Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry

DRAFT GUIDANCE

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

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GRZAN

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Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist potential applicants who plan to develop and submit an abbreviated new drug application (ANDA) to seek approval of a proposed combination product that includes both a drug constituent part and a delivery device constituent part.[2] The recommendations included in this guidance generally focus on the analysis of the proposed user interface for the generic[3] drug-device combination product (generic combination product) when compared to the user interface for the reference listed drug (RLD). For the purposes of this guidance, the term user interface refers to all components of the combination product with which a user interacts. This includes the delivery device constituent part of the combination product and any associated controls and displays, as well as product labeling and packaging.

In the early stages of development, potential applicants should carefully consider the design of the user interface of a proposed generic combination product and seek to minimize differences from the user interface for the RLD. To facilitate that process, this guidance provides general principles, including how to conduct threshold analyses for the identification and the assessment of differences in the design of the user interface for the proposed generic combination product when compared to its RLD.

Depending on the results of the threshold analyses discussed in this guidance, submission of additional data may be warranted, such as data from comparative use human factors studies, to assess the acceptability of differences identified in the user interface for the proposed generic

[1] This guidance has been prepared by the Office of Generic Drugs and the Office of Surveillance and Epidemiology in the Center for Drug Evaluation and Research (CDER), with the assistance of the Office of Combination Products and the Center for Devices and Radiological Health at the Food and Drug Administration.

[2] Products that include both a drug constituent part and a device constituent part are regulated as combination products. *See* 21 CFR Parts 3 and 4. Combination products within the scope of this guidance are those with a drug primary mode of action. Therefore, CDER will have primary jurisdiction for the review of these combination products and will coordinate with the Center for Devices and Radiological Health as appropriate.

[3] The term *generic* in this guidance refers to a product for which approval is sought under an ANDA.

combination product as compared to the user interface for the RLD. Applicants may consider modifying the design of the generic combination product to minimize differences from the RLD to avoid conducting comparative use human factors studies. To the extent an applicant conducts comparative use human factors studies, this guidance provides recommendations on the design and conduct of such studies.

FDA's guidance documents do not generally establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) (the Hatch-Waxman Amendments) created, among other things, section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Under section 505(j), an ANDA applicant can rely on FDA's previous finding that the RLD is safe and effective so long as the ANDA applicant demonstrates that the proposed drug product and the RLD are the same with respect to active ingredient(s), dosage form, route of administration, strength, and, with certain exceptions, labeling.[4] An ANDA must also include sufficient information to demonstrate that the proposed product is bioequivalent to the RLD, and that the ANDA meets the approval requirements relating to chemistry, manufacturing, and controls (CMC). An ANDA generally is not required to be the same as the listed drug it references in certain respects. For example, a generic drug generally can differ from its RLD in certain respects with regard to the device or with respect to inactive ingredients.

Drug products that are approved in ANDAs are generally considered by FDA to be therapeutically equivalent to their RLD. Products classified as therapeutically equivalent can be substituted with the full expectation that the generic product will produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling.[5]

These general principles apply to products submitted in ANDAs, including drug-device combination products.[6] A generic combination product classified as therapeutically equivalent to the RLD can be expected to produce the same clinical effect and safety profile as the RLD under the conditions specified in labeling. This does not mean, however, that the proposed generic combination product and its RLD need to be identical in all respects. FDA recognizes that an identical design may not always be feasible and, in certain instances, differences in the design of the user interface for a generic combination product as compared to the RLD may exist without

[4] See, e.g., sections 505(j)(2)(A) and 505(j)(4) of the FD&C Act and 21 CFR 314.94 and 21 CFR 314.127.

[5] *Therapeutic equivalents* are approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. *See* 21 CFR 314.3; *See* also FDA's *Approved Drug Products with Therapeutic Equivalents* (the Orange Book), preface to the 36th edition, at page vii.

[6] See, e.g., sections 505(j)(2)(A), 505(j)(4), and 503(g)(1) of the FD&C Act.

precluding approval of the generic combination product under an ANDA.[7] In some instances in which differences exist, certain additional information and/or data relating to the user interface of the proposed generic combination product, such as data from comparative use human factors studies, may be appropriate to support approval of the proposed generic combination product in an ANDA.[8] The extent to which differences between the proposed product and the RLD affect the approvability of the proposed ANDA product will be evaluated on a case-by-case basis.

FDA does not consider the comparative use human factors studies described in this guidance to be clinical investigations intended to demonstrate the safety or effectiveness of the proposed generic combination product. Rather, the comparative use human factors studies described in this guidance are intended to confirm that the differences in device and labeling between the generic combination product and RLD are acceptable and that the proposed generic combination product can be substituted with the full expectation that the generic combination product will produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling. FDA intends to consider whether the generic combination product can be substituted for the RLD without the intervention of a health care provider and/or without additional training prior to use of the generic combination product.

III. SCOPE

This guidance addresses generic combination products that include a drug and a delivery device intended to administer a drug product. Such products include, for example, products where the delivery device constituent part and the drug constituent part of the product are a single entity (e.g., pre-filled syringe, auto-injector),[9] and products where the two constituent parts are co-packaged (e.g., drug in a vial packaged in the same box with a syringe).[10]

The recommendations in this guidance generally focus on the analysis of the proposed user interface for the generic combination product when compared to the user interface for the RLD and are not intended to address all of the information necessary to support approval of a generic combination product, including the delivery device constituent part. For example, as applicable, a general description of the entire delivery device constituent part should be provided in the CMC section of the ANDA. There should be complete CMC information for the product, including the design of the delivery device constituent part and development information. The delivery device constituent part should be shown to be compatible for use with the final formulation of the drug constituent part through appropriate studies, including, for example, extractable/leachable studies, performance testing, and stability studies. In addition, comparative in vitro performance testing data may be needed to support the delivery device constituent part of the proposed generic combination product. Potential applicants should refer to relevant FDA

[7] FDA has previously discussed the assessment of differences between a proposed generic combination product and its RLD in two citizen petition responses. *See* FDA Response to King Pharmaceuticals (Jul. 29, 2009) (Docket No. FDA-2009-P-0040) and FDA Response to Dey Pharma L.P. (May 27, 2010) (Docket No. FDA-2009-P-0578). This guidance clarifies certain aspects of those responses and represents the Agency's current thinking regarding the topics addressed herein.

[8] See, e.g., sections 505(j)(2)(A), 505(j)(4), and 503(g)(1) of the FD&C Act.

[9] 21 CFR 3.2(e)(1).

[10] 21 CFR 3.2(e)(2).

guidance documents and other resources that provide information on what data and information should be included to support the delivery device constituent part(s) of a proposed generic combination product.[11]

IV. CONSIDERATIONS FOR THE USER INTERFACE FOR A PROPOSED GENERIC COMBINATION PRODUCT

This section discusses certain data and information that may be needed to support the design of the user interface of the proposed generic combination product to support approval of the product in an ANDA. Such data and information should support that the generic combination product may be substituted with the full expectation that the generic combination product will produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling.[12] FDA intends to consider whether the generic combination product can be substituted for the RLD without the intervention of a health care provider and/or without additional training prior to use of the generic combination product. FDA expects that data and information comparing the user interface of the proposed generic combination product to the RLD's user interface will be submitted to support an ANDA application.

A. General Considerations

When developing a generic combination product for submission in an ANDA, it is important that applicants carefully consider the overall design of the user interface and should generally seek approval of a presentation approved for the RLD.[13]

FDA recognizes that a potential applicant of a proposed generic combination product may develop a user interface that has certain differences from the user interface approved for the

[11] Additional guidances that provide the Agency's current thinking on this topic or otherwise set forth relevant principles include, but are not limited to:

- Draft Guidance for Industry: MDI and DPI Drug Products; CMC Documentation (when finalized, this guidance will reflect FDA's current thinking on this topic)
- Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products; CMC Documentation
- Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products
- Draft Guidance to Industry and FDA Staff: Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4; (when finalized, this guidance will reflect FDA's current thinking on this topic)

[12] There has been some confusion regarding whether FDA expects for ANDA approval that a generic combination product be used in accordance with the labeling for the RLD. FDA does not necessarily expect for approval that a generic combination product can be used according to the RLD labeling per se, but rather it is critical that the generic combination product can be substituted for the RLD without additional physician intervention and/or retraining prior to use. To this end, a comparative use human factors study as described in this guidance could be designed to account for how a particular proposed generic combination product might be used when substituted for the RLD. See also footnote 7.

[13] If a sponsor is proposing a presentation for which the RLD is not approved (e.g., seeking approval of a generic combination product as a pre-filled syringe in instances when the RLD was approved in a vial), FDA strongly encourages the sponsor to discuss the proposed presentation with FDA via controlled correspondence and/or pre-ANDA meeting package prior to product development or submission of an ANDA.

RLD. FDA may accept such design differences if they are adequately analyzed, scientifically justified, and do not preclude approval in an ANDA. In general, FDA expects that end-users of generic combination products, including but not limited to lay-persons, such as patients, and/or caregivers, can use the generic combination product when it is substituted for the RLD without the intervention of the health care provider and/or without additional training prior to use of the generic combination product.

FDA intends to consider any differences in the design of the user interface of a proposed generic combination product and the RLD, and assess the need for additional data, such as data from comparative use human factors studies, on a case-by-case basis. The following sections describe our current thinking and recommendations for identifying and evaluating design differences between a proposed generic combination product and its RLD.

B. Analysis of the User Interface of a Generic Combination Product

For purposes of this guidance, FDA recommends that potential applicants analyze the overall user interface of a proposed generic combination product to identify differences in design when compared to the RLD. Potential applicants are strongly encouraged to utilize the threshold analyses described below throughout product development and seek to minimize differences from the RLD. These threshold analyses may also assist potential applicants in identifying differences in the user interface of a proposed generic combination product and determine whether certain data, including data from comparative use human factors studies (as described further in this section), should be submitted to support approval of a proposed combination product submitted in an ANDA.

To conduct a comparative analysis of the user interface of a proposed generic combination product and its RLD, potential applicants should examine, among other things, the external critical design attributes of the proposed delivery device constituent part in comparison to the external critical design attributes of the RLD. External critical design attributes are those features that directly affect how users perform a critical task[14] that is necessary in order to use or administer the drug product. To identify the external critical design attributes, a potential applicant should examine the overall external operating principles of the delivery device constituent part by evaluating all the tasks that an end-user needs to perform to prepare and administer the product. Among those tasks, certain ones will be identified as critical to the use of the product, and the external critical design attributes of the product would be those features that end-users rely on to safely and effectively perform those identified critical tasks. FDA recommends that potential applicants consider the external critical design attributes of the RLD beginning in the early stages of their development program.

[14] For additional information on critical tasks, see FDA draft guidance for industry *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development*, Section III.B.1: *Critical Tasks*. When final, this guidance will reflect FDA's current thinking on this topic.

1. Threshold Analyses

Three types of threshold analyses can be used throughout the development program for the purposes of identifying, evaluating, and minimizing differences in design. These analyses should also be conducted after the design for the user interface of a proposed generic combination product has been finalized by the potential applicant and is representative of the commercial product.

FDA recommends that potential applicants carefully evaluate the risks associated with any differences identified in the user interface that may affect the ability of the patient, caregiver, or other user[15] to use the product. In particular, patient and caregiver end-user groups may lack the expertise that a health care provider user group is expected to possess. Patient and caregiver user groups may be less accustomed to navigating differences in the user interface of a generic combination product than health care providers. As a result, there is concern that patients or caregivers who encounter different user interfaces, such as differences in external critical design attributes, may be at increased risk for a use-related error that may impact their ability to use a generic combination product when substituted for the RLD.

a. Types of Threshold Analyses

The following three types of analyses are recommended as part of the threshold analyses to compare the user interface of the proposed generic combination product to the user interface of its RLD:

i. *Labeling comparison*: FDA recommends a side-by-side, line-by-line comparison of the full prescribing information, instructions for use, and descriptions of the delivery device constituent parts of the generic combination product and its RLD.[16]

ii. *Comparative task analysis*: FDA recommends that potential applicants conduct a comparative task analysis between the RLD and the proposed generic combination product.[17]

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[15] For additional information about end user group considerations, see FDA draft guidance for industry *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development*, Section III.B.2. Intended Users and Use Environment. When final, this guidance will reflect FDA's current thinking on this topic.

[16] ANDAs are required to include information to show that the labeling proposed for the generic drug is the "same" as the RLD, with certain limited exceptions, such as for changes required because of differences approved under a suitability petition (see section 505(j)(2)(C) of the FD&C Act and 21 CFR 314.93), or because the generic drug and the RLD are produced or distributed by different manufacturers (see section 505(j)(2)(A)(v) of the FD&C Act). Labeling differences that stem from permissible differences in design between the user interface for the proposed generic combination product and its RLD may fall within the scope of permissible differences in labeling for a product approved under an ANDA.

[17] To conduct a comparative task analysis, sponsors should systematically dissect the use process for each product, i.e., both the proposed generic product and the RLD, and analyze and compare the sequential and simultaneous manual and intellectual activities for end-users interacting with both the products. FDA recommends that sponsors analyze the differences with the goal to characterize the potential for use error. Also see the Association for the Advancement of Medical Instrumentation/American National Standards Institute HE75: 2009-Human factors

iii. *Physical comparison of the delivery device constituent part*: FDA recommends that the potential applicant of the proposed generic combination product acquire the RLD to examine (e.g., visual and tactile examination) the physical features of the RLD and compare them to those of the delivery device constituent part for the proposed generic combination product.

b. Outcomes of Threshold Analyses

After completing the threshold analyses, the following outcomes are possible[18]:

i. *No design differences*: When no differences are identified between the user interface of the proposed generic combination product and the user interface for the RLD, it is likely that certain information and/or data, such as data from comparative use human factors studies, will not be necessary to support approval of the ANDA.

ii. *Differences in design*: If differences are identified between the design of the user interface of a proposed generic combination product and the user interface of its RLD, the sponsor should focus on whether the difference(s) involves an external critical design attribute that may potentially impact whether the proposed generic combination product can be substituted for the RLD[19] and seek to establish and categorize the differences as follows:

- *Minor design difference*: FDA views a design difference as minor if the differences in the user interface of the proposed generic combination product, in comparison to the user interface of the RLD, do not affect an external critical design attribute. Minor differences in design are likely to be viewed by FDA as acceptable provided that the data and information submitted by the applicant demonstrate that the differences are in fact minor. For example, such data and information may be collected through threshold analyses described in section IV.B.1.a of this guidance, that demonstrate that the differences in design do not involve an external critical design attribute that can impact whether the proposed generic combination product can be substituted for the RLD. Similarly, for those products that would be expected to be administered only by a health care provider, the risks associated with substitution may be adequately addressed through threshold analyses rather than a comparative use human factors study. As mentioned previously, patient and caregiver end-user groups may be less accustomed to navigating differences in user interfaces among drug products than health care providers.

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engineering—Design of medical devices. The standard can be accessed at http://my.aami.org/aamiresources/previewfiles/HE75_1311_preview.pdf.

[18] Prior to submitting an ANDA for a generic combination product, potential applicants are strongly encouraged to contact FDA via controlled correspondence and/or pre-ANDA meeting package to discuss the applicant's proposed product. This communication should include a prototype of their proposed generic combination product, a sample RLD, and the results of threshold analyses described in this guidance.

[19] In assessing the significance of differences of design, potential applicants should consider the impact of the identified difference(s) in the context of the overall risk profile for the product.

- *Other design differences*: FDA may not view a design difference as minor if any aspect of the threshold analyses suggests that differences in the design of the user interface of a proposed generic combination product as compared to the RLD *may* impact an external critical design attribute that involves administration of the product. In such cases, the potential applicant should first strongly consider modifying the design of the user interface (e.g., delivery device constituent part) to minimize differences from the RLD. Alternatively, if such differences are present in the final design of the user interface of the proposed generic combination product, FDA may request that applicants provide additional information and/or data, such as data from a comparative use human factors study, to address whether the differences identified in the user interface introduce a risk that might impact the clinical effect or safety profile of the generic combination product as compared to the RLD when the generic combination product is substituted for the RLD. Based on the results of additional studies, FDA may or may not determine that the design difference(s) between the user interface of the proposed generic combination product and the RLD is acceptable for a proposed generic combination product.

2. Studies to Evaluate Differences That May Not Be Minor as Observed in Threshold Analyses

If the threshold analyses determine that a design difference may not be minor, as described in section IV.B.1 of this guidance, potential applicants should first consider modifying the design of the user interface (e.g., delivery device constituent part) for the proposed generic combination product to minimize differences from the RLD. Alternatively, FDA may request data to support that the user interface design difference(s) will not preclude approval of the generic combination product in an ANDA. Such data may be gathered in a comparative use human factors study that evaluates user performance of the critical tasks related to the external critical design attributes that are found to be different. In addition, there may be instances in which a comparative use human factors study is limited to the patient, caregiver and/or health care provider end-user group(s) that are most likely to be impacted by the differences in the design of the presentation of the proposed generic combination product compared to its RLD.

Comparative Use Human Factors Studies

Comparative use human factors studies may be warranted to provide the data to assess whether differences that may not be minor in the design of the user interface of a proposed generic combination product would preclude its approval under an ANDA. The objective of the comparative use human factors studies described in this guidance is to demonstrate that the use

error rate, associated with a change in an external critical design attribute for the proposed user interface, does not preclude approval of the proposed product in an ANDA.[20]

See Appendix A of this guidance for considerations on the design and conduct of comparative use human factors studies, when appropriate, to evaluate differences that may not be minor, as observed in threshold analyses.

APPENDIX A

Considerations for comparative use human factors studies to evaluate differences that may not be minor as observed in threshold analyses, where appropriate: [21]

i. Study Design Considerations

A comparative use human factors study, as discussed in this guidance, should be designed to provide sufficient data to confirm that the use error rate, for the critical task(s) as impacted by the differing external critical design attribute of the delivery device constituent part for the proposed generic combination product, is not worse than the corresponding use error rate for the RLD when used by patients and caregivers in representative use scenarios and use environments consistent with the labeled conditions of use. The comparative use human factors studies described in this guidance would generally be simulated-use studies[22] where the participants, who are representative of the patients and caregivers, are asked to simulate the use of the proposed generic combination product without actually administering the product.

For the purpose of the comparative use human factors studies described here, the risks associated with the user interface are derived from errors that occur in using the delivery device constituent part of the proposed generic combination product. FDA would generally accept a proposed generic combination product that had the same rates of error as the RLD, as demonstrated by an adequately designed comparative use human factors study or studies. However, we also recognize that lower error rates for a proposed generic combination product compared to error rates for the RLD would not necessarily preclude a finding of therapeutic equivalence. Therefore, lower bounds on error rates are generally not necessary in comparative use human

[20] Potential applicants should note that the objective of a comparative use human factors study differs from the objective of human factors validation studies. Specifically, human factors validation studies are not designed to assess differences in use error rates for specific external critical design attributes between two products. Therefore, the human factors validation report and studies, as described in FDA's guidance entitled, "Applying Human Factors and Usability Engineering to Medical Devices," are separate and distinct from the comparative use human factors study described in Appendix A.

[21] Potential applicants are strongly encouraged to discuss their proposed design of a comparative use human factor study, including determining the value of *d* for the specific proposed test product, prior to conducting a comparative use human factors study. This can be done through pre-ANDA meeting request or controlled correspondence submitted to FDA.

[22] For more information on simulation techniques, see FDA draft guidance for industry *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development*, Section D.1. Human Factors Simulated Use Validation Studies. When final, this guidance will reflect FDA's current thinking on this topic.

factors studies described here. For this reason, instead of using equivalence designs, noninferiority (NI) study designs are generally appropriate in such situations. NI tests comparing use error rates with the delivery device constituent part of a proposed generic combination product to those of the RLD are similar to usual statistical tests for a difference, but translated to account for allowable differences in error rates between the proposed generic combination product and its RLD.

In comparing pharmaceutical products, NI tests are often conducted to indirectly demonstrate that a proposed product is more efficacious than a placebo.[23] In contrast, a comparative use human factors study with an NI design as described in this guidance is intended to help confirm one aspect of the substitutability of a proposed generic combination product for its RLD, and not for determining differences relative to a placebo.

Careful consideration should be given to the design of the NI study. Using the result of the threshold analyses described earlier as a guide, a risk assessment should be done to identify the external critical design attributes and their impact to critical task performance for each end-user group, use scenario, and use environment consistent with the approved conditions of use for the RLD. FDA recommends that patient and caregiver (if applicable) end-users of the RLD be considered for inclusion in the comparative use human factors study. The risk assessment should explore risks for the various subgroups of the current patient and caregiver end-user groups and may identify an appropriate subpopulation on which to focus the comparative use human factors study. For example, in some cases, the risk assessment may determine that only a certain patient subpopulation (or subpopulations) is likely to experience difficulty administering the product, and thus the comparative use human factors study may be most appropriately focused on the identified patient subpopulation(s). If substitution is demonstrated in a higher-risk subgroup, an applicant would generally not be expected to conduct comparative use human factors studies in lower-risk subgroups.

The primary endpoint for a comparative use human factors study in the context of a generic combination product will be the rates of errors observed when using the proposed generic combination product when compared to the use rates when using the RLD. In this guidance, we use the notation ER_T and ER_R to represent the error rates observed when using the presentation associated with the proposed generic combination product (T) and that of the RLD (R), respectively.

The goal of a comparative use human factors study with an NI design intended to support the approval of a generic combination product is to demonstrate that for each critical task impacted by a change in critical external design attribute, ER_T is no greater than $ER_R + d$, where d is some acceptable deviance above ER_R. In determining the margin d, the variability in ER_R, which is an expected observation when conducting an experiment on any product, should be considered as well as the risk any difference in outcomes will pose to patients. That is, the value of d will

[23] For additional insight, see the draft guidance for industry *Non Inferiority Clinical Trials*. When final, this guidance will reflect FDA's current thinking on this topic.

differ between products, depending on the indication(s) and the clinical consequences associated with failing to perform the critical tasks appropriately.[24]

The results of the risk assessment should be considered when determining the NI margin (*d)* between ER_R and ER_T. The best choice of *d* enables creating a statistical test through which one can demonstrate that the error rate using the proposed generic combination product will not be unacceptably greater than that of the RLD while acknowledging and allowing for the inherent variability in use error rates.[25]

An example of a simple and direct approach to an NI test comparing ER_T and ER_R can be summarized as follows:

- Determine the allowable margin (*d*) by which ER_T could exceed ER_R.
- Calculate the study sample size considering assumed error rates and *d*.
- Observe error rates for the critical task(s) during the experiment.
- Perform the statistical hypothesis test:
    - H_0: $ER_T - ER_R > d$
    - H_A: $ER_T - ER_R \leq d$

Rejecting the null hypothesis (H_0) in favor of the alternative hypothesis (H_A) supports the claim of NI as defined by *d*. Typically, the acceptable Type I error probability (α) will be set at 5%.

The NI test may be performed by comparing the upper bound of the appropriate level confidence interval for the difference in event rates to *d*. This would be 95% if the type 1 error as stated above is set at 5%. If the upper bound is less than *d*, NI is demonstrated.

Paired designs and parallel designs are appropriate approaches to the NI studies discussed here. A paired design in which each end-user uses both presentations and acts as his or her own control will generally be applicable and more efficient with respect to resources than a parallel design. When using a paired design, subjects should be randomly assigned to the sequence of use, such as AB or BA in order to control for the effects associated with order, such as user learning. Parallel group designs in which end-users are randomized to groups using one or the other presentation are also viable in situations where paired designs are not possible. Sponsors are advised to propose and discuss study designs with FDA before initiating studies.

ii. Sample Size Considerations

The sample size of a comparative use human factors study should be adequate to support a demonstration that design differences of a generic combination product do not impact the product's clinical effect or safety profile compared to the RLD. The sample size required to support a showing that the difference between ER_R and ER_T is negligible depends on conditions

[24] The acceptable margin should be decided in consultation with the FDA before the study is conducted.

[25] Note that if we were to set *d=0*, the condition would be tantamount to requiring that the proposed product presentation be superior to that of the RLD, which is not the goal for this testing.

under which the experiment is run. The sample size of a paired design, as mentioned above, will depend on the margin (*d*), within-subject correlation, the underlying use error rates, desired statistical power and allowable Type I error probability.

Within-subject correlation can be thought of as the "closeness" of individual's outcomes using both devices. For example, a high level of this correlation can be interpreted to mean that a given person being able to properly use one device tends to imply that same person will have a high likelihood of being able to operate the other. This correlation is one reason paired designs often require fewer subjects than parallel designs.

The table below shows some examples of power simulations under assumed experimental conditions for a paired comparison of error rates. These numbers are provided as examples only, and sample sizes for specific product studies will depend on the settings under which they are conducted. The desired sample size for each user group population or set of circumstances will be a function of the assumed use error probability, the within subject correlation, and statistical power to rule out the chosen d. In general, these sample sizes can range from 50 to 100 or more when the d =.10 and desired statistical power ranges from 75% to 90% and use error probabilities range from 15% to 30%. Sample sizes generally will be smallest as the within subject correlation approaches one.

Power of Paired Design to Compare Use Error Rates under Various Assumptions.

Power (%)	Within-subject Correlation	Use Error Probability (%)	Sample Size
85	0.90	10	45
83	0.90	20	50
80	0.90	30	55
80	0.90	40	60
80	0.70	10	55
81	0.70	20	75
81	0.70	30	90
81	0.70	40	100
80	0.50	10	70
80	0.50	20	110
80	0.50	30	135
81	0.50	40	155

Simulated power given selected sample sizes, assuming equal success probabilities, a= 0:05 and d = 0:10 and using the method of Tango [Statist. Med. 17, pp. 891-908 (1998)]. 2500 simulated clinical trials were used for each table line.