Developing an R Shiny App for Dissolution Profile Similarity Analysis

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Introduction

f2 analysis is commonly used to assess dissolution profile similarity. However, for highly variable dissolution profiles, conventional *f2* analysis is not applicable. In such cases, bias-corrected and accelerated (BCa) *f2* bootstrapping and Mahalanobis distance (MSD) analysis can be used for dissolution similarity analysis by incorporating the variabilities. The purpose of this project is to develop an R Shiny tool that provides a user-friendly platform for reviewers to conduct conventional *f2,* non-BCa and BCa *f2* bootstrapping and MSD analyses for dissolution profile comparison in ANDA reviews.

Methods

Several different functions were programmed into the back-end of the App. Traditional *f2* values were calculated according to the 1997 FDA guidance for industry[1] using the following equation.

$$f_2 = 50 \cdot \log[100 \cdot \left(1 + \frac{\sum_{t=1}^{n}(R_t - T_t)^2}{n}\right)^{-0.5}]$$

Non-BCa intervals were calculated using the bootstrapping technique, which is a resampling method that relies on taking random samples from the original sample thousands of times. From these samples, *f2* calculations are performed and the mean of the 5th and 95th percentile is taken, resulting in a more accurate estimation of the *f2* value. The BCa confidence interval was calculated using an existing function called 'bootstrap_f2' in the R package "disprofas" by Dr. Dahinden[2]. In the function, Dr. Dahinden used the jackknifing method in addition to bootstrapping to predict the *acceleration parameter,* $\hat{a}$, in BCa calculations. A bias correction factor, $\hat{z_0}$, is also used. The equations used to calculate are shown below, respectively.

$$\hat{a} = \frac{\sum_{i=1}^{n}(\hat{\theta}_{(\cdot)} - \hat{\theta}_{(i)})}{6\{\sum_{i=1}^{n}(\hat{\theta}_{(\cdot)} - \hat{\theta}_{(i)})^2\}^{3/2}} \quad \hat{z}_0 = \Phi^{-1}\left(\frac{\#\{\hat{\theta}_b^* < \hat{\theta}\}}{B}\right)$$

In the function 'mimcr', Dr. Dahinden uses covariance matrices to calculate the Mahalanobis distance[3], which is used in model-independent MSD tests. The equation used is shown below:

$$D_M = \sqrt{[(x_2 - x_1)' S_{pooled}^{-1}(x_2 - x_1)]}$$

In addition to this method proposed by Dr. Tsong in 1996[4], 'mimcr' also uses a method done by Dr. Hoffelder in 2016[5] that relies on a "Critical F" value and a "Probability p" value. Dr. Tsong's conclusion is adopted in FDA reviews rather than Hoffelder's as Tsong's calculations are in accordance with FDA guidelines.

To validate the app, 50 dissolution datasets were used from 9 different Abbreviated New Drug Applications (ANDAs). These datasets were chosen because they have medium to high variability and have prior-calculated *f2* bootstrapping and MSD analysis results.

App Development

Started with a basic understanding of *f2* calculations and implemented such calculations into simple code.

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Programmed *f2* bootstrapping manually and inputted the same data as normal *f2* calculations.

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Conducted literature review to get a basic understanding of how BCa functioned. Found several pre-written R functions for BCa and determined which one was most accurate.

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Started the development of the App. Determined what inputs each function needs and first programmed the frontend User Interface (UI). Adjustments were made to the UI to make it more user-friendly.

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Programmed the back-end server that implemented all the functions that were previously tested into the App. Updated the UI to better accommodate what server outputs needed.

↓

Started learning how MSD calculations worked and investigated both model-independent and model-dependent MSD tests. Found and implemented an existing R function for model-independent MSD tests.

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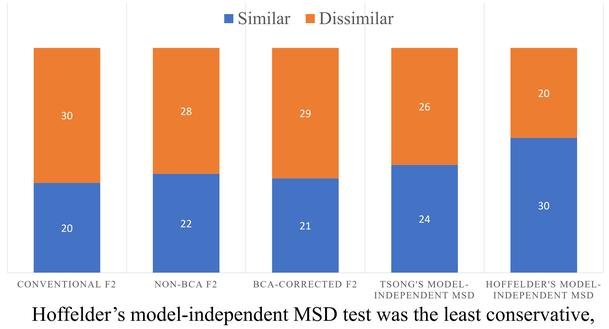
Used ANDA data from previous reviewers to validate the accuracy of the App. Made several UI updates and bug fixes to increase the readability of the App. Continued testing the App with data from multiple ANDAs.

Results and Discussion

Dissolution datasets from different ANDAs that compared a reference listed drug (RLD) to the test product were used for validation. The App calculated *f2* values are similar to reviewer calculated *f2* values (Table 1). The model-independent MSD tests also yielded similar results to previous reviewers (Table 2). All *f2* bootstrapping values were taken from a sample of 10,000 bootstrap replicates. The data obtained to compare *f2* values (not highly variable) are from a different ANDA than the data used in the MSD test (highly variable). Data from multiple other ANDAs were inputted to the App and compared with previous results. On average, BCa resulted in a more conservative value but on some occasions when the data were skewed towards lower *f2* values, the corrected *f2* value was higher than the traditionally calculated *f2* value. Most conventional *f2* or *f2 bootstrapping* values seemed to be more conservative (lower *f2* value) than model-independent MSD tests, which were even more conservative than model-dependent MSD tests dependent on the Weibull function as calculated by previous reviewers (Figure 1). BCa calculations were done with 2000 bootstrap replicates on a 95% confidence interval.

Figure 1. Conservativeness of different similarity tests



Hoffelder's model-independent MSD test was the least conservative, while the others were similar (Figure 1). Both bootstrapping techniques and Tsong's model-independent MSD test more readily account for variability in data. In the cases where the individual data were highly skewed, BCa was able to generate an appropriate *f2* value.

In addition to conventional *f2* calculations, non-BCa *f2*, BCa *f2*, and model-independent MSD, a function to calculate CV%, standard deviation, and mean were also added, which could help in determining whether data are highly variable. A guide on how to utilize the App, common errors in input, and required data format along with a documentation on how to add more functions to the App was written. The goal of such documents is to aid users who are unfamiliar with R in using the App as well as to make the written code more readable.

Table 1. Comparison of traditional *f2,* bootstrapped *f2,* and BCa bootstrapped *f2* values.

	RLD vs generic product (75 mg 0.1N HCl)	RLD vs generic product (75 mg pH 6.8)	RLD vs generic product (225 mg pH 4.5)
Reviewer calculated conventional f2	47.6	45.6	41.6
R Shiny App Conventional f2	47.7	44.7	41.1
Reviewer calculated non-BCa f2 bootstrap	48.6	44.4	40.8
R Shiny App calculated non-BCa f2 bootstrap	47.7	44.6	41.2
R Shiny App calculated BCa f2	48.2	44.8	41.7

Table 2. Comparison of Dr. Tsong's model-independent MSD test conclusions

	RLD (whole tablet) vs test (whole tablet) (25 mg pH 6.8)	Test (whole tablet) vs test (split tablet, mechanical) (100 mg pH 6.8)	Test (whole tablet) vs test (split, manual) (25 mg pH 6.8)
R Shiny App Calculated MSD	Dissimilar	Similar	Similar
Reviewer Calculated MSD	Dissimilar	Similar	Similar

Conclusion

- The developed R Shiny App appears to be efficient and user-friendly.
- R Shiny App was used for similarity analysis and majority of the results are consistent with previous reviewer's calculation.
- Based on the analyses, the order of the conservativeness (lower f2) of different similarity tests from most conservative to least conservative is conventional *f2*, BCa *f2*, non-BCa bootstrapped *f2*, Tsong's model-independent MSD, then Hoffelder's model-independent MSD.
- The development of the App also allows for standardization of such calculations and make these calculations more time efficient for reviewers.

DISCLAIMER

This poster represents the views of the presenters only and should not be construed to represent FDA's views or policies.

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References

(1) United States Food and Drug Administration (FDA). Guidance for industry: dissolution testing of immediate release solid oral dosage forms. 1997. https://www.fda.gov/media/70936/download
(2) Dahinden, Pius. "Bootstrap F2." *Disprofas*, CRAN, 10 Dec. 2021, Accessed 31 July 2023.
(3) Dahinden, Pius. "Model-independent multivariate confidence region (MIMCR) procedure." *Disprofas*, CRAN, 10 Dec. 2021, Accessed 31 July 2023.
(4) Tsong, Y., Hammerstrom, T., Sathe, P.M., and Shah, V.P. Statistical assessment of mean differences between two dissolution data sets. *Drug Inf J*. 1996; 30: 1105-1112. doi: 10.1177/009286159603000427
(5) Hoffelder, T. Highly variable dissolution profiles. Comparison of T2-test for equivalence and *f2* based methods. *Pharm Ind*. 2016; **78**(4): 587-592. https://www.ecv.de/suse_item.php?suseId=Z|pi|8430