and geographic location of trial enrollment should address the disease-modifying influence of ambient temperature and physical activity.