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Performing Reference-Scaled Average Bioequivalence (RSABE) in Phoenix® WinNonlin®

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PURPOSE

Traditional average bioequivalence (ABE) methodology requires prohibitively large sample sizes when used with highly variable drugs and drug products (HVDs/HVDPs), which are defined as products with intra-subject CV% of the reference greater than 30%. This increases the expense of BE studies, places more study subjects at risk, and ultimately limits the availability of generics.

Reference-scaled average bioequivalence (RSABE) methodology is increasingly used to demonstrate bioequivalence for HVDs/HVDPs. RSABE methodology allows the user to widen the acceptance criteria for BE. The extent to which the acceptance limits can be widened depends on the intra-subject variability for the reference product.

Specifics of RSABE methodology vary between regulatory agencies, but both the European Medicines Agency (EMA)[1] and the United States Food and Drug Administration (FDA)[2] require that subjects receive the reference drug more than once, e.g., replicated 3-period (RRT/RTR/TRR) or 4-period (RTRT/TRTR) crossover designs, so that the BE analysis accounts for within-subject variability. For both the EMA and the FDA, RSABE can be employed if the reference product within-subject variability, CV_{WR} , is greater than 30%, which corresponds to a within-subject standard deviation $s_{WR} \geq 0.294$.

- For the EMA, the possibility to widen the acceptance criteria based on high intra-subject variability applies to Cmax, but does not apply to AUC where the acceptance range should remain at 80.00 – 125.00% regardless of variability.
- For the FDA, RSABE can be employed for a specific PK parameter if it has $s_{WR} \geq 0.294$, whereas the two one-sided tests procedure must continue to be used for PK parameters with $s_{WR} < 0.294$.

Although the Phoenix WinNonlin software provides a BE module to perform average bioequivalence, this module is not currently designed for a complete RSABE analysis. The purpose of this work is to show how RSABE can be performed in Phoenix WinNonlin 6.3 using reusable projects and workflows for both the EMA and FDA approaches.

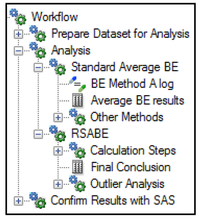
METHODS

Reusable Projects and Workflows in Phoenix

Phoenix projects and workflows were created in order to demonstrate that RSABE can be performed in Phoenix, and to also provide to users projects that can be re-executed with their own datasets from full and partial replicate studies. 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 operations as needed to complete an analysis.

Data Entry and Workflow to Prepare Dataset for Further Analysis

For both the EMA and FDA methodology, the user can import their own data, map their data columns to contexts (Subject, Sequence, Period, Formulation, Dependent), and enter basic information about their data: reference name, data already ln-transformed or to be ln-transformed, sequence names, full or partial replicate design. A data processing workflow will automatically prepare the dataset for further analysis by ABE and RSABE.



Workflow for ABE

For both the EMA and FDA methodology, a workflow is provided for Average BE analysis using three possible models.

Ratio (%)	ABE 90%CI Lower	ABE 90%CI Upper	CV_{wr}(%)	Extended_Lower_Bound	Extended Upper Bound
115.66	107.11	124.89	46.96	71.23	140.40

Workflow for RSABE – EMA Approach

For the EMA approach to RSABE, a workflow is provided that starts with the EMA's preferred method[3] of using only the reference drug data to estimate CV_{WR}. Since only reference data is used, the LinMix object is used instead of the Bioequivalence object to compute CV_{WR}. For $CV_{WR} > 30$ and $CV_{WR} \leq 50$, the workflow computes the scaled expanded limits that are acceptable for bioequivalence. For $CV_{WR} \geq 50$, the expanded limits are set to the largest allowable limits. A final workflow computes studentized intrasubject residuals for the reference drug, and plots these in both a Box plot and a QQ plot, and flags possible outliers[4].

	Average Bioequivalence (ABE)			Referenced Scaled Average Bioequivalence (RSABE)		
Assessment	Ratio (%)	90% CI Lower	90% CI Upper	sWR [>=0.294]	Point Estimate [0.80, 1.25]	Critical Bound [<=0]
USE RSABE: Criteria Met	115.66	107.10	124.89	0.446	1.15	-0.092

Workflow for RSABE – FDA Approach

For the FDA approach to RSABE[2], a workflow is provided that computes a point estimate for the geometric mean ratio, that estimates s_{WR}, and that computes the 95% upper confidence bound for the chi-square distributed test statistic. The workflow then provides an assessment of whether RSABE is applicable ($s_{WR} \geq 0.294$) and whether RSABE is shown (point estimate within [0.8, 1.25] and upper confidence bound ≤ 0).

Workflow for Comparing Results with SAS Results

In both the EMA and FDA executed projects, a workflow is provided that includes the equivalent SAS code as given by the EMA[3] and the FDA[2]. This workflow allows users to compare results using the Phoenix workflows with the results of the SAS runs. Note: only users with Phoenix Connect and SAS will be able to re-execute this workflow.

RESULTS

Test data from the EMA[3] (pgs. 24-31) were used for validation of both full and partial replicate designs. For the FDA workflow, the Phoenix results match SAS results obtained by using SAS code supplied by the FDA for Progesterone[2] (in chart below). For the EMA workflow, the Phoenix results match CV_{WR} documented by the EMA[3] (page 22, method C) and also match SAS results for CV_{WR} obtained by using SAS code supplied by the EMA[3] (page 23) which uses only reference drug data.

FDA 4-period	pointest	s_{WR}	critbound
Phoenix	1.1546	0.44645	-0.09208
FDA SAS code	1.1546	0.44645	-0.09208
FDA 3-period	**pointest**	**s_{WR}**	**critbound**
Phoenix	1.0226	0.11397	-0.00397
FDA SAS code	1.0226	0.11397	-0.00397

EMA 4-period	Ratio (%)	$CV_{WR, meth.C}$	CV_{WR}
Phoenix	115.66	47.3	46.964
EMA Doc/SAS	115.66	47.3	46.964
EMA 3-period	**Ratio (%)**	**$CV_{WR, meth.C}$**	**CV_{WR}**
Phoenix	102.26	11.5	11.171
EMA Doc/SAS	102.26	11.5	11.171

CONCLUSIONS

RSABE can be performed in Phoenix WinNonlin 6.3 using reusable template projects and workflows for both EMA and FDA approaches. These template projects require minimal input from the user in order to be used with any input dataset from a replicated 3-period or 4-period crossover design.

The Phoenix template projects and example executed projects are available for free download at: https://s3.amazonaws.com/Certara-Presentations/2013/AAPS/Assets/AAPS_2013_RSABE.zip

REFERENCES

1. European Medicines Agency CHMP, Guideline on the Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev.1/Corr, London, 20 January 2010
2. Draft Guidance on Progesterone, US FDA Guidance for Industry, Recommended Apr 2010; Revised Feb 2011
3. European Medicines Agency CHMP, Questions & Answers: Positions on specific questions addressed to the pharmacokinetics working party, EMA/618604/2008 Rev.7, London, 13 February 2013, pg. 20 - 31
4. European Generics Medicines Assoc., Revised EMA Bioequivalence Guideline – Questions and Answers, Summary of the Discussions held at the 3rd EGA Symposium on Bioequivalence, London, 1 June 2010, pg. 20