

Acceptance Program Guidelines

Determination of Efficacy in Product Evaluation



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Council on Scientific Affairs

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Scope:

These guidelines list the general requirements for demonstrating superiority, equivalency, and “at least as good as” properties for products in cases where the definition of those properties is based on mean values. Product acceptance often entails a suitable comparison of efficacy between the product and an existing product or appropriate control (e.g., superior to a control or equivalent to an existing, approved product). The present guidelines are not intended to serve as stand-alone requirements for any agent or product; rather, they provide a general setting to which specific product-related guidelines refer.

Properties of superiority, equivalence, or “at least as good as” can be considered in varying contexts, such as the determination of product efficacy, product safety, product stability, etc. However, a clearer discussion of these properties can be enjoyed when they are phrased in the terminology of a specific context. Thus, in the material that follows, the discussion of superiority, equivalence, and “at least as good as” is presented in the language and context of studies of product efficacy. However, it must be stressed that these concepts are by no means limited to efficacy considerations.

I. INFORMATION TO BE SUBMITTED TO SUBSTANTIATE EFFICACY IN PRODUCT EVALUATION

1. Cover Page

A Name of company

B Product name

2. Table of Contents

3. Clinical Studies

At least two independent clinical studies are required for superiority, equivalency, or "at least as good as" demonstration. Such studies should conform to the general principles detailed in the specific guidelines for the product. Furthermore, such studies must demonstrate a level of efficacy for the control or contrasted product that is consistent with published and/or available clinical data when possible. If the results for the control product are not consistent with these data, appropriate justification for the difference must be provided. In each case, the specific product guidelines enumerate particular clinical parameters (e.g., plaque index, decayed-missing-filled surfaces [DMFS], etc.) to which the following general principles are applied. Any exceptions to the criteria that follow are specified in the specific product guideline documents.

Note: The following material is written from the perspective that a lower score on a given clinical outcome parameter represents a "better" state of dental health. This is certainly true for many clinical parameters, such as gingival index, plaque index, DMFS, etc. In the event that circumstances entail the use of a parameter for which higher scores represent "better" states of dental health (such as scratchometer measurements obtained in hypersensitivity trials), the "sidedness" inherent in the following material should be reversed to appropriately accommodate the parameter being used.

A Demonstration of superiority

The superiority of a given therapeutic test agent entails that that agent will provide a meaningful, additional health benefit over the Control product(s) to which it is being compared (see Section 4 for additional details).

In demonstrating superiority in the efficacy of any given Test agent over a given Control agent, the magnitude of "additional health benefit" must be specified. This is done in terms of a percentage, which is designated in these guidelines as "S%." Thus, the Test agent is considered as providing superior efficacy to the Control agent if the mean outcome response for the Test agent is no greater than (100 - S%) of the mean outcome response for the Control agent.

For example, if S% is specified as 10%, the Test agent will be deemed superior to the Control agent if its mean response does not exceed 90% (i.e., 100 - S%) of the mean response for the Control agent.

Once the value of S% has been specified for a given outcome parameter (see Section 4), the following two criteria must be successfully attained for the results of a given study to support superiority:

- (i) The mean value of the outcome parameter for the Test agent must be shown to be significantly improved compared to the mean value for the Control agent in a one-sided test performed at the $\alpha=0.05$ level of significance.
- (ii) The *observed* mean value of the outcome parameter for the Test agent must be shown to be no greater than (100 - S%) of the *observed* mean value for the Control agent.

B Demonstration of Equivalency

The equivalence of a given Test agent to a given Control agent entails that the therapeutic benefits provided by those agents are so close as to suggest that the two agents could be used interchangeably without any meaningful effect on therapeutic outcome.

In demonstrating the equivalence of a given Test agent to a given Control agent, a quantitative definition of what is meant by “closeness of therapeutic benefits” must be provided. This is done by specifying two percentages, L% and U%, where L% (for “lower”) is less than 100% and U% (for “upper”) is greater than 100% (together, these two percentages are sometimes referred to as defining the “range of equivalence”). The Test agent is considered equivalent to the Control agent if its observed mean outcome response lies within the range from L% to U% of the true mean outcome response for the Control agent.

For example, if L% is set equal to 90% and U% is set equal to 110%, a Test agent will be deemed equivalent to a Control agent if the observed mean outcome response for the Test agent is greater than 90% of the response for the Control agent and less than 110% of the response for the Control agent.

Once the values of L% and U% have been specified (in these guidelines, L% is 90% and U% is 110%), the following criterion must be successfully attained for the results of a given study to support equivalence:

- (i) The results of the study must support the inference that the *observed* mean score associated with the Test agent lies between 90% and 110% of the *observed* mean score associated with the Control agent.

This criterion can be addressed in any number of ways. Among the methods currently in use are the Fieller Confidence Interval approach and the “Two One-sided Tests” approach.

(a) Fieller Confidence Interval approach

Construct a 90% confidence interval for the ratio of observed mean scores using Fieller’s theorem (the ratio considered is Test mean divided by the Control mean). The criterion above is met if the resulting confidence interval lies entirely within the range of values from L% to U%.

(b) “Two One-sided Tests” rule

Perform a one-sided hypothesis test ($\alpha=0.05$) to determine whether it can be concluded that the observed mean response for the Test agent is less than U% of the observed mean response for the Control agent, and separately perform a one-sided hypothesis test ($\alpha=0.05$) to determine whether it can be concluded that the observed mean response for the Test agent is greater than L% of the observed mean response for the Control agent. The criterion above is satisfied if statistical significance is attained in both of these tests.

- (ii) When a study involves both a placebo agent (negative control) and previously Accepted products (positive control), compared Accepted products must be found to be statistically significantly better than placebo for principal outcome variables in the equivalency studies.

c Demonstration of “at least as good as”

To say that a given therapeutic Test agent is “at least as good as” a given Control agent, the benefit provided by the Test agent must be adequately large enough so that individuals who might switch from using the Control agent to the Test agent will not undergo a meaningful loss of benefit and, in fact, may enjoy a greater benefit than provided by the Control agent.

“At least as good as” might better be understood by considering its relationship to the property of “equivalence.” For equivalence of a Test and Control agent, the mean outcome score for the Test agent is not too much higher nor too much lower than that of the Control agent—that is, the observed mean responses are “close.” The property of “at least as good as” requires that the mean of the Test agent not be too much higher than that of the Control agent; it does not require that the mean of the Test agent be not too much lower than the mean for the Control agent. Thus, this property requires that the observed mean score for the Test agent does not vary too much from that for the Control agent “on the ineffective side.”

In demonstrating that a given Test agent is “at least as good as” a given Control agent, a quantitative definition of what is meant by “large enough therapeutic benefits” must be provided. This is done by specifying a single percentage, which is designated as U% (note that U% is greater than 100 %). The Test agent is considered as “at least as good as” the Control agent if the Test agent’s observed mean outcome response is no greater than U% of the observed mean outcome response for the Control agent.

For example, if U% is set equal to 110%, then a Test agent will be deemed as “at least as good as” a Control agent if the observed mean outcome response for the Test agent is no greater than 110% of the response for the Control agent.

Once the value of U% has been specified (in these guidelines, U% is 110%), the following criterion must be successfully attained for the results of a given study to support that the Test agent is “at least as good as” the Control agent:

- (i) The results of the study must support the inference that the observed mean score associated with the Test agent lies at or below 110% of the observed mean score associated with the Control agent.

This criterion can be addressed in various ways. For example, the Fieller approach to equivalence described above can be invoked, with the criterion satisfied when the entire 90% Fieller Confidence Interval consists of values no greater than 110%. Alternatively, a single, one-sided test can be performed ($\alpha = 0.05$) to determine if the observed mean score associated with the Test agent is less than 110% of the observed mean score associated with the Control agent.

4. **Efficacy Requirements for Superiority**

As indicated in Section 3, the results from two independent clinical studies must result in a statistically significant improvement in an oral health benefit for superiority to be demonstrated over a compared product. Furthermore, for the listed products, this additional benefit must conform quantitatively to the values given in the Table. The magnitude of the increased benefit depends somewhat on the type of product and its role in a total dental health regimen. If the type of product is not listed in the Table, the advice of the Council on Scientific Affairs must be sought.

5. **Additional Requirements for Specific Products**

- A Dental floss and other interdental cleaners
Demonstration of superiority or equivalency for interproximal plaque removal must comply with the gingivitis reductions given in the Table.
- B Agents to slow or arrest periodontitis
Demonstration of superiority or equivalency for these products is based on improvement in periodontal attachment levels. For superiority, the studies must demonstrate a statistically significant improvement over scaling and root planing and/or the product(s) to which it is compared.
- c Chemotherapeutic agents to control gingivitis
Demonstration of superiority for plaque reduction must comply with the gingivitis reductions listed in the Table.

- D Fluoride-containing dentifrices
Demonstration of superiority or equivalency for caries prevention also is considered. The quantitative improvement in caries prevention for demonstration of superiority must be equivalent to the caries reduction value in the Table.
- E Products designed to regenerate periodontal tissues
Demonstration of superiority related to oral health benefits, (e.g., gain in periodontal attachment and alveolar bone formation) requires two studies unless there is a predicate device. If a predicate device exists, only one clinical study is required. Demonstration of equivalence requires two clinical studies.
- F Products for the diagnosis or management of periodontitis
Clinical studies for demonstration of superiority or equivalency should compare the novel diagnostic methods system with conventional methods (e.g., periodontal probes, radiographs, etc.).

6. **Appendices**

Detailed description of clinical evaluation methods and any other defined areas.

II. REFERENCES FOR FURTHER EXPLANATION

The following references were used in the development of these guidelines. They can be consulted for a more detailed discussion of issues addressed in these guidelines.

- A Proskin HM, Kingman A, Naleway C, Wozniak WT. Comparative Attributes for the Description of the Relative Efficacy of Therapeutic Agents: General Concepts and Definitions, and Application to the American Dental Association Guidelines for the Comparison of the Clinical Anticaries Efficacy of Fluoride Dentifrices. *J Clin Dent* 1995; 6:176-184.
- B Imrey PB, Chilton NW, Pihlstrom BL, et al. Proposed Guidelines for American Dental Association Acceptance of Products for Professional Non-Surgical Treatment of Adult Periodontitis. *J Periodont Res* 1994; 29 348-360.

Table—Additional Oral Health Benefit Required For Demonstration of Superiority

Type of Therapeutic Product	Oral Health Benefit (S%) Required	100†-†S%
Manual toothbrushes	15% reduction of gingivitis	85
Powered toothbrushes	15% reduction of gingivitis	85
Dental floss and other interdental cleaners*	15% reduction of gingivitis	85
Oral irrigators	15% reduction of gingivitis	85
Adjunctive dental therapies	15% reduction of gingivitis	85
Chemotherapeutic agents to control gingivitis*	20% reduction of gingivitis	80
Fluoride-containing dentifrices*	10% improvement in caries reduction	90
Products to regenerate periodontal tissues*	25% gain in periodontal attachment (see Section 5E)	75
Other product categories*	Seek specific Council direction on appropriate S% value	

* Additional requirements for these product categories, see Section 5.

