

Guidance for Industry

Uncomplicated and Complicated Skin and Skin Structure Infections — Developing Antimicrobial Drugs for Treatment

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GUIDANCE FOR INDUSTRY¹

Uncomplicated and Complicated Skin and Skin Structure Infections Developing Antimicrobials for Treatment

I. INTRODUCTION

This is one in a series of guidance documents intended to assist the pharmaceutical industry in the development of antimicrobial drug products for the treatment of infections. The information presented here should help applicants plan clinical studies, design clinical protocol(s), implement and appropriately monitor the conduct of clinical studies, collect relevant data for analysis, and perform appropriate types and numbers of analyses of study data. Clinical trials planned and conducted as recommended in this guidance should yield the information necessary for the Agency to determine whether the antimicrobial under study is safe and effective in the treatment of the specific infection. For general information on related topics, the reader is referred to the guidance *Developing Antimicrobial Drugs — General Considerations for Clinical Trials (General Considerations)*.

This guidance for industry focuses on developing antimicrobials for the treatment of uncomplicated and complicated skin and skin structure infections.

II. BACKGROUND

Over the years, the Agency has issued guidance to the pharmaceutical industry on how to design, carry out, and analyze the results of clinical trials for the development of antimicrobials for the treatment of infections in a variety of forms. Guidance has been provided verbally during various industry and FDA meetings, in letters written to sponsors, and in general guidance on related issues. This guidance is the result of efforts to collect all pertinent information and present it in

¹ This guidance has been prepared by the Office of Drug Evaluation IV, representing the Division of Anti-Infective Drug Products, the Division of Special Pathogens and Immunological Drug Products, and the Division of Anti-Viral Drug Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on developing antimicrobials for the treatment of uncomplicated and complicated skin and skin structure infections. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

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one location. Where appropriate, this guidance contains relevant information from several sources, including *Clinical Evaluation of Anti-Infective Drugs (Systemic)* (1977); IDSA's "Guidelines for the Evaluation of Anti-Infective Drug Products" (1992) (IDSA guidance);² *Points to Consider: Clinical Development and Labeling of Anti-Infective Drug Products* (1992) (*Points to Consider*), an FDA guidance on issues related to evaluating new drug applications for anti-infective drug products; and *Evaluating Clinical Studies of Antimicrobials in the Division of Anti-Infective Drug Products* (February 1997), a draft guidance discussed at a March 1997 advisory committee meeting on anti-infective drug products, which will be superseded by this guidance once it is issued in final form.

III. UNCOMPLICATED AND COMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS

A. Regulatory Synonyms

A number of synonyms have been used in the past in discussions of uncomplicated and complicated skin and skin structure infections including *skin and skin structure infections* and *skin and soft tissue infections*.

B. Study Considerations

1. Study Characteristics

A statistically adequate and well-controlled multicenter trial is recommended establishing safety and effectiveness (i.e., similar or superior effectiveness to an approved product). The total number of patients should include 20% each of the following infections: simple abscesses, impetiginous lesions, furuncles, and cellulitis. Protocols used to study an investigative product for treatment of these infections should have very clear inclusion, exclusion, and outcome definitions, as the primary effectiveness parameter for this infection should be clinical outcome. At least 50% of the clinically evaluable patients should also be microbiologically evaluable so that adequate numbers of evaluable cases with specific pathogens are available to assess general effectiveness for specific pathogens. NDAs with studies, in which only one or two specific categories of uncomplicated skin and skin structure infections were studied should be approved for only those specific infections.

Please note four caveats:

² This guidance appeared in IDSA's (Infectious Disease Society of America) supplement to *Clinical Infectious Diseases*, formerly *Reviews of Infectious Diseases*.

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- The simple growth of transient or resident skin flora in a culture should not constitute a microbiologically evaluable patient. Pathogens listed in the INDICATIONS AND USAGE section of the product label should be those established in the submitted data that also reflect contemporary beliefs about pathogenicity in these types of skin infections. In addition, the microbiologic culture sample should be obtained in such a manner that biologically meaningful conclusions can be reached based on the data.
- The large majority of the microbiologically unevaluable patients in this trial should be patients with diagnoses where low pathogen recovery is the norm (such as cellulitis). Such cases should be supported as probable bacterial infections by a prospective rigid case definition.
- Analysis of treatment outcomes in these infections should be stratified by the presence or absence of therapeutic surgical intervention(s). In certain circumstances where it appears the surgical treatment was required as an adjunct or follow-up therapy due to failure of the investigative agent to successfully treat the uncomplicated skin infection, the patient should be evaluated as a treatment failure.
- Analyses of the data should also generally confirm (by comparing the direction of the independent 95% confidence intervals testing) the successful outcome rates established for the overall clinically evaluable and for the clinically and microbiologically evaluable subset of patients. Likewise, the analyses should establish the correlation between clinical cure and bacterial eradication in the clinically and microbiologically evaluable subset of patients.

In addition, adequate microbiologic data and specific human pharmacokinetic/dynamic data supportive of clinical effectiveness in this disease entity should be submitted. Such studies would include, but not be limited to, tissue distribution studies that demonstrate that, at the dosing regimen requested in NDA, the investigative agent diffuses into skin and superficial skin structure tissues or other validated surrogate marker in quantities adequate to achieve and maintain skin and superficial skin structure levels equal to or above the expected MIC₉₀ of the claimed pathogens for an adequate time period.

If an applicant chooses to perform more than one adequate and well-controlled trial in this indication (e.g., to establish a sufficient overall safety database for the product), specific pharmacokinetic/dynamic data relative to this indication should not ordinarily be necessary.

2. Study Characteristics for Complicated Skin and Skin Structure Infections

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One statistically adequate and well-controlled multicenter trial is recommended establishing safety and effectiveness (i.e., similar or superior in effectiveness to an approved product or to an approved method of treating these types of infections). In the study of this indication, patients with infected ulcers, burns, and major abscesses or other skin structure infections requiring surgical intervention with antimicrobial drug therapy, and infections of the deeper soft tissues should be enrolled. Numbers of patients with each type of these infections should be such that this indication can be approved. NDAs with studies in which only one or two specific types of these infections were studied should be approved for only those specific infections. Protocols used to study an investigative product for treatment of these infections should have very clear inclusion, exclusion, and evaluability criteria and outcome definitions, as the primary effectiveness parameter for this infection should be clinical outcome. Nonetheless, at least 70% of the clinically evaluable patients should also be microbiologically evaluable so that adequate numbers of evaluable cases with specific pathogens will be available to assess general effectiveness for specific pathogens. Analysis of treatment outcomes in these infections should be stratified by the presence or absence of therapeutic surgical intervention(s). In certain circumstances, where it appears the surgical treatment was required as an adjunct or follow-up therapy due to failure of the investigative agent to successfully treat the infection, the patient should be evaluated as a treatment failure.

Analyses of the data should also generally confirm (by means of comparing the direction of the independent 95% confidence intervals testing) the successful outcome rates established for the overall clinically evaluable and for the clinically and microbiologically evaluable subset of patients. Likewise, the analyses should establish the correlation between clinical cure and bacterial eradication in the clinically and microbiologically evaluable subset of patients.

In addition, adequate microbiologic data and specific human pharmacokinetic/dynamic data supportive of clinical effectiveness in this disease entity should be provided. Such studies would include, but not be limited to, tissue distribution studies that demonstrate that, at the dosing regimen requested in the NDA, the investigative agent diffuses into skin and deeper soft tissues or other validated surrogate marker in quantities adequate to achieve and maintain skin and superficial skin structure levels equal to or above the expected MIC90s of the claimed pathogens for an adequate time period.

If an applicant chooses to perform more than one adequate and well-controlled trial in this indication (e.g., to establish a sufficient overall safety database for the product), specific pharmacokinetic/dynamic data relative to this indication should not ordinarily be necessary.

3. Disease Entity Definition

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Because of the vast array of skin and skin structure infections possible, it would be very difficult to study each individually. Additionally, because broad categories of skin and skin structure infections tend to share common pathogens (e.g., superficial skin infections, impetigo, erysipelas, cellulitis, and simple abscesses are all predominantly caused by either *Streptococcus pyogenes* or *Staphylococcus aureus*) and similar responses to similar antimicrobial therapy, this cluster of diseases has been studied under the umbrella of skin and soft tissue infections and, more recently, in two broad categories: Uncomplicated skin and superficial skin structure infections and complicated skin and soft tissue infections.

The uncomplicated category includes such clinical entities as simple abscesses, impetiginous lesions, furuncles, and cellulitis. Infections that can be treated by surgical incision alone, such as cases of isolated (meaning one solitary area of infection) furunculosis or folliculitis, should not be included in the clinical trials.

The complicated category includes infections either involving deeper soft tissue or requiring significant surgical intervention, such as infected ulcers, burns, and major abscesses or a significant underlying disease state that complicates the response to treatment. Superficial infections or abscesses in an anatomical site, such as the rectal area, where the risk of anaerobic or Gram-negative pathogen involvement is higher, should be considered complicated infections.

There are clinical situations where it may be difficult to categorize the infection into one of these broad categories. Additionally, there are clinical situations that fall outside these categories: the treatment of active infections in burn patients or the prophylaxis against infections in this same group. Infections that occur infrequently (e.g., necrotizing fasciitis), are complicated by an underlying condition that may impair proper evaluation of the anti-infective agent's effect (e.g., a secondarily infected atopic dermatitis or eczema), are complicated by an immune deficiency in the patient (e.g., the development of ecthyma gangrenosum in neutropenic patients), or involving infections of prosthetic materials (e.g., catheter tunnel infections), should not be included in the primary clinical studies supporting the approval of the new agent. Though data about the efficacy of an agent in such situations is very valuable information, the rarity and/or the complicating factors involved would make proper evaluation of the study agent difficult.

Lesions that are superficial should be of an extensive enough nature that antimicrobial therapy is warranted.

4. Breakdown of Disease Entities

The sponsor should make an effort to include a wide array of disease entities when studying either uncomplicated or complicated skin and skin structure infections. Thus, in

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order to adequately evaluate the efficacy of an agent against uncomplicated skin infections, the sponsor should enroll a comparable number of patients with impetiginous lesions, simple abscesses, and cellulitis. For complicated skin infections, a similar mix of infected ulcers, complicated or extensive abscesses and deeper soft tissue infections should be included. The two categories (uncomplicated and complicated) should be studied separately because of the different pathogens and pathophysiology involved. In the event that a sponsor does not have an adequate profile of disease entities studied, the product package insert may reflect this by stating which disease entities were actually studied in adequate numbers.

5. Other Considerations

This is a microbiologically driven indication, and all efforts should be made to ensure a good yield on pre-therapy cultures. There are conditions where the percentage of patients with growth of pathogen on pre-therapy cultures is low, such as seen in cellulitis, but other conditions usually have high percentages of positive pre-therapy cultures.

For uncomplicated skin and skin structure infections, the two most commonly seen pathogens are *Staphylococcus aureus* and *Streptococcus pyogenes*. In fact, this indication traditionally has only included these two pathogens, since other organisms are not uniformly agreed upon to be pathogens in this indication, but rather seen as colonizers or contaminants. If a sponsor proposes the addition of another organism in this indication (uncomplicated skin and skin structure infections), they should provide a scientific rationale as to why they see this organism as being a true pathogen in these infections.

For complicated skin and skin structure infections, the possible pathogens are numerous and dependent on the clinical situation, the location of the lesion/infection, and past medical history of the individual patient. Additionally, it is often difficult to separate a colonizer from a pathogen, since the same organism can be either one, depending on the clinical setting. Thus, it is very important that microbiologic specimens are obtained properly, and that the methods used are described in detail in the study protocol and report.

Another problem with complicated skin and skin structure infections is that there may not be any one organism which is found commonly. Thus, the organisms listed in this indication may be dependent on the overall study results and may reflect which organisms were found most commonly. Qualifying statements, such as “This organism was studied

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in less than 10 clinical cases” have been used previously when this indication has been granted, to alert the clinician that the actual experience with a certain organism may not be extensive.

It is important to include an adequate mix of clinical conditions when studying either uncomplicated or complicated skin and skin structure infections. This should help in obtaining an adequate microbiologic profile with which to make a reasonable decision regarding approval or non-approval.

C. Inclusion Criteria

To be enrolled in a study evaluating skin and skin structure infections, the patient should have an infection consistent with one of the two categories presented above: either an uncomplicated skin and superficial skin structure infection or a complicated skin and skin structure infection. The patient enrollment should include both males and females. All patients should have a microbiologic specimen obtained prior to the initiation of therapy.

The sponsor should also elaborate upon the information that follows. This would allow the reviewer at the FDA to properly picture the patient’s disease entity.

- Anatomical site of infection
- Extent of infection (i.e., length, width)
- Superficial or deep involvement
- Description of actual infected site, including erythema, swelling, tenderness, extension of redness, heat
- Cause of infection (i.e., trauma, spontaneous, bite)
- Underlying medical conditions (i.e., diabetes mellitus)
- Previous medical/surgical therapy for the infection being studied
- Picture of the infected site (optional but potentially helpful)

D. Exclusion Criteria

Several points to consider include:

1. Infections that have a high cure rate after surgical incision alone (such as isolated furunculosis) or after aggressive local skin care (such as a minor skin infection) should not be enrolled.
2. Prior anti-infective use, even up to the day of patient enrollment, would exclude a patient, unless a culture is obtained showing the persistence of a pathogen. Because of the slow resolution of inflammation in many skin and skin structure

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infections (e.g., cellulitis), a clinical picture alone, without the positive culture, would be inadequate to enroll a patient on prior anti-infective therapy.

3. For complicated skin infections, medical conditions leading to difficulty in interpreting response (as may be the case in superinfected eczema where inflammation may be prominent for an extended period even after successful bacterial eradication) or where the response may be altered (e.g., as in immunocompromised patients), should be taken into account and such patients excluded when applicable.
4. With skin and skin structure infections being both a clinically and microbiologically driven indication (i.e., efficacy for both is needed for drug approval), patients who do not have an initial culture should be excluded. However, a negative culture would not discontinue a patient. That patient should still be followed for clinical efficacy.

E. Drug Dosing and Regimens

1. Investigational Agent

In clinical settings where the activity of the antimicrobial agent can be affected by environmental factors, studies should be done to evaluate this. For example, an agent that is less active in an acidic environment (as seen with aminoglycosides) may need to be given at a higher dose when treating an abscess.

2. Comparator Agent

Due to the multiple presentations of these infections and, thus, the use of multiple treatment regimens in clinical practice, there is the potential problem that a clinical trial may have no one comparator agent used frequently enough to compare with the investigational agent. In light of this, the sponsor should clearly specify the comparator (or give one or two appropriate options) to be used in the trial.

It is also appropriate to compare agents administered via different routes of administration. For example, an investigational topical agent could be compared to an approved *first-line* oral agent, or an investigational oral agent could be compared to an approved *first-line* intravenous agent. In all such cases, the sponsor should first discuss the study design with the FDA so as to resolve such issues as blinding.

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3. Adjunctive Therapy

With both uncomplicated and complicated skin and skin structure infections, adjunctive therapy is commonly used. Included among these are: daily dressing changes; use of topical solutions including antimicrobial agents such as Betadine; daily debridement. Because these are considered to be "standards of therapy," the disqualification of patients who receive adjunctive therapy may lead to major enrollment problems. Thus, the sponsor should clearly specify which adjunctive therapies are to be allowed and which would potentially disqualify a patient. With proper blinding and randomization, both the investigational agent arm and the comparator arm should have comparable use of these adjunctive therapies.

4. Minimum Duration of Therapy

The length of therapy needed may vary from condition to condition, with complicated skin structure infections most likely needing longer courses. The course of therapy chosen should be based on appropriate preclinical data and discussed with the agency prior to study initiation.

5. Switch in Therapy

The sponsor should select the criteria necessary to allow a switch from an intravenous agent to an oral agent prior to study initiation. This is usually based upon the afebrile period prior to the switch (e.g., 24 or 48 hours with the patient being afebrile would allow for the switch to be made) and also upon certain clinical criteria (e.g., extent of erythema, formation of granulation tissue). These criteria should be discussed with the FDA prior to study initiation. Prior to switching, a full assessment (including cultures) of the patient should be done.

F. Evaluation

1. Pre-Therapy Visit

Microbiologic Tests: At the time of enrollment, all patients (regardless of the disease type) should have appropriate cultures obtained. Following are several caveats.

For superficial skin infections, open impetigo, and open superficial wound infections, after vigorous debridement of an infected area, a swab from the base of the lesion, sent for aerobic culture should suffice. However, in cases where such a lesion is in an anatomical site where anaerobes are potential pathogens (e.g., rectal area lesions or when a foul-smelling discharge from a postoperative wound is present), anaerobic cultures should be

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obtained as well. Antimicrobial susceptibility testing should be done on potential pathogens isolated.

For cellulitis and erysipelas, a leading edge needle aspiration culture should be obtained and sent for aerobic culture and antimicrobial susceptibility testing. In addition, two sets of aerobic blood cultures should be obtained as well.

For complicated skin and skin structure infections, deep cultures (such as from a biopsy, needle aspiration, surgically obtained specimens or fluids/pus) of an area contiguous to the infected burn, ulcer or wound should be obtained. Swabs are not acceptable. Specimens should be sent for aerobic, anaerobic, mycobacterial and fungal cultures, as the clinical picture indicates. For anaerobic cultures, proper anaerobic transport methods should be followed. In addition, two sets of blood cultures (both aerobic and anaerobic) should be obtained prior to study drug initiation. Antimicrobial susceptibility should be performed on the isolated pathogens.

Only microorganisms accepted as pathogens should be considered as valid when determining the microbiologic evaluability of a patient. Patients who grow only transient or resident skin flora on the pre-therapy culture should be found to be microbiologically unevaluable. A list of accepted pathogens should be created by the sponsor prior to study initiation, and should be discussed with the FDA. This is especially important in complicated skin and skin structure infections where the potential number of pathogens is great.

In all cases, Gram's stains of the specimen are helpful and should be encouraged. This is of special importance in cases where prior anti-infective therapy was initiated.

Safety studies: Please refer to the General Comments section for full details.

Prior anti-infective therapy: As noted previously, prior anti-infective use, even up to the day of patient enrollment, would be acceptable if a culture is obtained showing the persistence of a pathogen. Because of the slow resolution of inflammation in many skin and skin structure infections (such as cellulitis) a clinical picture alone, without the positive culture, would be inadequate to enroll a patient on prior anti-infective therapy.

2. On-Therapy Visit

Assessments During Therapy: Please refer to the General Comments section for more details. It should be noted that the number and timing of assessments during therapy may vary depending upon the study drug and the diagnoses (uncomplicated or complicated). Additionally, interventions, (i.e., daily debridements, dressing changes), are allowed if the

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study protocol clearly defines their limits. Such interventions should be considered the standard of care and should not be done only to help the efficacy rate of the study drug. There are situations in which an intervention should be considered a sign of a clinical failure, and these should be discussed with the FDA and spelled out in the study protocol. An example of this would be an unplanned incision and drainage (I&D) of an abscess several days after therapy had been started.

In situations where an intravenous agent may be switched to an oral agent, the sponsor should discuss within FDA prior to study initiation which criteria may be needed to qualify a patient for such a switch. Commonly used criteria are a period of apyrexia and appearance of the skin infection. A full assessment (including attainment of microbiologic specimens for culture and Gram's stain) should be performed prior to the transition being made.

3. End-of-Therapy Visit

Medication Related Questions: Please refer to the *General Considerations* guidance for more information. In regard to the study medication, several important points to consider are:

- a. Patients should receive between 80-120% of the proposed duration of therapy.
- b. There may commonly be situations where patients receive a course of therapy longer than the protocol specifies. In general, patients who receive greater than 120% of the protocol specified course should be found unevaluable. However, if an extension of therapy (meaning greater than 120% of the intended course) is found to be a common occurrence, the sponsor may be asked to recommend a longer course.
- c. Daily dressing changes, with the application of antimicrobials, (i.e., Betadine) can be allowed if specified in the study protocol and if the patients are properly randomized.

4. Post-Therapy Visit

Timing: The timing of the test-of-cure visit (the visit whose assessments should be used to evaluate the clinical and microbiological response) should be at least seven days after the tissue levels of the study drug have gone lower than the MICs of the expected pathogens. Thus, for most anti-infectives, an appropriate window for the test-of-cure follow-up visit would be 7 to 14 days after completion of therapy. For such agents where

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tissue levels remain elevated for days after completion of therapy, a window of 14 to 21 days would be more appropriate. Please refer to the General Comments section for more details.

Assessments: All clinical assessments performed at the pre-therapy and on-therapy visits should be done at the follow-up visits. In cases where a case report form or tabulation only allows the investigator to state if a patient was cured/improved/not cured and does not leave room for reporting clinical assessments, the FDA retains the right to find all such patients as unevaluable.

Appropriate microbiologic specimens should be obtained in all patients at the follow-up visits, if there is a focus to culture. In situations where the skin infection has healed to the extent that microbiologic specimens can not be obtained, patients should be seen as *presumed eradications*. The specimens obtained should be cultured in the same way as at the pre-therapy visit. An important aspect to follow in all follow-up cultures is the development of resistance to the study drug. Thus, if a pathogen is isolated on a follow-up culture, antimicrobial susceptibility testing should be done.

The need for safety studies, and the type of safety studies needed should depend upon the study drug and should be discussed with the FDA prior to study initiation.

G. Outcome Categories

With demonstration of both clinical and microbiologic efficacy needed for an investigational drug to be approved for the treatment of either complicated or uncomplicated skin and skin structure infections, all patients should have pre-therapy cultures. However, with a percentage of pre-treatment cultures inevitably showing no growth of pathogen, patients can be found to be either clinically and microbiologically evaluable or clinically evaluable alone, depending upon the circumstances as described below:

1. Clinical Outcome

The following criteria should be met:

- No violations of inclusion/exclusion criteria
- Pre-treatment culture obtained
- An adequate description of the patient's infected area/lesion has been provided (as has been described before)

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- Adequate length of therapy i.e., 80-120% of the protocol specified course (usually in days, not doses) or at least 2 full days of therapy for patients deemed to be failing while on therapy
- No use of concomitant antimicrobial therapy
- Adequate follow-up visit (at or after the timing for the test-of-cure visit), with a full description of the infected area provided in the patient's record, and a culture obtained (if an appropriate site to culture is available)

2. Clinical and Microbiological Outcome

- Meet clinical criteria as described above
- Growth of pathogens on an adequate pre-treatment culture, and antimicrobial susceptibility testing
- Adequate follow-up visit, with repeat culture and antimicrobial susceptibility testing (if an appropriate site to culture is available)

3. Efficacy Outcome

A separate clinical and microbiologic evaluation should be done on each patient. The options for a response should be either *cured* (or *eradicated* for microbiologic response) or *not cured* (or *not eradicated*), with all unevaluable patients considered unevaluable.

4. Clinical Response

Patients who have the following at the test-of-cure visit (or at a later date if they failed to come to this visit), should be considered cured:

Total resolution of all signs and symptoms of the infection, or improvement of the above to such an extent that no further antimicrobial therapy is necessary.

5. Microbiological Response

This should be done both on a patient level and a pathogen level. Patients who have the following at the test-of-cure visit (or a later date if they failed to come to this visit) should be considered as having had their pathogen eradicated:

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- No growth of either the pre-treatment pathogen or of a new potential pathogen on a post-therapy culture **or**
- A post-therapy culture was not obtained due to lack of culturable material, secondary to an adequate clinical response

All clinical failures should have a repeat culture and antimicrobial susceptibility testing, especially in an age where resistance development is not uncommon.

6. Clinical and Microbiological Response Resolution

In the vast majority of cases, the clinical and microbiologic cure rates should be consistent, with an explanation provided for cases where they are not. Two such situations are:

a. Clinical Cure/Microbiological Not Cure

In such situations, consideration should be given to whether the repeat positive culture is showing the growth of a true pathogen or of a colonizer/contaminant. In a large number of skin and skin structure infections (such as in burns), the most common pathogens are also common skin flora, which may make evaluation of culture results difficult.

b. Clinical Not Cured/Microbiological Cure

In complicated skin and skin structure infections, either underlying medical conditions or a large inflammatory component to the underlying process (such as seen in decubitus ulcer) may make it difficult to adequately evaluate the patient clinically. In such cases, a longer post-treatment follow-up period should be considered. However, in no situation should a microbiologic response alone be viewed as proof of clinical efficacy.

7. Therapeutic Response

This refers to a combined overall efficacy response where patients who have been deemed as both clinically cured and microbiologically eradicated are called overall cures. All other combinations of results are seen as failures. The majority of cases should have the same response both clinically and microbiologically, and an effort should be made to explain discrepancies. Please refer to the *General Considerations* guidance for more details concerning the use of *therapeutic response*.

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8. Safety Outcome:

Please refer to the General Comments section for full details.

H. Statistical Considerations

Analyses should include the intent-to-treat analysis, clinical and microbiological outcome.