Diabetic Foot Infections: Developing Drugs for Treatment

Guidance for Industry

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

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Clinical/Antimicrobial

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TABLE OF CONTENTS

Contains Nonbinding Recommendations

Diabetic Foot Infections: Developing Drugs for Treatment Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment of diabetic foot infections (DFIs) without concomitant bone and joint involvement.[2] Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and clinical trial designs for the development of drugs to support an indication for treatment of DFI. Development of drugs for the treatment of acute bacterial skin and skin structure infections, defined as cellulitis/erysipelas, wound infection, and major cutaneous abscess, is addressed in a separate guidance.[3]

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* (September 1998) and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001), respectively.[4] Diabetic foot infections encompass cellulitis, ulcers, and bone and joint infections located at or distal to the malleoli. Bone and joint infections are excluded from the scope of this guidance.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only s recommendations, unless specific regulatory or statutory requirements are cited. The use of the

[1] This guidance has been prepared by the Division of Anti-Infectives in the Office of Infectious Diseases in the Office of New Drugs in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, references to *drugs*, include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262) that are regulated as drugs.

[3] See the guidance for industry *Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment* (October 2013). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs.

[4] In addition to consulting guidances, sponsors are encouraged to contact the Division to discuss specific issues that arise during drug development.

word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Foot infections in diabetic patients account for substantial morbidity and often underlie the need for lower extremity amputations. Frequently, the inciting event is a superficial neuropathic foot ulcer. Diabetic peripheral neuropathy predisposes to foot ulcer formation, as many diabetic patients sustain repeated, localized foot trauma that is not perceived as being painful. Concomitant peripheral vascular insufficiency results in poor wound healing and predisposes superficial wounds to progress into deep ulcers before medical attention is sought. DFIs can be further complicated by the development of abscesses, joint infections, and osteomyelitis. Treatment is multifactorial, requiring debridement of devitalized tissue, drainage of any abscesses, reperfusion in cases of critical limb ischemia, off-loading (removing pressure on the infected wound), optimizing glycemic control, administration of appropriate antibacterial therapy, and application of dressings that allow for moist wound healing and control of excess exudation.

Important considerations for developing antibacterial drugs for DFI include the types of bacteria that are associated with DFI, which can be either monomicrobial or polymicrobial. Monomicrobial infections with aerobic gram-positive cocci such as *Staphylococcus aureus* or β-hemolytic streptococci typically occur in patients who have not recently received antibacterial therapy.[5] Patients who have chronic wounds or who have recently received antibacterial therapy are more prone to developing polymicrobial infections. These infections can involve pathogens such as aerobic gram-positive cocci, including methicillin-resistant *Staphylococcus aureus,* and gram-negative organisms, including drug-resistant gram-negative pathogens. Patients with limb ischemia or necrotic wounds may be infected by anaerobic pathogens.

Of note, the guidance for industry *Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment* does not address DFI due to the differences between DFI and other ABSSSI related to definitions, clinical manifestations, microbiology, management, and measurement of clinical outcomes;[6] therefore, a separate guidance was deemed necessary.

III. DEVELOPMENT PROGRAM

Sponsors should consider the following when developing drug products for diabetic foot infection.

[5] Johns Hopkins ABX Guide. The Johns Hopkins University; 2022.

[6] See the guidance for industry *Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment*.

A. General Drug Development Considerations

1. Early Phase Development Considerations

In assessing the efficacy of antibacterial drugs for the treatment of DFI, the sponsor should consider providing phase 1 data demonstrating adequate drug penetration into the outer skin layers. We recommend sponsors discuss with the Agency the type of technique to evaluate drug penetration before study initiation.

2. Drug Development Population

The drug development population should include subjects with diabetes mellitus who have a bacterial infection of the foot, located at or distal to the malleoli. Of note, development of drugs for bone and joint infections is out of the scope of this guidance.

The use of a classification system characterizing the extent of the lesion and systemic signs and symptoms may be considered to define the study population (Schaper 2004; Lipsky et al. 2020; Lipsky 2009; Senneville et al. 2023).

3. Efficacy Considerations

Noninferiority (NI) trials are interpretable and acceptable to support approval of a drug for the treatment of DFI, provided an acceptable NI margin is clearly justifiable. Superiority trials comparing the investigational drug to an active control are also readily interpretable and provide direct evidence of treatment benefit.

In general, two adequate and well-controlled trials are needed to support the effectiveness of the investigational drug. A single adequate and well-controlled trial supported by other independent confirmatory evidence, such as a trial in another related infectious disease indication (e.g., acute bacterial skin and skin structure infections), can potentially provide evidence of effectiveness in support of an indication for the treatment of DFI. Sponsors should discuss their anticipated approach to demonstrating substantial evidence of effectiveness with FDA early in development, such as at a pre-investigational new drug application meeting, and no later than at an end-of-phase 2 meeting.[7]

4. Safety Considerations

In general, a safety database of approximately 500 subjects or more is recommended to support approval of a drug for the treatment of DFI. If the same or greater dosage and duration of therapy were used in clinical trials for other infectious disease indications, the safety information from those clinical trials may be part of the overall preapproval safety database. For new drugs that

[7] See the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

have an important clinical benefit compared with existing therapies, depending on the benefit demonstrated, a smaller preapproval safety database may be appropriate. Sponsors should discuss the appropriate size of the preapproval safety database with the FDA during clinical development.

B. Phase 3 Efficacy Trial Considerations

Sponsors are encouraged to discuss proposed study designs and investigative approaches with the Agency before initiating clinical trials for antibacterial drugs for the treatment of DFI.

1. Trial Design

Trials should be active-controlled, prospective, randomized, and double-blinded using an NI or superiority trial design. Add-on superiority trials can also be performed.

2. Trial Population

The clinical trial population for efficacy trials should include subjects with DFIs of varying depths and extent of involvement. Surgical incision and drainage of abscesses or wound debridements could influence treatment outcomes among subjects with DFI. Planned surgical debridements should be performed during the first 48 hours after randomization. Subjects needing surgical debridement after 48 hours should be considered as having a clinical failure.[8] Topical antibacterial drugs should be avoided. Minor prespecified procedures performed at the bedside (e.g., suture removal, needle aspiration, superficial debridement of devitalized tissue, or routine wound care) are permitted.

3. Entry Criteria

Subjects with type 1 or 2 diabetes mellitus with a foot infection that started at or below the malleoli and does not extend above the knee, without concomitant osteomyelitis and infectious arthritis, can be enrolled in DFI clinical trials. Infection should be defined by the presence of at least two of the following (Lipsky et al. 2012; Lipsky et al. 2019; Senneville et al. 2023):

- Local swelling or induration
- Erythema around the wound
- Local tenderness or pain
- Local warmth
- Purulent discharge (thick, opaque to white or sanguineous secretion)

Investigators should enroll subjects with moderate to severe DFIs, including patients who may have vascular insufficiency and neuropathy and who are representative of the population in which antibacterial drug treatment is recommended. Enrollment of subjects with mild infections

[8] Sponsors can discuss with the FDA a different window for planned surgical debridements.

could potentially drive results toward NI as these infections are associated with a higher incidence of spontaneous resolution.

The International Working Group on the Diabetic Foot (IWGDF) DFI criteria can be used to define moderate and severe infection (Lipsky 2019). Under this classification, moderate infection is defined as erythema extending ≥2 cm from the wound margin, and/or tissue involvement deeper than skin and subcutaneous tissues (e.g., muscles and tendons), and no systemic inflammatory response signs, while severe infection is defined as any foot infection associated with two or more of the following systemic manifestations:

- Temperature >38°C or <36°C
- Heart rate >90 beats/min
- Respiratory rate >20 breaths/min or PaCO2 < 4.3 kPa (32 mmHg)
- White blood cell count >12 000/mm^3, <4000/mm^3, or >10% immature (band) forms

If the subject has multiple sites of DFI, the one with the highest IWGDF classification and the largest size will be designated as the primary DFI.

The method of measuring lesion size should be the same across all trial sites. Methods to assess lesion size include, but are not limited to, the following: (1) manual measurement of length and perpendicular width, (2) digital planimetry, and (3) computer-assisted tracings.

Recommended general exclusion criteria include the following:

- Subjects with medical conditions that would alter the interpretation of the primary endpoint (e.g., subjects with severe neutropenia)
- Subjects with suspected or confirmed osteomyelitis
- Subjects with suspected or confirmed septic (infectious) arthritis
- Subjects who have received more than 24 hours of effective antibacterial drug therapy for the treatment of DFI
- Subjects with gangrene requiring amputation
- Subjects with necrotizing fasciitis
- Subjects with an infected prosthesis
- Subjects likely to require revascularization of the primary site of infection or critical ischemia involving the infected limb
- Subjects with a burn wound or an underlying inflammatory skin disease that may obscure determination of response, such as atopic dermatitis

- Subjects with documented or suspected fungal, parasitic, or viral pathogens as a causative pathogen

- Subjects with acute gout, acute Charcot neuro-osteoarthropathy, acute fracture in the affected foot, or deep venous thrombosis of the affected extremity.

4. Prior Antibacterial Drug Therapy

Ideally, subjects enrolled in a DFI noninferiority clinical trial would not have received prior antibacterial drug therapy for the current DFI episode because such therapy can obscure potential treatment differences between an investigational drug and a control drug and therefore bias toward a finding of no difference.

However, consideration can be given for the enrollment of a limited number of subjects who have received less than 24 hours of potentially active antibacterial therapy for the current DFI episode before enrollment (e.g., at most 25% of the patient population).

5. Clinical Microbiology Considerations

All subjects should have pretherapy specimens obtained aseptically from acceptable sources such as leading-edge needle aspirates of an infected wound, surgically debrided tissue, abscess contents, and blood. DFI lesion cultures and/or blood cultures should be repeated only if clinically indicated (e.g., if a subject is deemed a clinical failure or if purulence and discharge from the DFI lesion continues at any time after screening).

An adequate clinical specimen for microbiological evaluation should be sent to the laboratory for microscopic examination (e.g., Gram stain) and culture. Specimens should be processed according to standard methods. In vitro antimicrobial susceptibility testing should be performed using standardized methods on appropriate bacterial isolates. Potential pathogenic isolates should be saved and sent to the central laboratory for final confirmation, antimicrobial susceptibility testing, and additional testing. Blood cultures should be obtained before administration of antibacterial therapy.

Wound swabs are generally not appropriate. Sinus tract cultures are unreliable and should be avoided. The sponsor's approach to wound microbiology should be discussed with the Agency before study initiation.

The investigator should assess bacteria isolated from culture specimens as either pathogens, colonizers, or contaminants, and should provide a summary of the assessment.

Only bacteria designated as pathogens should be considered in determining the microbiological evaluability of an enrolled subject. A list of accepted pathogens should be discussed with and submitted to the Agency.

6. Assessment for Osteomyelitis

Subjects should be screened for bone and joint infections before enrollment, and those with suspected or confirmed bone and joint infections should be excluded from DFI clinical trials as they may have less favorable outcomes resulting from slower healing times. Additionally, the management of these subjects may differ because they often require surgical resection and prolonged duration of antibacterial drug treatment. These factors can influence the selection of the primary endpoint, timing of evaluation of the endpoint, and justification of NI margins. A diagnosis of osteomyelitis may be established either by a positive probe to bone test or by imaging. In subjects with open, infected foot ulcers that do not probe to bone and for subjects with sepsis related to a foot infection, magnetic resonance imaging should be considered. Sponsors should discuss with the FDA before initiation of the trial if alternative methods of detection of osteomyelitis are planned.

7. Randomization, Stratification, Covariate Adjustment, and Blinding

Trials should be controlled, randomized, and double-blinded. If subjects with ulcer and non-ulcer–related infections are enrolled in the trial, then the randomization and outcome analyses should be stratified by the presence or absence of a foot ulcer to account for the differences in the natural history of the disease entities. To improve the precision of treatment effect estimation and inference, sponsors may consider adjusting for prespecified prognostic baseline covariates (e.g., severity of infection, degree of vascular insufficiency, level of glycemic control) in the primary efficacy analysis and propose methods of covariate adjustment.[9]

8. Specific Populations

Sponsors should include geriatric subjects without any upper age limit in clinical trials.[10] Any exclusion criteria pertaining to comorbidities should be avoided unless essential for ensuring patient safety (e.g., because of important drug-drug interactions with drugs required in the treatment of a comorbidity). The trials should also include obese subjects (defined as body mass index of at least 30 kg/m^2), as obese subjects with diabetes are at an increased risk of diabetic foot infection (Glovaci et al. 2019). Sponsors should characterize the pharmacokinetics of the drug in obese subjects before phase 3 studies to inform the selection of an appropriate dosage for this population. Adequate characterization of pharmacokinetics of the study drug in patients with renal insufficiency should be planned in early development (i.e., phase 1 studies) so such patients can be included with appropriate dosage modifications in phase 3 studies.[11] Similarly, subjects

[9] See the guidance for industry *Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products* (May 2023).

[10] See the ICH guidances for industry *E7 Studies in Support of Special Populations: Geriatrics* (August 1994) and *E7 Studies in Support of Special Populations: Geriatrics; Questions and Answers* (February 2012).

[11] See the draft guidance for industry *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing* (September 2020). When final, this guidance will represent the FDA's current thinking on this topic.

with hepatic impairment should be enrolled, provided the pharmacokinetics of the drug have been evaluated in these subjects and/or appropriate dosage has been defined.[12]

9. Dose Selection

Sponsors should integrate the findings from animal models[13] and information from phase 1 and, if appropriate, phase 2 trials for the purposes of selecting appropriate dosages, and duration of therapy to be evaluated in phase 3 clinical trials.

10. Use of Active Comparators

In general, the active comparator used in clinical trials should be considered standard of care for this indication. When evaluating standard of care, sponsors should consider recommendations by authoritative scientific bodies (e.g., the Infectious Diseases Society of America) and other information that reflects current clinical practice.

11. Concurrent Antibacterial Drug Therapy

Ideally, concurrent antibacterial drug therapy should be avoided except in an add-on trial when it is part of the study therapy. Concomitant antibacterial drug therapy with a spectrum of activity that overlaps with the spectrum of the investigational drug should not be administered during the trial, except as rescue therapy, as it will limit assessment of the efficacy of the investigational drug. The need for rescue therapy will generally be interpreted as failure of the study drug. Concomitant antibacterial drugs for bacteria that are not susceptible to the study drug may be acceptable. Sponsors should discuss with the FDA any plans for concomitant antibacterial drug therapy in advance of trial initiation. The ability to maintain study blinding with the use of concomitant antibacterial drug therapy should be addressed.

12. Adjunctive Measures

As part of the current standard of care for DFI, various modalities are used in wound management to encourage healing and closure. Some examples of the measures that could be employed include non-weight bearing (off-loading) and debridement. The contribution of each modality to the overall treatment outcome can be difficult to assess. The sponsor should prespecify and document which adjunctive modalities are permitted under the protocol.

13. Minimum Duration of Treatment:

In general, the minimal duration of treatment for DFI without concomitant osteomyelitis or septic arthritis is 7 to 14 days. For subjects who require a prolonged course of antibacterial drug

[12] See the guidance for industry *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling* (May 2003).

[13] We support the principles of the 3Rs, to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if they wish to use a nonanimal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method is adequate to meet the regulatory need.

therapy, the sponsor should define criteria for prolonging study drug treatment and discuss these with the Agency before study initiation.

14. Intravenous to Oral Therapy Switch

For drugs that only have an intravenous (IV) formulation available, we recommend that subjects receive the IV formulation alone until the assessment of the primary efficacy endpoint.

For drugs that have both an IV and an oral formulation, a switch to the oral formulation may be appropriate before the primary efficacy outcome assessment, provided that the pharmacokinetics of the oral formulation have been evaluated to ensure adequate exposure and to determine an appropriate dosage. If an IV-to-oral switch is incorporated into the protocol, the sponsor should specify the objective criteria necessary to permit the switch and discuss the criteria with the FDA before study initiation.

15. Efficacy Endpoints

a. Primary efficacy endpoint

The primary endpoint should be resolution or improvement of all signs and symptoms of DFI to the extent that no further antibacterial drug therapy is needed and none of the following events have occurred: receipt of rescue therapy, unplanned surgical debridement, amputation, or death. Sponsors should predefine these criteria to allow for uniformity of clinical assessments among investigators across sites. Alternative definitions of clinical response should be discussed with the FDA before initiation of clinical trials.

To preserve the integrity of randomization, the timing of all post-baseline assessments should be based on a window defined by the time from randomization (i.e., around a fixed time point) rather than a window defined by the time from the end of therapy (EOT). In general, the primary endpoint should be evaluated at the test-of-cure visit approximately 21 days post-randomization. The treatment effect should also be evaluated at the EOT and other follow-up visits to evaluate for durability of the treatment effect.

The investigator's assessment of clinical response should be performed by the same investigator on the same subject throughout the study, whenever possible, to ensure uniformity of assessments.

b. Secondary endpoint considerations

An endpoint defined as the composite of death, unplanned amputation, and infectious complications at 21 days post-randomization should be considered, as this objectively measures key patient benefits. Other secondary endpoints may include clinical response assessed at EOT or all-cause mortality at a fixed time point post-randomization (e.g., 21 days).

c. Additional endpoint considerations

For the primary and secondary outcome classifications, subjects with any unplanned surgical debridement, except for minor prespecified procedures, or other unplanned adjunctive interventions after 48 hours, should be considered clinical failures. Subjects who have amputations or who develop osteomyelitis of underlying bone despite study drug therapy would be considered clinical failures.

In instances where an overlying foot ulcer has healed completely without clinical evidence of infection, the subject's microbiological response would be presumptive eradication.

Endpoints based on patient-reported outcomes can be considered. Sponsors should discuss proposed patient-reported outcome instruments with FDA.

16. Trial Procedures and Timing of Assessments

Entry visit
At this visit sponsors should collect appropriate demographic, history, and physical examination information, including lesion size measurements, evaluation for osteomyelitis, neuropathy, peripheral vascular disease, microbiological specimens, safety laboratory tests, and imaging studies.

On-therapy visits
At 48 to 72 hours after initiating study drug and other on-therapy visits, sponsors should provide a clinical assessment of the primary DFI site (including lesion size measurement) and assess all signs and symptoms as specified by the protocol. Safety and laboratory tests, as appropriate, should be evaluated.

EOT visit
At this visit, sponsors should evaluate the lesion size in the same manner as at the entry and on-therapy visits, as specified by the protocol. Safety and laboratory tests, as appropriate, should be evaluated. Subjects who discontinue study therapy prematurely should not be discontinued from the study but should continue to be followed per the protocol. The protocol should specify criteria to guide the duration of study treatment.

Test-of-cure visit
This visit should occur at Day 21 plus/minus 2 days post-randomization, which would correspond to 7 to 14 days following the EOT. As indicated above, the primary endpoint should be evaluated at this visit. Sponsors should assess the maintenance of clinical response and any new safety effects, evaluate for osteomyelitis, and obtain safety laboratory tests, as appropriate, at this visit.

Day-28 post-randomization follow-up visit
At this visit, all-cause mortality, durability of clinical response, and follow-up of any adverse events should be assessed.

17. Statistical Considerations

The trial hypotheses, the estimands of interest, and the analysis methods should be prespecified in the protocol and in a detailed statistical analysis plan. The primary efficacy analysis should be based on the difference in the proportions of subjects achieving a successful clinical response. Subgroup analyses should assess the primary endpoint in the baseline subgroups of subjects who did and did not receive prior antibacterial therapy. Additional sensitivity/exploratory analyses should be performed for factors that could modify the primary analysis findings.

Analysis populations

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

- Safety population — All subjects who received at least one dose of drug during the trial.
- Intent-to-treat (ITT) population — All subjects who were randomized.
- Microbiological intent-to-treat (micro-ITT) population — All subjects randomized to treatment who have a baseline bacterial pathogen known to cause DFI. Patients should not be excluded from this population based upon events that occur after randomization (e.g., lost to follow-up). In an NI trial, this analysis population should exclude subjects with baseline bacterial pathogens against which the control drug does not have antibacterial activity.
- Per-protocol, clinically evaluable, or microbiologically evaluable populations — Subjects who follow important prespecified components of the trial can then be defined as part of a per-protocol or other evaluable population (i.e., ITT subjects who follow important components of the trial can be defined as the clinically evaluable population, or micro-ITT subjects who follow important components of the trial can be defined as the microbiologically evaluable population).

For both NI and superiority trials, the primary analysis should be based on the ITT population. In general, the ITT population, instead of the micro-ITT population, should be the primary analysis population because the definitions of DFI described are most consistent with bacterial infection even for cases in which purulent material is not easily obtained (e.g., cellulitis). Generally, it is not appropriate to consider analyses of the per-protocol, clinically evaluable, or microbiologically evaluable populations as primary because population membership is based on post-randomization events or characteristics of subjects. However, consistency of the results should be evaluated in all populations.

Sample size

The appropriate sample size for a clinical trial should be based on the number of subjects needed to answer the research question posed by the study. The sample size is influenced by several factors, including the prespecified type I (α=.05, two-sided) and type II error ($\beta \leq 0.2$) rates, the expected clinical response rate, and the NI margin (for NI trial) or the magnitude by which the study drug is expected to be superior to the control in a superiority trial. Sample size should be

based upon the number of subjects needed to draw conclusions in the ITT primary analysis population.

An estimate of the sample size for an NI trial with 1:1 randomization is approximately 442 subjects per arm based on the following assumptions: (1) the NI margin is selected at 10%, (2) the two-sided type I error is 0.05, (3) the type II error is 0.10 (90% power), and (4) 70% of subjects achieve clinical response in both arms.

Selection of NI[14] margins

If a sponsor chooses to design an NI trial for DFI, then the NI margin should be prespecified to determine an appropriate sample size for the trial. The NI margin that should be used in this circumstance is determined by the amount of potential loss of efficacy relative to the active control that the trial will attempt to rule out statistically. Sponsors should provide data to justify the selection of the NI margin. The selection of an appropriate NI margin should be based upon the following:

- Previous evidence of the magnitude of the benefit of the control antibacterial drug over placebo from a compilation of all relevant placebo-controlled or superiority trials of an antibacterial drug over another antibacterial drug. The degree of benefit anticipated must account for the variability across previous trials in the degree of beneficial effect observed. The planned trial should be sufficiently similar to the studies considered in the historical evidence on important factors including inclusion criteria, patient and disease characteristics, clinical endpoint(s), duration of treatment, timing of assessment, and other relevant factors.

- Consideration of the potential loss of efficacy relative to the control drug by an amount that is clinically acceptable.

In general, a 10% NI margin would be acceptable; however, sponsors can propose alternative NI margins with a justification provided for the acceptance of that margin.

The appendix provides an example of an NI margin justification. Sponsors should discuss with the FDA a clinically appropriate NI margin in advance of trial initiation.

18. Labeling Considerations

The DFI treatment indication should include the approved age groups[15] and information about the use of the drug in patients without concomitant osteomyelitis or septic arthritis. Additionally, this indication should list the genus and species of the bacteria identified in clinical trials that supported the indication. For example:

[14] See the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016).

[15] See section II.A.2. in the draft guidance for industry *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (July 2018). When final this guidance will represent the FDA's current thinking on this topic.

"DRUG-X is indicated for the treatment of adults with diabetic foot infections (without concomitant osteomyelitis or septic arthritis) caused by … [list genus and species of bacteria]."

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APPENDIX: JUSTIFICATION FOR A NONINFERIORITY MARGIN FOR DIABETIC FOOT INFECTIONS

Background

The first step in the consideration for a noninferiority (NI) trial design is determining the treatment effect of the active-comparator drug that can be reliably distinguished from placebo (M_1). This determination is based on the evidence from previously conducted trials using reliable efficacy endpoints. Because no historical, randomized, placebo-controlled trials for patients with diabetic foot infection (DFI) could be identified, direct estimation of the treatment effect was not possible. Therefore, we considered retrospective case series comparing the pre- with the post-antibacterial drug era. Various outcome measures were considered, including control of infection rates, mortality rates, and rates of major amputations.

Retrospective case series comparing the pre- with the post-antibacterial drug era:

Two publications (McKittrick 1946; Regan et al. 1949) discussed the treatment effect of antibacterial drugs on rates of mortality and rates of major amputations in patients with DFI as assessed by the treating physicians in the pre- and post-antibacterial drug era. An additional publication (McKittrick 1949) assessed infection control in the post-antibacterial drug era. These studies generally included subjects with serious DFI, such as infections with gangrene and presumably osteomyelitis for which amputation was often required. Patients with osteomyelitis are not considered for this guidance because they require a prolonged duration of antibacterial drug therapy, typically 4 to 6 weeks, usually in conjunction with surgical intervention.

Regan (1949) stated that changes in surgical procedures with more aggressive surgeries likely led to a strong reduction in the infection rate. For example, 105/140 (75%) of the amputations performed between 1930 and 1939 resulted in infections of the stump after amputation versus 1/28 (3.5%) of amputations performed between 1940 and 1944 using a more aggressive surgical approach. The potential for confounding is also observed by the reduction in mortality for all amputations performed from 1933 to 1939 (35.0%) versus 1940 to 1944 (8.8%), which was primarily attributed to improvements in surgical protocols, although sulfonamide use appeared to be an additional factor (Regan et al. 1949).

Outcome of major amputations

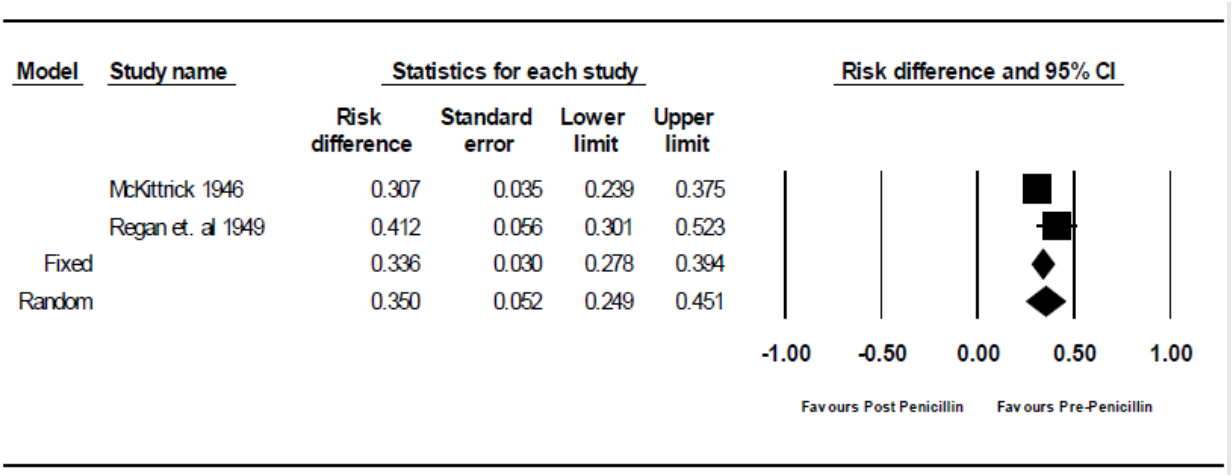
Table 1 shows for both studies the proportion of major amputations out of all amputations of lower extremities in diabetic patients before and after the introduction of penicillin. These results show that a substantial reduction in major amputations occurred after the introduction of penicillin. The treatment difference (before and after penicillin) was 30.7% in McKittrick (1946) and 41.2% in Regan et al. (1949) (Table 1). In Figure 1, a meta-analysis of both studies using a random effect model based on the DerSimonian-Laird approach shows a treatment difference of 35.0% (95% CI: 24.9%, 45.1%).

Table 1: Proportion of Patients with Amputations Receiving Major Amputations, Pre-Penicillin Versus Post-Penicillin

Publication	Before Penicillin[1] n/N (%)	After Penicillin[2] n/N (%)
McKittrick 1946	680/1036 (65.6%)	80/229 (34.9%)
Regan et al. 1949	99/140 (70.7%)	36/122 (29.5%)

n = Number of patients with major amputations, N = Number of patients with any type of amputation (major or minor).
[1] *Before Penicillin* refers to years of 1923 to 1941 (McKittrick 1946) and 1933 to 1939 (Regan et al. 1949).
[2] *After Penicillin* refers to 1944 to1945 (McKittrick 1946) and 1945 to 1948 (Regan et al. 1949).

Figure 1: Meta-Analysis of the Proportion of Major Amputations Performed, Pre-Penicillin Versus Post-Penicillin



Outcome of mortality

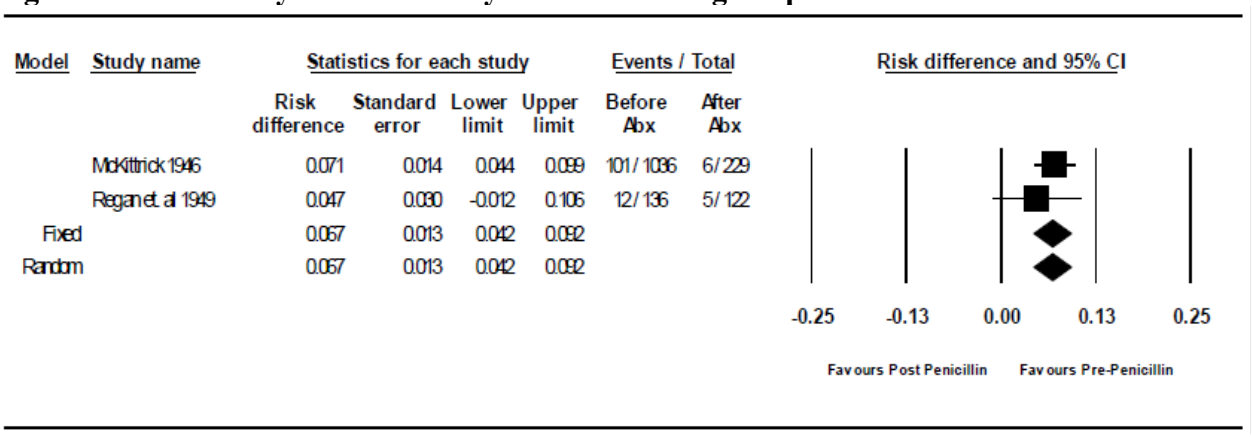
The two publications discussed above (McKittrick 1946; Regan et al. 1949) also discuss the mortality of patients undergoing amputations. Table 3 shows post-amputation mortality rates pre and post the use of penicillin. These results show a modest reduction occurring after the introduction of penicillin. The treatment difference was 7.1% in McKittrick (1946) and 4.7% in Regan et al. (1949) (Table 2). In Figure 2, a meta-analysis of both studies shows a treatment difference of 6.7% (95% CI: 4.2%, 9.2%) using a random effects model. The reduction in mortality rate post penicillin use helps to support an overall treatment benefit attributable to antibacterial drug use.

Table 2: Mortality Rates After Amputation,[1] Before Penicillin Versus After Penicillin

Publication	Mortality Rate		
	Before Penicillin[2] n/N (%)	After Penicillin[3] n/N (%)	Difference (%)
McKittrick (1946)	101/1036 (9.7%)	6/229 (2.6%)	7.1%
Regan et al. (1949)	12/136 (8.8%)	5/122 (4.1%)	4.7%

[1] Amputations include both minor and major amputations.
[2] *Before Penicillin* refers to 1923 to 1941 (McKittrick 1946) and 1940 to 1944 (Regan et al. 1949)
[3] *After Penicillin* refers to 1944 to 1945 (McKittrick 1946) and 1945 to 1948 (Regan et al. 1949)

Figure 2: Meta-Analysis of Mortality Rates Following Amputation



Outcome of control of infection rates

Regan et al. (1949) discussed the treatment effect of antibacterial drugs on the control of diabetic lower extremity infection rates in patients receiving minor amputations in the pre- and post-antibacterial drug era. McKittrick (1949) also discussed control of infection rates after the introduction of penicillin. In Regan et al. (1949), "control of infection" required that the wound heal completely, or stumps take skin grafts without subsequent re-amputation. In McKittrick (1949), "control of infection" required that the wound heal without need of re-amputation or death.

These results show that a substantial improvement in control of infection rates occurred after the introduction of penicillin. The treatment difference in Regan et al. (1949) was 39.7% (21.0% to 58.4%). Treatment comparisons could not be made based on the 1949 McKittrick paper; however, control of infection rates in the after-penicillin period were observed to be 72.1%.

Table 2: Control of Infection Rates Among Cases with Local (Minor) Amputations

Publication	Pre-Penicillin (1933–1939) n/N (%)	Post-Penicillin (1945–1948) n/N (%)	Difference (95% CI)
Regan et al. (1949)	19/41 (46.3%)	74/86 (86.0%)	39.7% (21.0-58.4)
McKittrick et al. (1949)	NA	155/215 (72.1%)	—

Discussion

There are major limitations with determining an NI margin for patients with DFIs. For example, the older studies of antibacterial drug treatment in diabetic lower extremity infections (Regan et al. 1949; McKittrick 1946; McKittrick et al. 1949) were not performed in a prospective and well-controlled manner but rather were based on retrospective analyses of case series. Analyses of case series can involve treatment imbalances, uncontrolled confounding variables, lack of standardized methodologies, missing/unreported data, and various types of biases (e.g., evaluator biases, recall biases). These studies also lacked details regarding important study design features such as inclusion/exclusion criteria, baseline characteristics, extent of antibacterial drugs used (e.g., extent of sulfonamide use during early 1940s), and definitions used for "control of infection" (e.g., timing of assessment and the success/failure criteria). These studies were also conducted in a much earlier time period involving large differences with respect to treatment modalities, including management of diabetes mellitus patient populations and disease etiologies. This can result in higher baseline mortality/morbidity rates and estimated treatment effects compared with what would be observed in current clinical trials for DFI.

There are also limitations specific to the analyses of the treatment effect using major amputations and mortality, which may not be applicable in current clinical trials of DFIs. Analyses using mortality may be affected by low incidence rates resulting in smaller estimates of the treatment effect. Analyses using major amputations may involve serious confounding because of improvements in surgical protocols that were attributed to reduced mortality and postoperative incidence of infections from 1940 to 1945 (Regan et al. 1949).

These studies also included patients with more serious infections, including those with gangrene, and presumably osteomyelitis where amputation was often required. Current populations addressed in this guidance have less serious infections (e.g., no osteomyelitis) and are less likely to have an amputation. Despite these differences, these publications strongly point to a large effect of antibacterial drugs in the treatment of DFI.

Summary and Selection of Noninferiority Margin for DFI

Data from the Regan et al. (1949) study support a difference of at least 20% based on the lower 95% confidence limit for the difference in control of infection rates between the pre-penicillin and post-penicillin periods. These scientific data provide support for the selection of an NI margin of 10% that preserves some of M_1 based on an endpoint of control of infection. Sponsors

should discuss the selection of an NI margin with the FDA in advance of trial initiation, in particular for a margin selected at greater than 10%.

APPENDIX REFERENCES

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