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# Reference-Scaled Average Bioequivalence (RSABE) Approach For Drugs With A Narrow Therapeutic Index (NTID) Using Phoenix™ WinNonlin®

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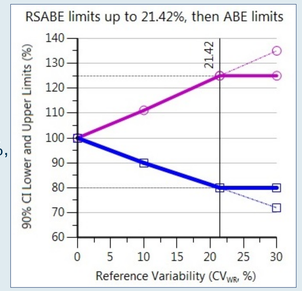
## PURPOSE

Drugs with a narrow therapeutic index (NTIDs) have a narrow range between therapeutic and toxic dose levels. Traditional average bioequivalence (ABE) methodology may be unacceptable for NTIDs, because small differences (*e.g.,* 20%) in drug exposure may lead to serious therapeutic failures and/or adverse drug reactions. The usual average ABE limits of 80.00 to 125.00% are not considered sufficient for NTIDs, and several regulatory agencies have narrowed the limits for bioequivalence, typically to 90.00 to 111.11%.

The US FDA guidance for warfarin sodium (2012) proposed a new bioequivalence methodology for NTIDs as an extension of RSABE to scale bioequivalence limits to the within-subject variability of the reference product, and to compare within-subject variabilities of test ($\sigma_{WT}$) and reference ($\sigma_{WR}$) products. For NTIDs, a fully replicated design must be used, and the test formulation must pass the following three criteria:

1) RSABE, scaled to the reference variability, *e.g.,* 90% CI within limits of 90.00-111.11% for reference formulations with $CV_{WR}$ = 10%,
2) unscaled ABE, within 90% CI limits of 80.00-125.00%,
3) the upper bound of the 90% CI of the ratio $\sigma_{WT}/\sigma_{WR}$ must be ≤ 2.5.

The purpose of this work is to show how RSABE for NTIDs can be performed in Phoenix WinNonlin using reusable workflows (i.e. templates).




## OBJECTIVE(S)

- to demonstrate that RSABE and other tests for Narrow Therapeutic Index drugs (NTIDs) can be performed in Phoenix WinNonlin,
- to provide users with WinNonlin projects that can be re-executed with their own datasets from fully replicated studies for NTIDs.

## METHOD(S)

Template workflows were created in a Phoenix WinNonlin project to test the three criteria for an RSABE analysis of NTI drugs per the FDA Warfarin Guidance and to summarize the results. A Phoenix project is a file that saves users' input data, code, documents, workflows, and execution results. A Phoenix workflow is an object in which users group together as many Phoenix tools as needed to complete an analysis.

Phoenix WinNonlin has a ready-to-use tool to test Average BE, so workflows were developed for the first and third criteria, that is, for RSABE using NTID-specific constants, and for a test on the ratio of the test-to-reference variability:

$$95\%\text{ upper confidence bound}\left(\left(\overline{Y}_T-\overline{Y}_R\right)^2-\theta\, s_{WR}^2\right)\le 0$$
$$\text{where } \theta\equiv\left(\frac{\ln(\Delta)}{0.10}\right)^2 \text{ and } \Delta=1/0.9$$

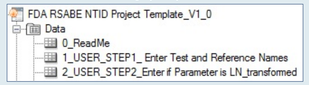
$$\text{Upper limit of 90\% confidence interval for } \sigma_{WT}/\sigma_{WR}\le 2.5$$
$$\left(\frac{s_{WT}/s_{WR}}{\sqrt{F_{\alpha/2}(\nu_1,\nu_2)}},\frac{s_{WT}/s_{WR}}{\sqrt{F_{1-\alpha/2}(\nu_1,\nu_2)}}\right)$$

## RESULT(S)

A Phoenix template project was created to perform an analysis for narrow therapeutic index drugs (NTIDs) per the FDA's three criteria in the Warfarin Guidance. The analysis includes these workflows:

Data Entry and Workflow to Prepare Dataset for Further Analysis

The user can simply import their own data, map their data columns to contexts (Subject, Sequence, Period, Formulation, Parameter Data), and enter basic information about their data: reference name, test name, and data to be or already ln-transformed. A data processing workflow will automatically prepare the dataset for further analysis by ABE, RSABE, and the upper 90% limit test.




Workflow for RSABE for FDA Approach

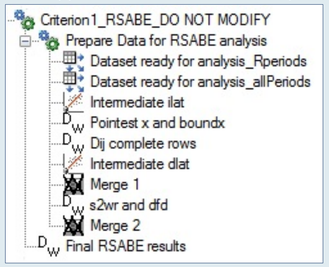
A workflow is provided that computes $s_{WR}$, an estimate of $\sigma_{WR}$, which is the within-subject standard deviation of the reference product, for the PK parameter being tested. This workflow also computes a point estimate for the geometric mean ratio and computes the 95% upper confidence bound for the $\chi^2$ distributed test statistic. The workflow then provides an assessment of whether RSABE is shown (point estimate within 0.8000 and 1.2500 and upper confidence bound ≤ 0). The reference-scaled method is almost the same as in the FDA Progesterone Guidance for highly-variable drug products (HVDs), but a different regulatory constant and upper BE limit is used for NTID's.

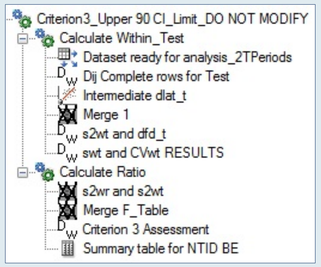
Workflow for Average Bioequivalence

A workflow is provided for Average BE analysis using the FDA's recommended model for replicated data, to test one of the criteria for NTID's -- the drug must still meet the usual 80.00% and 125.00% limits for Average BE for the 90% confidence interval of the test-to-reference ratio for AUC and Cmax.

Workflow for Upper 90% Criterion for Ratio of Test to Reference Variability

A workflow is provided that computes the upper bound of a 90% confidence interval of the ratio $\sigma_{WT}/\sigma_{WR}$, and tests whether the upper bound is less than or equal to 2.5 to check the third BE criterion for NTID's.




Workflows for Final Tables

Two workflows are provided to compile the conclusions from the three criteria and to list any subjects not used in analyses due to missing observations.

| | | Referenced Scaled Average Bioequivalence (RSABE) | | | Average Bioequivalence (ABE) | | | Criterion on Ratio sWT/sWR | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Criterion | Assessment [Needs to Pass All 3 Criteria] | Point Estimate [0.80, 1.25] | Critical Bound [<=0] | $s_{WR}$ | Ratio_%Ref_ | 90% C.L. Lower | 90% C.L. Upper | Upper 90% C.L. [<=2.5] | Ratio | $s_{WT}$ |
| 1 | Passed RSABE [Critical Bound <=0] | 0.9851 | -0.0098 | 0.124 | | | | | | |
| 2 | Passed unscaled ABE [CI within 80.00-125.00%] | | | | 98.51 | 93.90 | 103.35 | | | |
| 3 | Passed Upper 90% CL Ratio <=2.5 | | | | | | | 0.684 | 0.448 | 0.0557 |

## CONCLUSION(S)

RSABE for Narrow Therapeutic Index (NTI) drugs following the three criteria in FDA guidances can be performed in Phoenix WinNonlin 6.4, 7.0, and 8.0, using reusable template projects and workflows. The template projects require minimal input from the user in order to be used with any input dataset from a replicated 4-period crossover design.

The Phoenix template projects and example executed projects are available for free download at Certara University:
http://www.certarauniversity.com/lms/index.php?r=course/details&id=318

For EMA, Health Canada, and Japan PMDA guidelines, only the Average BE analysis in Phoenix WinNonlin is required, but with tightened 90% confidence interval limits: on a case-by-case basis for the EMA but generally to 90.00 to 111.11%; 90.0% to 112.0% for Health Canada for AUC but not tightened for Cmax; and 90.00 to 111.11%; for PMDA for AUC and Cmax.

## REFERENCES

1. Draft Guidance on Warfarin Sodium, US FDA, Recommended Dec 2012.
2. Draft Guidance on Progesterone, US FDA, Recommended Oct 2015.
3. Draft Guideline on the Investigation of Bioequivalence, EMA CHMP, 24 July 2008, Section 4.1.9
4. Guidance Document - Comparative Bioavailability Standards: Formulations Used for Systemic Effects, Health Canada, May 2012, Section 2.1.1.6

FDA Guidances that refer to the Warfarin Guidance for NTID methodology:
5. Draft Guidance on Tacrolimus, US FDA, Finalized Sep 2009, Revised Dec 2012
6. Draft Guidance on Phenytoin Sodium, US FDA, Recommended May 2007; Revised Dec 2014
7. Draft Guidance on Levothyroxine Sodium, US FDA, Recommended Dec 2014.
8. Draft Guidance on Carbamazepine, US FDA, Recommended May 2008; Revised Mar 2015
9. Draft Guidance on Sirolimuse, US FDA, Recommended Oct 2005; Revised May 2007; Sep 2008; Oct 2010, Sep 2015
10. Draft Guidance on Rivaroxaban, US FDA, Recommended Sept 2015
Draft Guidance on Cyclosporine, US FDA, Recommended Mar 2015; Revised Apr 2016
11. Draft Guidance on Dabigatran Etexilate Mesylate, US FDA, Recommended Jun 2012; Revised Sept 2015, Jul 2017
12. Draft Guidance on Digoxin, US FDA, Recommended Jun 2005; Revised Aug 2017

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