FDA Guidance for ABSSSI Trials: Implications for Conducting and Interpreting Clinical Trials

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Recent guidance from the US Food and Drug Administration (FDA) on the conduct of clinical trials for acute bacterial skin and skin structure infection (ABSSSI) has changed the framework for clinical trial design and conduct. Notable changes included new disease state definitions, new primary endpoint definitions and the timing of assessments at these endpoints, and updated guidance on patient inclusion/exclusion criteria. Supportive evidence and statistical justification for the proposed noninferiority margins were described in detail.

Although the updated guidelines are still considered drafts and have been adopted in some trials, they serve as the basis for study protocol discussions between pharmaceutical companies and the FDA in advancing the development of promising new agents. Not only will the new trial designs impact researchers and sponsors responsible for drug development programs, but they will also affect healthcare providers participating in clinical trials and the ways in which clinicians develop patient treatment plans based on the results of those trials. This review provides a summary of key changes that will impact future clinical trial design and outcomes.

In August 2010, the US Food and Drug Administration (FDA) issued its first revision of draft guidance for industry regarding development of drugs for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) [1]. The update affects nearly all areas of clinical trial conduct, from a new primary endpoint designation and timing of assessment to clarification of appropriate patient populations. The elements that are reasonably attributable to assessment of antibiotic effects are described, and confounding or secondary factors are eliminated [1]. Of note, the 2010 draft guidance remains in draft format, as certain areas still require additional investigation and work before finalization. Despite the “draft” nature of the current guidance document, its principles are being incorporated into ongoing and future clinical trial design for a number of novel antibiotics. This paper provides a summary of key points in the new guidance for ABSSSIs (Table 1), with insights into how these changes will impact the conduct of future clinical trials as well as the comparison of study results with those obtained using older study designs.

UPDATED GUIDANCE

Subject Population for Clinical Trials

Notable changes have been made in the definition of skin infection types and severity for consideration in ABSSSI trials, including new requirements for lesion size and severity. The new draft guidelines focus on acute bacterial infections and eliminate patients with chronic skin and skin structure infections. Previous guidelines distinguished uncomplicated (small abscesses, impetiginous lesions, furuncles, and cellulitis) from complicated skin and skin structure infections (infective cellulitis, wound infections, major abscesses, infected burns, skin ulcers, and diabetic foot ulcers) that involve deeper soft tissue, which might also require surgical intervention and/or are associated with underlying disease that complicates the management of the infection [2, 3]. Beyond these descriptive terms, there were no minimum lesion size criteria for enrollment, and patients with otherwise “uncomplicated wounds”...
Table 1. Summary of Key Points of New Guidance for Acute Bacterial Skin and Skin Structure Infection Trials

- Eligible patients
  - Patients with cellulitis/erysipelas, wound infections, major cutaneous abscesses, and burn infections
  - Lesions should have a minimum surface area of 75 cm²; for wound infections, major cutaneous abscesses, and burn infections, erythema and/or induration should extend ≥5 cm from the peripheral margin of the infection
  - Systemic signs of infection (e.g., fever) and/or proximal lymphadenopathy are required

- Exclusion of patients with diabetic foot infections
- Exclusion of patients receiving drugs with antipyretic properties
- Number of patients enrolled with abscesses should be ≤30% of the total study population
- Primary endpoint is cessation of spread of the primary lesion and resolution of fever 48–72 hours after enrollment
- Prior antibiotic therapy is only allowed
  - If there was objective clinical progression documented despite this therapy
  - As a single dose of short-acting antibiotics ≥3 days prior to enrollment
  - As treatment for an indication other than ABSSSI with antibiotics inactive against pathogens that are associated with ABSSSI

Adapted with permission from: Corey GR, Stryjewski ME. New rules for clinical trials of patients with acute bacterial skin and skin-structure infections: do not let the perfect be the enemy of the good. Clin Infect Dis 2011; 52(Suppl 7):S469–76.

Abbreviation: ABSSSI, acute bacterial skin and skin structure infection.

could be moved to the complicated category when infection location suggested increased risk of anaerobic or gram-negative pathogen involvement [3]. In addition, the previous FDA guidance did not differentiate between acute and chronic skin/skin structure infections.

In the new draft guidance, eligible ABSSSI subjects include those with erysipelas/cellulitis, wound infections, major cutaneous abscesses, or burn infections. The proportion of subjects with major cutaneous abscesses is limited to 30% or less of the total study population in order to minimize the potentially confounding impact of incision and drainage in assessing treatment effect [1]. The exclusion of chronic infections (e.g., diabetic foot infections and decubitus ulcer infections), human and animal bites, and necrotizing fasciitis avoids infections with microbiological heterogeneity and/or the need for a more complicated treatment regimen that could confound a direct assessment of early antimicrobial outcome [1]. The exclusion of chronic infections, systemic signs and symptoms may include leukocytosis, as well as increased serum c-reactive protein levels, procalcitonin levels, and erythrocyte sedimentation rates [2]. These new ABSSSI severity criteria not only identify infections that require systemic therapy for resolution but also set the stage for a better assessment of treatment effect. The new draft guidance identifies cessation of the spread of redness, edema, and/or induration of the lesion or the reduction in lesion size (length, width, and area) of redness, edema, and/or induration plus resolution (absence) of fever (i.e., temperature <37.7°C at 3 consecutive recordings using the same methodology every 6 hours between 48 and 72 hours) as the new objective criteria for clinical success [1]. The current FDA guidelines state that patients on agents with antipyretic properties cannot be enrolled in ABSSSI studies.

The second new element of note is the timing of this primary efficacy assessment, that is, at 48–72 hours after enrollment [1]. This is in stark contrast to the previous guidance, which recommended the test-of-cure visit to take place between 7 and 21 days after completion of therapy, depending on how long drug tissue levels are known to persist [3]. By utilizing an earlier endpoint in the new guidance, the clinical interpretation of a successful response is more focused on the impact of a treatment effect, while minimizing the confounding influence of the host immune response and natural lesion healing processes.
Evaluation of clinical response early in the course of therapy reflects a time point “... at which prior evidence had demonstrated reliable and reproducible drug effects” [4].

In setting the early response criteria, the FDA referred to historical evidence of a treatment difference between antimicrobial therapy with sulfa drugs and a placebo (ultraviolet light) over the first several days of therapy, from 2 studies published in 1937 (Table 2). In the FDA review, it was found that the magnitude of the difference in response between the treatments was approximately maximal at 48–72 hours after initiation of therapy. After that point, the difference between the 2 treatments rapidly waned over time. Of note, outcome measures in these early studies included whether “lesions continued to spread” and the “temperature became normal,” which the FDA has adopted into the new ABSSSI guidance.

The updated recommendations for an early endpoint are also supported by a recent review of the historical and modern literature [4]. The respective findings are particularly important when considering that the design of active-control noninferiority clinical trials, such as those used for the evaluation of novel ABSSSI therapies, requires a reliable assessment of the past performance of the active control [8]. This information is currently not available for the assessment of clinical response at the end of therapy or subsequent follow-up [9]. Finally, the rate of late failure in ABSSSI is low and a relatively short course of antibiotics “... can have a profound effect on patient outcome” [4], further underscoring the greater relevance of early response assessment.

For the same reason, the guideline also recommends exclusion of patients with prior systemic or topical antimicrobial treatment within 14 days of enrollment (except a single dose of a short-acting antibiotic 3 or more days prior to enrollment), unless prior treatment failure or inappropriate prior therapy can be objectively documented [1, 2]. The rational for excluding patients on prior antibiotic therapy is that such therapy within this time period can be expected to have a greater confounding effect on an early endpoint assessment of treatment response as opposed to later assessment, as was the case previously with skin and skin structure infections.

While early response may be the most suitable primary endpoint for comparing efficacy between different drugs, overall clinical response is the patient’s ultimate goal. Assessment of late response should therefore also be incorporated into trial design [5, 9] in order to provide important information on the sustainability of the therapeutic effect, which is more consistent with clinicians’ expectations [4]. To determine whether the early clinical response is sustained over time, the new guidance also recommends lesion size assessments at a fixed time point 10–14 days post randomization (ie, generally at the end of therapy) and at additional follow-up visits after completion of therapy (eg, 21–28 days post randomization) [1].

### Table 2. Results of 2 Historic Studies That Formed the Basis for Setting Clinical Response Margins

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<tbody>
<tr>
<td></td>
<td>Ultraviolet Light</td>
<td>Prontosil</td>
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<tr>
<td>At 48 h</td>
<td>75/98 (76.5%)</td>
<td>100/102 (98%)</td>
</tr>
<tr>
<td>At 72 h</td>
<td>86/98 (87.8%)</td>
<td>101/102 (99%)</td>
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<tr>
<td>At 96 h</td>
<td>91/98 (92.9%)</td>
<td>102/102 (100%)</td>
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<tr>
<td>Resolution of fever</td>
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<tr>
<td>At 48 h</td>
<td>43/89 (48.3%)</td>
<td>70/92 (76.1%)</td>
</tr>
<tr>
<td>At 72 h</td>
<td>55/89 (61.8%)</td>
<td>84/92 (91.3%)</td>
</tr>
<tr>
<td>At 96 h</td>
<td>66/89 (74.2%)</td>
<td>86/92 (93.5%)</td>
</tr>
<tr>
<td>Did not have fever</td>
<td>9</td>
<td>10</td>
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The greatest treatment effect for both efficacy endpoints was observed at 48 hours after initiation of therapy.


Abbreviation: CI, confidence interval.

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**Figure 1.** The relationship between confidence intervals, data margins, and the conclusions drawn from superiority, equivalence, and noninferiority trial designs. Adapted with permission from: Mascha EJ. Equivalence and noninferiority testing in anesthesiology research. Anesthesiology 2010; 113:779–81.
Statistical Considerations

When designing clinical trials and the corresponding data analysis plans, the hypothesis (or clinical question of interest) is set to determine whether a new treatment is superior, equivalent, or noninferior to another therapy [10, 11]. Trials are then designed to test the selected hypothesis using well-defined endpoint measurements, identification of an appropriately representative patient population, and an assessment of how the new therapy response compares with an accepted standard (i.e., either a placebo or another therapy). Since an infinite number of patients cannot be enrolled in clinical trials, an a priori margin (Δ) is established to judge the probability that a treatment is the same or different from the chosen accepted standard [11] (Figure 1).

Due to ethical and feasibility concerns, noninferiority trials are favored in the development of new antimicrobial drugs, where there is already an accepted standard of care [4]. Due to the relatively high efficacy of available antibiotics, even in the face of increasing resistance to older agents, superiority trials against an FDA-approved comparator are unlikely to enroll the large numbers of patients required to demonstrate significant differences. For the same reason, placebo-controlled superiority trials are not conducted in serious infections such as ABSSSI, where it would be unethical to expose patients to risk of high morbidity or even death when effective treatment alternatives exist. Noninferiority trials are often chosen when evaluating a new treatment that is expected to demonstrate acceptable efficacy in the primary outcome measure, with potentially fewer side effects, an easier dosing regimen, and/or improved quality of life than a comparator regimen [10]. The latter elements are not factored into the statistical analysis but may provide an informative and valuable alternative in clinical practice.

The focus of noninferiority analyses is on the lower margin (−Δ): if the lower limit of the confidence interval is higher than (i.e., further to the right of) the lower margin, the trial is deemed a “success.” What happens at the upper margin is not a primary concern in a noninferiority trial. The noninferiority margin itself depends on the effect size of antibiotics compared with placebo, termed “M1.” From M1, a conservative noninferiority margin (M2) can then be derived to preserve treatment effect. This M1 effect size for skin infections is substantial. Based on historical data, estimates as high as 14% for major abscesses, 29% for cellulitis/erysipelas, and 42% for infected wounds and ulcers have been suggested [12] but have not been widely accepted as useful noninferiority margins. Other authors have suggested that noninferiority margins <10% are not feasible [5]. In the current ABSSSI draft guidance, the FDA estimates M1 to be 12% for the endpoint of cessation of spread of the lesion and resolution of fever at 48–72 hours after start of therapy [1]. An M2 of 10% has been used as the noninferiority margin (−Δ) in several recent clinical trials in the setting of ABSSSI [13–15] and appears to be sufficiently conservative to preserve the 12% treatment effect that antibiotics provide for ABSSSI.

DISCUSSION

Compared with the previous 1998 FDA skin infection draft guidance, the new 2010 ABSSSI draft guidance proposes a number of significant changes in clinical trial design. The most prominent difference comes in the form of a new primary efficacy endpoint, assessing treatment response in a much more objective fashion at a much earlier time point after initiation of therapy. In its current form, the draft guidance recommends cessation of lesion spread plus absence of fever at 48–72 hours after enrollment.

While the selection of this endpoint was pragmatically based on the only relevant historical datasets available, it may also be more relevant and objective from a clinical standpoint. Response at a later time point is influenced by several nonpharmacological factors, including the positive impact of surgical intervention and host response, patient risk factors, and microbiology. Assessing response at 7–14 days after the end of therapy (corresponding to the primary endpoint recommended in the old FDA guidance) may thus have made it easier to demonstrate noninferiority [16]. A recent example is the pooled results from 2 identical phase 3 trials with ceftaroline, which demonstrated noninferiority over vancomycin/aztreonam for treatment of complicated skin and skin-structure infection using the traditional endpoint of test-of-cure at 8–15 days after end of therapy [13]. However, a post hoc analysis of the same data but limited to the subpopulation that met the new criteria for ABSSSI suggested a better response with ceftaroline than the comparator at day 3 of therapy [17]. This retrospective analysis was hampered by several limitations [16, 17] but underscores the importance of evaluating response early in the course of treatment and supports the use of an early over a late endpoint [13].

Early assessment of clinical response may seem premature to some, but this approach actually has significant therapeutic relevance [16] and reflects real-life clinical practice, where it is customary for a clinician to evaluate treatment response after 2–3 days of therapy and change the antibacterial regimen if rapid improvement is not observed. This approach is also reflected in the current Infectious Diseases Society of America treatment guidelines for the management of skin and soft-tissue infections, which recommend evaluation of clinical response after 24–48 hours [18]. Potentially better clinical utility aside, there also appears to be a very high concordance between clinical response at the early time point and response at the end of therapy. For instance, a recent, large phase 3 ABSSSI trial comparing tedizolid phosphate with linezolid showed
concordance rates between early (day 3) and late (7–14 days after end of therapy) response in excess of 80%. Of note, only about 2% of patients with an early response were deemed clinical failures at the post therapy follow-up [14]. These results confirm that the therapeutic effect seen early on is sustained until later time points.

The new guidelines also provide more stringent enrollment criteria [2], which will help limit variability within and across clinical trials and facilitate the more objective assessment of a measurable clinical response. Nevertheless, the development of stricter criteria is not without its own set of feasibility challenges. For instance, excluding patients with prior antibiotic therapy is likely more scientifically valid than permitting the enrollment of individuals with prior treatment shortly before start of a study drug. However, this approach creates challenges for conducting clinical trials, since otherwise eligible patients have often received prior treatment; excluding such patients can therefore unduly prolong the time to reach the required sample size. Similarly, assessment of an area of redness and induration is by itself a subjective process [4], and optimal measurement techniques need to be developed that address measurement across asymmetric skin lesions [19]. It is currently unclear how quantification of irregular wound dimensions and wound depth may impact outcome assessment, as most lesion-measurement methods to date have not been assessed in acute lesions but only in chronic skin lesions [2]. Furthermore, the size requirement has been critiqued by some as being too restrictive, as the necessary surface area may exceed the size of some body parts, such as hands and feet, particularly in children and smaller adults [5]. In these cases, the size of the lesion could potentially be judged proportionate to body region [5], and the current FDA guidance stipulates that the definitions of ABSSSI will vary for children according to total body surface area [1].

Another challenge is the recognition that the fever component may not apply to all patients, since systemic signs at the time of enrollment can include either fever or lymph node enlargement. Of note, most trial designs in this setting required at least 1 such sign to be present at enrollment, despite the lack of demonstrated association between these signs and both disease severity and clinical outcome [2]. Requiring fever at enrollment could even result in trial populations that do not reflect clinical reality since few patients in the United States are febrile when presenting for consultation [5]. For instance, a recent single-center study found that <15% of adult patients requiring hospitalization for skin and soft-tissue infections had fever at presentation [20]. For those relatively few patients with fever upon presentation, repeat temperature measurements can be difficult to obtain and are often inaccurate since there is no single definition of fever and there are many sources of error in the measurement of body temperature [2, 4]. In addition, the added burden on investigators of repeated temperature and lesion size measurements might result in a larger number of protocol deviations and investigator fatigue, with subsequent lack of interest in pursuing this type of research. Institutions and investigators will need to review their current protocols to ensure that systems are in place to accurately collect these new data. However, this guidance is evolving, and it is hoped that these issues will continue to be addressed by the FDA in order to provide increasingly optimal trial design and clinically applicable outcomes.

In the recently published ESTABLISH 1 trial for ABSSSI, for instance, the primary endpoint was cessation of lesion spread and absence of fever at 48–72 hours [14], as recommended in the current FDA guidance. After publication of the new guidance, the Foundation for the Institutes of Health (FNIH) recommended that the absence of fever not be a component of the primary outcome measure due to the reasons summarized above. In the recently completed ESTABLISH 2 trial, the primary endpoint was therefore restricted to a ≥20% reduction in lesion area at 48–72 hours—without consideration of body temperature [21]. The FNIH did recognize the clinical importance of fever resolution (and achieving stability of physiologic parameters in general) and therefore suggested that fever be included in a sensitivity analysis and/or be part of a subsequent evaluation. In line with this suggestion, primary response with and without temperature as part of the objective outcome measure was compared in the large patient populations of both ESTABLISH trials. These analyses confirmed that the response rates in both treatment arms were comparable with both approaches [14, 21, 22]. In keeping with the evolution of the ABSSSI endpoints, a planned integrated analysis of the 2 trials will utilize the primary endpoint of the ESTABLISH 2 trial.

In contrast to the current FDA recommendations to use objective lesion size measurements, the European Medicines Agency (EMA) still evaluates subjective investigator assessment of clinical response at 7–14 days after end of therapy as the primary endpoint in ABSSSI trials. A potential compromise between the early-response primary endpoint currently recommended in the FDA guidance and that required by both the older FDA guidance and the EMA could be to incorporate a requirement for early treatment success into an objectively determined, late test-of-cure assessment to indicate overall clinical response [5].

In summary, the FDA has advanced a new path for the development of drugs in the ABSSSI indication, and further refinements are still being explored. A motivation for this initiative has been an earnest desire to improve the science and quality of the studies that lead to drug approval. Requiring changes in lesion size as part of efficacy evaluation and the use of an early response assessment on the basis of historical data from the 1930s is still hotly debated [23]. Further improvement of primary endpoints and increased selectivity when enrolling appropriate patients will enhance the scientific and clinical
validity of such studies [9] but also will pose new challenges in the design and conduct of those trials. Although the draft guidance continues to evolve in terms of defining the exact parameters for clinical response [4, 9], it already requires changes in how ABSSSI clinical trials are designed, how investigators conduct these trials, and, importantly, how clinicians interpret the data and incorporate the results into the clinical management of patients. Beyond the US approval processes, the new guidance adopted by the FDA for ABSSSI becomes different from that currently stipulated by European regulatory agencies, and this lack of harmonization is a definite and costly challenge for sponsors seeking multinational approval of new antibiotics. Further revisions and refinements to this guidance, including the development of patient-reported outcome measures, are currently in progress and are expected to further facilitate the development of new antibiotics for ABSSSI [9].

Notes

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