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**SUBJ: The Infectious Diseases Society of America's Comments on Docket #FDA-2010-D-0433; Draft Guidance for Industry on Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment; 75 Federal Register 52755; August 27, 2010**

Dear Sir/Madam:

The enclosed comments on the above-referenced Food and Drug Administration (FDA) Draft Guidance concerning Acute Bacterial Skin and Skin Structure Infections (ABSSSI) are submitted by the Infectious Diseases Society of America (IDSA). IDSA represents more than 9300 infectious diseases physicians and scientists devoted to patient care, prevention, public health, education, and research in the area of infectious diseases. Our members care for patients of all ages with serious infections, including meningitis, pneumonia, tuberculosis and HIV/AIDS, antibiotic-resistant bacterial infections such as those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and gram-negative bacterial infections such as *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, and, finally, emerging infections such as the 2009 H1N1 influenza virus as well as bacteria containing the newly emerging New Delhi metallo-beta-lactamase (NDM-1) enzyme that makes bacteria resistant to a broad range of antibacterial drugs.

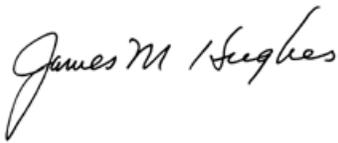
For the past decade, IDSA has raised concerns about the imbalance between the dwindling antibiotic pipeline and the significant and concomitant need for new, safe and effective antibacterial drugs to treat an increasing number of serious and life-threatening drug-resistant infections. In 2004, concluding that immediate government action was essential, IDSA published its report "Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates a Public Health Crisis Brews." The report examined all aspects of the government's response to the pipeline problem and focused significantly on the need for FDA to provide clear and workable written guidance to industry about how to design antibacterial clinical trials in a way that safe and efficacious drugs could achieve FDA approval. Now, six years later, the drug pipeline and resistance problems have only grown worse as more companies have withdrawn from antibiotic research and development and ever-more resistant "bad bugs" have spread across the United States in health care settings and communities, devastating the lives of the young and the old, the healthy and the frail. There is no doubt that the lack of clear and feasible FDA guidances has contributed in a significant way to the growing crisis.

To advance the development of clear and practical FDA guidance (for ABSSSI and other indications), over the past several years IDSA leaders have: a) expended significant time and energy considering trial designs, b) conducted extensive literature reviews, c) participated in FDA Anti-Infective Advisory Committee meetings and workshops, and d) participated in a recent effort sponsored by the Foundation for the National Institutes of Health (FNIH).

It is based on this significant expertise that IDSA raises serious concerns about the ABSSSI Draft Guidance, its conclusions, and its potentially negative impact on the availability of new, life-saving drugs for our patients should the Draft Guidance be finalized without extensive revision.

Specific areas of concern and recommendations for revisions are summarized below, first in an executive summary, with subsequent expansion of these points in greater detail.

Sincerely,

A handwritten signature in cursive script that reads "James M. Hughes". The signature is written in black ink and is positioned above the typed name.

James M. Hughes, MD, FIDSA  
IDSA President

Enclosures: Executive Summary and Expanded Comments

**Executive Summary**

1. The estimate of 12% absolute treatment effect (M1) of antibacterial therapy for ABSSSI is substantively lower than estimates derived from other available, credible historical and modern data.
2. IDSA is unable to accept “cessation of lesion spread” as defining success of therapy. Success requires evidence that the inflammatory response is resolving--not that the process has stabilized. Furthermore, the proposed endpoint lacks assay sensitivity. Given that drugs (prontosil rubrum & sulfanilamide) which are clearly inferior in efficacy to modern antibacterial therapy had a 99% success rate in the studies used by FDA to justify the “cessation of lesion spread” endpoint, that endpoint cannot distinguish less effective from more effective therapy.
3. Based on historical and modern data, IDSA proposes a 28-day (i.e., test-of-cure) composite primary efficacy endpoint that incorporates mortality and resolution of defined, objective signs and symptoms of infection.
4. If “cessation of lesion spread” is to be used as a primary efficacy endpoint despite the above concerns, it should be converted into a clinically meaningful endpoint, which can be done with only minor modification. It is true that if lesions continue to progress by day 3 (which is very rare with modern antibacterial therapy), the patient is failing therapy. Cessation of lesion spread is necessary, but not sufficient, to define clinical success of antibacterial therapy for ABSSSI. Therefore, IDSA suggests the definition of success for the primary efficacy endpoint include both: 1) no worsening by day 3 and 2) resolution of infection without relapse at test-of-cure. This design is achievable by using either a composite primary endpoint, a co-primary endpoint, or a hierarchical primary endpoint, for which both elements of the hierarchy are met for designation as a treatment success.
5. The Draft Guidance should specify the M2 margin, or a range of acceptable M2 non-inferiority (NI) margins, to provide clarity and uniform guidance to all sponsors, and minimize the risk of shifting goalposts. IDSA proposes that the M2 margin range between 10 and 15%. The sponsors of study drug should justify the margin, within that range, for each study by weighing the relative merits and limitations of the drug under consideration with those of licensed drugs (e.g., Is it active against extreme drug-resistant or pan-drug resistant pathogens? Does it have substantial safety advantages? Does it have a new mechanism of action?).
6. The need for international harmonization of endpoints for registrational studies deserves emphasis. A decision to abandon previously acceptable endpoints will immediately eliminate any harmonization between U.S. and European guidances, and thereby substantially negatively impact availability of antibacterial agents in the future.
7. An arbitrary lesion size (75 cm<sup>2</sup>) is not a validated index of disease severity. Sepsis criteria (Systemic Inflammatory Response Syndrome (SIRS) plus known or suspected infection) have

been extensively validated as markers of disease severity, and should be used as disease severity criteria for enrollment into ABSSSI studies.

8. Historical evidence of sensitivity to drug effect exists for antibacterial agents for the treatment of major abscesses and wound (surgical site and traumatic) infections. Sufficient disease severity for these infections can be objectively ensured by requiring the presence of 2/4 SIRS criteria. Therefore, such infections should be included in ABSSSI treatment trials if: a) surrounding cellulitis is present, as proposed in the current Draft Guidance; OR b) if  $\geq 2/4$  sepsis criteria are present, irrespective of the presence of surrounding cellulitis.
9. Because of its invasive nature and low yield, soft tissue biopsy culture of inflamed skin in patients with clinical cellulitis/erysipelas should not be required. If used by sponsors, a detailed description of the procedure is required for both patients (informed consent) and the clinical trial physician investigators.
10. Requiring temperature measurements every 4 hours is not necessary, and will not provide meaningful information beyond that which is achieved by the standard in-patient protocol of every 8 hours plus additional measurements whenever patients complain of fever or chills. Temperature measurements every 4 hours will only add to the cost and complexity of these studies, and will increase inappropriately the rate of “failures” since missing information will result in an indeterminate result and therefore a failure in an ITT analysis. Furthermore, IDSA suggests that FDA revisit its criterion for determining that a patient is afebrile and the requirement that that threshold must be reached for the patient to be considered a success at day 3.

FDA must balance the risks of approving possibly less effective therapy with the benefit of enabling feasible regulatory requirements that result in clinically relevant safety and efficacy data. IDSA is deeply concerned by the growing public health crisis engendered by the lack of new antibacterial development, converging with rising antibacterial resistance. IDSA believes it is possible to implement clinical trials that assess drug safety and efficacy in a clinically relevant and statistically valid manner. Extreme statistical conservatism must be balanced with physician and patient needs if the public health need is to be addressed.

## **Expanded Comments**

The following represents an expansion of the points made in the Executive Summary:

### **1) Estimate of the efficacy of antibacterial therapy.**

There are fundamental problems with the manner in which the estimate of a 12% absolute treatment effect of antibacterial therapy for ABSSSI has been calculated. That estimate is vastly lower than far more plausible estimates derived from other available historical and modern data.

Despite the existence of a large number of other studies addressing the issue (summarized below), the only data FDA has been willing to accept regarding the efficacy of antibacterial therapy for ABSSSI are the two studies published in 1937 by Snodgrass and Anderson, in which sulfonamide therapy was compared to UV lamp therapy.<sup>8-9</sup> The Snodgrass and Anderson studies are indeed important single components of an overall, global understanding of antibacterial efficacy for ABSSSI. However, the substantial methodological limitations of these studies do not support their use as a singular gold-standard for defining antibacterial efficacy. We acknowledge that all other data available are limited as well (see below); hence, all data available, including Snodgrass and Anderson, are limited in their quality. Rather than inappropriately elevating Snodgrass and Anderson to gold-standard status, a solution to the problem of suboptimal historical data is to consider all of the available data and to carefully balance the limitations of the data available with the public health need to enable new antibacterial agents to become available.

In the absence of randomization or true blinding, Snodgrass and Anderson was an alternation study which, while actively controlled, was still subject to multiple forms of unexplained bias, just as is the case for retrospective and single cohort descriptions. The background medical therapy and standard of care of medicine were different than in the modern era, just as is true for most other historical studies. For example, all patients in the Snodgrass and Anderson studies were put on a mandatory liquid diet, with a specified formula (including for example Horlick's malted milk, arrowroot, etc., while forbidding the intake of onions). As well, all patients received a mandatory liquid paraffin enema on admission which was repeated "when necessary." Thus, it is of dubious value to single out these studies as a gold-standard for establishing Historical Evidence of Sensitivity to Drug Effect (HESDE) for ABSSSI. These studies do not mirror the quality or relevance of a modern, randomized, double-blinded, controlled trial.

Based on IDSA's analyses, the Snodgrass & Anderson studies massively underestimate the absolute treatment effect of antibacterial antibiotics in a patient population with cellulitis for the following reasons:

1. Monotherapy with prontosil rubrum or sulfanilamide is far less efficacious than beta-lactam therapy. We summarized previously the difference in efficacy between sulfonamide monotherapy and parenteral penicillin therapy for skin infections based on a systematic review of historical literature between 1900-1950.<sup>10</sup> Penicillin resulted in a statistically significantly higher clinical cure rate for cellulitis relative to sulfonamide therapy [7% higher (95% confidence interval (CI): 4-10%)].<sup>10</sup> Penicillin also reduced mortality from erysipelas/cellulitis

2. by 5 to 10-fold vs. sulfonamides,<sup>10</sup> underscoring the marked superiority of beta-lactam therapy vs. sulfonamides.
3. The historical literature, across all serious infections, including cellulitis, abscess, wound infection, pneumonia, bacteremia, endocarditis, meningitis, and others demonstrates the marked superiority of penicillin as compared to sulfonamide therapy. The literature on this point is substantive and consistent.
4. With the availability of penicillin in the late 1940s, monotherapy with sulfonamides became less clinically relevant and ultimately became totally irrelevant in the 1960s with the availability of dihydrofolate reductase inhibitors, which are synergistic when used in combination with sulfonamide para-aminobenzoic acid (PABA) analogues. To base an estimate of antibacterial efficacy for any disease on drugs which have been irrelevant for more than 40 years is illogical and difficult to defend. The result is a gross under-estimation of the treatment effect of modern antibiotics.
5. The Snodgrass and Anderson studies did not compare sulfonamide therapy to placebo, but to ultraviolet (UV) lamp therapy. UV lamp therapy was an efficacious treatment relative to placebo, as acknowledged by FDA in the Draft Guidance. Indeed, IDSA's summary demonstrated that UV lamp therapy actually reduced mortality of cellulitis by an absolute 2.4% (95% CI 1.3-3.6%) relative to placebo.<sup>10</sup> Hence, FDA's analysis comparing sulfonamide therapy to UV lamp therapy is highly conservative when used as an estimate of antibacterial efficacy relative to placebo.
6. In addition, FDA applied the 95/95 method (i.e., comparing the lower bound of the 95% CI of the success rate with antibacterial therapy with the upper bound of the 95% CI of the success rate without antibacterial therapy), thereby calculating the smallest possible estimate of antibacterial efficacy. In another guidance, FDA acknowledged that the 95/95 method is intrinsically conservative.<sup>11</sup> Despite the intrinsically conservative nature of the 95/95 method and the other conservative factors mentioned above, the FDA Draft Guidance then applies an additional discount to the estimate of antibacterial efficacy for cellulitis. The concept of discounting has become popular at public meetings. However, IDSA is unable to locate any FDA or International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance which provides a rationale for, or a justification of, the application of a further discount on top of the conservative calculations resulting from the 95/95 method and other conservative calculation features, as delineated above. The ICH E9 guidance, the ICH E10 guidance<sup>12-13</sup> and the recent FDA guidance on the conduct of non-inferiority studies<sup>14</sup> do not discuss "discounting" non-inferiority margins in addition to setting an M2 margin which preserves a clinically meaningful fraction of M1. Discounting presents a façade of mathematical precision, but it results in an arbitrary, overly conservative mathematical calculation that provides no logical justification regarding first, how much to "discount" and second, how much of the discounted M1 estimate to "preserve" when setting M2.

7. Furthermore, the issue of how much of the treatment effect to “preserve” when setting M2 is not and never should be a statistical question; it is a clinical question. Qualified experts in clinical medicine, who care for patients and know the current challenges and needs for improving treatment, possess the expertise required to define how much of a potential decrease in treatment benefit can be justified as a trade-off against the critical need to develop new efficacious and safe drugs and have them available for clinical use.
8. IDSA has published a peer-reviewed estimate of the treatment effect size of beta-lactam antibacterial therapy for cellulitis based on an analysis of published studies between 1900 and 1950. The estimate of beta-lactam antibacterial efficacy for cellulitis is a 32% (95% CI 28-36%) absolute improvement in clinical cure versus placebo/no therapy.<sup>10</sup>
9. In a modern dose-escalation study of complicated skin and skin structure infection (cSSSI), patients receiving 2 doses of dalbavancin had an absolute 32% higher cure rate than patients receiving 1 dose of dalbavacin.<sup>15</sup> Because this study occurred in the modern era, background medical therapy was relevant to modern non-inferiority studies. We emphasize that the modern dataset provides a conservative estimate of antibacterial efficacy versus placebo because 1 dose of dalbavancin was almost certainly more efficacious than placebo would have been had it been concurrently studied. The ~32% estimate of antibiotic treatment benefit is virtually identical to the estimate of antibiotic treatment effect generated by IDSA based on historical data.
10. Finally, the severity of FDA’s underestimate of antibacterial efficacy is underscored by the magnitude of the survival benefit of antibacterial therapy versus placebo/no therapy for cellulitis. IDSA found that penicillin reduced the mortality of cellulitis by an absolute 11% (relative risk reduction of ~30-fold) versus placebo/no therapy.<sup>10</sup> The mortality analysis is robust and is based on data from more than 23,000 patients.<sup>10</sup> It is not logical to conclude that treatment which reduces mortality by 11% only results in a composite (clinical + mortality) benefit of 12% relative to placebo. In essence, this 12% estimate argues that effective antibiotics markedly reduce mortality but result in no clinical benefit at all aside from mortality (i.e., do not improve signs or symptoms of infection, but do markedly reduce death from infection). Such an estimate is not plausible.

## **2) Lack of Clinical Relevance of the Proposed Primary Efficacy Endpoint**

FDA proposes to use the endpoint from the Snodgrass and Anderson studies as the endpoint for modern non-inferiority clinical trials. The proposed endpoint is relevant to clinical failure of modern antibiotics, but is irrelevant as a definition of clinical success of modern antibiotics.

A simple example illustrates this concept. A patient with a skin infection presents to a physician and antibacterial therapy is initiated. The patient returns in 3 days with a lesion of the same size (i.e., not progressing). The patient is informed that he is a treatment success. Clearly that conclusion would not be justified; neither the patient nor the physician would accept such a conclusion. The expectation is continuous and progressive improvement resulting in elimination of the infection with no relapse after discontinuation of therapy. This is not a statistical issue. The

proposed efficacy endpoint lacks common sense. Cessation of progression of a skin infection is not acceptable as a definition of ultimate treatment success.

Another critical point is that the proposed endpoint lacks assay sensitivity (i.e., cannot distinguish more effective from less effective drugs). As FDA demonstrates in the Draft Guidance, in the Snodgrass and Anderson studies prontosil rubrum and sulfanilamide resulted in a 99% success rate of cessation of lesion spread and 91% rate of defervescence at day 3. As stated above, 1930s oral sulfonamide therapy was clearly significantly less effective than later beta-lactam therapy, and certainly is less effective than modern antibacterial therapy. Yet, despite the clear inferior efficacy of sulfonamides, they resulted in very high success rates using the proposed endpoint. Given such a high success rate (99%) of less effective therapy, it is not possible for the endpoint to distinguish more effective from less effective therapy. The endpoint intrinsically lacks assay sensitivity based on the very historical data used by FDA to justify the endpoint.

In the Draft Guidance, FDA proposes clinical response at the end of therapy as a secondary endpoint to ensure that the 3-day cessation of spread endpoint is clinically relevant. As we all know, secondary endpoints are hypothesis-generating rather than hypothesis-confirming as they are susceptible to the complexities of multiple comparisons. In the absence of correcting for multiple comparisons, a secondary endpoint cannot be used as a definition of treatment success. Indeed, primary endpoints are prospectively defined precisely because doing so eliminates the concern about multiple comparisons. FDA would unlikely accept cessation of lesion spread at day 3 as a secondary endpoint for this exact reason.

### **3) The need for a primary endpoint that reflects cure at test-of-cure (e.g., day 28)**

IDSA believes that a 28-day composite objective endpoint that incorporates mortality and resolution of objectively defined signs and symptoms of infection should be the primary efficacy endpoint for ABSSSI studies. As mentioned, IDSA's estimate of antibacterial efficacy for cellulitis using this endpoint is a 32% (95% CI 28-36%) absolute improvement versus placebo/no therapy.<sup>10</sup> IDSA chose this endpoint because a 28-day endpoint is consistent with a Test-of-Cure endpoint occurring 1-2 weeks after End-of-Therapy in modern studies,<sup>16-18</sup> and because 28-day follow up was available in many of the historical studies reviewed. IDSA used an objective, auditable definition of clinical response (defined in reference 6), and cited all the studies used in performing its analysis to facilitate reproduction and re-analysis by the agency. IDSA is willing to make the raw database available to FDA for re-analysis. The estimate of antibacterial efficacy in treatment of cellulitis is based on data from more than 4000 patients in historical datasets. Furthermore, as mentioned, the estimate based on historical studies is remarkably similar to the estimate from a modern dose-escalation dataset of cSSSI, in which patients receiving 2 doses of dalbavancin had a 32% higher cure rate than patients receiving 1 dose of dalbavacin.<sup>15</sup>

### **4) Facile modification of the proposed endpoint into a clinically relevant endpoint**

If FDA wishes to use the day 3 cessation of lesion spread endpoint despite its lack of assay sensitivity, one simple solution is to convert the proposed 3 day endpoint into a clinically meaningful endpoint. It is true that if lesions continue to progress by day 3 (which is very rare with modern antibacterial therapy), the patient is failing therapy. Cessation of lesion spread is

necessary but not sufficient to define clinical success of antibacterial therapy for ABSSSI. Therefore, IDSA suggests that to be defined as a success for the primary efficacy endpoint, patients have to experience both: 1) no worsening of lesion spread by day 3 and 2) resolution of infection without relapse at test-of-cure. This design is achievable by using either a composite primary endpoint, a co-primary endpoint, or a hierarchical primary endpoint, for which both elements of the hierarchy must be met for success to be achieved.

During the FNIH discussions, FDA expressed concern that inclusion of clinical response in a composite primary efficacy analysis would disrupt justification of the non-inferiority margin based on historical data of the cessation of lesion spread endpoint. This concern is easily mitigated. First, as described above, a far greater historical dataset is available than just the Snodgrass and Anderson studies, and the historical data do support a substantial antibacterial effect for resolution of ABSSSI at day 28 after presentation (timing of test-of-cure).<sup>10</sup> Second, the only way the composite endpoint of cessation of lesion spread plus clinical resolution at test-of-cure would have a smaller estimate of HESDE than cessation of lesion spread alone would be if antibacterial therapy worsened clinical cure rates versus placebo after improving cessation of lesion spread at day 3 versus placebo. Even if antibacterial therapy was of no benefit relative to placebo for mediating clinical cure, as long as it was of no harm, the absolute difference in efficacy of the composite endpoint between antibiotics and placebo would be the same as the absolute difference in efficacy for cessation of lesion spread. It is simply not plausible that antibiotics would improve cessation of lesion spread by day 3 relative to placebo but result in worse clinical cure rates thereafter relative to placebo. Therefore, if the composite endpoint requires success in both elements (cessation of lesion spread and clinical cure at test-of-cure), the absolute effect size of antibacterial therapy can be safely assumed to be at least as big (on an absolute basis) for the composite endpoint as for cessation of lesion spread.

Finally, a hierarchical endpoint obviates the concern completely, since each endpoint is separately considered, and the success at test-of-cure would not even be analyzed for patients who failed cessation of lesion spread at day 3 of therapy. However, if this solution is to be undertaken, the margin of non-inferiority for cessation of lesion spread at day 3 should be 10%, and no smaller, and the margin for clinical response at test-of-cure should be 10-15% depending on the relative merits of the experimental drug to other therapy, as delineated below.

### **5) Defining M2 for ABSSSI**

The FDA Draft Guidance does not define the M2 for trials of ABSSSI, but instead indicates that sponsors should justify the M2 for each individual study. As a result of an unacceptably low estimate of M1, the FDA Draft Guidance caps M2 at 12%. Realistically, this creates a precedent which could ultimately lead to an M2 requirement of approximately 6% (half of 12%) in the future. A 6% M2 for skin infections is unacceptably and unnecessarily low, and will likely prevent sponsors from conducting new pivotal studies of antibiotics for ABSSSI. We understand that at least one sponsor thus far has been told that a 10% M2 margin is acceptable for a planned phase III protocol. Nevertheless, we are not aware of a precedent in which FDA allowed the M2 to be as large as 83% of the M1. To avoid the potential for shifting goalposts in the future, and to ensure that sponsors receive consistent guidance, we believe that a specific M2, or a specific range

of appropriate M2s, should be listed in the Draft Guidance. Furthermore, we believe that an M2 margin of less than 10% is not appropriate for this indication, based on the substantial size of M1 and the clinical need for new drugs, as discussed above.

Ultimately, in the face of the limitations of the available historical literature, no scientific study is going to satisfy the desire to have an absolute, precisely defined estimate of the efficacy of antibacterial therapy for ABSSSI. Only large, randomized, double-blinded placebo-controlled trials in the modern era can possibly provide the degree of scientific rigor required to definitively answer this question, and those trials will never be conducted. Hence, this is not a scientific issue. Rather, the issue that must be addressed to benefit public health is how best to balance the equally concerning problems of the need to ensure approved drugs are safe and efficacious, and the need to facilitate the critical development of new antibacterial agents. The Draft Guidance fails, in our opinion, to balance these concerns, and remains solely focused on setting a non-inferiority margin that is far too low.

IDSA has previously proposed non-inferiority margins of 10-15% depending on the specific subset of disease types included in the pivotal studies for ABSSSI.<sup>10</sup> IDSA reiterates that margins of this range are appropriate for ABSSSI. In the face of substantial and robust evidence of a very large M1 (i.e., 30% for cellulitis), no statistical or mathematical model can rationally be applied to select the M2. All such statistical and mathematical methods will be arbitrary. Rather, IDSA suggests that the appropriate method to select M2 should be to weigh the relative merits of the drug under consideration. Regulators and physicians, as experts in public health needs, should be willing to accept a small increase in statistical imprecision regarding treatment effect size in return for facilitating development of critically needed new drugs. For example, a margin of 10% would be appropriate for a drug with few advantages over drugs already available. A margin of 15% would be appropriate for a drug with substantial advantages over other drugs on the market (e.g., activity against extreme drug resistant or pan-drug resistant bacteria that cannot be treated by any other drugs on the market, and/or substantial safety advantages).

One possible means by which sponsors can make margin selection more objective is to use numerical criteria based on these factors. As an illustrative example:

Clinically/Microbiologically Relevant Issues	Points
<b>Availability of other classes of antimicrobials</b>	
None	3
One	2
Two	1
Three or more	0
<b>Safety of compound at effective dosage</b>	
Substantially more safe	2
More safe	1
As safe as standard therapy	0
<b>Class of compound</b>	
New	3
Substantial Improvement of existing class	2
Improvement in existing class	1
No identifiable improvement in existing class	0

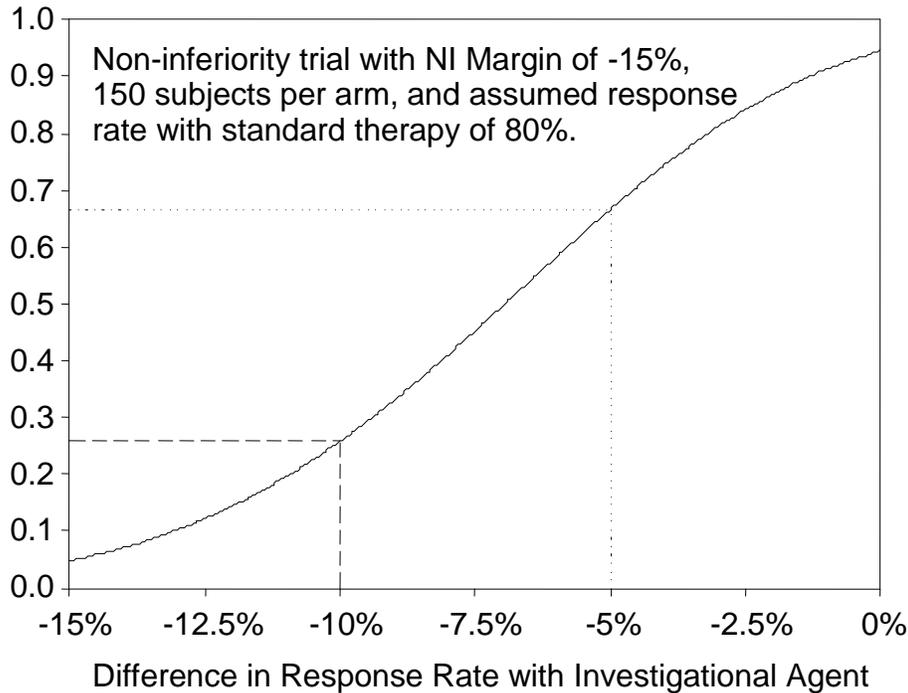
Higher numerical scores (e.g.,  $\geq 5$ ) indicate a margin of closer to 15%, middle scores (e.g., 3-4) indicate a 12.5% margin, and lower scores ( $\leq 2$ ) indicate a margin of 10% is appropriate.

One concern about non-inferiority margins of 10-15% is that such a margin means that society is willing to use, and FDA will approve, drugs that are 10-15% less efficacious than comparator drugs. However, use of a 15% absolute non-inferiority margin in a pivotal phase III clinical trial does not mean that the agency is likely to approve a drug that is 15% worse than the comparator drug. Rather, the key to understanding the implications of a 15% non-inferiority margin, in terms of the likelihood of regulatory approval of a substantially inferior antibacterial agent, is to examine the power curve for such a trial (Figure 1). In the example shown, the trial is designed to have a power of 95% to demonstrate non-inferiority with a margin of 15%, an  $\alpha$  of 0.05, and a treatment success rate of 80% with the comparator drug. The power is defined for the alternative hypothesis that the two drugs are exactly equivalent in efficacy. Although the pre-planned non-inferiority margin is -15%, the actual probabilities that non-inferiority will be established if the true effect of the new agent is -15%, -10%, or -5% relative to the comparator drug is 5%, 26%, or 67%, respectively. Hence, it is highly unlikely that an experimental drug which is 15% less efficacious than the comparator drug would result in a positive trial result.

Furthermore, FDA typically requires that two, independent non-inferiority trials be conducted to support approval of a new drug for a particular indication. If the true effect of the new agent is -15%, -10%, or -5% relative to the comparator drug, the probability of obtaining two positive non-inferiority trials is 0.25%, 6.7%, or 44%, respectively. Thus, with a margin of -15%, the new agent has only a 1 in 400 chance to achieve non-inferiority in two trials if its true efficacy is indeed 15% worse than the comparator drug. The new agent must have an effect better than -5% relative to the comparator drug to even have a 40% chance of yielding two successful trials to support regulatory approval.

Why take any chance that the approved drug could be inferior in efficacy to the comparator drug? As the non-inferiority margin shrinks, the required study sample size—and hence study cost and required time to complete enrollment—markedly increases. If new antibacterial agents are critically needed, we must balance the feasibility of conducting studies against a desire to reduce the chances of approving a truly inferior agent by narrowing the non-inferiority margin. While patients may be harmed if inefficacious drugs are allowed to reach the market, they also may be harmed if they have an infection for which no efficacious antibacterial agents have been developed. Furthermore, if the criteria for study conduct are so strict that it is infeasible to enroll meaningful numbers of patients in the United States, or the trial results are not generalizable post-approval, we risk that the observed safety and efficacy of the drug in its pivotal studies will not be informative regarding the safety and efficacy of the drug for patients in the U.S. The key is to create a regulatory pathway that balances these competing risks.

Probability of Establishing Non-inferiority as a Function of the True Response Rate of the Investigational Agent



**Figure 1. The power curve for a clinical trial with a non-inferiority margin of -15%, an  $\alpha$  of 0.05, and an expected 80% success rate in the comparator arm.** The power curve for a trial shows the probability of a positive trial (demonstrating non-inferiority) as a function of the true difference in efficacy between the treatment arms. In the example shown, the trial has a power of 95%, or a probability of 0.95, for demonstrating non-inferiority of the experimental drug if both the experimental and comparator drugs yield a success rate of 80% (a difference of 0%). The probability of a positive trial (i.e., establishing non-inferiority) is graphed on the vertical axis against the true difference in success rate between the experimental and comparator drugs (i.e., experimental drug success rate – comparator drug success rate) on the horizontal axis. For example, if the experimental drug is associated with an absolute difference of -5% relative to the comparator drug, the trial has a 67% chance of achieving a positive outcome (i.e., establishing non-inferiority). If the experimental drug is associated with a -10% difference, the trial has only a 26% chance of achieving a positive outcome. Finally, if the experimental drug is associated with a -15% absolute difference in outcome relative to the comparator drug, the trial has only a 5% chance of achieving a positive outcome.

In summary, when considering the design of a clinical trial, sponsors should justify the non-inferiority margin (M2) by providing an analysis of the potential benefits of the experimental drug relative to other drugs on the market. Sponsors and regulatory agencies should avoid arbitrary and unjustified statistical discounting of the already conservative estimates of historical effect size, and should avoid arbitrarily selecting the fraction of the discounted clinical benefit to “preserve” the non-inferiority margin (M2). Rather, sponsors and regulatory agencies should select the margin for an individual study based upon an assessment of the relative merits of the specific candidate drug and key features of the proposed study design; clinical, not statistical, reasoning is the relevant methodology. Factors include relative advantages of the experimental drug versus drugs already on the market (e.g., antibacterial spectrum of activity, novel mechanism of action, safety, dosing), and the inclusion of specific disease subtypes for which HESDE is greater or smaller than for cellulitis (see below).

#### **6) The Need for International Harmonization**

An additional major concern is the potential for placing FDA requirements in sharp juxtaposition to those of the European Medicines Agency and other foreign regulatory agencies. Infectious diseases know no geographical boundaries and the development of safe and efficacious antibacterial agents is a global public health need. Thus international harmonization of regulatory requirements is critical to the development of new therapies. This apparently unilateral decision by FDA to abandon previously acceptable endpoints is a huge step backwards in this regard. Requiring pharmaceutical sponsors to conduct separate clinical development programs for the U.S. and elsewhere will be costly, time-consuming, and expose many more patients to experimental drugs than would otherwise occur.

#### **7) How to define severe infection**

FDA proposes to use a cellulitic area of 75 cm<sup>2</sup> to ensure that patients are sufficiently ill to derive meaningful benefit from antibacterial therapy. IDSA agrees with the concept of enrolling substantially ill patients. Unfortunately, the choice of 75 cm<sup>2</sup> area of cellulitis is arbitrary and not based on science, and there are no data to indicate that it is either sensitive or specific for identifying substantially ill patients. Rather than choosing an arbitrary, unvalidated lesion size to ensure severe or complicated cellulitis, a scientifically validated method would be to require that patients enrolled in ABSSSI studies meet sepsis criteria. Sepsis criteria are among the most thoroughly validated disease severity criteria in all of medicine. Seminal studies by Roger Bone in the 1980s validated sepsis criteria (i.e.,  $\geq 2$  of 4 SIRS criteria + known or suspected infection) in tens of thousands of patients.<sup>19</sup> These criteria unequivocally distinguish patients with a step-increase in risk of mortality compared to patients without these criteria. Not only are these criteria validated to define severe infection, they are far more flexible than requiring an arbitrary lesion size or just requiring fever. Elderly, immunocompromised, and hemodialysis patients, and patients taking antipyretics all may be severely ill in the absence of a fever. Sepsis enables such patients to be captured as long as 2 of the 4 SIRS criteria are met. IDSA strongly recommends that sepsis criteria be used to define enrollment criteria in ABSSSI studies in lieu of requiring any specific size of cellulitis.

**8) Major abscesses and wound infections should be enrolled in ABSSSI irrespective of accompanying cellulitis**

The FDA Draft Guidance only acknowledges the Snodgrass and Anderson studies of erysipelas/cellulitis as establishing HESDE. Hence, patients with a major abscess or wound infection who do not have 5 cm of surrounding cellulitis would be excluded from enrollment in ABSSSI studies. IDSA believes this is a mistake and should be reconsidered.

IDSA believes major abscesses and wound infections should be enrolled in ABSSSI studies because: 1) there is substantial HESDE of the value of antibacterial therapy for the treatment of both wounds and major abscesses;<sup>10</sup> 2) physicians commonly encounter these infections,<sup>20,21</sup> and, for the sake of public health, must know which drugs are efficacious in treating them. Excluding these disease subsets from ABSSSI studies will put physicians in the unacceptable position of not knowing how to treat these infections, and will therefore put patients with these infections at unacceptable risk, particularly with rising rates of antibiotic-resistant organisms causing both abscesses and wound infections for which available therapy is inefficacious; and 3) in clinical practice<sup>21</sup> and in previous cSSSI clinical trials, cellulitis comprises one third or less of enrolled patients. Exclusion of 2/3 of eligible patients will functionally result in far more difficult to conduct studies. When added to smaller non-inferiority margins, these studies could become so difficult to conduct as to close ABSSSI off as a viable indication.

IDSA has summarized HESDE for both infected wounds and major abscesses.<sup>10</sup> While there are limitations to the historical datasets, just as for cellulitis, the effect size for wound infections was certainly greater than for cellulitis. Pre-penicillin, wounds that did heal typically took many months to do so, and wounds often ended up resulting in amputation or functional loss. Again, these studies are cited in the relevant IDSA publication,<sup>10</sup> and the objective criteria used to define clinical failure at day 28 are auditable. Before concluding that the data are invalid or unavailable, FDA should audit the data and reproduce the analyses.

There continues to be great confusion in the literature and in public meetings regarding the efficacy of antibacterial therapy for complicated or major abscesses. The definition of a complicated abscess has never been definitively established. Based on our recommendation above, we define a complicated abscess (which should be included in ABSSSI studies) as an abscess with the presence of  $\geq 2/4$  SIRS criteria (i.e., an abscess in a patient who meets sepsis criteria). For emphasis, patients with evidence of a systemic inflammatory response are at increased risk of complications: e.g., bacteremia, relapse, need for hospitalization. A simple incision and drainage is inadequate.

If we use a definition that includes evidence of a systemic host response, **there are no prior placebo-controlled trials of treatment of complicated abscesses.** All published placebo controlled trials of the treatment of abscesses included only patients without fever or other evidence of systemic inflammatory response. These lesions are uncomplicated, by previous terminology, and are therefore not relevant to enrollment in a study of antibiotic treatment effect for cSSSI.

**Furthermore, almost all studies of uncomplicated abscesses have been highly underpowered. Yet most have still shown trends to measurable benefit of adjunctive antibacterial therapy in addition to incision and drainage (Table 2).** IDSA members have recently summarized these data.<sup>22</sup> The review of previously published studies suggests that there may be a 5-10% excess failure rate when an active antibiotic is withheld after incision and drainage of an uncomplicated abscess (Table 2). The 95% CI for outcomes in previous underpowered studies all included differences of this magnitude. Meta-analysis of the reviewed studies is not likely to elucidate the issue given the mixture of observational and randomized trials, the discordant types of antibiotics and doses used, and the clear heterogeneity of results. Rather, we hope that the two ongoing National Institute of Allergy and Infectious Diseases (NIAID)-funded placebo-controlled trials of **uncomplicated** abscesses [NCT00730028 & NCT00729937] will finally clarify the issue by providing an adequately powered comparison of an active antibacterial agent vs. placebo for **uncomplicated** abscess. Until such time as adequately powered studies are available, we urge caution in interpreting available data, and recommend against concluding that adjunctive antibacterial therapy is of no benefit in the treatment of incised and drained, **uncomplicated** abscesses.

**Furthermore, we reiterate that these studies did not evaluate patients with systemic illness (i.e., complicated abscess). Patients with complicated abscess had substantial clinical benefit from antibacterial therapy, independent of surgical therapy, in historical literature.**<sup>10</sup> Patients with complicated abscess in the pre-antibiotic era often progressed to bacteremia, which caused substantial morbidity and mortality. Indeed, we found a 6% mortality of patients with complicated abscess treated without antibiotics in the historical datasets. No mortality was detected in similar patients treated with antibiotics. The relevance of the historical data is supported by a recent study published in *Clinical Infectious Diseases*, which reported that 10% of patients with a skin abscess presenting to the hospital for care were bacteremic.<sup>21</sup> With antibacterial therapy, none of those patients died. Such patients unquestionably benefit from antibacterial therapy.

The Draft Guidance indicates that wounds and abscesses can be evaluable for ABSSSI treatment studies if the lesions are surrounded by cellulitis. However, another means to include patients with abscess and wound infection in a study of ABSSSI is to require that these infections occur in the presence of sepsis criteria, just as for cellulitis. Use of sepsis criteria will enable a sufficient ill population to be enrolled to ensure that antibacterial therapy is required, and to enable constancy with the historical datasets demonstrating HESDE for these infections. Therefore, patients with infected wounds and abscesses should be enrolled in and considered evaluable for primary efficacy analysis in ABSSSI trials if: a) there is sufficient surrounding cellulitis, per the Draft Guidance; OR b) if the patient meets sepsis criteria, irrespective of surrounding cellulitis.

**Table 2. Studies Comparing Active Antibacterial Therapy vs. Inactive Therapy/Placebo for Uncomplicated Cutaneous Abscesses**

1 <sup>st</sup> Author / Yr	Results	Difference (95% CI*)	P value
Randomized Controlled Trials			
Schmitz 2010 <sup>1</sup>	<ul style="list-style-type: none"> <li>• <u>Treatment failure</u>: 15/88 (17% TMP-SMX) vs. 27/102 (26% placebo)</li> <li>• <u>Recurrence</u>: 4/46 (9% TMP-SMX) vs. 14/50 (28% placebo)</li> </ul>	<ul style="list-style-type: none"> <li>• 9% (-2.2, 21.1)</li> <li>• 19% (4.4, 34.2)</li> </ul>	<ul style="list-style-type: none"> <li>• 0.1</li> <li>• 0.02</li> </ul>
Duong 2009 <sup>2</sup>	<ul style="list-style-type: none"> <li>• <u>Treatment failure</u>: 3/73 (4% TMP-SMX) vs. 4/76 (5% placebo)</li> <li>• <u>Recurrence</u>: 9/70 (13% TMP-SMX) vs. 19/72 (26% placebo)</li> </ul>	<ul style="list-style-type: none"> <li>• 1% (-7.0, 9.3)</li> <li>• 13% (-0.7, 27.8)</li> </ul>	<ul style="list-style-type: none"> <li>• 0.5</li> <li>• 0.04</li> </ul>
Llera 1985 <sup>3</sup>	<ul style="list-style-type: none"> <li>• <u>Treatment failure</u>: 1/27 (3.7% cephadrine) vs. 1/23 (4.3% placebo)</li> </ul>	<ul style="list-style-type: none"> <li>• 0.6% (-14.4, 15.6)</li> </ul>	<ul style="list-style-type: none"> <li>• 0.9</li> </ul>
Macfie 1977 <sup>†4</sup>	<ul style="list-style-type: none"> <li>• <u>Recurrence</u>: 0/57 (0% clindamycin) vs. 3/41 (7% placebo)</li> </ul>	<ul style="list-style-type: none"> <li>• 7% (-2.8, 17.4)</li> </ul>	<ul style="list-style-type: none"> <li>• 0.07</li> </ul>
Observational Studies			
Ruhe 2007 <sup>5</sup>	<ul style="list-style-type: none"> <li>• <u>Treatment failure</u>: 16/312 (5% active antibiotics) vs. 29/219 (13% discordant antibiotics)</li> </ul>	<ul style="list-style-type: none"> <li>• 8% (2.6, 13.6)</li> </ul>	<ul style="list-style-type: none"> <li>• 0.001</li> </ul>
Paydar 2006 <sup>‡6</sup>	<ul style="list-style-type: none"> <li>• <u>Treatment failure (intention to treat)</u>: 2/178 (1% active antibiotics) vs. 22/263 (8% discordant antibiotics)<sup>‡</sup></li> </ul>	<ul style="list-style-type: none"> <li>• 7% (3.8, 11.4)</li> </ul>	<ul style="list-style-type: none"> <li>• 0.001</li> </ul>
Lee 2004 <sup>7</sup>	<ul style="list-style-type: none"> <li>• <u>Treatment failure</u>: 0/26 (0% active antibiotics)<sup>ϕ</sup> vs. 4/37 (11% discordant antibiotics)</li> </ul>	<ul style="list-style-type: none"> <li>• 11% (-2.5, 24.1)</li> </ul>	<ul style="list-style-type: none"> <li>• 0.1</li> </ul>

TMP-SMX = trimethoprim-sulfamethoxazole

\* The 95% CI in the study by Schmitz et al is reported as it was in the manuscript, without continuity correction; all other CI's in this table were re-calculated with continuity correction.

<sup>†</sup>2 study arms in which abscess cavities were sutured shut are not included; clindamycin given at very low dose (150 mg po q6 h)

<sup>‡</sup>When patients lost to follow up were excluded, failure rates were 2/166 (antibiotics) vs. 1/242 (no antibiotics), but the “failure” in the no antibiotic arm was subsequent development of necrotizing fasciitis requiring leg amputation

<sup>ϕ</sup>Includes 5 patients who were treated initially with an active antibiotic and 21 patients who initially received a discordant antibiotic but who were switched to an active antibiotic after culture results became available.

**9) Soft tissue cultures for patients with cellulitis should not be required**

Blood cultures and cultures of abscesses and wounds are informative and relevant. Cultures of cellulitic skin, obtained by invasive means such as leading edge cultures or punch biopsies, are not necessary, have a poor yield, and are of no clinical relevance.<sup>23-26</sup> They also may subject patients to unnecessary pain and risk of injury. These cultures should not be required in FDA guidance. Although sponsors may wish to pursue such sampling to improve microbiological recovery, the risks and benefits of the procedure should be explicitly described in the informed consent document.

**10) Requiring temperature measurements every 4 hours is not necessary**

Standard nursing procedure is to check temperature once per shift (i.e. once per 8 hours) and again whenever a patient has signs or symptoms consistent with fever (e.g., complaints of feeling feverish or having the chills, or an appearance of sweating, flushing, or rigors). Deviation from standard nursing protocol will substantially add to the cost and logistical complexity of conducting these studies, and the information gained will be negligible and not worth the problems it causes. Requiring fever measurements every 4 hours, 24 hours per day for 3 days for inpatients will require substantial study coordinator resources, since nursing staff will not do this. Furthermore, requiring fever measurements every 4 hours will increase inappropriately the rate of “failures” since missing information will result in an indeterminate result and, therefore, be analyzed as failure in an intent-to-treat (ITT) population analysis. Further, this increases chances of bias toward the null and could lead to a false conclusion of noninferiority.

FDA acknowledges in its Draft Guidance that the use of short-acting drugs with antipyretic effect does not meaningfully inhibit ability to measure fever as an element of response to therapy. Because anti-pyretics are short-acting and not dosed on a fixed schedule but rather upon patient request, the return of fever subsequently confirms that the patient is not cured. The absence of return of fever confirms that the patient is responding to therapy. Whether the analysis of return of fever or absence of return of fever occurs in 4 hours or 8 hours (once per shift) is irrelevant. The fever either will return or it will not. Furthermore, when fever returns, patients typically notify the nurse that they are feeling febrile and would like another dose of anti-pyretic, resulting in a temperature measurement by the nurse at the time. In this case, the temperature is recorded irrespective of how many hours have elapsed since the previous measurement.

For example, if a patient’s fever returns only once between hours 5 and 7, and resolves before hour 8 and never occurs again, AND the fever is so clinically insignificant as to fail to result in the patient notifying the nurse that he/she feels feverish, that is not a relevant event. If the fever returns at hour 5 and either persists until or recurs again after hour 8, or if the fever occurs only between hours 5 and 7 but results in the patient informing the nurse that he/she felt feverish, the event will be captured.

Therefore, temperature should be measured once per nursing shift and whenever patients complain of symptoms or health care providers note signs or symptoms consistent with fever (e.g., sweating,

chills, new erythema on the head or neck not related to the primary infection, patient complaints, etc.).

Furthermore, in patients with the presence of fever at baseline, it is clinically inappropriate to consider those who have persistence of some degree of fever at Day 3 as a clinical failure. Consider the following clinical scenario, which reflects successful, not unsuccessful, treatment: the patient presents with a temperature of 40°C; has a progressive decrease in temperature after initiation of treatment (along with improvement in well-being plus cessation of lesion spread); has a temperature of 38.1°C at day 3; and has resolution of the lesion and is afebrile by end-of-therapy and test-of-cure.

IDSA also believes that it is unnecessary and clinically inappropriate to define the afebrile state as 37.6°C, with an “intermediate” zone of 0.4°C. How were these thresholds determined? Furthermore, if reducing uncertainty due to variability in temperature measurement is the goal, did FDA’s decision take into account that several “afebrile” temperature readings are required?

Accordingly, IDSA suggests that FDA revisit its criterion for determining that a patient is afebrile and the requirement that that threshold must be reached for the patient to be considered a success at day 3.

### **Summary**

FDA demonstrates an ongoing, legitimate concern that they not approve new antibacterial agents that are ineffective for the treatment of the disease under study. However, sufficient historical and modern data are available to demonstrate antibacterial efficacy vs. placebo/no therapy for cellulitis, wound infections, and abscess, including using an endpoint that incorporates cure at the test-of-cure study visit. In IDSA’s view, FDA should demonstrate recognition and concern that antibacterial resistance rates continue to rise rapidly; untreatable infections are occurring as reported in the literature; and new antibacterial agents are needed to treat these infections. FDA must balance the risks of approving less effective therapy with the benefits of removing the current, substantial barrier to new antibacterial development. Our deep concern is the public health crisis engendered by the lack of new antibacterial development, converging with the rising crisis of antibacterial resistance. A singular focus on statistics cannot address the public health need. Extreme statistical conservatism must be balanced with clinical reality if the needs of the public are to be addressed.

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