Guidance for Industry
Acute Bacterial Skin and Skin Structure Infections:
Developing Drugs for Treatment

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

August 2010
Clinical/Antimicrobial
Revision 1
Guidance for Industry
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This draft guidance, when finalized, will represent the Food and Drug Administration’s (FDA’s) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment of acute bacterial skin and skin structure infections (ABSSSI), impetigo, and minor cutaneous abscesses. Specifically, this guidance addresses the Food and Drug Administration’s (FDA’s) current thinking regarding the overall development program and clinical trial designs for systemic drugs to support an indication for treatment of ABSSSI, and topical or systemic drugs to support an indication for treatment of impetigo or minor cutaneous abscesses. This guidance is intended to serve as a focus for continued discussions among the Division of Anti-Infective and Ophthalmology Products and the Division of Special Pathogen and Transplant Products, pharmaceutical sponsors, the academic community, and the public. This guidance does not address lower extremity infections in neurologically compromised patients, such as the diabetic foot infection or pressure sore infection. Currently, there are ongoing efforts in the scientific community regarding clinical trial designs and endpoints for ABSSSI. As the science of clinical trial design for this indication evolves, we expect that this guidance may be revised.

1 This guidance has been prepared by the Division of Anti-Infective and Ophthalmology Products and the Division of Special Pathogen and Transplant Products in the Center for Drug Evaluation and Research (CDER) 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 In addition to consulting guidances, sponsors are encouraged to contact the divisions to discuss specific issues that arise during drug development.

4 We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.
This guidance revises the draft guidance for industry Uncomplicated and Complicated Skin and Skin Structure Infections — Developing Antimicrobial Drugs for Treatment published in 1998. Once final, this guidance will be considered the FDA’s current thinking regarding the development of drugs to treat ABSSSI. It also supersedes, with regard to development of drugs to treat ABSSSI, more general guidance issued many years ago (i.e., Clinical Evaluation of Anti-Infective Drugs (Systemic) and Clinical Development and Labeling of Anti-Infective Drug Products, as well as the joint FDA/Infectious Disease Society of America’s General Guidelines for the Clinical Evaluation of Anti-Infective Drug Products). This guidance does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry E9 Statistical Principles for Clinical Trials and E10 Choice of Control Group and Related Issues in Clinical Trials. This guidance focuses on specific drug development and trial design issues that are unique to the study of ABSSSI.

II. BACKGROUND

In general, the majority of skin infections are caused by Gram-positive bacteria such as Streptococcus pyogenes and Staphylococcus aureus. Methicillin-resistant Staphylococcus aureus (MRSA) is also an important pathogen in skin and skin structure infections. Because broad categories of skin infections tend to share common bacterial pathogens, clinical trials include several clinical disease entities under one or more general categories. Over the past several decades, skin infections have been characterized into two broad categories: (1) uncomplicated skin and skin structure infections (uSSSI); and (2) complicated skin and skin structure infections (cSSSI) with the synonym of skin and soft tissue infections also being used.

Since the 1998 draft guidance published, there have been public discussions about the definitions of skin and skin structure infections included in the general categories of uSSSI and cSSSI, clinical trial designs, and endpoints used in support of anti-infective drugs approved for the indications of the treatment of uSSSI and/or cSSSI. Many issues were discussed at the Anti-Infective Drugs Advisory Committee (AIDAC) meeting in November 2008. These discussions have focused on clinical trial designs for ABSSSI and other important issues such as the following:

5 Beam, TR, DN Gilbert, and CM Kunin, 1992, General Guidelines for the Clinical Evaluation of Anti-Infective Drug Products, Infectious Disease Society of America and the Food and Drug Administration, Clinical Infectious Diseases, Nov.15, Supplement 1:S5-32.

6 The Anti-Infective Drugs Advisory Committee meeting, November 18, 2008. Transcripts and briefing information can be found at the FDA Web site at http://www.fda.gov/ohrms/dockets/ac/cder08.html#AntiInfective.
Based on these discussions and data available from clinical trials of antibacterial drugs, the types of skin infections that should be included in clinical trials to support an indication for treatment have been re-evaluated and are termed acute bacterial skin and skin structure infections. In addition, there are ongoing efforts in the scientific community to develop and evaluate new efficacy endpoints for ABSSSI that are assessed at an earlier time point than endpoints used in previously conducted trials. Important changes from the 1998 draft guidance that are based on these discussions have been incorporated into the appropriate sections below, including the definitions of ABSSSI and the proposed primary efficacy endpoints.

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Definitions of Acute Bacterial Skin and Skin Structure Infection

The definitions of the clinical disease entities are based on the types of infections commonly encountered in clinical trials of skin and skin structure infections. The definitions of ABSSSI apply to enrollment criteria for enrolling adults and adolescents in clinical trials and are intended to support an indication for the treatment of ABSSSI. Therefore, they may differ in some respects from the treatment guidelines or other clinical decision tools for consideration of antibacterial drug therapy. The definitions of ABSSSI for use in enrollment criteria for children will vary, depending on the total body surface area of the pediatric populations targeted for enrollment. The definitions are divided into two general categories: (1) ABSSSI for which a reliable estimate of a treatment effect of antibacterial drug therapy can be described and either noninferiority or superiority trial designs are recommended; and (2) milder skin infections for which a treatment effect of antibacterial drug therapy has not been characterized and superiority trial designs are recommended.

(1) ABSSSI for which a reliable estimate of a treatment effect of antibacterial drug therapy can be described and either noninferiority or superiority trial designs are recommended:

- **Cellulitis/erysipelas:** A diffuse skin infection characterized by spreading areas of redness, edema, and/or induration of a minimum surface area of 75 cm² (e.g., length of 15 cm and width of 5 cm), accompanied by lymph node enlargement or systemic symptoms such as fever greater than or equal to 38 degrees Celsius (or 100.4 degrees Fahrenheit)
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- **Wound infection:** An infection characterized by purulent drainage from a wound with surrounding redness, edema, and/or induration of a minimum surface area of 75 cm² (e.g., the shortest distance of redness, edema, and/or induration extending at least 5 cm from the peripheral margin of the wound), accompanied by lymph node enlargement or systemic symptoms such as fever greater than or equal to 38 degrees Celsius.

- **Major cutaneous abscess:** An infection characterized by a collection of pus within the dermis or deeper that is accompanied by redness, edema, and/or induration of a minimum surface area of 75 cm² (e.g., the shortest distance of redness, edema, and/or induration extending at least 5 cm from the peripheral margin of the abscess), accompanied by lymph node enlargement or systemic symptoms such as fever greater than or equal to 38 degrees Celsius.

- **Burn infection:** An infection characterized by purulent drainage, redness, edema, and/or induration of a minimum surface area of 75 cm² (e.g., the shortest distance of redness, edema, and/or induration extending at least 5 cm from the peripheral margin of the burn infection), accompanied by lymph node enlargement or systemic symptoms such as fever greater than or equal to 38 degrees Celsius.

The hallmark of these definitions is the minimum surface area of redness, edema, and/or induration (i.e., 75 cm² of cellulitis). The reason for this is as follows: (1) it provides a patient population for which the treatment effect of antibacterial drug therapy would be expected to be similar to the treatment effect observed in historical studies of cellulitis/erysipelas; and (2) it provides an extent of disease to clearly and objectively document the infection and to follow clinical improvement or deterioration. We recommend that the ABSSSI clinical trial population include patients with a mixture of the clinical disease entities defined above. Because surgical incision and drainage might influence treatment outcomes among patients with major cutaneous abscesses, we recommend that patients with major cutaneous abscesses should not comprise more than 30 percent of the clinical trial population (note that major cutaneous abscess includes patients with a minimum surface area of surrounding redness, edema, and/or induration of 75 cm²).

Patients with infections such as infections of animal or human bites, necrotizing fasciitis, diabetic foot infection, decubitus ulcer infection, myonecrosis, ecthyma gangrenosum, and catheter-site infections should not be enrolled in ABSSSI clinical trials. The treatment regimens for these infections are usually more complex than the treatment regimens provided in the context of an ABSSSI clinical trial. Sponsors who wish to develop a drug for one or more of these indications should consult with the FDA.

(2) Definitions for adults and children with milder skin infections for which a superiority trial design is recommended:

- **Minor cutaneous abscess:** An infection characterized by a collection of pus within the dermis or deeper that is accompanied by redness, edema, and/or induration of less...
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than 5 cm from the peripheral margin of the abscess for adults and adolescents and is not accompanied by systemic symptoms. The maximum size of the minor cutaneous abscess for enrollment criteria for children younger than approximately 13 years of age depends on the total body surface area of the child that is enrolled. The definition of minor cutaneous abscess for this pediatric population should be discussed with the FDA during protocol development.

- **Impetigo:** A distinct skin infection characterized by multiple, erythematous, yellowish, or crusted lesions on exposed surfaces of the body.

2. **Drug Development Population**

The intended clinical trial population should include adults and children with ABSSSI, or with the milder skin infections of minor cutaneous abscesses or impetigo. Sponsors are encouraged to discuss pediatric drug development with the FDA early in the course of clinical development, including the potential extrapolation of adult efficacy data, appropriate pharmacokinetic studies in pediatric patients to support the selection of a dose, the pre-approval safety database in children, and as appropriate when children are included in clinical trials the definitions of ABSSSI in the pediatric population (e.g., the minimum surface area of redness, edema, and/or induration for each pediatric population subgroup based on total body surface area).

3. **Efficacy Considerations**

The goal of ABSSSI clinical trials should be to demonstrate an effect of antibacterial drug therapy on the clinical course of ABSSSI caused by commonly implicated bacterial pathogens such as *S. aureus* or *S. pyogenes*. At least two adequate and well-controlled trials that establish safety and efficacy should be conducted for treatment of ABSSSI. Either noninferiority or superiority trials are recommended for the indication of treatment of ABSSSI disease entities of cellulitis/erysipelas, wound infection, major cutaneous abscess, or burn infection.

Previously conducted clinical studies were examined to evaluate the natural history of ABSSSI in the absence of antibacterial drug therapy and to estimate the effect of treatment of ABSSSI with an antibacterial drug. Two previously conducted published clinical studies were identified that included comparison of ultra-violet (UV) light therapy to therapy with a sulfonamide antibacterial drug. The endpoints used in these previously conducted clinical studies (e.g., resolution of fever and cessation of spread of the lesion) were assessed at a number of time points during the first several days of therapy, including at 48 to 72 hours after initiation of antibacterial drug therapy (see the Appendix for a discussion about the historical studies). Given that these studies were conducted a number of years ago and that recent trials in skin infections have used other endpoints assessed at other time points, we recommend that before conducting a phase 3 trial using the endpoint of cessation of spread of redness, edema, and/or induration and resolution of fever at 48 to 72 hours, sponsors should perform additional developmental work (e.g., in a phase 2 trial) to develop how this endpoint will be measured, and to evaluate its performance.

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7 See reference numbers 1 and 2 in the references section at the end of this guidance.
The developmental work for the endpoint should incorporate assessment of the accuracy and reliability of the proposed lesion size measurement method(s) to help identify the best measurement method(s) to minimize potential errors in lesion size measurement. Sponsors can consider daily measurements of lesion size for the first 3 days of treatment as well as lesion size at end-of-therapy and other follow-up visits to better characterize a primary endpoint based on cessation of the spread of the lesion and other secondary endpoints that evaluate lesion size(s). In addition, it also can be valuable to evaluate the inclusion and exclusion criteria. Information to establish methods for endpoint assessment and evaluating its performance in the population of interest (e.g., response rate for a particular endpoint) can be important in planning and conducting phase 3 trials (e.g., for sample size calculations).

At least two adequate and well-controlled superiority trials are recommended for the indication of treatment of impetigo or treatment of minor cutaneous abscesses.

B. Specific Efficacy Trial Considerations

1. Clinical Trial Designs, Populations, and Inclusion Criteria

Patients with cellulitis/erysipelas, wound infection, major cutaneous abscess, or burn infection as defined in this guidance can be enrolled in a noninferiority trial using an active control. A superiority clinical trial using an active control also can be conducted; placebo-controlled trials are not recommended.

The following are recommended inclusion criteria:

- Clinical documentation of cellulitis/erysipelas, wound infection, major cutaneous abscess, or burn infection
- Documentation of a minimum surface area of 75 cm² based on length and/or width of redness, edema, and/or induration as described in section III.A.1., Definitions of Acute Bacterial Skin and Skin Structure Infection
- Documented fever, defined as an oral or tympanic temperature greater than or equal to 38 degrees Celsius

We recommend that patients with impetigo or minor cutaneous abscesses be enrolled in a superiority trial using the test antibacterial drug versus placebo or an active control.

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8 We reviewed the baseline patient temperatures from selected databases of cSSSI trials and found the proportions of patients with documented temperature greater than or equal to 38 degrees Celsius at baseline varied between approximately 30 percent to approximately 90 percent of clinical trial patients. Although we recommend the documentation of fever as an inclusion criterion based on the historical data, sponsors can choose to put forth proposals seeking to justify inclusion criteria that would not include documentation of fever. Additional developmental work may help to further define methods for assessing fever as a baseline inclusion criterion.
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2. General Exclusion Criteria

Recommended general exclusion criteria for all trials include the following:

- Any recent use of antibacterial drug therapy in a clinical trial designed to show noninferiority. We recommend exclusion of patients who received systemic or topical antibacterial drugs within 14 days of enrollment (or within a longer period of time for prior use of an antibacterial drug with a long half-life). However, patients who received prior antibacterial drug therapy can be eligible for clinical trial entry in certain situations:
  - The clinic notes or photographs objectively document the clinical progression of ABSSSI (i.e., not by patient history alone)
  - Patients received a single dose of a short-acting antibacterial drug 3 or more days before clinical trial enrollment (e.g., administration of a single dose of an antibacterial drug for surgical prophylaxis)
  - Patients recently completed a treatment course with an antibacterial drug for an infection other than ABSSSI and the drug does not have antibacterial activity against bacterial pathogens that cause ABSSSI

- Patients with medical conditions that would alter the interpretation of a primary endpoint, such as patients with neutropenia or compromised immune function.
- Patients with suspected or confirmed osteomyelitis.
- Patients with suspected or confirmed septic arthritis.
- Patients with complex skin infections, such as diabetic foot infections. (Patients with diabetes and ABSSSI, for example cellulitis, can be enrolled into ABSSSI trials).
- Chronic use of an antipyretic drug (e.g., daily use of naproxen).

3. Clinical Microbiology Considerations

Because MRSA is an important pathogen in ABSSSI, a sponsor developing a drug for ABSSSI should assess activity against MRSA in nonclinical studies and in phase 1 and phase 2 clinical trials. The phase 3 clinical trials should include patients with MRSA.

An adequate clinical specimen for microbiologic evaluation should be obtained from all patients and sent to the laboratory for microscopic evaluation (e.g., Gram stain), culture, and in vitro antibacterial susceptibility testing performed on appropriate organisms isolated from the
specimen. Specimens should be processed according to recognized methods. If the specimen is kept at room temperature, the Gram stain should be performed and the specimen plated for culture within 2 hours from the collection time. Alternatively, these tests can be performed within 24 hours of collection if the specimen is stored at 2 to 8 degrees Celsius before processing. The specimen for microscopic evaluation (e.g., Gram stain) and culture should be collected before administration of antimicrobial therapy and can be obtained by any one of the following means:

- A punch biopsy or aspirate of the leading edge of redness for patients with cellulitis/erysipelas
- Biopsy, needle aspiration, or surgically obtained specimens of purulent material from an infected wound or burn (a swab is not recommended)
- Using sterile techniques that minimize potential isolation of normal skin flora, aspiration of purulent material from a cutaneous abscess

In ABSSSI trials that enroll patients with cellulitis/erysipelas, wound infection, major cutaneous abscess, or burn infection as described in this guidance, aerobic and anaerobic blood cultures at two separate sterile venipuncture sites are recommended before initiation of investigational drug therapy.

All isolates considered to be possible pathogens taken from patients enrolled in clinical trials should be saved in the event that additional testing of an isolate is needed (e.g., pulse field gel electrophoresis for strain identification). Sponsors conducting clinical trials outside the United States should characterize the pathogen and describe similarities and differences among isolates identified in the United States. For microbiological assessment, the investigator should collect the following information:

- The anatomic location of where the specimen was obtained.
- The specimen identification number.
- A description of how the sample was obtained, processed, and transported to the laboratory.

- Data from in vitro susceptibility testing of the isolates to both the investigational drug and other antibacterial drugs that may be used to treat ABSSSI caused by the pathogens targeted by the investigational drug. In vitro susceptibility testing should be performed by using standardized methods unless otherwise justified. Sponsors should describe the exact methodology used for susceptibility testing if a standardized method was not used.

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10 Standard methods for in vitro susceptibility testing are developed by organizations such as the Clinical and Laboratory Standards Institute, Wayne, PA.
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335 • Characterization of virulence factors associated with the bacterial pathogens (e.g.,
336 Panton-Valentine Leukocidin-positive isolates of \textit{S. aureus} or emm-types of \textit{S. pyogenes}).
339
340 The use of rapid diagnostic tests to determine the presence of the bacterial pathogens should be
discussed with the FDA before initiation of clinical trials.
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4. Randomization, Blinding, and Stratification

Patients should be randomized for receipt of the trial drug at enrollment. All trials should be
multicenter, well-controlled, and double-blind unless there is a compelling reason for single-
blind or open-label trials. If trials are single-blind or open-label, sponsors should discuss
potential biases with the FDA and how the biases will be addressed.
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5. Choice of Comparators

Noninferiority clinical trials for the evaluation of treatment of ABSSSI should include an FDA-
approved drug for cSSSI, ABSSSI, or an appropriate-related skin infection indication. In
addition, we recommend that the comparator drug also be one recommended for use based upon
current treatment guidelines. The dosages, regimens, and infusion rates in the labeling should be
used. Placebo or an antibacterial drug that is FDA-approved for the condition studied should be
used for clinical trials of patients with minor cutaneous abscess or impetigo designed for
superiority.

6. Prior Antibacterial Drug Therapy

In general, patients who have received prior effective antibacterial drug therapy for ABSSSI
should not be eligible for enrollment into a clinical trial. If there is clinical documentation that
the ABSSSI is progressing on the prior antibacterial drug therapy (i.e., persistent fever,
progression of redness, edema, and/or induration from cellulitis, increased amounts of pus from
the wound infection), a patient can be eligible for clinical trial enrollment. If the clinical trial
includes patients with ABSSSI who progress despite antibacterial drug therapy, we recommend
limiting the enrollment of these patients and the results should be evaluated in this subgroup to
assess any potential effects of the prior antibacterial drug therapy on efficacy outcomes.

7. Concurrent Antibacterial Drug Therapy

In general, concurrent antibacterial drugs should not be administered in the trial to evaluate the
efficacy of the test antibacterial drug versus the control. Certain patients with ABSSSI may
require broad spectrum antibacterial coverage that is beyond the antibacterial activity of the test
drug or control drug. To the extent possible, any additional antibacterial drug to provide a broad
spectrum antibacterial coverage should not have overlapping antibacterial activity with the test
drug.
Other infections can occur in patients being treated for ABSSSI, and enrollment in a trial should not preclude treatment of other infections. However, the use of other concurrent antibacterial drug therapy will confound efficacy results and should be considered a clinical failure in the primary analysis populations, unless there is documentation that the nontrial antibacterial drug does not demonstrate activity in the treatment of ABSSSI.

8. Adjunctive Therapy

Adjunctive therapy is often used in ABSSSI treatment, including the following:

- Daily dressing changes
- Use of topical solutions including nonspecific antimicrobial drugs such as povidone-iodine
- Debridement
- Hyperbaric oxygen treatments
- Surgical interventions planned at the initiation of treatment

Sponsors should specify which adjunctive therapies are to be permitted in the clinical trials. With proper blinding and randomization, both the investigational drug group and the active-control drug (or placebo) group should have comparable use of these adjunctive therapies. Sponsors should analyze the clinical outcomes stratified by the presence or absence of adjunctive therapies (e.g., daily debridement). We recommend that topical treatments with specific antibacterial activity should not be used as adjunctive therapy in ABSSSI clinical trials.

Many patients will take systemic antipyretic drugs for relief of clinical symptoms associated with fever (e.g., chills, warmth). For patients enrolled in clinical trials, oral or tympanic temperature should be recorded every 6 hours or 4 times per day during the first 3 days of therapy. If the temperature is greater than 38 degrees Celsius, the patient may take a short-acting antipyretic drug for relief of symptoms associated with fever. If the patient takes a short-acting antipyretic drug for each episode of fever and does not take an antipyretic drug in the absence of fever, consecutive temperature recordings of the resolution of fever would be attributable to the effect of the antibacterial drug. The resolution of fever would not be attributed to the antipyretic drug because, in the absence of fever, an antipyretic drug would not have been taken.

For example, if a patient takes one dose of acetaminophen for each temperature recording of greater than 38 degrees Celsius during the first 36 hours of therapy, and then has temperature recordings of less than 37.7 degrees Celsius during 48 to 72 hours and an antipyretic drug is not taken, the resolution of fever at 48 to 72 hours can be attributed solely to the effect of the antibacterial drug. With this approach of taking one dose of a short-acting antipyretic drug only in the event of a fever, consecutive temperature recordings of less than 37.7 degrees Celsius would not be influenced by antipyretic drugs. For relief of pain, analgesic drugs without antipyretic activity should be used. Alternatively, protocols should provide an algorithm for use of drugs for relief of pain that ensures the endpoint of resolution of fever is attributed solely to the effect of the antibacterial drug without the influence of an analgesic drug.
9. Efficacy Endpoints and Timing of Assessments

We recommend a responder variable for clinical outcome at 48 to 72 hours as the primary endpoint based on the timing of efficacy endpoints in the historical studies that were used to support a noninferiority margin (see the Appendix). As stated in section III.A.3., Efficacy Considerations, before initiating phase 3 clinical trials sponsors should develop a standardized method to assess this endpoint and evaluate its performance in phase 2 clinical trials. Some of the issues to be addressed in phase 2 clinical trials pertain to the lack of clarity regarding the clinical observations early in the course of treatment for ABSSSI. For example, because of the rapid spread of redness, edema, and/or induration in some patients at the time of presentation with ABSSSI, the lesion may continue to spread during a short period of time after administration of the first doses of antibacterial drug therapy. Because events that occur after randomization and may be influenced by trial drug have potential to bias treatment effects, comparison to the lesion documented at trial entry (baseline) is recommended. Phase 2 trials and phase 3 clinical trials should plan to follow patients for the duration of therapy and for a period of observation after completion of therapy.

Primary efficacy endpoint and timing of assessments for a noninferiority trial in ABSSSI

(clinical response or clinical failure at 48 to 72 hours):

- **Clinical response:** Cessation of the spread of the redness, edema, and/or induration of the lesion or reduction in the size (length, width, and area) of redness, edema, and/or induration at 48 to 72 hours after enrollment and resolution (absence) of fever (i.e., temperature less than 37.7 degrees Celsius at 3 consecutive recordings by the same methodology every 6 hours between 48 and 72 hours)

- **Clinical failure:** Death; continued fever (i.e., temperature greater than or equal to 37.7 degrees Celsius); increase in the size (length, width, and area) of redness, edema, and/or induration of the lesion; or administration of rescue antibacterial drug therapy or administration of nontrial antibacterial drug therapy for treatment of ABSSSI before the primary efficacy endpoint assessment

Secondary efficacy endpoints and timing of assessments for a noninferiority trial in ABSSSI:

Patients should be evaluated for continued clinical improvements and sustained clinical response for the duration of antibacterial drug therapy and for a period of observation after completion of antibacterial drug therapy. These evaluations for important secondary efficacy endpoints can be useful for the determination of overall evidence of efficacy. The clinical evaluation of patients and the timing of the secondary efficacy endpoints should be considered to ensure that clinical improvement can be objectively documented, recognizing that patients will still have signs or symptoms that may require additional time to completely resolve. The secondary outcome definitions and the timing of assessments are as follows:
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- **Clinical response:** Cessation of the spread of the lesion at 48 to 72 hours, and resolution of the infection at 10 days post-randomization and at additional follow-up visits following completion of therapy

- **Clinical failure:** Protocols should prospectively define clinical failures at 48 to 72 hours, at a fixed time point 10 to 14 days post-randomization, and at additional follow-up visits, and should include but may not be limited to the following:
  - Deaths (all-cause mortality) from the start of trial drug
  - Incision and drainage of the ABSSSI site that was not planned before randomization or specified in the protocol
  - Persistent purulent drainage (for a duration of at least 48 hours) from a wound infection at the same or greater intensity as enrollment
  - Initiation of rescue antibacterial drug treatment or initiation of nontrial antibacterial drugs for treatment of ABSSSI
  - Initiation of nontrial antibacterial drugs for treatment of any other infection unless there is documentation that the nontrial antibacterial drug does not demonstrate activity in the treatment of ABSSSI
  - Patients who otherwise do not meet the definition of clinical success

Patients designated as clinical failures for the primary efficacy endpoint at 48 to 72 hours yet overall show clinical signs of improvement (e.g., cessation of spread of the lesion and decrease in temperature from 39.2 degrees Celsius to 37.9 degrees Celsius) can remain on the assigned treatment and can be counted as a clinical response at the secondary efficacy endpoint at a fixed time point 10 to 14 days post-randomization. If patients are clinical responders at the primary endpoint assessment at 48 to 72 hours, and are then offered rescue therapy after this assessment (see section III.B.10.f., Rescue therapy), those patients should be counted as clinical failures at the secondary efficacy endpoint that evaluates sustained clinical response at the fixed 10- to 14-day time point after randomization.

Additional important secondary analyses should include absolute and percent change from baseline in the reduction of the lesion size (length, width, and area) at 48 to 72 hours and at the post-therapy visits. The following are additional considerations for the timing of secondary endpoints:

- **Visit (fixed time point 10 to 14 days post-randomization):** This visit should be the trial visit at trial day 10 to 14 post-randomization to evaluate clinical response or clinical failure as secondary efficacy endpoints. In general, the administration of antibacterial

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11 Sponsors should provide documentation of the surgical operative notes.
Follow-up post-therapy visits: These trial visits should evaluate the maintenance of clinical response after completion of therapy (e.g., trial days 21 to 28 post-randomization). Sponsors should use a prospective definition of clinical failures at follow-up visits, outlined above in Clinical failure. For drugs that have evidence of prolonged tissue levels, the sponsor should propose appropriate timing for follow-up visits after completion of therapy.

Note: These important secondary endpoints are intended to assess the robustness of the overall evidence and consistency of treatment effect. However, if sponsors intend to pursue efficacy claims based on a superiority hypothesis of these secondary endpoints, then the analysis should be prespecified that, control the family-wise type I error rate, and the findings replicated in at least two clinical trials. The analysis plan should be discussed with the FDA before trial initiation.

Patient-reported outcome measures in ABSSSI:

Use of a patient-reported outcome (PRO) instrument is advised when measuring aspects of disease (or its treatment) that are best measured from the patient perspective (e.g., pain intensity). A PRO measure designed to capture the important symptoms of ABSSSI can be considered a direct measure of treatment benefit and can be used in a superiority trial to support labeling claims. Development of a new instrument should begin well in advance of phase 3 clinical trials so that the instrument can be qualified as well-defined and reliable at the time it is incorporated into the phase 3 protocol. The use of a PRO measure may have limited utility as a primary efficacy endpoint in a noninferiority trial of ABSSSI because of the difficulty in estimating a treatment effect over placebo based on a PRO measure. The use of a PRO measure as a secondary or exploratory endpoint in phase 3 noninferiority trials may help to characterize its usefulness as an efficacy endpoint in future trials.12

Primary efficacy endpoint of clinical success for a superiority clinical trial in impetigo or minor cutaneous abscess:

We recommend a fixed time point at the completion of investigational drug therapy (see section III.B.10.c., End-of-therapy visit) for the objective assessment of clinical resolution of impetigo or minor cutaneous abscess.

10. Trial Procedures and Timing of Assessments

a. Entry visit

12 For more information, see the guidance for industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.
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At the entry visit, the following information at a minimum should be obtained and recorded on the case report form:

- History and physical examination
- Underlying medical conditions (e.g., diabetes mellitus) and drug allergies
- Previous medical or surgical therapies for the infection being studied
- Baseline signs and symptoms of ABSSSI (or impetigo or minor cutaneous abscess)
- Vital signs and record of temperature with method of measurement to be consistent among individuals throughout the trial (e.g., oral temperatures throughout the clinical trial)
- The extent of the infection (e.g., measurements of width and length) documented at or near the time of the first administration of clinical trial drug therapy
- Cause of the infection (e.g., traumatic wound, spontaneous abscess)
- Microbiological specimens obtained before administration of antibacterial drug therapy: adequate clinical specimens for Gram stain and culture; blood cultures (aerobic and anaerobic) from two separate venipuncture sites obtained using sterile procedures
- Laboratory tests: hematology, chemistry, and other tests as appropriate
- Concomitant medications
- Optional standardized photography of the ABSSSI site; can be helpful for subsequent review

b. On-therapy visits during 72 hours following enrollment

The evaluations during the first 72 hours are of critical importance for the assessment of the primary endpoint. Patients should have recordings of temperature at least 4 times per day (e.g., every 6 hours) for 72 hours, which can be recorded on case report forms for hospitalized patients or recorded on patient diary cards in an outpatient setting (ensuring that patients are dispensed a thermometer and are instructed on methods for obtaining an accurate temperature (e.g., sublingual placement of the oral thermometer, oral temperature should not be obtained while consuming hot beverages)). The areas of redness, edema, and/or induration should be evaluated and the measurements and observations documented on a case report form at least once per day for 72 hours. This can be accomplished in the hospital setting or with daily visits to a clinic for the first 72 hours.

The 72-hour assessment should address the following:
Contains Nonbinding Recommendations

Draft — Not for Implementation

- Review of adverse events
- Review of the recordings of oral or tympanic temperature taken every 6 hours (a consistent method of temperature measurement should be used in individual patients in the trial)
- Evaluation and measurements of the infection site (e.g., objective characterization of cessation of (or absolute and percent reduction in length, width, and area from baseline) the amount of redness, edema, and/or induration)
- Review of signs and symptoms of ABSSSI (or impetigo or minor cutaneous abscess)
- Administration of a PRO instrument (e.g., pain intensity by a validated pain scale), if used
- Completion of an abbreviated physical examination, as appropriate
- Performance of laboratory tests, as appropriate
- Review of concomitant medications including the use of analgesic or antipyretic drugs
- Record of planned and unplanned adjunctive therapies and operative notes
  
  c. End-of-therapy visit

The end-of-therapy visit at the completion of investigational drug therapy should be used to evaluate the primary endpoint in trials enrolling patients with impetigo or minor cutaneous abscess. An end-of-therapy visit also can be incorporated into clinical trials of ABSSSI to assess whether discontinuation of antibacterial drug therapy is appropriate.

  d. Visit at a fixed time point 10 to 14 days post-randomization

The post-therapy visit at a fixed time point 10 to 14 days post-randomization should be used to evaluate the secondary endpoint of clinical response or clinical failure. In general, this visit should correspond to the completion of therapy or within several days after completion of therapy and address the following:

- Review of adverse events
- Evaluation and objective measurements of the infection site and overall assessment as clinical response or failure
- Completion of physical examination including vital signs
- Performance of laboratory tests, as appropriate
- Review of concomitant medications
- Record of planned and unplanned adjunctive therapies
At the post-therapy visit, investigators should document findings from on-therapy office visits (e.g., history, physical examination, and laboratory test results) on the patient case report form. If the investigator contacted the patient by telephone or by another interactive technology, the investigator should capture on the case report form documentation of the specific questions asked, how they were asked, and the responses given by the patients. If a patient diary is used to capture patient symptoms during the trial, this information in the diary should also be collected at the post-therapy visit and recorded on the patient case report form.

e. Follow-up post-therapy visits

The evaluation of the maintenance of clinical response should occur at 1 or 2 weeks after completion of therapy (e.g., at trial day 21 to 28 post-randomization) and address the following:

- Review of medical history
- Review of adverse events
- Evaluation of the infection site and assessment as clinical response or failure
- Completion of physical examination
- Performance of laboratory tests, as appropriate
- Review of concomitant medications
- Record of planned and unplanned adjunctive therapies

It is important that all patients be followed for at least 28 days after enrollment to capture 28-day all-cause mortality data. If a follow-up post-therapy clinical trial visit for the evaluations as above is scheduled before the 28-day time point, the 28-day assessment can be performed by telephone contact or by another interactive technology in patients who were considered to be clinical successes and had no adverse events noted at or after the post-therapy visit. For patients with adverse events occurring at or after the post-therapy visit, investigators should perform an assessment that includes a medical history, physical examination, appropriate laboratory evaluations, and identification of any new adverse events. All adverse events should be followed until resolution.

f. Rescue therapy

It is important for investigators to distinguish patients who are worsening or not improving (i.e., where rescue antibacterial drug therapy is appropriate) from patients who are slow to improve but still may remain on assigned therapy and thereby achieve clinical success. As such, patients with ABSSSI who are characterized as clinical failures at the 48- to 72-hour primary endpoint assessment may not require rescue therapy if overall there appears to be slow clinical improvement on their assigned treatment. For patients who clearly and objectively are worsening or not improving and require rescue therapy, specimens for microbiological evaluation (see section III.B.3., Clinical Microbiology Considerations) should be obtained in these patients before initiation of the rescue antibacterial drug therapy. Patients who receive rescue antibacterial drug therapy should continue to have protocol-specified assessments identical to patients who continue to receive their originally assigned treatment.
11. **Statistical Considerations**

The trial hypothesis and the analysis methods should be stated in the protocol and/or the statistical analysis plan before initiation of the trial. The trial should be adequately powered to detect differences between treatment arms if differences exist. If sponsors choose to test multiple primary or secondary hypotheses, the statistical issues of the overall (family-wise) type 1 error rate and multiplicity should be discussed with the FDA during protocol development and should be incorporated into the statistical analysis plan.

a. Analysis populations

The definitions for the statistical analysis populations are provided as follows:

- Safety population — All patients who received at least one dose of drug during the trial.
- Intent-to-treat (ITT) population — All patients who were randomized.
- Microbiological intent-to-treat (MITT) population — All patients randomized to treatment assignment who have a baseline bacterial pathogen known to cause ABSSSI, impetigo, or minor cutaneous abscess. Patients should not be excluded from this population based upon events that occur post-randomization (e.g., lost to follow-up).
- Per-protocol or clinically evaluable population — Patients who meet the definition of ITT population and who follow important components of the trial as specified in the protocol.
- Microbiologically evaluable population — Patients who meet the definition of the MITT population and who follow important components of the trial as specified in the protocol.

For superiority trials, the ITT population should be considered the primary analysis population and the MITT should be considered a critical secondary analysis population. It is important to note that analyses of the per-protocol population and the microbiologically evaluable population are subgroup analyses because they exclude patients based on events that occur after randomization. However, consistency of the results should be evaluated on all populations.

For noninferiority trials, the ITT population should be considered the primary primary analysis population. The results based on a per-protocol population should closely correspond to the results based on the ITT population in a noninferiority trial, because missing information might result in biases toward a conclusion of noninferiority. For example, missing information counted as failures in an ITT population might bias the treatment groups to appear similar and the exclusion of patients after randomization in a per-protocol population might also bias the treatment groups to appear similar. There is no single way to deal with missing data and sponsors should make every attempt to limit loss of patients from the trial. There are several approaches to assess the robustness of the results based on missing observations and these methods should be specified in the protocol as additional analyses. Therefore, consistency of the results in all populations should be evaluated and any inconsistencies in the results of these analyses should be explored and explanations provided.
Based on the clinical trial population and the extent of antibacterial activity of the test drug and the control drug, there are other considerations for the analysis populations that sponsors may wish to discuss with the FDA. For example, an ABSSSI clinical trial population might include patients suspected of having either Gram-positive or Gram-negative pathogens, yet the test antibacterial drug being evaluated has activity against only Gram-positive pathogens and the protocol specifies that Gram-negative coverage may be added when Gram-negative infection is suspected or identified. Because the test antibacterial drug would not be expected to have activity against Gram-negative pathogens, analysis populations characterized by the type of infection (e.g., Gram-positive infections for an agent with Gram-positive activity) should be discussed with the FDA in advance of initiation of phase 3 clinical trials.

b. Noninferiority margins

Noninferiority trials are only appropriate and recommended if there is reliable and reproducible evidence of treatment effect for the comparator drug, based on historical studies for the proposed endpoint and patient population. Noninferiority trials may be appropriate when enrolling patients with cellulitis/erysipelas, wound infection, major cutaneous abscesses, or burn infections as described in this guidance for the indication of ABSSSI (see the Appendix). Based on the evaluations of patients during the first 72 hours of therapy (as described in section III.B.10.b., On-therapy visits during 72 hours following enrollment), the recommendation for primary efficacy endpoint in a noninferiority clinical trial is the cessation of spread of the lesion and resolution of fever at 48 to 72 hours after initiation of clinical trial therapy, although there are no recent data available for validating the sensitivity of this endpoint compared to the historical evidence of treatment effect. The noninferiority margin described in the Appendix applies to a clinical trial that enrolls patients with ABSSSI definitions and disease spectrums defined in this guidance (see section III.A.1., Definitions of Acute Bacterial Skin and Skin Structure Infection). Sponsors should justify the noninferiority margin for the proposed trial design and population enrolled and discuss the justification of the margin with the FDA during clinical development.

Superiority trials are recommended for the indications of the treatment of impetigo or minor cutaneous abscess.

c. Sample size

The appropriate sample size for a clinical trial should be based on the number of patients needed to answer the research question posed by the trial. The sample size is influenced by several factors including the prespecified type I and type II error rates, the expected success rate, and the noninferiority margin, or the amount by which an investigational drug is expected to be superior.

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13 See the draft guidance for industry Non-Inferiority Clinical Trials. 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 Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

14 Noninferiority clinical trial designs for skin and skin structure infections were discussed at the November 18, 2008, AIDAC meeting; the committee voted that the noninferiority trial design was not appropriate for specific uncomplicated skin infections including impetigo and minor cutaneous abscesses (see http://www.fda.gov/ohrms/dockets/ac/08/htm/AntiInfective).
(for a superiority trial). The appropriate sample size should be estimated using a two-sided type I error of 0.05 (\(\alpha=0.05\)) and adequate statistical power (e.g., 80 percent or more).

d. Missing data

There is no single optimal way to deal with missing data from clinical trials. Sponsors should make every attempt to limit loss of patients from the trial. The methods of how missing data will be analyzed should be specified in the protocol. Higher proportions of missing data will limit the interpretability of the results as discussed in section III.B.11.a., Analysis populations.

e. Secondary endpoints and other analyses of interest

Sponsors should evaluate the secondary endpoint of clinical response and clinical failure at the post-therapy visit at a fixed time point 10 to 14 days post-randomization in noninferiority ABSSSI clinical trials. The robustness of the secondary efficacy data should be evaluated by comparing any differences among the results of the primary efficacy analysis at 48 to 72 hours post-randomization, and any differences should be thoroughly explored and explanations provided. Sponsors can present other secondary analyses on other endpoints of interest such as:

- Outcomes at other time points on therapy or after completion of therapy
- Mortality endpoints
- Outcomes between patients with bacteremia versus patients without bacteremia
- Response based on patient demographic characteristics, such as age, geographic region, underlying medical conditions, and microbiological etiology
- Response based on baseline microbiological confirmation
- Time to complete resolution of signs and symptoms of ABSSSI
- Clinical failures and relapses after the post-therapy visit
- Clinical responses by subgroups of ABSSSI (e.g., responses in patients with wound infections)


Currently, there are no surrogate markers recommended by the FDA as substituting for clinical outcomes in ABSSSI trials that would meet the criteria for accelerated approval under subpart H. Sponsors who wish to propose a surrogate marker for a clinical outcome should discuss this with the FDA early in the drug development process.
Risk-benefit considerations should depend on the populations being studied and the safety profile of the drug being investigated. A noninferiority trial or superiority trial using an active-controlled comparator drug in patients with ABSSSI can provide useful risk-benefit information relative to an approved comparator drug.

Superiority trials are recommended for evaluation of drugs for treatment of impetigo or minor cutaneous abscess. Although there may be a small treatment effect attributable to antibacterial drugs, impetigo and minor cutaneous abscesses are often self-limited infectious diseases with nonantibacterial drug treatments (e.g., surgical incision and drainage for minor cutaneous abscesses). Complications from impetigo or minor cutaneous abscesses are rare, and there were no reports of serious complications among patients randomized to receive placebo in historical clinical studies of impetigo or minor cutaneous abscesses. Antibacterial drugs have adverse effects associated with their administration. Therefore, the overall risk to patients with impetigo or minor cutaneous abscess receiving placebo may be similar to the overall risk to patients receiving an antibacterial drug. Rescue antibacterial drugs can be administered (open-label) at the time a nonresponder or failure endpoint is assigned as a measure to mitigate risk to patients randomized to receive placebo. All trial designs should provide appropriate provisions for patient safety.

C. Other Considerations

1. Pharmacokinetic/Pharmacodynamic Considerations

The pharmacokinetic/pharmacodynamic (PK/PD) characteristics of the drug should be evaluated using in vitro models or animal models of infection if not previously performed. Before the initiation of clinical trials, sponsors should identify the PK/PD index best associated with antibacterial effect and the magnitude of the PK/PD index necessary to achieve the desired endpoint. The results from PK/PD assessments should be integrated with the findings from phase 1 PK assessments to help identify appropriate dosing regimens for evaluation in phase 2 and phase 3 clinical trials. We recommend a dose-response trial design as an option for early clinical trials (e.g., phase 2 clinical trials) to weigh the benefits and risks when selecting doses and ensure that suboptimal doses or excessive doses (beyond those that add to efficacy) are not used, offering some protection against unexpected and unrecognized dose-related toxicity.

Sponsors should consider a sparse sampling strategy from all patients in phase 2 and phase 3 clinical trials to allow for the estimation of drug exposure in each patient. Collection of PK data in phase 2 clinical trials can be used to explore the exposure-response relationship and to confirm that the proper dosing regimen is selected for further evaluation in phase 3 clinical trials. Collection of PK data in phase 3 clinical trials may help to explain potential questions regarding efficacy or safety that might arise from the clinical trials.

Noninferiority clinical trial designs for skin and skin structure infections were discussed at the November 18, 2008, AIDAC meeting; the committee voted that the noninferiority trial design was not appropriate for specific uncomplicated skin infections including impetigo and minor cutaneous abscesses (see http://www.fda.gov/ohrms/dockets/ac/cder08.html#AntInfective).
A retrospective exposure-response analysis based on the population PK model from patients in phase 3 clinical trials should be performed to assess the relationship between PK/PD indices and observed clinical and microbiologic outcomes. The relationship between drug exposure and clinically relevant adverse events should also be explored to identify potential risks with different dosing regimens (if applicable) and specific patient populations (e.g., patients with renal impairment).

2. **Dose Selection and Formulations**

The findings from nonclinical toxicology studies, animal models of infection, pharmacokinetics, pharmacodynamics, in vitro susceptibility profiles of target pathogens, safety and tolerability information from phase 1 trials, and safety and antibacterial activity information from phase 2 dose-ranging trials should be integrated for purposes of selection of appropriate doses to be evaluated in phase 3 clinical trials. Nonclinical data should document activity against commonly implicated pathogens for ABSSSI. An assessment of drug penetration at the site of action (e.g., skin blister or microdialysis studies) can be used as supportive evidence that the selected doses are likely to achieve drug concentrations sufficient to exert both an antimicrobial and clinical effect. If appropriate, we recommend microdialysis in patients with ABSSSI because it minimally alters the integrity of skin and allows differences in drug concentrations between healthy subjects and infected patients to be considered. In addition, the pharmacokinetics of the drug in specific populations (e.g., pediatric patients, geriatric patients, patients with renal or hepatic impairment) should be evaluated before initiation of phase 3 clinical trials to determine whether dose adjustments are necessary. This may prevent the exclusion of such patients from phase 3 clinical trials.

For drugs that only have an intravenous (IV) formulation available, we recommend that clinical trials be conducted with the IV formulation alone without a switch to an oral antibacterial drug to allow for proper assessment of both efficacy and safety of the test drug. Patients do not need to be hospitalized to be enrolled and can receive the IV formulation of the drug as an outpatient.

For drugs that have both an IV and oral formulation, a switch to the oral drug may be appropriate provided that pharmacokinetics of the oral formulation have been adequately evaluated to ensure comparable exposure and to determine an appropriate dosing regimen. Appropriate clinical response criteria that allow for IV to oral switch should be specified in the clinical trial protocol.

If practice patterns allow, hospitalized ABSSSI patients can be enrolled in oral antibacterial drug trials. Appropriate criteria that allow for treatment with an oral drug should be specified in the protocol.

3. **Other Clinical Microbiology Issues in Clinical Trials**

If sponsors want to include less commonly implicated bacterial pathogens in clinical trials for ABSSSI, such as *Staphylococcus haemolyticus*, *Streptococcus dysgalactiae*, *Streptococcus agalactiae*, *Streptococcus anginosus* group, *Enterococcus faecalis*, or Gram-negative bacteria,
they should provide data sufficient to substantiate the clinical relevance of the particular bacterial pathogen in ABSSSI.

4. Safety Considerations

The protocols should specify the methods to be used to obtain safety data during the course of the clinical trials. Both adverse event information and safety laboratory data should be collected during the trial. All patients should be evaluated for safety at the time of each trial visit or assessment, regardless of whether the test drug has been discontinued. All adverse events should be followed until resolution, even if time on clinical trial would otherwise have been completed.

A sufficient number of patients including those older than 65 years and pediatric patients should be evaluated at the exposure (dose and duration) proposed for use to draw appropriate conclusions regarding drug safety.

5. Labeling Considerations

The labeled indication should be based on the types of patients enrolled in the clinical trials.

- For clinical trials enrolling patients with ABSSSI as defined in this guidance, the labeled indication should be for the treatment of ABSSSI caused by specific bacteria identified in patients in the clinical trials. The clinical disease entities studied for ABSSSI among the patients enrolled in the clinical trials should be reflected in the CLINICAL STUDIES section of labeling. For example:

  “Drug X is indicated for the treatment of acute bacterial skin and skin structure infections due to....”

- For clinical trials in patients with impetigo or minor cutaneous abscesses, the labeled indication should reflect the clinical disease entities in labeling. For example:

  “Drug X is indicated for the treatment of impetigo due to....”
APPENDIX:
JUSTIFICATION FOR A NONINFERIORITY MARGIN FOR ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS

Background

Acute bacterial skin and skin structure infections are common and encompass a variety of disease presentations and severity. A clinical trial design using an active-comparator antibacterial drug is recommended for the clinical disease entities of ABSSSI as defined in this guidance (i.e., cellulitis/erysipelas, wound infection, major cutaneous abscess, and burn infection). One type of trial design using an active-comparator is the noninferiority clinical trial using a prespecified noninferiority margin. The first step sponsors should consider for a noninferiority trial design is determining the treatment effect of the active-comparator drug that can be reliably distinguished from placebo (M1). This step is supported by evidence from previously conducted trials using reliable efficacy endpoints. The results from previously conducted placebo-controlled trials, where the effect of a drug can be reliably distinguished from placebo, provide the strongest evidence for M1. When evaluating M1, the population in which the control drug was studied, the endpoint assessed, and the timing of assessment are critical factors in evaluating how the information on treatment effect derived from previously conducted trials might be applied in a future trial. This Appendix summarizes our efforts to identify a treatment effect of antibacterial drugs in the treatment of skin and skin structure infections.

A literature search was conducted to identify published articles that describe the effects of antibacterial drug treatment for skin infections. For the types of ABSSSI defined in this guidance (i.e., cellulitis/erysipelas, wound infection, major cutaneous abscess, and burn infection), there were no placebo-controlled trials in the historical literature. We identified two controlled studies that evaluated antibacterial drugs versus nonantibacterial treatments in patients with cellulitis/erysipelas. In addition, approximately 30 active-controlled or uncontrolled studies were available in the literature, but these studies did not help to identify a treatment effect over placebo. Finally, seven placebo-controlled studies of skin infections of a lesser severity (i.e., impetigo and minor cutaneous abscesses) were available in the literature.

Controlled studies in cellulitis/erysipelas

Two controlled studies were identified in the scientific literature that compared outcomes in patients with cellulitis/erysipelas treated with an antibacterial drug versus nonantibacterial drug therapy. Investigators at Ruchill Hospital in Glasgow, Scotland, conducted two controlled clinical studies of patients admitted to their hospital ward with erysipelas. During the 1930s, the use of UV light was a routine method employed in the hospital because previous studies

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16 See the draft guidances for industry Non-Inferiority Clinical Trials and Antibacterial Drug Products: Use of Noninferiority Studies to Support Approval. When final, these guidances will represent the FDA’s current thinking on these topics. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

17 See reference numbers 1 and 2 in the references section at the end of this guidance.
In the first study (Study 1), approximately 312 patients admitted from May 1936 to February 1937 received one of four open-label treatments for erysipelas:

- UV light
- Prontosil (a sulfonamide antibacterial drug that is metabolized to sulphanilamide)
- UV light plus Prontosil
- Scarlet fever antitoxin

In the second study (Study 2), approximately 270 patients admitted from February 1937 to August 1937 received one of two open-label treatments for erysipelas:

- UV light
- Sulphanilamide (a sulfonamide antibacterial drug)

The authors stated that the duration of these clinical observations would be compared among the different treatment groups.

In Study 1, UV light treatments were administered daily “when considered necessary.” Prontosil was administered “until the temperature became normal.” After completion of treatment when the clinical improvement was noted, patients did not receive any additional therapies beyond this point in time for Study 1. For Study 2, UV light treatments were administered daily “when considered necessary.” Patients did not receive any additional UV light therapy beyond the point in time when clinical improvement was noted, which was identical to Study 1. Sulphanilamide was administered at higher doses “until the temperature of the patient became normal.” In the sulphanilamide treatment group, this antibacterial drug was administered at a lower dose for the duration of hospitalization. Because the protocols appeared to be similar, including the prespecified clinical endpoints for both studies, we combined the relevant treatment groups into Table 1: the UV light and Prontosil treatment groups from Study 1 and both treatment groups...
from Study 2. The deaths that were observed in the studies were excluded from the efficacy analyses (the deaths by treatment arm are tabulated below).

<table>
<thead>
<tr>
<th>Table 1. Results of Studies 1 and 2 as Reported in the Articles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>UV light</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Deaths</td>
</tr>
<tr>
<td>“failed UV therapy”</td>
</tr>
<tr>
<td>N evaluable for cessation of spread of lesion</td>
</tr>
<tr>
<td>Cessation of spread of lesion at 48 hours</td>
</tr>
<tr>
<td>Cessation of spread of lesion at 72 hours</td>
</tr>
<tr>
<td>Cessation of spread of lesion at 96 hours</td>
</tr>
<tr>
<td>Did not have fever</td>
</tr>
<tr>
<td>N evaluable for resolution of fever</td>
</tr>
<tr>
<td>Resolution of fever at 48 hours</td>
</tr>
<tr>
<td>Resolution of fever at 72 hours</td>
</tr>
<tr>
<td>Resolution of fever at 96 hours</td>
</tr>
<tr>
<td>N that was not “toxic” at baseline</td>
</tr>
<tr>
<td>N evaluable for cessation of “toxemia” at 48 hours</td>
</tr>
<tr>
<td>Cessation of “toxemia” at 48 hours</td>
</tr>
<tr>
<td>Recurrence of erysipelas</td>
</tr>
<tr>
<td>Complications</td>
</tr>
<tr>
<td>Average duration of therapy</td>
</tr>
</tbody>
</table>

*Patients continued to receive sulphanilamide during entire hospitalization, which resulted in numerically lower rates of recurrence and complications for this treatment group.

The prespecified analysis plan was the comparison of the duration of the clinical findings noted in Table 1, and the articles provided the results at day 1 through day 5 of treatment. Although a specific time point was not prespecified as a primary analysis, the articles highlighted the results of the clinical observations at the 48-hour time point, which appeared to have the largest treatment difference. UV light therapy and antibacterial drug treatments were administered for an average of approximately 2 or 3 days. The administration of antibacterial drug therapy was not summarized by the duration of administration in Study 1. Rather, administration of drug therapy was summarized by the average cumulative dose (5 grams total), which can be inferred.
to be approximately 2 or 3 days of antibacterial drug therapy. For some of the study patients, the
48- or 72-hour assessment was an end-of-therapy assessment because UV light or antibacterial
therapy was discontinued during this time frame.

To estimate a treatment effect of an antibacterial drug over placebo, we evaluated the results of
the cessation of spread of the lesion and resolution of fever after 48 hours, 72 hours, and 96
hours of therapy, as depicted in Tables 2 and 3. The duration of toxemia, which was an estimate
of clinical well-being by clinician evaluation of signs and symptoms such as headache, insomnia,
vomiting, and prostration, among others, was not fully characterized and the articles noted that
“the precise duration of toxemia [sic] is difficult to assess clinically.” Therefore, we did not
include cessation of toxemia in an estimate of treatment effect, although as shown in Table 1 the
proportion of patients with cessation of toxemia at 48 hours in the antibacterial drug treatment
groups was numerically higher.

Table 2 summarizes the clinical outcomes and treatment differences at 48-hour, 72-hour, and 96-
hour time points among patients with erysipelas assigned to 1 of 2 treatment groups: a
sulfonamide antibacterial drug (Prontosil) or UV light therapy.\textsuperscript{18}

Table 3 summarizes the clinical outcomes at 48 hours, 72 hours, and 96 hours among patients
with erysipelas assigned to 2 treatment groups: a sulfonamide antibacterial drug
(sulphanilamide) or UV light therapy.\textsuperscript{19}

\textsuperscript{18} See reference number 1 in the references section at the end of this guidance.
\textsuperscript{19} See reference number 2 in the references section at the end of this guidance.
**Table 3. Clinical Assessment at 48-, 72-, and 96-Hour Time Points for Study 2**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cessation of spread of erysipelas at 48 hours</th>
<th>Resolution of fever at 48 hours</th>
<th>Cessation of spread of erysipelas at 72 hours</th>
<th>Resolution of fever at 72 hours</th>
<th>Cessation of spread of erysipelas at 96 hours</th>
<th>Resolution of fever at 96 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>UV light</td>
<td>89/122 (73.0%)</td>
<td>53/112 (47.3%)</td>
<td>101/122 (82.8%)</td>
<td>67/112 (59.8%)</td>
<td>115/122 (94.3%)</td>
<td>77/112 (68.8%)</td>
</tr>
<tr>
<td>Sulphanilamide</td>
<td>129/130 (99.2%)</td>
<td>94/125 (75.2%)</td>
<td>130/130 (100%)</td>
<td>113/125 (90.4%)</td>
<td>130/130 (100%)</td>
<td>122/125 (97.6%)</td>
</tr>
<tr>
<td>Treatment difference</td>
<td>26.3% (17.5%, 35.1%)</td>
<td>27.9% (15.1%, 40.7%)</td>
<td>17.2% (10.2%, 25.3%)</td>
<td>30.6% (19.2%, 41.2%)</td>
<td>5.7% (0.9%, 11.9%)</td>
<td>28.8% (19.2%, 38.6%)</td>
</tr>
</tbody>
</table>

The greatest treatment effect was noted at the 48-hour time point for both efficacy endpoints. A similar or even greater treatment effect was noted for resolution of fever at 72- and 96-hour time points. Because the 48-hour data for cessation of spread of lesion and resolution of fever represented the greatest treatment effects, we used these data to estimate a treatment effect on the clinical endpoints of cessation of spread of the lesion and resolution of fever. Figures 1 and 2 describe the DerSimonian and Laird random effects meta-analysis of the results of the 2 studies at each clinical endpoint at the 48-hour time point.

**Figure 1. Meta-Analysis for Cessation of Spread of Lesion at 48 Hours**

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Treatment difference and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment difference</td>
<td>Standard error</td>
</tr>
<tr>
<td>Prontosil</td>
<td>0.215</td>
<td>0.045</td>
</tr>
<tr>
<td>Sulphanilamide</td>
<td>0.263</td>
<td>0.041</td>
</tr>
<tr>
<td>Overall</td>
<td>0.241</td>
<td>0.030</td>
</tr>
</tbody>
</table>

-0.40 -0.20 0.00 0.20 0.40

Favors UV  Favors Antibacterial
### Figure 2. Meta-Analysis for Resolution of Fever at 48 Hours

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Treatment difference and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment difference</td>
<td>Standard error</td>
</tr>
<tr>
<td>Prontosil</td>
<td>0.278</td>
<td>0.069</td>
</tr>
<tr>
<td>Sulphanilamide</td>
<td>0.279</td>
<td>0.081</td>
</tr>
<tr>
<td>Overall</td>
<td>0.278</td>
<td>0.046</td>
</tr>
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The results of the two random effects meta-analyses in patients with erysipelas demonstrate that there is a statistically significant treatment difference for the clinical endpoints of cessation of the spread of cellulitis/erysipelas and resolution of fever at 48 hours with the use of sulfonamides compared to UV light. The evaluation of treatment differences in the meta-analyses and the associated lower bound of the 95 percent confidence intervals (CI) accounts for some of the uncertainties and associated variability of the estimate of the treatment differences shown in Figures 1 and 2.

We performed two additional analyses of the data presented in the two articles. Deaths and patients who failed UV therapy were excluded from the meta-analyses described in Figures 1 and 2. We included deaths and patients who failed UV therapy as treatment failures (i.e., did not have cessation of spread of the lesion and did not have resolution of fever) in DerSimonian and Laird random effects meta-analyses. We note that the articles do not describe when during the trial these deaths occurred. The treatment differences and 95 percent CI were similar to the results described in Figures 1 and 2. In addition, we used the results as reported in the publications to estimate the proportion of patients that achieved cessation of spread of the lesion and resolution of fever as a responder endpoint. We assumed a worst-case scenario where we estimated the greatest proportion that might have achieved a successful responder endpoint in the UV light groups and the least proportion in the antibacterial drug groups. For the responder endpoint of cessation of spread of lesion and resolution of fever, an estimate of the treatment difference was 26.4 percent with a lower bound of the two-sided 95 percent CI of 17.4 percent. On the basis of these historical data, early objective clinical assessments at 48 to 72 hours after enrollment appear to show the strongest statistically significant differences in the treatment effect of a sulfonamide antibacterial drug over UV light therapy.

The treatment effect of sulfonamides compared to UV light in cellulitis/erysipelas caused by *S. pyogenes* or *S. aureus* for the endpoints of cessation of spread of lesion and the resolution of fever at a 48-hour endpoint was estimated to be approximately 18 percent based on the lower bound of the two-sided 95 percent CI for the two meta-analyses. A conservative estimate of the treatment effect based on a responder endpoint of cessation of spread of lesion and resolution of fever at 48 hours was 17.4 percent (lower bound of the two-sided 95 percent CI). These data show a treatment difference of approximately 17 percent for a responder primary endpoint of cessation of spread of lesion and resolution of fever at a 48- to 72-hour time point. Given the uncertainties and limitations of this data, further discounting is recommended to arrive at an estimate of M1.
Other Pertinent Data From Historical Studies

Several historical studies compared the observed clinical outcomes among patients with cellulitis/erysipelas treated with UV light therapy as the comparator rather than other topical therapies.20 These studies showed that patients treated with UV light had better outcomes in terms of resolution of local signs and fever. For example, in one study the average time to resolution of symptoms of the infection was 4.5 days for 79 patients treated with UV light and 8.7 days for 151 patients treated with Magnesium sulfate and glycerin pack therapy.21 Therefore, the treatment effect of antibacterial drug therapy over placebo is likely to be greater than the estimate of the treatment effect based on a UV light control group.

There are historical studies that describe the outcomes of patients with skin infections before the widespread availability of antibacterial drug therapy. One article from Boston City Hospital summarized the outcomes of 122 cumulative cases of *S. aureus* bacteremia. The article did not provide detailed descriptions of the cases, but 12 cases appeared to have skin abscesses as the sole source of bacteremia, with each patient receiving surgical incision and drainage. Only eight patients survived.22 This article did not provide additional information for the determination of a treatment effect of antibacterial drug therapy over placebo, but demonstrates that morbidity (bacteremia) and mortality was observed in patients with skin abscesses caused by *S. aureus* before availability of antibacterial drug therapies.

Other than the two studies that compared a sulfonamide antibacterial drug to UV light therapy, none of the other studies supported a Historical Evidence of Sensitivity to Drug Effects (HESDE) on a clinical outcome measurement at an early time point after initiation of therapy.

Two studies provide some support for early on-therapy clinical evaluations for a primary endpoint in noninferiority studies of ABSSSI. For example, skin infections of the hand caused by *S. aureus* or *S. pyogenes* that involved underlying tendon-sheaths showed a mean time to resolution of fever at 3.7 days (standard deviation (SD) ± 2.6 days) for patients that received penicillin therapy and at 12.0 days (SD ± 8.8 days) for patients that did not receive penicillin therapy.23 Another study evaluated a primary endpoint of “days to no advancement of cellulitis” between patients receiving IV antibacterial drugs in a hospital or at home, and found that approximately 85 percent of all patients in the study had no advancement of cellulitis at a day 2 time point.24 A recent review examined a number of publications reporting results for patients with skin infections and also supported, in general, the treatment effect of an antibacterial drug in erysipelas and cellulitis.25

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20 See reference numbers 3-7 in the references section at the end of this guidance.
21 See reference number 5 in the references section at the end of this guidance.
22 See reference number 8 in the references section at the end of this guidance.
23 See reference number 9 in the references section at the end of this guidance.
24 See reference number 10 in the references section at the end of this guidance.
25 See reference number 11 in the references section at the end of this guidance.
The antibacterial drugs used in the Snodgrass papers were sulfonamides. It is reasonable to generalize the effect size of observed for the sulfonamides used in the Snodgrass studies to other antibacterial drugs approved for complicated skin and skin structure infections (or related indications for skin infections) that are also recommended for use in current treatment guidelines. It is reasonable to expect that other antibacterial drug therapies that are both FDA-approved and recommended in treatment guidelines would have at least the effect of a sulfonamide drug in the treatment of ABSSSI. The paper by Spellberg et al. provides some information regarding the observed effect of sulfonamides and penicillin suggesting that the effect of penicillin (during the era when penicillin resistance was not prevalent) was at least as great if not greater than sulfonamides.

A review of other historical studies of cellulitis/erysipelas and skin infections that would be characterized as ABSSSI did not provide additional information of sufficient quality to evaluate the HESDE at an on-therapy endpoint of 48 to 72 hours for a clinical outcome measurement. However, untreated skin infections can be severe, with associated morbidity (bacteremia) and mortality, and early on-therapy clinical evaluations of cessation of spread of cellulitis and resolution of fever as important components of a primary endpoint has some support from historical studies.

Other Studies of Skin and Soft Tissue Infections: Minor Cutaneous Abscess

Placebo-controlled studies that enrolled patients with cutaneous abscesses are available in the literature. Three studies that assessed antibacterial drug therapy versus placebo for the treatment of cutaneous abscesses (incision and drainage was allowed in both treatment groups) did not identify differences in successful outcomes between treatment groups. These studies included patients with varying sizes of the cutaneous abscess and did not characterize the size of the surrounding redness, erythema, and/or induration. In these studies that likely enrolled patients with minor cutaneous abscesses, surgical incision and drainage alone appears to result in high rates of successful outcomes regardless of the presence of systemic antibacterial drug therapy.

For example, the determination of clinical cure by resolution of signs and symptoms (e.g., resolution of purulent wound drainage and erythema) at a 1-week end-of-therapy assessment did not differ significantly between the treatment groups that received placebo versus an antibacterial drug; 90.5 percent versus 84.1 percent, respectively.

Placebo-controlled studies in patients with varying sizes of cutaneous abscesses that did not characterize the surrounding soft tissue involvement with redness, edema, and/or induration did not demonstrate a treatment effect of antibacterial drugs over placebo in studies where patients received incision and drainage. Minor cutaneous abscesses respond

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26 See reference numbers 1 and 2 in the references section at the end of this guidance.
27 See reference number 11 in the references section at the end of this guidance.
28 See reference numbers 12-14 in the references section at the end of this guidance.
29 See reference number 13 in the references section at the end of this guidance.
to surgical incision and drainage alone. Superiority clinical trials are recommended for clinical trials enrolling patients with minor cutaneous abscesses.

Active-Controlled Clinical Trials

The active-controlled noninferiority trials evaluated clinical responses at a point in time after the completion of therapy, a test-of-cure visit, as the primary efficacy endpoint. In general, clinical trials incorporated daily or early clinical assessments, but these results were not routinely reported or systematically examined from the active-controlled trials. Therefore, the active-controlled trials that were used to support approval of antibacterial drugs for treatment of complicated and uncomplicated skin and skin structure infections are not useful for inclusion in a HESDE in the treatment of ABSSI, based on a noninferiority clinical trial using an efficacy endpoint of 48 to 72 hours after initiation of therapy.

Summary and Selection of Noninferiority Margin for ABSSI

The overall data support the estimate of M1 to be approximately 12 percent for antibacterial drugs in the treatment of cellulitis/erysipelas for an endpoint of cessation of spread of the lesion and resolution of fever at 48 to 72 hours. We believe it is reasonable to generalize this treatment effect to patients with wound infection, major cutaneous abscess, or burn infection where there is a significant component of cellulitis (as defined in section III.A.1., Definitions of Acute Bacterial Skin and Skin Structure Infection) using an endpoint at 48 to 72 hours after clinical trial enrollment. This estimate of M1 has several limitations as described below:

- The HESDE for treatment of ABSSI was derived only from two studies
- The estimate of M1 was drawn from patients with cellulitis/erysipelas; there were no other studies of patients with other ABSSI skin infections, such as wound infections, burn infections, or major cutaneous abscesses with surrounding cellulitis that incorporated a placebo or a nonantibacterial drug therapy control group
- The endpoint that was used to estimate a treatment difference of approximately 17 percent was an endpoint at 48 hours of therapy for each clinical observation; the historical studies did not evaluate clinical success as a responder endpoint of both cessation of spread of the lesion and resolution of fever
- The treatment effect was less robust for cessation of spread of the lesion at 72 hours after initiation of therapy
- The treatments were open-label and randomization was not clearly described leading to the potential for bias
- Lack of clarity on how the measurements of lesion size were taken in the Snodgrass studies and the associated measurement error

The two studies used to support M1 have the following strengths:
The investigators prespecified the endpoints of objective daily clinical observations of cessation of spread of lesion and resolution of fever.

Analyses of the comparison of the duration in time to cessation of spread of lesion and time to resolution of fever were prespecified analyses.

The treatment differences for resolution of fever were similar between the 48-hour and 72-hour time points.

Patients received similar background treatment on admission to an “erysipelas ward” in the hospital.

Maintaining antibacterial drug therapy in Study 2 reduced the proportion of “recurrences” of erysipelas.

One of the UV light treatment groups may have had fewer patients that were severely ill thereby diminishing an antibacterial drug treatment effect. Twelve “severely ill” patients initially scheduled to receive UV light in Study 2 were removed from the study and received antibacterial drug. None of the 12 patients were expected to survive, but 9 survived and recovered.

UV light therapy appears to have a better treatment effect compared to other nonantibacterial drug therapies.

The treatment effect based on the analyses of the two endpoints appears to be similar to the treatment effect based on the analysis of the estimates of a responder endpoint, using conservative estimates of the proportion that achieved a successful responder endpoint of cessation of spread of the lesion and resolution of fever at 48 hours.

Given these strengths and limitations, the estimate of the treatment effect over placebo from the lower bound of the 95 percent CI of the treatment difference of approximately 17 percent provide a conservative estimate of the treatment effect. However, this treatment effect should be further discounted to account for the uncertainties listed above. We recommend discounting the treatment effect of 17 percent by approximately 30 percent to account for these uncertainties.

Thus, an M1 of approximately 12 percent for the endpoint of cessation of spread of the lesion and resolution of fever at 48 to 72 hours appears to be appropriate in the patient population with ABSSSI as defined in section III.A.1, Definitions of Acute Bacterial Skin and Skin Structure Infection. As noted above, if UV light therapy has a treatment effect over placebo, then the true treatment effect of a sulfonamide drug over placebo without UV light may be higher than 17 percent.

These scientific data provide support for an endpoint of cessation of lesion spread and resolution of fever at 48 to 72 hours (i.e., before the completion of drug therapy). From a clinical perspective, clinicians evaluate patients at earlier time points to assess the response to therapy and whether a change in clinical or antimicrobial management is necessary. Patients would be
expected to maintain clinical success during the remainder of administration of investigational drug therapy and after completion of investigational drug therapy; data on clinical outcome at later time points should be captured in the conduct of the clinical trial and reported as secondary efficacy endpoints. Because the clinical evaluations at the end of therapy inform clinicians about a decision to discontinue therapy, and recurrences were noted after a short duration of antibacterial drug therapy (Study 1), we recommend a fixed time point at 10 to 14 days post-randomization as the time of the evaluation of the secondary efficacy endpoint of clinical success or clinical failure.

The clinical studies that were reviewed in general did not offer concise definitions or provide minimum areas of involvement with skin infection. Observational studies of patients presenting with more severe skin infections suggested the potential for morbidity and mortality outcomes in the absence of antibacterial drug therapy. Studies of patients with cutaneous abscesses did not identify a treatment effect of antibacterial drug therapy, perhaps because of the enrollment of patients with smaller or minor cutaneous abscesses that respond readily to incision and drainage alone.

Prontosil or sulphanilamide was used in the clinical studies from which the treatment effect was derived. For future trials it is reasonable to generalize that antibacterial drugs that are FDA-approved for complicated skin and skin structure infections, ABSSSI, or other appropriate-related indications and that are recommended in current treatment guidelines would have at least the effect observed for the sulfonamides used in those clinical studies.

The bacterial pathogens *S. aureus* and *S. pyogenes* were the predominant bacterial pathogens isolated from patients in the historical studies and still represent the most common bacterial pathogens isolated in current studies of ABSSSI. With a sufficiently large area of skin structure or soft tissue involvement with infection that resembles cellulitis/erysipelas, the data that support a noninferiority margin for cellulitis/erysipelas can be extended to wound infections, burn infections, and major cutaneous abscesses. Therefore, precise definitions of skin infections that provide minimum areas of skin involvement are important. A minimum surface area of redness, edema, and/or induration of approximately 75 cm² as defined is recommended for ABSSSI as defined in section III.A.1., Definitions of Acute Bacterial Skin and Skin Structure Infection, for the following reasons: (1) it provides a patient population for which the treatment effect of antibacterial drug therapy would be expected to be similar to the treatment effect observed in historical studies of cellulitis/erysipelas; and (2) it provides an extent of disease to clearly and objectively document the infection and to follow clinical improvement or deterioration over time. When the trial is completed, the applicability of the HESDE to the actual population enrolled in the trial should be assessed.

An M1 of 12 percent is estimated for patients with ABSSSI as defined in this guidance using an endpoint of cessation of spread of the lesion and resolution of fever at 48 to 72 hours of therapy. A sufficiently conservative noninferiority margin (M2) should be selected to preserve the treatment effect that antibacterial drugs provide for ABSSSI.
REFERENCES FOR APPENDIX

8. Skinner, D and CS Keefer, 1941, Significance of Bacteremia Caused By Staphylococcus aureus, Archives of Internal Medicine, 68:851-875.
1372 Contains Nonbinding Recommendations
1373 Draft — Not for Implementation
1375 Abscesses Caused By Community-Acquired Methicillin-Resistant \textit{Staphylococcus aureus},