FTNIR Spectrometry of Micafungin Sodium Quality

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RAPID COMMUNICATION

Abstract

Intra-lot and inter-lot variability in the spectra of micafungin was detected in the Drug Quality Study (DQS) using Fourier transform near-infrared spectrometry (FTNIR). Two vials of 6 vials sampled from Fresenius Kabi lot ACP106 appeared 7.9 and 14.0 standard deviations (SDs) from the center of the rest of the vials on the DQS FTNIR screening assay. Spectra of 48 vials from 7 lots in the library showed 2 outliers at 8.3 and 9.8 SDs from the center of the rest of the library, suggesting they represent different material.

Introduction

The University of Kentucky's (UK) Drug Quality Study was established in August of 2019 to engage in consumer-level quality assurance testing for drugs used within UK HealthCare's pharmacies. DQS currently screens medications, using FTNIR and Raman spectroscopy, for quality defects indicated by variability in absorbance peak intensities and locations. Through 16 months of continuous monitoring, DQS has assembled a spectral library containing medications typically used in an inpatient care setting. Statistical analyses using DQS' spectral library can now be performed to identify potential intra-lot and inter-lot variability in medications under review. Using MedWatch, DQS reports its findings in an effort to hold manufacturers accountable for GMP requirements and to improve patient outcomes by exerting positive pressure on the pharmaceutical supply chain. At all levels, DQS staff are committed to achieving service excellence by pursuing compliance with the standards set forth by our patients and broad GxP requirements.

Drug Product

Mycamine (micafungin sodium) is an antifungal medication used to treat infections caused by the *Candida* fungus, and is also used to prevent *Candida* fungal infections in stem cell transplant patients.

Mycamine is a sterile, lyophilized product for intravenous (IV) infusion that contains micafungin sodium, a semisynthetic lipopeptide (echinocandin) synthesized by a chemical modification of a fermentation product of *Coleophoma empetri* F-11899. Micafungin inhibits the synthesis of 1, 3-beta-D-glucan, an integral component of the fungal cell wall.

In May 2020, Fresenius Kabi announced the launch of Micafungin for Injection, a generic version of Mycamine (micafungin for injection; from Astellas Pharma)(Park, 2020). The launch occurred during the lockdowns at the beginning of the COVID-19 pandemic.

Issues

Intra-lot variability was detected in the spectra of micafungin manufactured by Fresenius Kabi. Two vials of 6 vials sampled from Fresenius Kabi lot ACP106 appeared 7.9 and 14.0 SDs from the center of the rest of the vials on the DQS FTNIR screening assay, suggesting they represent different material.

Inter-lot variability was detected in spectra of 48 vials from 7 lots (Fresenius Kabi lots ACP102, ACP103, ACP104, ACP105, ACP106, ACP107, and ACP109) in the library of micafungin vials. Analysis of the library spectra showed 2 outliers at 8.3 and 9.8 SDs from the center of the rest of the library, suggesting they represent different material.

Methods

FTNIR (Fourier Transform Near-Infrared) Spectrometry

Using nondestructive analytical techniques, FTNIR spectra were collected for inventory belonging to lot AFN102 as part of routine medication quality screening. A representative sample of 12 individual vials were selected for screening from lot AFN102 and noted to be stored under proper conditions, in their original packaging at ambient room temperature. FTNIR spectra were collected noninvasively and nondestructively through the bottom of the vials using a Thermo Scientific Antaris II FTNIR Analyzer (Waltham, MA, USA).

Multiplicative Scatter Correction (MSC)

Multiplicative scatter correction (MSC) is a widely used spectrometric normalization technique. Its purpose is to correct spectra in such a way that they are as close as possible to a reference spectrum, generally the mean of the data set, by changing the scale and the offset of the spectra (Isaksson, 1988).

BEST (Bootstrap Error-Adjusted Single-sample Technique)

The BEST calculates distances in multidimensional, asymmetric, nonparametric central 68% confidence intervals in spectral hyperspace (roughly equivalent to standard deviations)(Dempsey, 1996). The BEST metric can be thought of as a "rubber yardstick" with a nail at the center (the mean). The stretch of the yardstick in one direction is therefore independent of the stretch in the other direction. This independence enables the BEST metric to describe odd shapes in spectral hyperspace (spectral point clusters that are not multivariate normal, such as the calibration spectra of many biological systems). BEST distances can be correlated to sample composition to produce a quantitative calibration, or simply used to identify similar regions in a spectral image. The BEST automatically detects samples and situations unlike any encountered in the original calibration, making it more accurate in chemical investigation than typical regression approaches to near-IR analysis. The BEST produces accurate distances even when the number of calibration samples is less than the number of wavelengths used in calibration, in contrast to other metrics that require matrix factorization. The BEST is much faster to calculate as well (O(n) instead of the O(n^3) required by matrix factorization.)

Principal Components (PCs)

Principal component analysis is the process of computing the principal components of a dataset and using them to execute a change of basis (change of coordinate system) on the data, usually employing only the first few principal components and disregarding the rest (Joliffe, 2016). PCA is used in exploratory data analysis and in constructing predictive models. PCA is commonly utilized for dimensionality reduction by projecting each data point onto only the first few principal components to obtain lower-dimensional data while preserving as much of the original variation in the data as possible. The first principal component is the direction that maximizes the variance of the projected data. The second principal component is the direction of the largest variance orthogonal to the first principal component. Decomposition of the variance typically continues orthogonally in this manner until some residual variance criterion is met. Plots of PC scores help reveal underlying structure in data.

Results and Discussion

Intralot Analysis

The raw, multiplicative scatter-corrected FTNIR spectra of lot ACP106 showed variation in apparent moisture content of one vial (vial 2) at 5160 cm^{-1} (see Figure 1). Transformation of the spectra of lot ACP106 to principal axes revealed that the majority of the spectral variation correlated to moisture content was on PCs 1 and 2. PC 1 accounted for 58.8% of the total spectral variation, while PC 2 accounted for 26.1% of the total spectral variation. Together, the first 3 PCs accounted for 93.5% of the total variation in the spectral library.

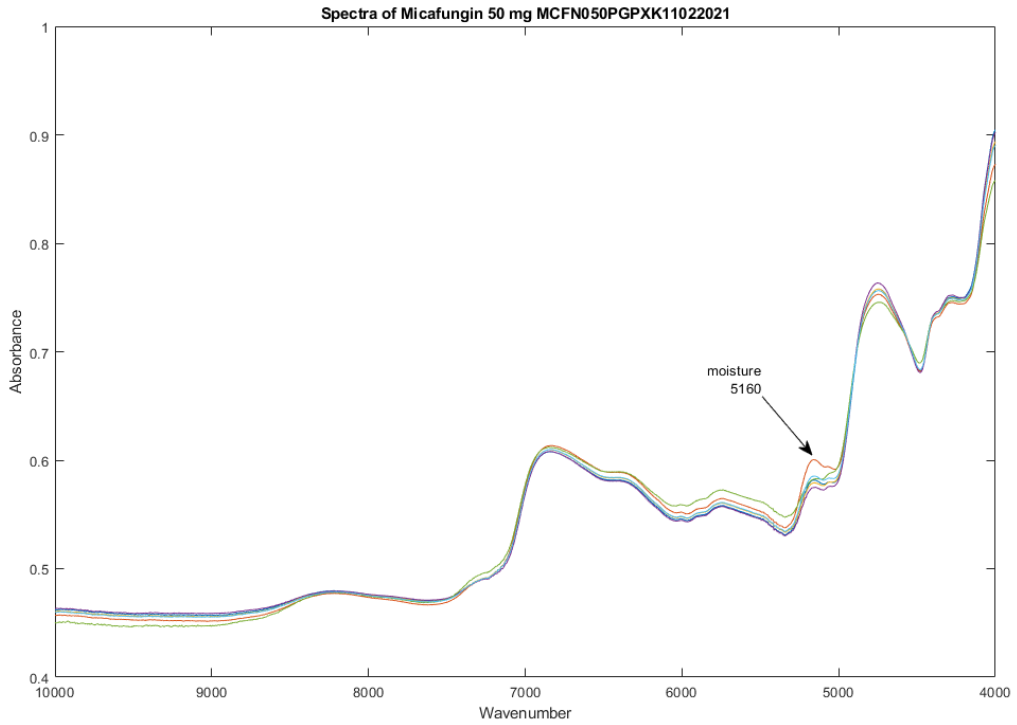

Figure 1. The raw, multiplicative scatter-corrected spectra of lot ACP106 show variation in apparent moisture content of vial 2 (red line, 7.9 SDs from center) at 5160 cm^{-1}.

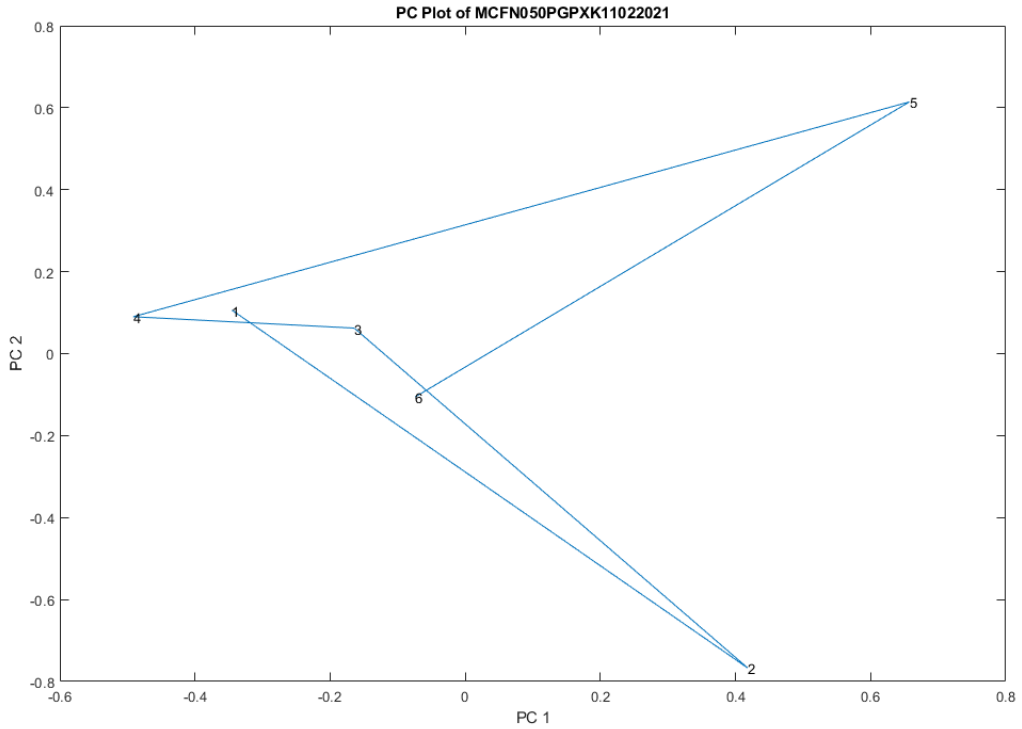

Figure 2. PC plot of the spectra of lot ACP106 (see Figure 1.)

Vial 2 lies 7.9 SDs from the center of the lot ACP106 spectra. Vial 5 is also separated 14.0 SDs from the remainder of the vials, but in a different direction (see Figure 2). The main difference between vial 5 and the rest of ACP106 is a feature at 5050 cm^{-1} (see Figure 3).

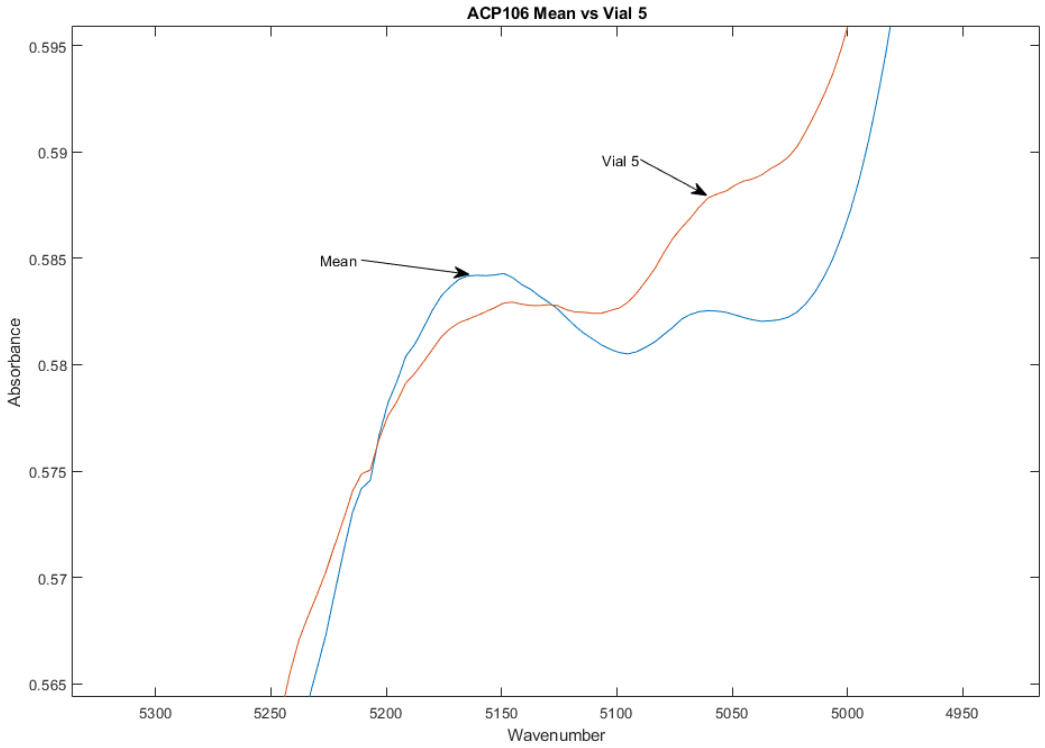

Figure 3. Spectra of the mean of lot ACP106 (blue line) and vial 5 (red line, 14.0 SDs from mean).

Plotting the loadings that form each PC can be helpful in isolating the important spectral features of each principal component.

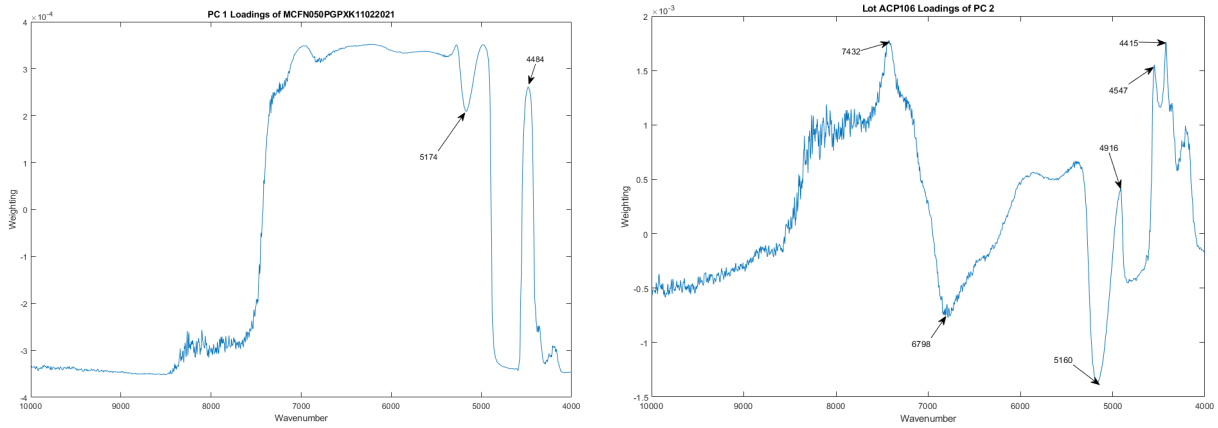

Figure 4. PC loadings for PC 1 (left) and 2 (right). Some important features are marked.

The moisture peak and other peaks that differentiate vials 2 and 5 are marked in Figure 4.

Interlot Analysis

Variations in the lots that comprise the micafungin spectral library that are similar to those observed in lot ACP106. The most prominent is the moisture peak at 5160 cm^{-1}, so moisture variations are probably common in the lyophilized drug product (see Figure 5).

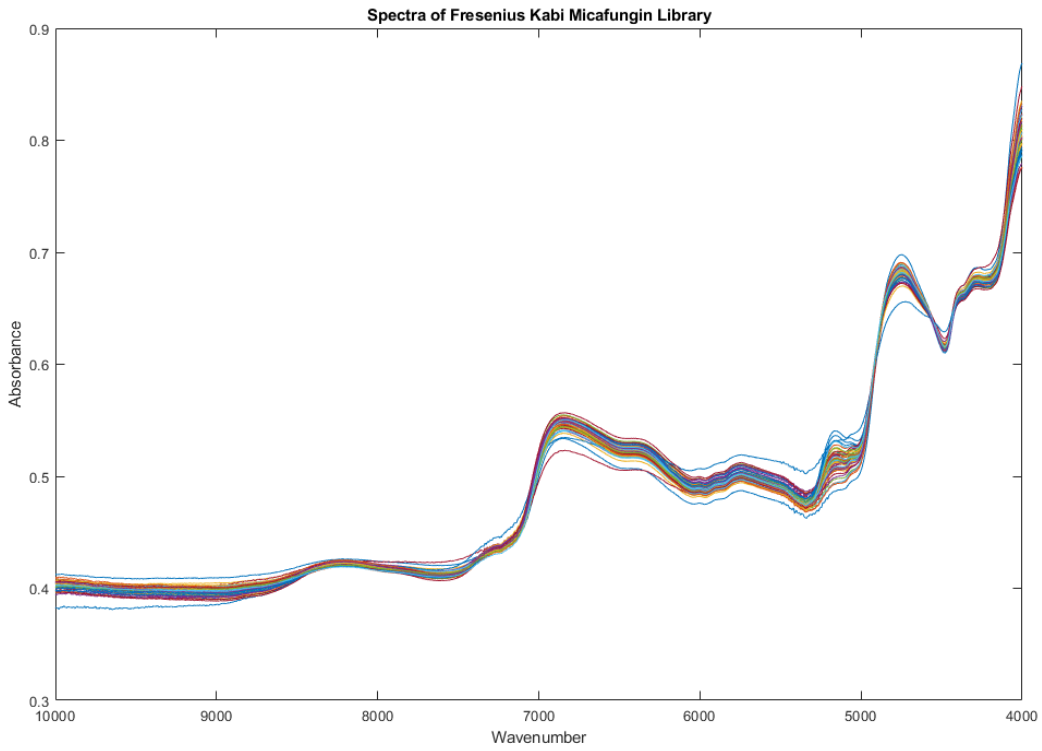

Figure 5. Spectra of 48 vials from 7 different lots of Fresenius Kabi micafungin that comprise the current spectral library. Moisture variations are apparent at 5160 cm^{-1}.

Transformation of the micafungin spectral library to principal axes helps to more easily visualize other spectral changes. PC 1 accounted for 41.8% of the total spectral variation, while PC 2 accounted for 22.9% of the total spectral variation. Together, the first 3 PCs accounted for 78.9% of the total variation in the spectral library.

A plot of the first 3 PCs of the spectral library appears in Figure 6. Several apparent outliers are visible. Vial 14 (8.3 SDs from the center of the spectral library) and vial 22 (9.8 SDs from the center of the spectral library) are definitely outliers, but vials 17 and 32 are also displaced in the same direction, although not as far. Figures 7, 8, and 9 are all different orthogonal views of the hyperspace plotted in Figure 6. The view in Figure 8 resembles a normal, well-controlled pharmaceutical process leading to homogeneous drug products, and illustrates the importance of examining multiple views of the spectral hyperspace to detect outliers.

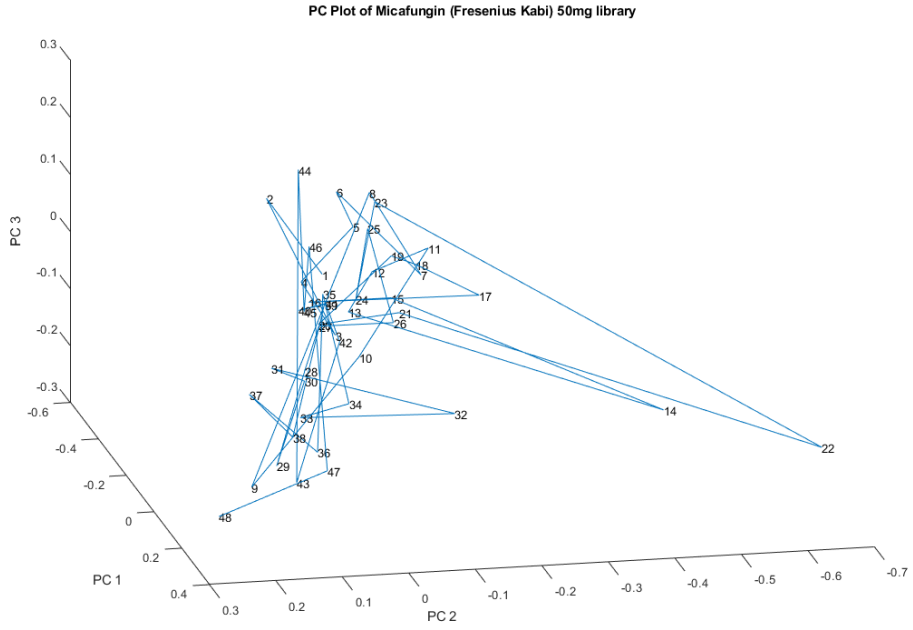

Figure 6. PC plot of the first 3 PCs of the micafungin spectral library. Vial 14 (8.3 SDs from the center of the spectral library) and vial 22 (9.8 SDs from the center of the spectral library) are outliers.

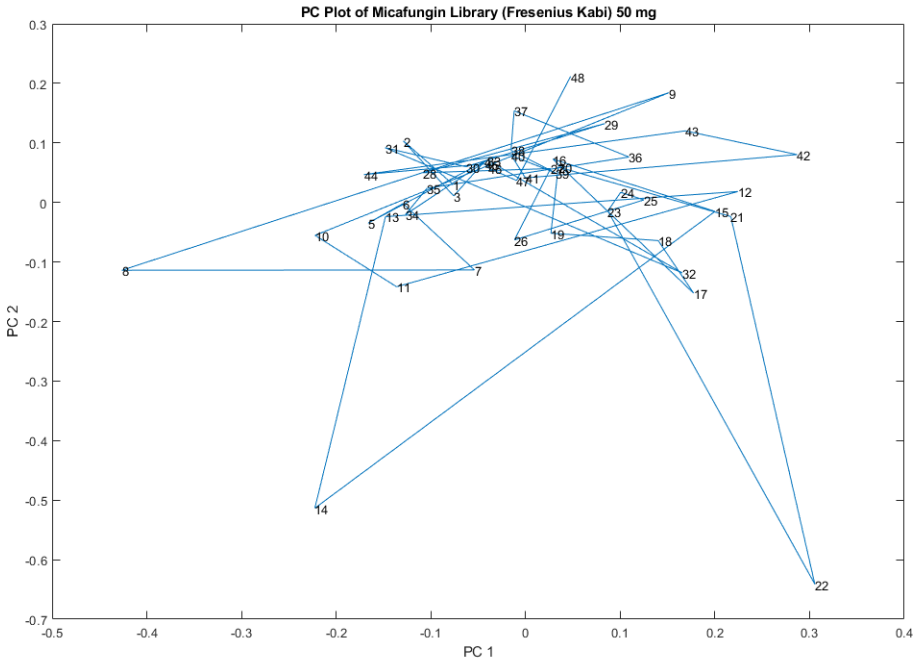

Figure 7. PC plot of PCs 1 and 2 of the micafungin spectral library. Vial 14 (8.3 SDs from the center of the spectral library) and vial 22 (9.8 SDs from the center of the spectral library) are outliers.

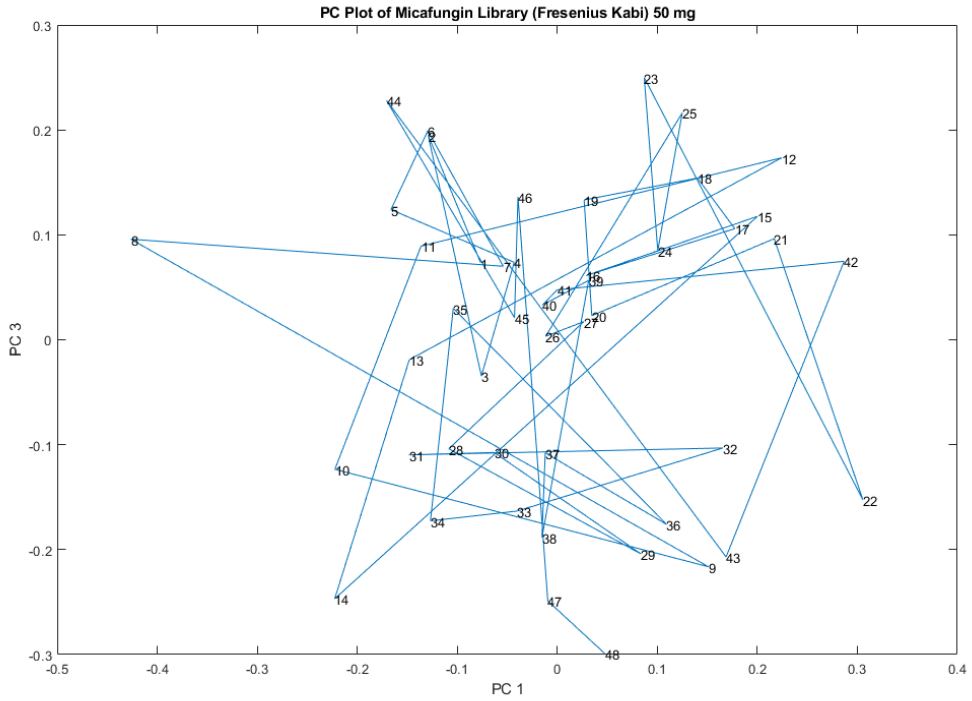

Figure 8. PC plot of PCs 1 and 3 of the micafungin spectral library. This view resembles a normal, well-controlled pharmaceutical process leading to homogeneous drug products.

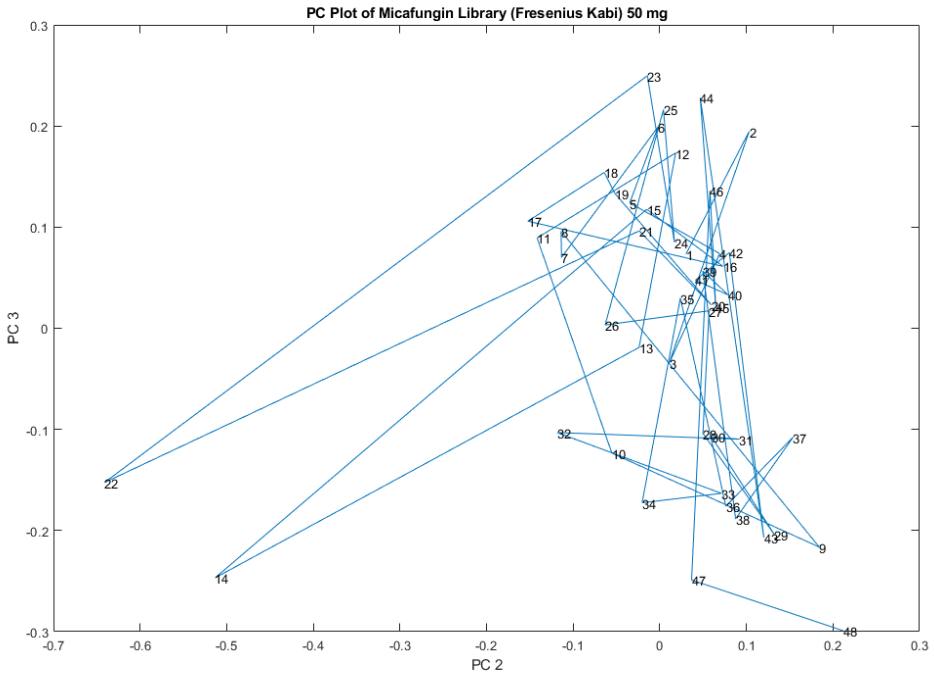

Figure 9. PC plot of PCs 2 and 3 of the micafungin spectral library. Unlike Figure 8 in which vials 14 and 22 are covered by the other vials of the library, this view shows vials 14 and 22 as outliers.

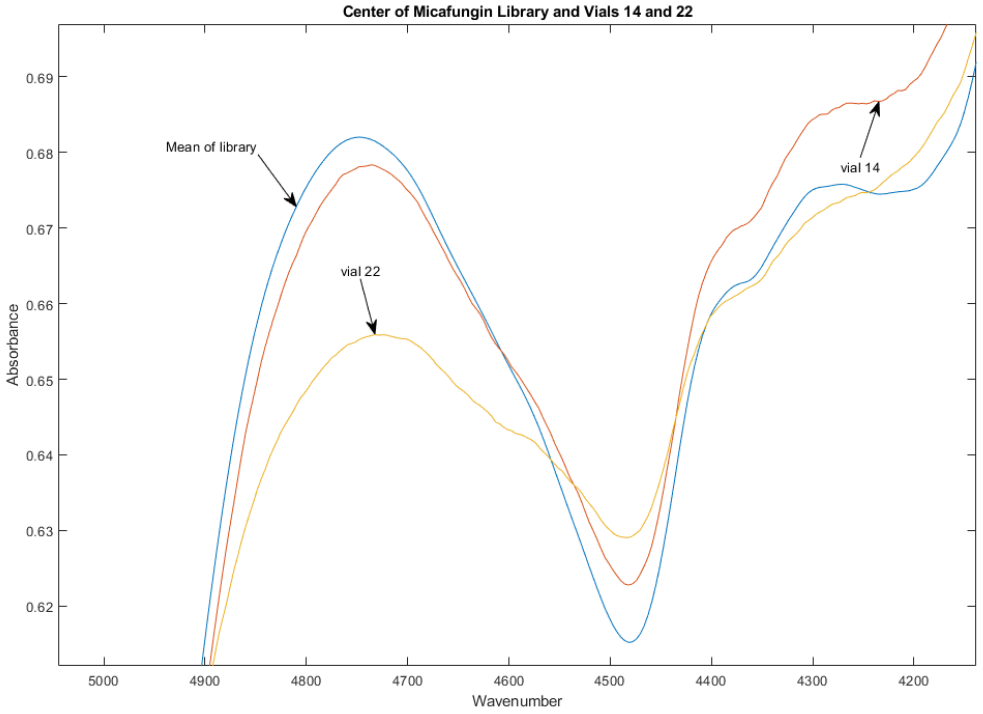

Figure 10. A comparison of the group mean of the spectral library (the center, or average spectrum, shown as the blue line) with the spectra of vial 14 (red line) and vial 22 (yellow line).

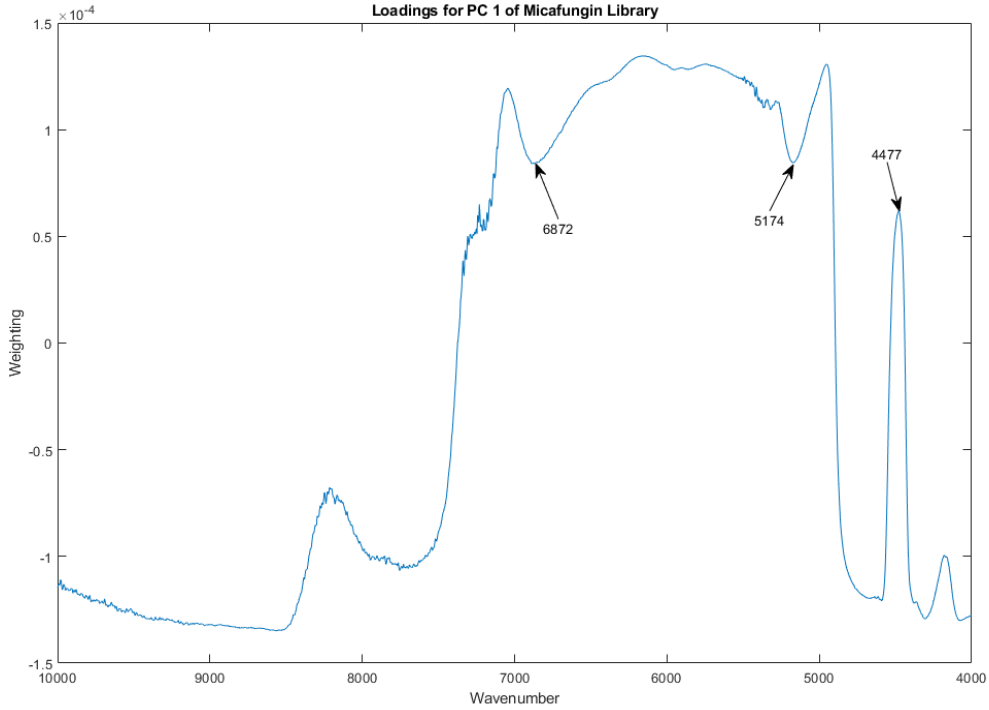

Figure 11. Loadings spectrum of PC 1 of the micafungin library.

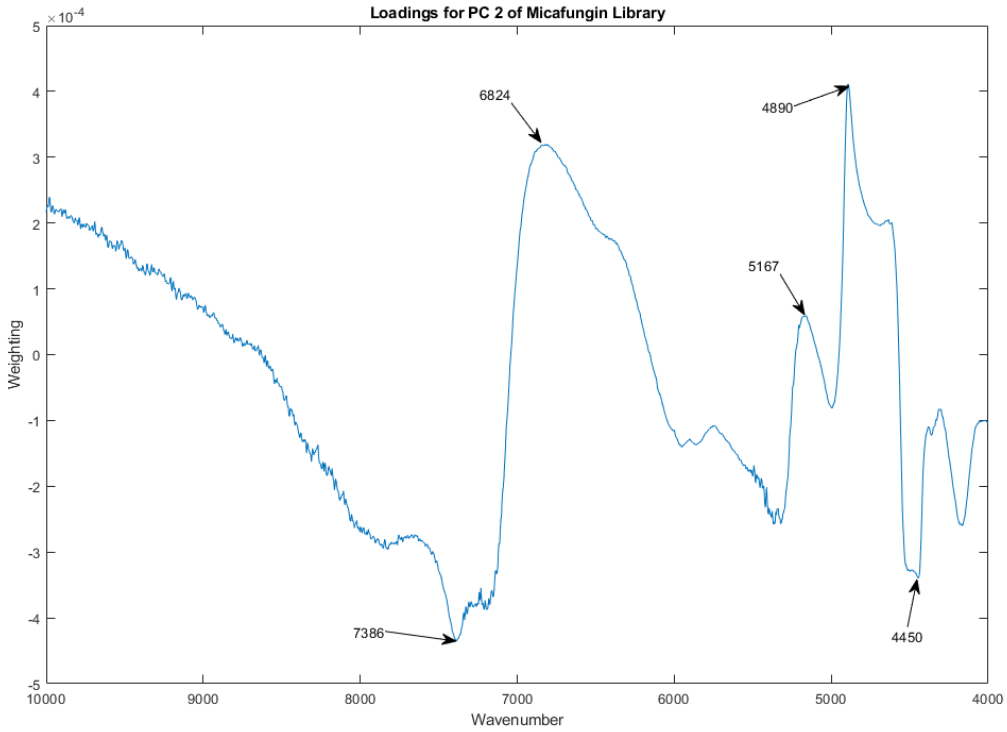

Figure 12. Loadings spectrum of PC 2 of the micafungin library.

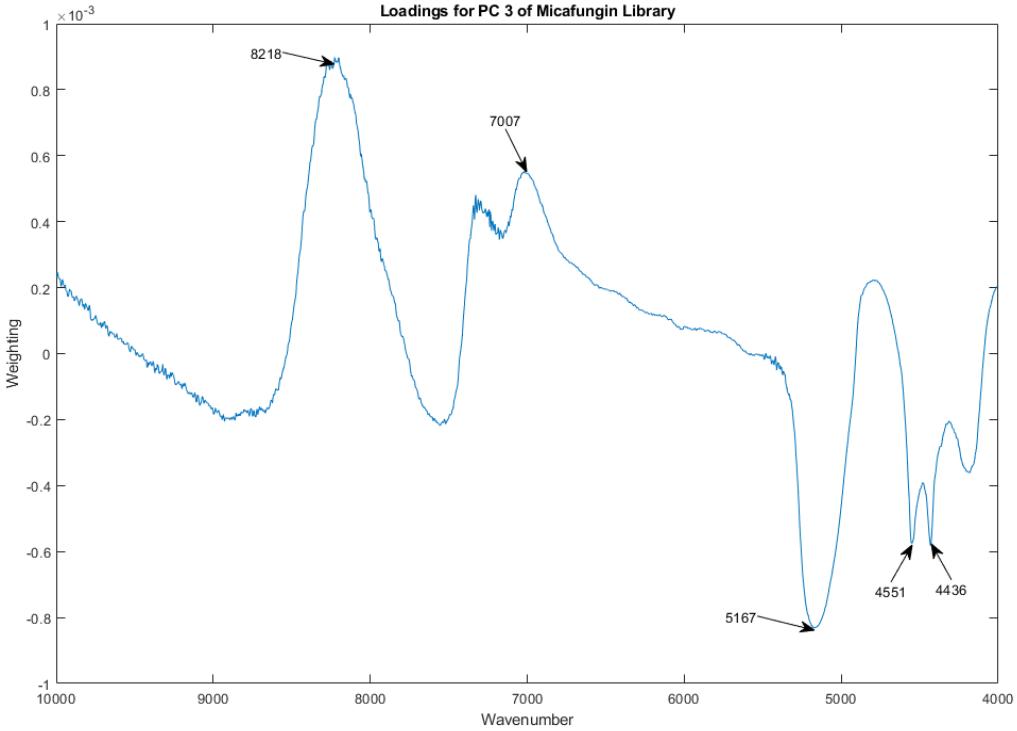

Figure 13. Loadings spectrum of PC 3 of the micafungin library.

Figure 10 is the comparison of the group mean of the spectral library (the center, or average spectrum) with the spectra of vial 14 and vial 22. On average, the library spectra have a larger peak at 4300 cm^{-1} than either vial 14 or vial 22, and a lower peak at 4750 cm^{-1}.

The principal component loadings spectra for PCs 1, 2, and 3 are provided in Figures 11, 12, and 13, respectively. Highly weighted bands in the PC loadings spectra correspond well to features in Figures 5 and 10.

Conclusions

Intra-lot and inter-lot variability in the spectra of micafungin was detected in the Drug Quality Study (DQS) using Fourier transform near-infrared spectrometry (FTNIR). Two vials of 6 vials sampled from Fresenius Kabi lot ACP106 appeared 7.9 and 14.0 standard deviations (SDs) from the center of the rest of the vials on the DQS FTNIR screening assay. Spectra of 48 vials from 7 lots in the library showed 2 outliers at 8.3 and 9.8 SDs from the center of the rest of the library, suggesting they represent different material.

Quality control is important in drug manufacturing. Good drugs lead to good patient outcomes. These FTNIR results do not prove an excess level of impurities or adulteration. However, they suggest that the manufacturing process may have been operating outside of a state of process control. Additional investigation is needed.

Acknowledgements

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