Variability in Content of Piperacillin and Tazobactam Injection

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RAPID COMMUNICATION

Abstract

Piperacillin and Tazobactam Injection is a combination product consisting of a penicillin-class antibacterial, piperacillin, and a beta-lactamase inhibitor, tazobactam, indicated for the treatment of patients with moderate to severe infections caused by susceptible isolates of bacteria. In the past decade some quality problems have been noted by the US Food and Drug Administration (FDA) with the Apotex Corp. manufacturing.

Intra-lot and inter-lot variability in the spectra of Piperacillin and Tazobactam Injection 3.375 g was detected in the Drug Quality Study (DQS) using Fourier transform near-infrared spectrometry (FTNIR). One vial of 6 (17%) sampled from lot AD103008F3 appeared 14.4 multidimensional SDs from the other vials, suggesting that it represents a different material.

Spectra of 132 vials from 19 lots in the spectral library contained 4 vials that were outside the group (21.0 SDs using a subcluster detection test), suggesting that the 4 library vials (3%) also contain differing materials.

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 potential quality defects indicated by variability in absorbance peak intensities and locations. Through years of continuous monitoring, DQS has assembled a spectral library containing

medications typically used in a health system setting. Statistical analyses using DQS' spectral library are 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 providing information on quality to augment the information on price that is already available. The increasing transparency is designed to improve 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

Piperacillin and tazobactam for injection is a combination penicillin-class antibacterial and β-lactamase inhibitor, which can be used in adults and children 2 months and older and indicated for treatment of intra-abdominal infections, skin and skin structure infections, female pelvic infections, community-acquired pneumonia and hospital-acquired pneumonia (FDA Apotex recall, 2018).

The drug is furnished by Apotex Corp. as a sterile lyophilized preparation. Lot AD103008F3 was originally the lot under test. The lots comprising the spectral library were AD002007F6, AD002008F6, AD002008F4, AD003014F4, AD004021F4, AD004019F6, AD005024F4, AD006033F5, AD011001F2, AD101005F4, AD101005F6, AD012006F2, AD103008F3, AD103017F2, AD012014F2, AD103002F1, AD103014F3, AD103020F3, and AD106038F3.

Related Reports

On May 14, 2018, Apotex Corp. voluntarily recalled 36 lots of Piperacillin and Tazobactam for Injection, USP 3.375 gram/vial and 4.5 gram/vial strengths, to the consumer/user level. The Piperacillin and Tazobactam for Injection were found to contain elevated levels of impurities that may result in decreased potency. The affected product was manufactured by Hospira Inc., a Pfizer Company and distributed in the US market by Apotex Corp (FDA Apotex recall, 2018).

The FDA Risk Statement read: "The decreased potency of Piperacillin and Tazobactam could result in worsening of the infection under treatment and under extreme circumstances lead to serious morbidities depending upon the severity of the illness. Elevated levels of impurities may result in various toxicities, such as liver, renal, and hematological toxicities. There have not been any reports of adverse events related to this recall to date" (FDA Apotex recall, 2018). Wholesalers/retailers/hospitals/institutions with an existing inventory of the lots subject to this recall were told to stop use and distribution of the remaining units and quarantine them immediately.

A similar recall of 21 lots of Piperacillin and Tazobactam for Injection, USP 4.5 grams, occurred in 2013 over concerns that the recalled lots showed precipitation or crystallization in IV bags or IV lines after reconstitution (PBR Staff Writer, 2013).

FDA Medwatch

An FDA Form 3500 Medwatch describing the findings of this Rapid Communication was filed on April 7, 2022 (FDA Form 3500, 2022).

Methods

FTNIR (Fourier Transform Near-Infrared) Spectrometry

Using nondestructive analytical techniques, FTNIR spectra were collected for inventory belonging to lot AD103008F3 as part of routine medication quality screening. A representative sample of 6 individual vials were selected for screening from lot AD103008F3 and noted to be stored under the conditions required by the manufacturer in their original packaging. 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.

Subcluster Detection

In typical near-infrared multivariate statistical analyses, samples with similar spectra produce points that cluster in a certain region of spectral hyperspace. These dusters can vary significantly in shape and size due to variation in sample packings, particle-size distributions, component concentrations, and drift with time. These factors, when combined with discriminant analysis using simple distance metrics, produce a test in which a result that places a particular point inside a particular cluster does not necessarily mean that the point is actually a member of the cluster. Instead, the point may be a member of a new, slightly different cluster that overlaps the first. A new cluster can be created by factors like low-level contamination, moisture uptake, or instrumental drift. An extension added to part of the BEST, called FSOB (Fast Son of BEST) can be used to set nonparametric probability-density contours inside spectral clusters as well as outside (Lodder, 1988), and when multiple points begin to appear in a certain region of cluster-hyperspace the perturbation of these density contours can be detected at an assigned significance level using r values, and visualized using quantile-quantile (QQ) plots. The detection of unusual samples both within and beyond 3 SDs of the center of the training set is possible with this method. Within the ordinary 3 SD limit, however, multiple instances are needed to detect unusual samples with statistical significance.

Results and Discussion

Intralot Analysis

It is not unusual for different lots of a drug to cluster in slightly different regions of near-IR spectral hyperspace. There can be a little drift in the manufacturing process from batch to batch that slightly alters the composition of the drug yet still represents the approved product. This drift is consequently reflected in the spectra. However, it is unusual for spectra of drugs from the same lot number to vary dramatically. A process that is in control generally produces the same drug over and over again, and as a result, the spectra are very similar.

In lot AD103008F3, 5 of the 6 (16%) near-IR spectra are similar (see Figure 1 and Figure 2). Vial 5 has the unusual spectrum that appears 14.4 SDs from the other 5 vials.

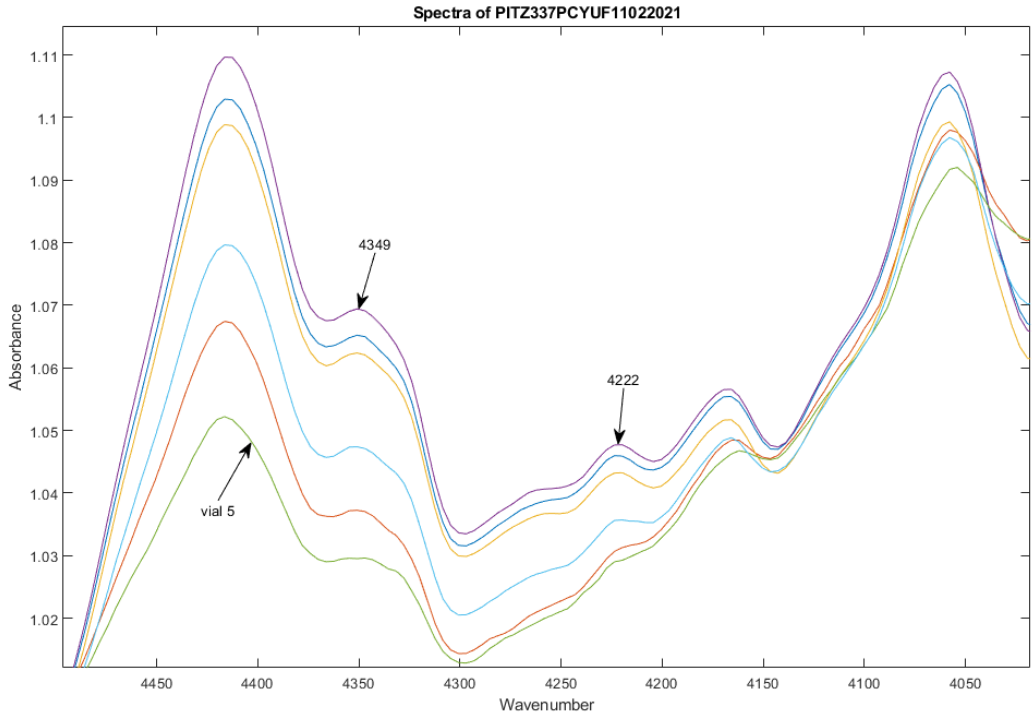

Figure 1. Spectra of 6 vials obtained from Lot AD103008F3. Peaks at 4222 and 4349 are diminished in vial 5 (green).

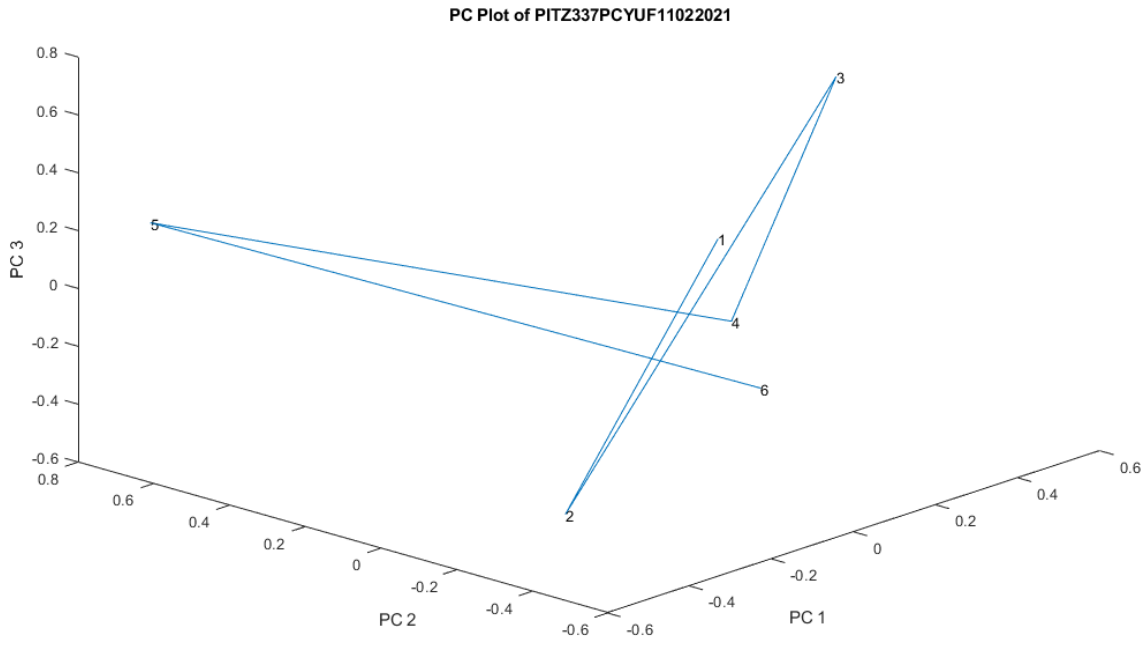

Figure 2. PC plot of the spectra of 6 vials obtained from Lot AD103008F3. Vial 5 (17% of the total vials measured) is 14.4 multidimensional SDs from the center of the cluster formed by the other 5 vials.

Interlot Analysis

The lots comprising the spectral library were collected together and the spectral data transformed to principal axes. The amount of variation contributed by each principal component to the total variation is shown in Table 1.

PC Number	Variation	Cumulative Variation
PC 1	43.2	43.2
PC 2	15.0	58.1
PC 3	13.4	71.5

Table 1. Percentage of spectral variation explained by each PC for the spectral library

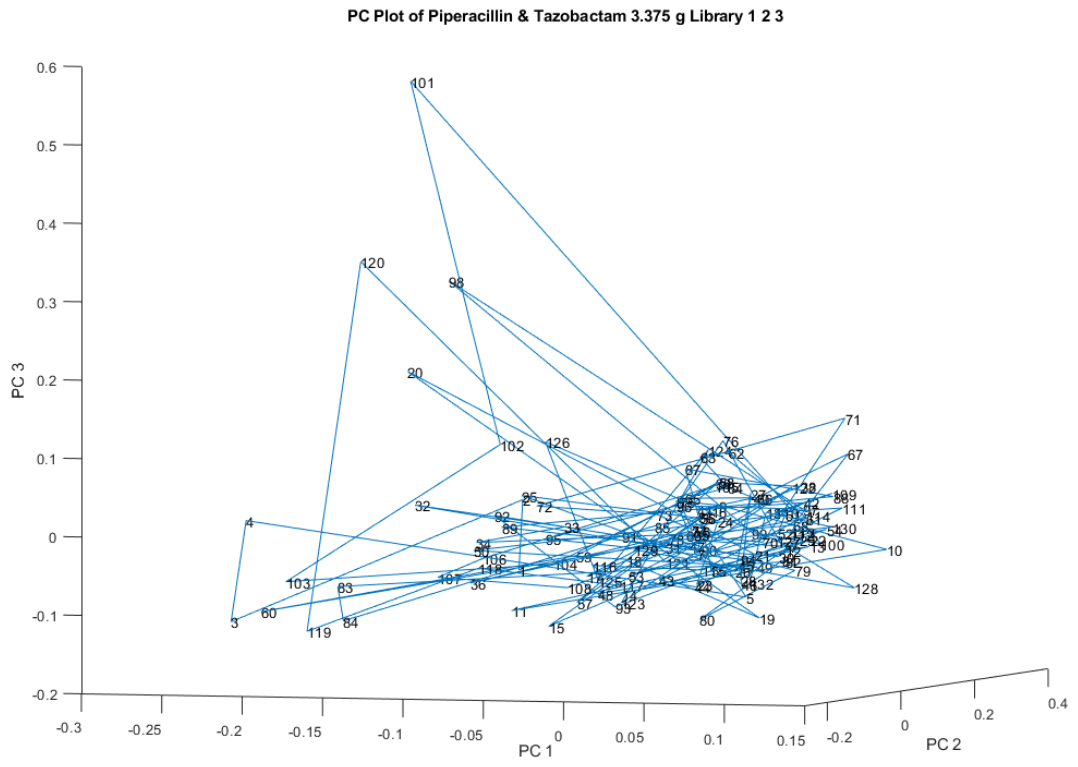

Figure 3. PC plot of the spectra of 132 vials from 19 lots in the spectral library for Apotex Piperacillin & Tazobactam 3.375 g. The outlier vials are vials 20, 98, 101, and 120 (3% of the total vials measured). The subcluster detection test marks these as 21.0 SDs from the other vials.

The 132 spectra of the vials comprising the spectral library were transformed to principal axes and the first 3 PCs are shown in Figure 3. The outlier vials are vials 20, 98, 101, and 120 (3% of the total vials measured). The subcluster detection test marks the set of these 4 vials as 21.0 SDs from the other vials.

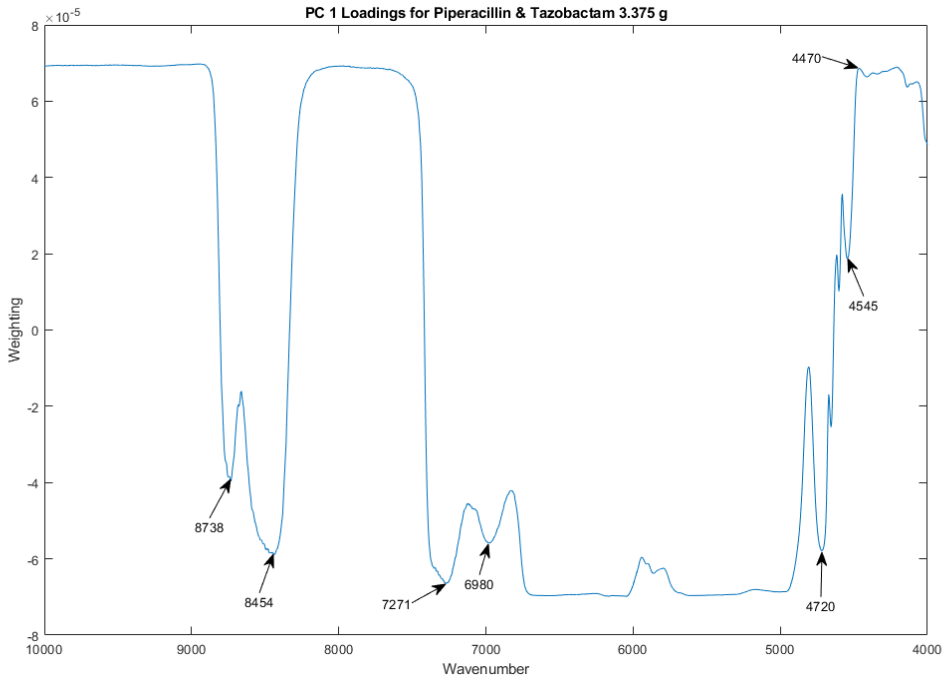

Figure 4. Plot of the loadings spectrum for PC 1 of the spectral library for Apotex Piperacillin & Tazobactam 3.375 g. In NIR spectra PC1 usually reflects some kind of baseline variation, even in scatter-corrected spectra.

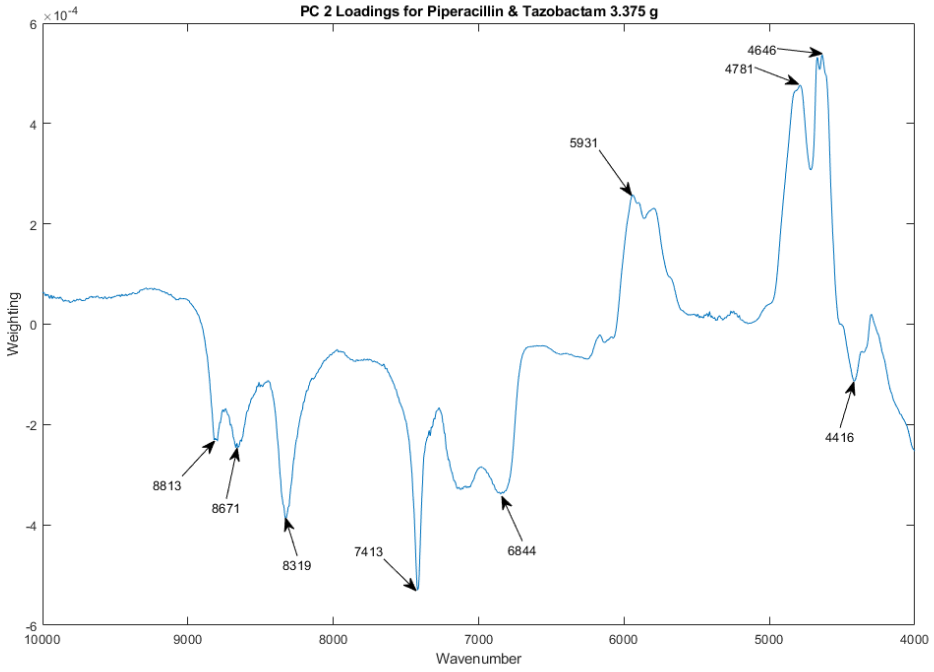

Figure 5. Plot of the loadings spectrum for PC 2 of the spectral library for Apotex Piperacillin & Tazobactam 3.375 g.

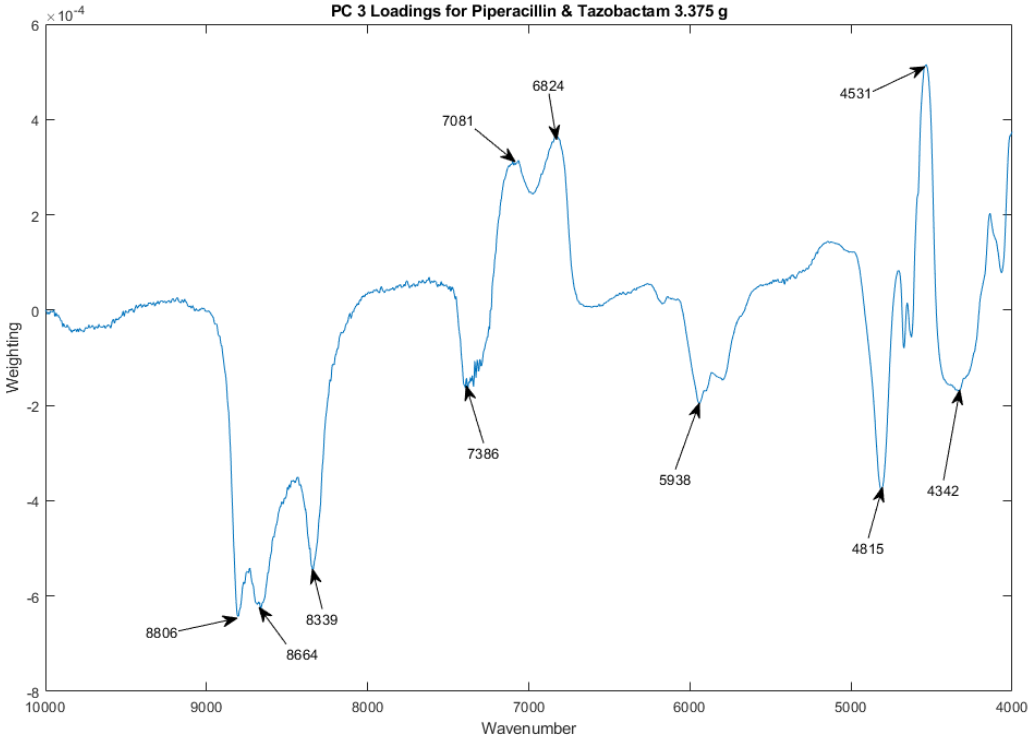

Figure 6. Plot of the loadings spectrum for PC 3 of the spectral library for Apotex Piperacillin & Tazobactam 3.375 g. The 4 outlier spectra are displaced most on PC 3.

Figure 4, Figure 5, and Figure 6 are the loadings of the wavenumbers for the 1st, 2nd, and 3rd PCs, respectively. Highly weighted loadings peaks of interest are marked. The 4 outlier spectra are displaced most on PC 3, which accounts for 13.4% of the total spectral variation.

Figure 7 is the QQ plot from the subcluster detection test on the 4 outliers (vials 20, 98, 101, and 120) in the spectral library. QQ plot from the subcluster detection test on PCs 1, 2 and 3 of the spectral library. (r_{lim}=0.96, r_{tst}=0.84, p=0.02) The clusters are 21.0 SDs apart by the subcluster detection metric. If the outliers had the same location and scale in spectral hyperspace as the main group of spectra, this graph would be a straight line with a slope of 1 and an intercept of zero.

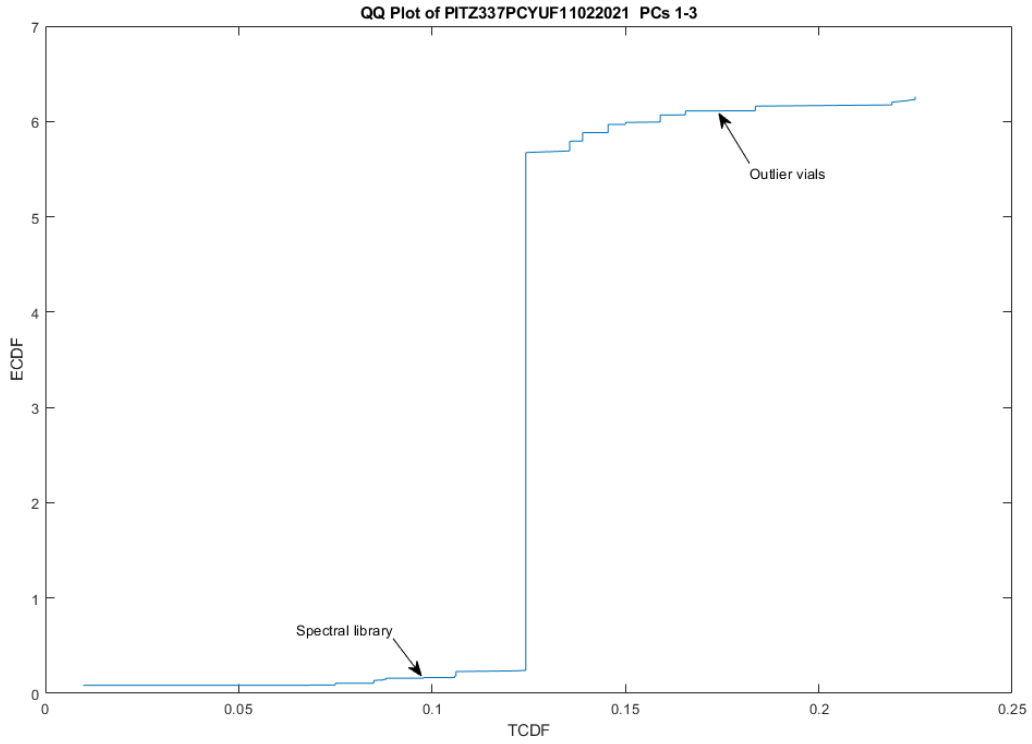

Figure 7. QQ plot from the subcluster detection test on PCs 1, 2 and 3 of the spectral library. (r_{lim}=0.96, r_{tst}=0.84, *p*=0.02) The clusters are 21.0 SDs apart by the subcluster detection metric.

Conclusions

Piperacillin and Tazobactam Injection is a combination product composed of a penicillin-class antibacterial, piperacillin, and a beta-lactamase inhibitor, tazobactam. The antibiotic is indicated for the treatment of patients with moderate to severe infections caused by susceptible isolates of bacteria. Over the past decade some quality problems have been noted in the drug by the US Food and Drug Administration (FDA).

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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

The project described was supported in part by NSF ACI-1053575 allocation number BIO170011 and the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant UL1TR001998. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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