

Spectroscopic Quality Monitoring of Cefepime

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RAPID COMMUNICATION

Abstract

Cefepime for Injection, a broad-spectrum fourth-generation cephalosporin, is indicated for treating serious infections including pneumonia, febrile neutropenia, urinary tract infections, and intra-abdominal infections. This study utilizes non-invasive Fourier transform near-infrared (FTNIR) spectrometry to evaluate the manufacturing quality and consistency of cefepime drug product. The investigation revealed significant intralot variability within a single manufacturing lot (5056KFPDL1). Principal Component Analysis (PCA) of this lot showed that the first two principal components (PCs) accounted for 99.72% of total spectral variation, and subcluster analysis identified two distinct groups of vials with statistical significance ($p=0.02$). Furthermore,

interlot variability was documented across a spectral library of 222 vials from 17 different manufacturing lots. Significant spectroscopic variations were observed between lots. PCA of the interlot library indicated that the first three PCs collectively captured 87.83% of total variation, revealing the existence of multiple distinct clusters or "families" of vials rather than a uniform population. While these results do not definitively prove impurities, they strongly suggest the manufacturing process may be operating outside of a state of process control, warranting further investigation to ensure pharmaceutical supply chain integrity.

Introduction

The University of Kentucky's (UK) Drug Quality Task Force (DQTF) was established in August of 2019 to engage in consumer-level quality assurance screening for drugs used within UK HealthCare's pharmacies ([Isaacs, 2025a](#)). The DQTF currently screens medications using Fourier transform near-infrared spectrometry (FTNIR) and Raman spectrometry for potential quality defects indicated by variability in absorbance peak intensities and locations. Through years of continuous monitoring, DQTF has assembled a spectral library containing medications typically used in a health system setting. Statistical analyses using the DQTF spectral library are performed to identify potential intra-lot and inter-lot variability in medications under review. Using Medwatch and publications in the scientific literature, the DQTF 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.

Drug Product

Cefepime for Injection is a cephalosporin antibacterial indicated for the treatment of the following infections caused by susceptible strains of designated microorganisms: pneumonia; empiric therapy for febrile neutropenic patients; uncomplicated and complicated urinary tract infections (including pyelonephritis); uncomplicated skin and skin structure infections; complicated intra-abdominal infections (used in combination with metronidazole) in adults ([Cefepime package insert, 2021](#)).

[Figure 1](#) is a photo of the drug product. Intralot analyses were done on lot 5056KFPDL1. The 17 lot numbers making up the spectral library were 0A0046A42, 0C0185A42, 0D0266A42, 0D0315A42, 0F0445A42, 0F0456A42, 0H0536A42, 0H0606A42, 0H0615A42, 1A0016A42, 1A0045A42, 1C0266A42, 1E0385A42, 1E0435A42, 1G0485A42, 1G0545A42, and 9M0685A42.



Figure 1. Vials of cefepime drug product from lot 5056KFPDL1.

Background

Recent studies

Recent studies involving cefepime appear to cluster around four key themes:

- A. The Cefepime vs. Piperacillin-Tazobactam (Pip-Tazo) Debate
- B. Cefepime-Induced Neurotoxicity (CIN) Risk and Mitigation
- C. New Formulations (Cefepime-Enmetazobactam) and Guideline Updates
- D. Dosing Optimization (Extended vs. Standard Infusion)

1. The Cefepime vs. Piperacillin-Tazobactam Debate

For years, a central debate in infectious diseases has been the choice between cefepime and piperacillin-tazobactam for broad-spectrum empirical coverage ([Patanwala, 2025](#)). The concern was a perceived trade-off: cefepime was associated with neurotoxicity, while piperacillin-tazobactam (especially with vancomycin) was associated with a higher risk of acute kidney injury (AKI).

- Most Important Study: The ACORN (Antibiotic Choice on Renal Outcomes) trial ([Radecki, 2024](#)). This was a large-scale, pragmatic, randomized controlled trial that directly compared

the two ([Patanwala, 2025](#)).

- Why It's Important: The ACORN trial is the most robust evidence to date on this topic. As discussed in recent analyses, the trial found no significant difference between cefepime and piperacillin-tazobactam in its primary outcome of AKI or 14-day mortality.
- Context: This finding was so significant because it challenged a large body of observational data suggesting piperacillin-tazobactam was more nephrotoxic. The trial's results suggest that for the general population of hospitalized adults, either agent is a reasonable choice, allowing clinicians to base decisions on other factors like local antimicrobial resistance, cost, or specific patient risk factors. Subsequent analyses and critiques of *other* conflicting observational studies have reinforced the ACORN trial's findings, highlighting the risks of bias in non-randomized studies.

2. Cefepime-Induced Neurotoxicity (CIN)

The most significant safety concern with cefepime remains neurotoxicity. The recent literature has moved from simply identifying this risk to *quantifying* it, defining its mechanisms, and proposing clear strategies for prevention.

- Most Important Studies: Several key systematic reviews and pharmacokinetic (PK/PD) analyses.
- Why They Are Important: These studies confirm that CIN is not just a rare event but a significant risk, *especially* in specific populations ([Liu, 2025](#)). The key findings are:
 - Primary Risk Factor: The strongest association is with renal impairment, particularly when the cefepime dose is not appropriately adjusted. A 2023 systematic review noted that in a majority of reported CIN cases, patients with renal impairment had *not* received a renal dose adjustment ([Ajibola, 2023](#)).
 - PK/PD Target for Toxicity: Neurotoxicity is strongly associated with high cefepime trough concentrations ([Taylor, 2025](#)). Multiple reviews and case studies cite a trough level above 20 mg/L as a major risk factor, increasing the risk fivefold ([Taylor, 2025](#)).
 - Clinical Implications: This has led to strong calls for Therapeutic Drug Monitoring (TDM) of cefepime in high-risk patients (e.g., critically ill, renal dysfunction, elderly). It also highlights the critical importance of simple, diligent renal dose adjustments.
 - New Findings: A 2024 case report even linked CIN to a *change in infusion time*, where a patient was stable on a 3-hour extended infusion but became neurotoxic after being switched to a 30-minute standard infusion of the same dose, suggesting the rapid peak concentration (C_{max}) may also be a risk factor ([Stratton, 2024](#)).

3. New Formulations and Official Guideline Updates

Recent developments have expanded cefepime's utility in fighting antimicrobial resistance (AMR), a change reflected in both new drug approvals and updated society guidelines.

- Most Important Studies: A 2025 network meta-analysis on a new drug combination and the 2024 IDSA guidance.
- Why They Are Important:
 - New Drug: Cefepime-Enmetazobactam: A new combination agent was approved by the FDA and EMA in 2024. A 2025 network meta-analysis found that cefepime-enmetazobactam was superior to piperacillin-tazobactam and showed significantly higher microbiological eradication rates than carbapenems for complicated urinary tract infections (cUTIs). This is a major development, providing a new, effective *carbapenem-sparing* option ([Wagenlehner, 2025](#)).
 - IDSA Guideline Update: The Infectious Diseases Society of America (IDSA) updated its guidance on AMR Gram-Negative Infections in 2024. This update *clarified* the role of cefepime against organisms with inducible AmpC β -lactamases, notably *removing* a previous warning against using cefepime for certain organisms (like *Enterobacter*) with elevated MICs (4-8 $\mu\text{g/mL}$). This official guidance solidifies cefepime's role as a reliable agent for many resistant pathogens ([Tamma, 2024](#)).

4. Dosing Optimization: Extended-Infusion

To overcome resistance and improve efficacy, particularly for difficult-to-treat pathogens like *Pseudomonas aeruginosa*, optimizing cefepime's pharmacodynamics has been a major focus.

- The most important studies are retrospective cohort studies and PK/PD analyses comparing extended-infusion (EI) to standard-infusion (SI) dosing.
- Those studies are important because cefepime is a time-dependent antibiotic, meaning its efficacy relies on the *time* its free concentration remains above the minimum inhibitory concentration (MIC)([Khole, 2023](#)).
 - Improved Outcomes: While foundational studies are older, recent high-quality retrospective studies (e.g., 2023) have confirmed their findings. These studies show that administering cefepime as an extended infusion (over 3-4 hours), compared to a standard 30-minute bolus, is associated with better clinical outcomes ([Stratton, 2024](#)).
 - Specific Benefits: These outcomes include reduced mortality in patients with *P. aeruginosa* infections], shorter time to clinical stability, and lower rates of treatment failure. While not all studies have shown a benefit (e.g., a 2017 pilot study in febrile neutropenia found no difference), the weight of the evidence, especially for severe infections, strongly supports the use of EI regimens.

Recalls

There is no direct product recall explicitly named for "Apotex Cefepime for Injection" in the U.S. or Canada at the time of submission. However, Apotex is currently facing significant manufacturing suspensions at its Richmond Hill, Ontario facility (where sterile injectables are made) following a serious FDA Warning Letter issued on October 31, 2025. This has led to recalls of other sterile products and confirmed shortages of APO-CEFEPIME in Canada ([Eglovitch, 2025](#)).

There were no active recalls found for Qilu Pharmaceutical's cefepime for injection in the U.S. or Canada.

Apotex Cefepime: Alerts & Manufacturing Issues

While a specific "recall" for cefepime has not been issued in the U.S., the manufacturing environment for Apotex sterile injectables is currently compromised.

FDA Warning Letter & Production Suspension (October 2025)

On October 31, 2025, the U.S. FDA issued a [Warning Letter 320-26-12](#) to Apotex regarding its facility in Richmond Hill, Ontario. The inspection found significant violations in sterile manufacturing processes, including:

- Failure to investigate leaks in container closures.
- Visible damage and deterioration to critical sterile equipment (e.g., glove breaches in barrier systems).
- Inadequate prevention of microbiological contamination.

As a result, Apotex temporarily suspended manufacturing and distribution of sterile solutions and small-volume sprays from this facility. While the voluntary recalls issued so far explicitly name other drugs (like ophthalmic solutions), the suspension of the facility affects the production and potential supply of other sterile injectables like cefepime ([Eglovitch, 2025](#)).

Philippine Recall (Astral Steritech Link)

Event: In 2023, the Philippine FDA issued a recall for Cefepime 1g and 2g Powder for Injection ([Advisory No. 2023-1589](#)). This product was manufactured by Astral Steritech Pvt. Ltd. (India). Apotex has historically partnered with Astral Steritech for some injectable products. The reason for this recall was Out-of-Specification (OOS) data and GMP issues at the sterile facility.

Canadian Market Status

Health Canada lists [APO-CEFEPIME \(DIN 02467518\)](#) as having a "Drug Shortage" status as of September 2025. This shortage is likely a direct downstream effect of the manufacturing suspension at the Richmond Hill plant.

Qilu Cefepime: Current Status

There are currently no FDA or Health Canada enforcement reports listing a recall for Qilu Pharmaceutical's Cefepime for Injection. [Qilu is an active packager and manufacturer for cefepime](#) (generic). While Qilu has had import alerts for other products in the past, none are currently flagged for their cefepime production lines.

FDA Medwatch

An FDA Form 3500 Medwatch describing the findings of this Rapid Communication was filed.

Methods

FTNIR (Fourier Transform Near-Infrared) Spectrometry

Using nondestructive analytical techniques, FTNIR spectra were collected from inventory as part of routine medication quality screening. A representative sample of individual vials were selected for screening 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)([Isaacs, 2025b](#)).

Smoothing

Data smoothing is a technique used to remove noise from data. This can be done by fitting a smooth curve to the data, such as a cubic spline. Cubic splines are piecewise cubic polynomials that are continuous and have continuous first and second derivatives. This makes them very smooth and resistant to noise. Cubic splines can be easily fitted to data using least squares ([Matlab, 2024](#))([Pollock, 1998](#)).

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 ([Jolliffe, 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 clusters 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 ([Isaacs, 2023](#))([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.

Artificial Intelligence Tools

Artificial intelligence (AI) tools, principally used for background information, include [Gemini](#) (Google LLC) and [GPT-4](#) (OpenAI). AI can be used in a variety of ways, including to brainstorm, organize thoughts, develop arguments, and edit.

Results and Discussion

Intralot analysis

Smoothed spectra graphs of batch

[Figure 2](#) displays the FTNIR spectra collected from individual vials within a single manufacturing lot (5056KFPDL1) of cefepime drug product. The figure specifically marks areas of peak variability with arrows at four wavenumbers: 4151, 4361, 4904, and 6495 cm^{-1} . Figure 2 is important because it visually demonstrates intra-lot variability: It provides the primary visual evidence that spectroscopic differences (variability in absorbance peak intensities and locations) exist among vials within the same manufacturing lot. The detection of this intra-lot variability is a core finding of the research conducted by the DQTF on spectroscopic quality monitoring of cefepime. This visual variability serves as the foundation for the more complex statistical subclustering analyses.

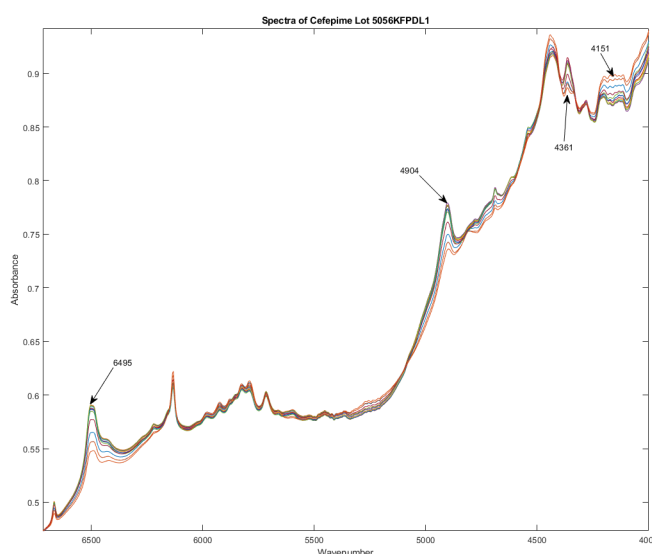


Figure 2. Spectra of vials from intralot analysis. Areas of peak variability are marked with arrows at 4151, 4361, 4904, and 6495 cm^{-1} .

[Figure 3](#) is a three-dimensional principal component (PC) scatterplot representing the spectral data of cefepime vials from lot 5056KFPDL1. The plot visualizes the relationships between individual samples in a reduced-dimensional coordinate system defined by the first three principal components. PC 1 represents the direction that maximizes the variance of the projected data, accounting for 86.90% of the total variation in the intralot analysis. PC 2 captures the largest variance orthogonal to PC 1, representing 12.82% of the variation. PC 3 accounts for a much smaller fraction (0.18%) of the variation. The variation described by PC 1 is greater than 90% in most well controlled pharmaceuticals. The figure shows various data points (representing individual vials) connected by lines, forming a geometric structure in the spectral hyperspace. The points are labeled with numbers corresponding to specific vials, illustrating how they are distributed relative to one another based on their spectroscopic characteristics.

PC Plots

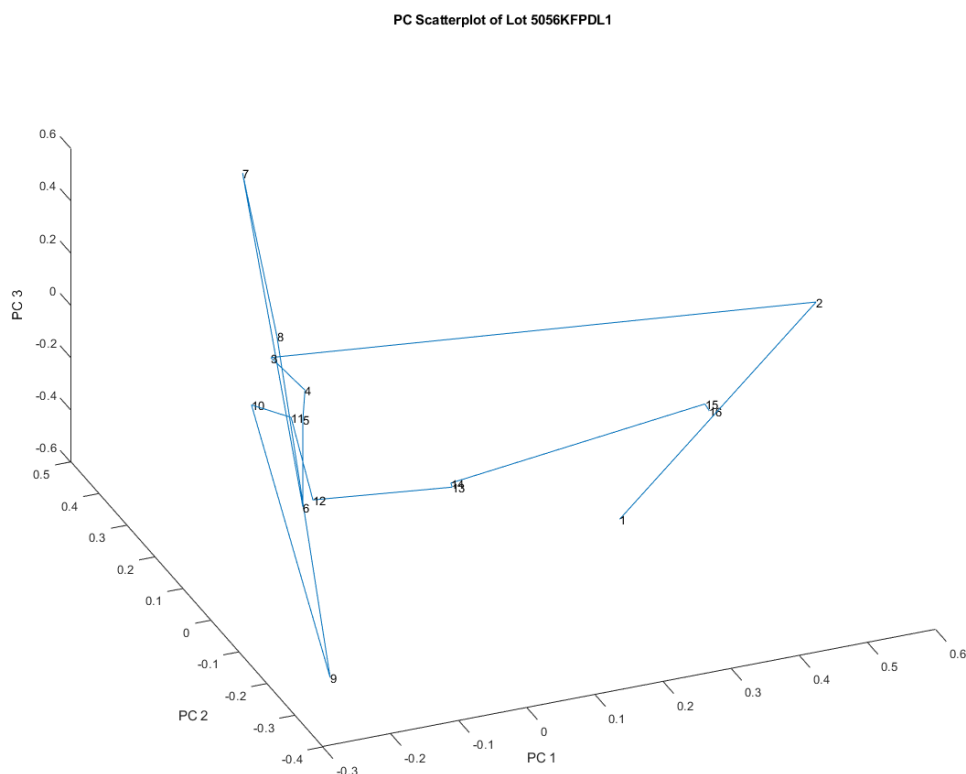


Figure 3. PC scatterplot of the spectra of the vials from [Figure 2](#).

QQ plot from Intralot Analysis

[Figure 4](#) is a QQ plot generated from the intralot subcluster analysis of cefepime lot 5056KFPDL1. The graph plots the ECDF on the y-axis against the TCDF on the x-axis. The plot features a distinct blue line representing the distribution of the vial spectra. A key characteristic of this line is a sharp, nearly vertical jump occurring between the TCDF values of approximately 0.03 and 0.044. The figure also includes specific statistical correlation coefficients such as $r_{tn} = 0.9946$, the correlation for the training group, $r_{ts} = 0.9132$, the correlation for the test "subcluster" group, and the r value for a significance level for $p=0.02$, 0.98947.

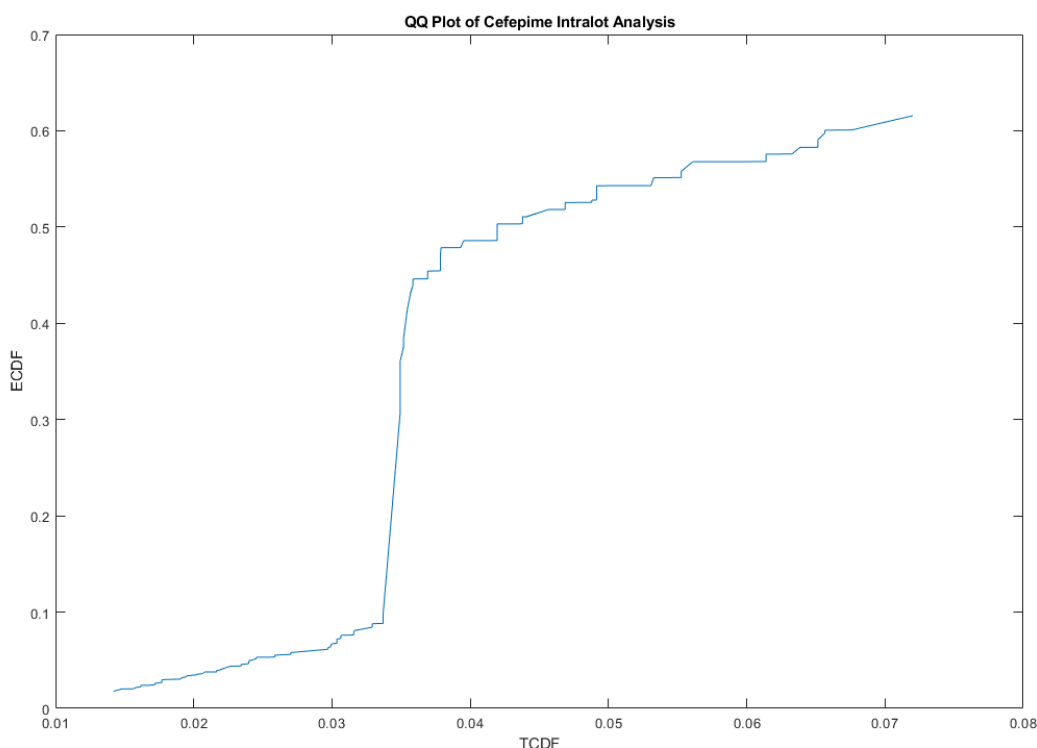


Figure 4. QQ plot from the intralot subcluster analysis showing 2 groups of vials in lot 5056KFPDL1. $r_{tn}=0.9946$, $r_{ts}=0.9132$. r for $p=0.02$ is 0.9894

[Table 1](#) summarizes the results of the Principal Component Analysis for the vials within lot 5056KFPDL1. It lists nine principal components (PCs) and the specific variation each accounts for. PC 1, which accounts for the vast majority of variation at 0.8690 (86.90%). PC 2 accounts for 0.1282 (12.82%). PC 3: accounts for a marginal 0.0018 (0.18%) of total variation. In a perfectly controlled manufacturing process, the variation should be extremely low and random. In a well-controlled pharmaceutical process, the first PC usually accounts for more than 90% of the total spectral variation.

The first two PCs alone explain 99.72% of the total spectral variation within the lot. By the sixth PC, essentially 100% of the variation is accounted for.

Table 1 is critical for establishing the statistical validity of the findings regarding manufacturing consistency within a single lot. Because PC 1 and PC 2 capture 99.72% of all variation, it proves that the 3D scatterplot in [Figure 3](#) is a near-perfect representation of the actual data. Nearly 87% of the differences between vials in this batch can be explained by a single set of spectral features (PC 1). PC loadings provide the weightings used to calculate the BEST distances and the subsequent QQ plot ([Figure 4](#)).

Table 1. Variation accounted for by each of the principal components of the spectra in the intralot vials

PC Number	Variation in this PC	Cumulative PC Variation
1	0.8690	0.8690
2	0.1282	0.9972
3	0.0018	0.9990
4	0.0008	0.9998
5	0.0002	0.9999
6	0.0000	1.0000
7	0.0000	1.0000
8	0.0000	1.0000
9	0.0000	1.0000

Interlot analysis

Smoothed spectra graphs of library

[Figure 5](#) displays the FTNIR reflectance spectra of 222 vials sourced from 17 different manufacturing lots comprising the cefepime spectral library for this manufacturer and dose of cefepime. The graph plots absorbance (y-axis) against wavenumber in cm^{-1} (x-axis) for the specific spectral region of 4000 to 4500 cm^{-1} . The figure highlights significant spectroscopic differences between these lots, specifically noting the variation in the relative size of absorbance peaks at three specific wavenumbers 4130 cm^{-1} , 4340 cm^{-1} , and 4360 cm^{-1} . [Figure 5](#) is a cornerstone of the study's interlot analysis for the following reasons: It provides the primary visual documentation that significant spectroscopic differences exist between different manufacturing lots of the same drug product. This variability in absorbance peak intensities and locations is the key indicator used by the DQTF to identify potential quality defects in medications. By documenting these variations, the figure supports the DQTF's mission to provide quality information that augments existing price data, aimed at improving the pharmaceutical supply chain. These spectra represent the "fingerprint" of the medication over time, allowing for the assembly of a library used to perform statistical analyses and identify lot-to-lot inconsistencies.

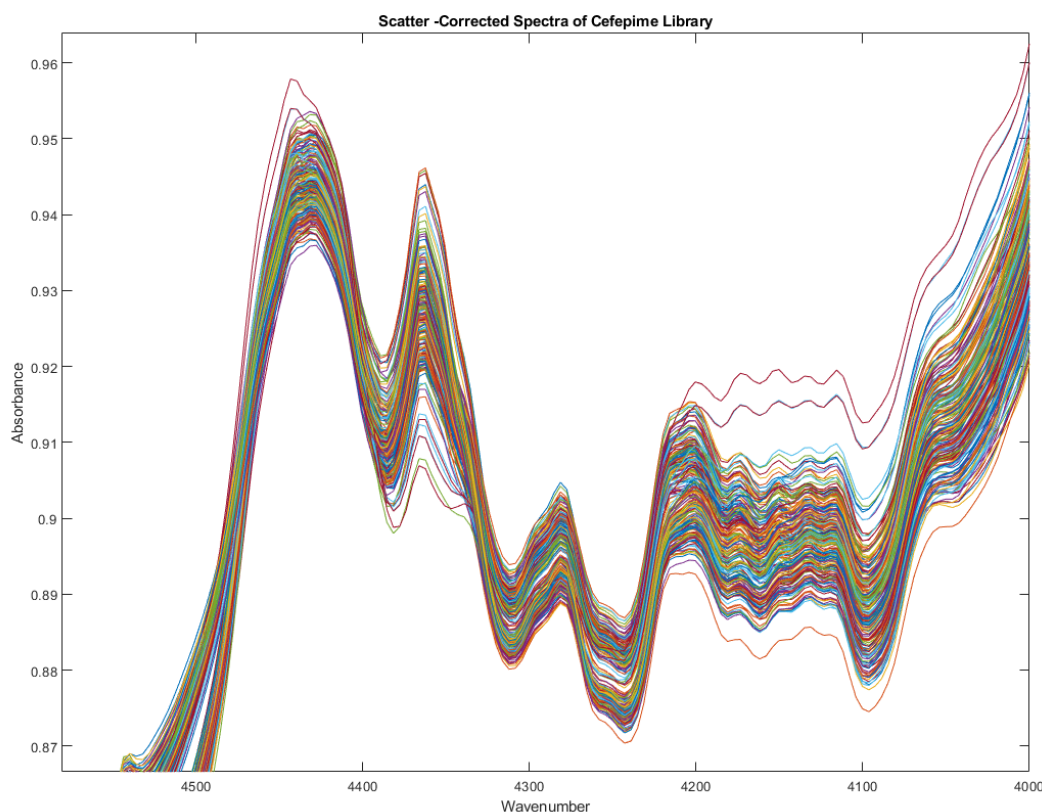


Figure 5. Spectra of 222 vials from 17 different lots in the cefepime spectral library in the region from 4000 to 4500 cm^{-1} . Note the variation in the relative size of the peaks at 4130, 4340, and 4360 cm^{-1} .

[Figure 6](#) displays the FTNIR spectra of the same 222 vials from 17 different manufacturing lots featured in the spectral library shown in [Figure 5](#), now focusing specifically on the wavenumber region from 4600 to 4950 cm^{-1} . This visualization highlights significant variations in the relative size and intensities of several key absorbance peaks within this range, most notably at 4620, 4690, 4770, 4810, and 4900 cm^{-1} . These differences represent spectroscopic "fingerprints" of the various lots and are a direct result of the nondestructive analytical techniques used by the DQTF to screen inventory for potential quality defects. The importance of [Figure 6](#) lies in its role as visual evidence of inter-lot variability, demonstrating that medications supposedly produced to the same standards can exhibit distinct spectroscopic differences. These variations in peak intensities and locations are utilized by the DQTF to identify medications that may have been manufactured outside of a state of process control. By documenting these inconsistencies across a broad library of samples, the researchers aim to increase transparency in the pharmaceutical supply chain and hold manufacturers accountable for Good Manufacturing Practice (GMP) requirements. Furthermore, this figure provides the raw spectral data that

serves as the basis for the more advanced multidimensional statistical analyses, such as the Principal Component Analysis scatterplots, which mathematically map these differences in spectral hyperspace.

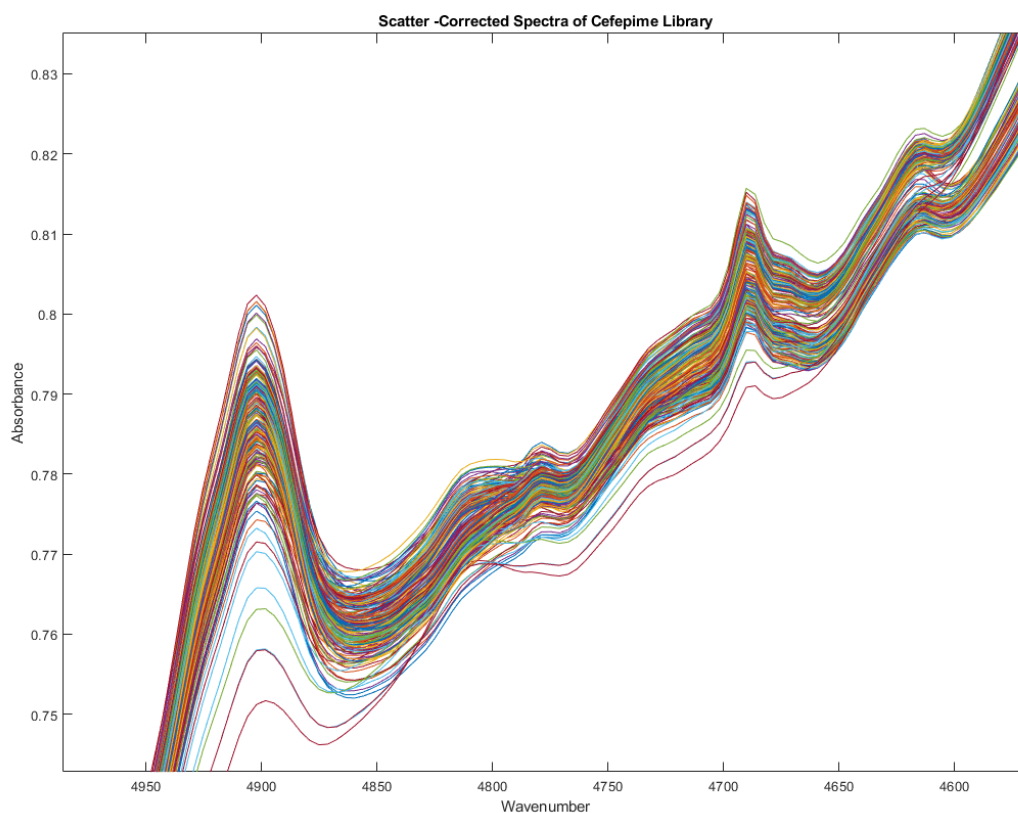


Figure 6. Spectra of 222 vials from 17 different lots in the cefepime spectral library in the region from 4600 to 4950 cm^{-1} . Note the variation in the relative size of the peaks at 4620, 4690, 4770, 4810, and 4900 cm^{-1} .

[Figure 7](#) presents the FTNIR spectra of the 222 cefepime vials from the 17-lot spectral library, specifically examining the higher wavenumber region from 5800 to 6500 cm^{-1} . In this specific spectral range, the graph highlights noticeable variation in the relative absorbance and size of peaks at wavenumbers 6140, 6210, and 6500 cm^{-1} . These spectroscopic differences across multiple vials and lots serve as primary visual evidence of inter-lot variability and suggest that different manufacturing runs or even vials may possess distinct chemical or physical characteristics despite being the same drug product. The phenomenon where certain peaks change in size while others remain stable occurs because near-infrared (NIR) spectra are essentially complex "fingerprints" of a sample's chemical composition and physical state. Each peak in a spectrum corresponds to a specific molecular vibration, such as the stretching or bending of chemical bonds like C-H, O-H, or N-H. If a specific chemical component such as an

active pharmaceutical ingredient, a specific impurity, or moisture varies in concentration, only the peaks associated with those specific molecular vibrations will show a change in absorbance. Conversely, peaks representing chemical structures that remain constant across all samples will appear uniform across the spectra. Furthermore, physical factors such as changes in particle size distribution or sample packing can also influence the scattering of light, leading to variations in certain regions of the baseline or specific peak intensities.

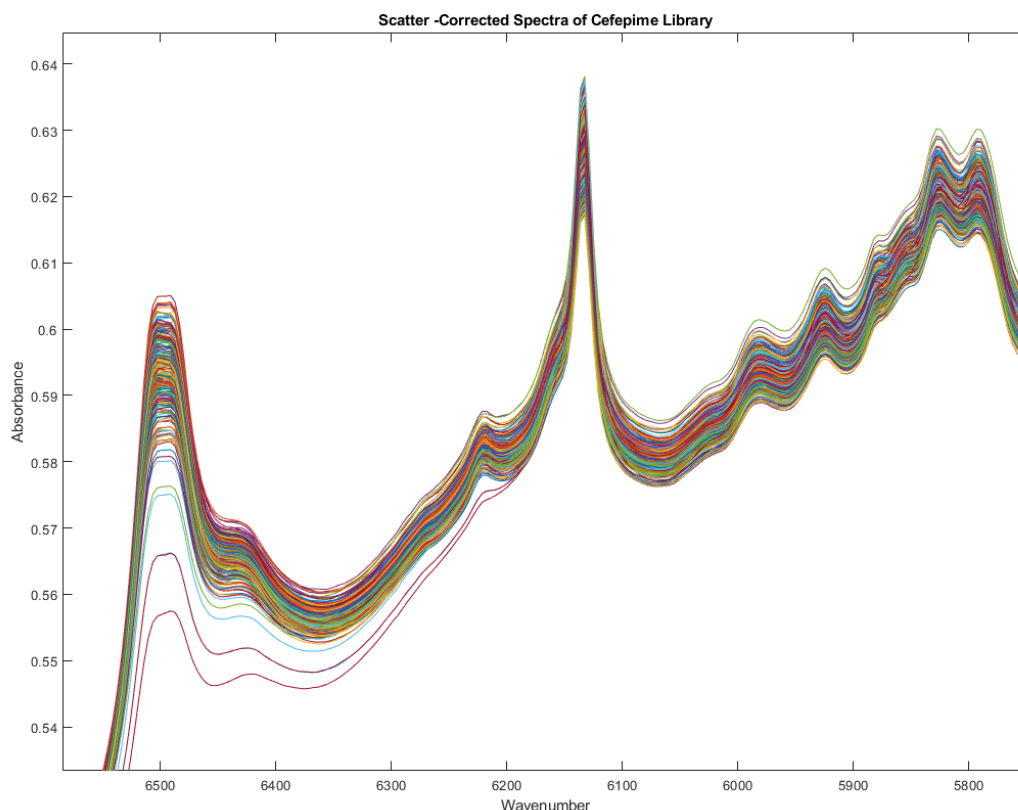


Figure 7. Spectra of the same 222 vials in [Figure 5](#) and [Figure 6](#) in the region from 4600 to 4950 cm^{-1} . Note the variation in the relative size of the peaks at 6140, and 6210, and 6500 cm^{-1} .

[Figure 8](#) is a three-dimensional scatterplot of the principal component (PC) scores for the 222 cefepime vials contained in the spectral library. The plot maps each vial's complex spectral data onto the first three principal components (PC1, PC2, and PC3), which essentially serve as a coordinate system for visualizing the most significant variances in the data. By plotting the scores in this three-dimensional space, the figure reveals the underlying structure of the data, showing how the vials relate to one another based on their unique spectroscopic "fingerprints".

The presence of multiple distinct groups, or clusters, indicates that the 222 vials do not belong to a single, uniform population but instead separate into different "families" based on spectral similarities. These clusters form because vials with similar chemical or physical properties—such as specific component concentrations, particle-size distributions, or sample packing—generate similar spectral data points that group together in the scatterplot. Conversely, the separation between these clusters implies significant differences in these properties between the groups, suggesting that different sets of vials (likely from different manufacturing lots) have distinct characteristics.

The existence of these distinct clusters is meaningful because it suggests the manufacturing process may be operating outside of a state of process control. In a tightly controlled manufacturing environment, one might expect all samples to cluster tightly in a single region. However, the separation into distinct groups and the presence of outliers indicate variability that could be caused by factors like moisture uptake or even low-level contamination. These groupings allow researchers to identify samples that deviate from the standard profile, flagging them for further investigation into potential quality defects.

PC Plots



Figure 8. Scatterplot of the PC scores of the spectral library of 222 cefepime vials showing multiple distinct groups and outliers..

[Figure 9](#) presents an alternative rotation of the three-dimensional scatterplot showing the principal component scores for the 222 cefepime vials in the spectral library. This visualization utilizes the same data points and principal components as the previous figure but viewed from a different angle in spectral hyperspace to provide a different perspective on the data structure. While the previous orientation highlighted distinct groupings, the clusters and individual groups are less clearly defined in this specific rotation.

Despite the groups being less clear, the figure still displays the distribution of labeled vials throughout the coordinate system. The lines connecting individual points help trace the relationships and relative distances between specific samples based on their spectroscopic characteristics. This type of multi-angle visualization is often used in exploratory data analysis to ensure that conclusions about clustering or outliers are robust and complete, and not merely a cursory look at a single viewing perspective.

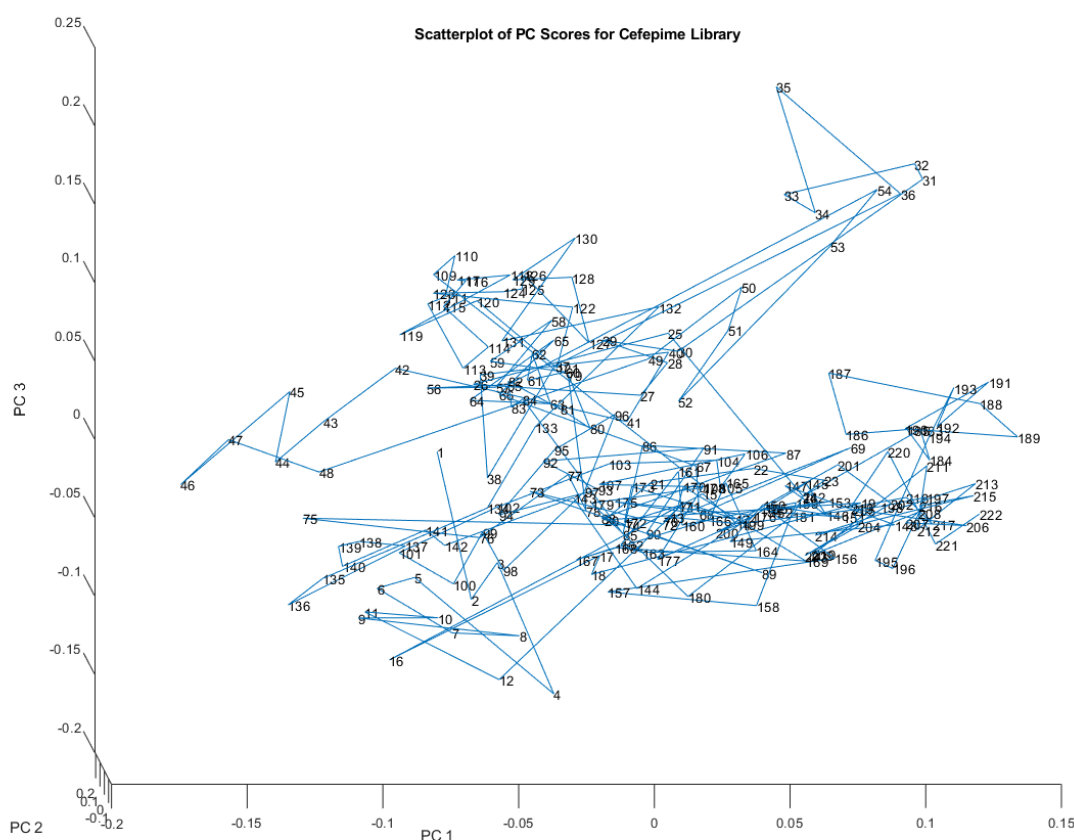


Figure 9. Another rotation of the same 222 vial spectra shown in [Figure 8](#). The groups are less clear in this view.

[Figure 10](#) presents a three-dimensional scatterplot that maps the principal component scores of the 222 cefepime vials from the spectral library using the fourth, fifth, and sixth principal components (PC 4, PC 5, and PC 6) as the coordinate axes. While the first three principal components typically capture the most significant variation in the dataset, this visualization explores the secondary and tertiary variances that remain after the primary data structure has been accounted for. By plotting the data in this specific coordinate system, researchers can identify more subtle relationships, outliers, and potential sub-groupings that may not have been obvious in the initial primary component views.

The distribution of points in this plot shows the vials spread across the spectral hyperspace, with various labels and connecting lines indicating the identity and relative positioning of specific samples. Although the lower-order principal components represent smaller percentages of the total variation, they are often crucial for detecting specific types of process deviations, such as subtle shifts in manufacturing, moisture uptake, or the presence of minor impurities. This figure is part of the comprehensive exploratory data analysis intended to characterize the inter-lot variability and ensure that no significant trends or clusters are overlooked in the broader spectral library.



Figure 10. Scatterplot using PCs 4-6 of the scores of the spectral library of 222 cefepime vials

[Figure 11](#) is a three-dimensional scatterplot showing the principal component scores of the 222 cefepime vials from the spectral library using the seventh, eighth, and ninth principal components as the coordinate axes. By plotting the data in this specific coordinate system, the figure visualizes very subtle variations that remain after the primary and secondary patterns of the data have been accounted for by the earlier principal components. These higher-order components represent a very small fraction of the total spectral variation, with principal components seven, eight, and nine accounting for only 0.61%, 0.35%, and 0.11% of the total variation, respectively.

The importance of [Figure 11](#) lies in its ability to detect extremely minor spectroscopic signatures or patterns that might be buried under larger sources of variability, such as major component concentrations or significant physical differences. By examining these subtle dimensions, researchers can look for evidence of very low-level impurities, slight differences in hydration states, or minor instrumental fluctuations that could indicate a subtle drift away from a state of process control. Including these high-order components in the exploratory analysis ensures a comprehensive evaluation of the spectral library, confirming whether any meaningful clusters or outliers exist even at the most minute levels of data variation.

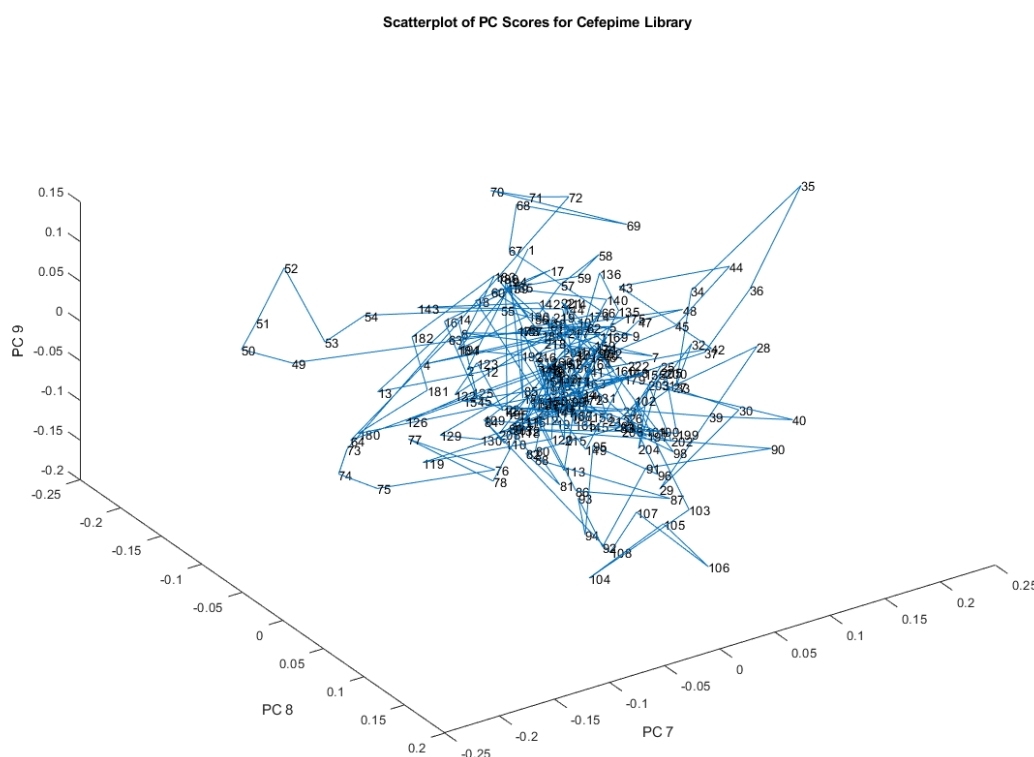


Figure 11. Scatterplot using PCs 7-9 of the scores of the spectral library of 222 cefepime vials.

[Table 2](#) presents the results of the Principal Component Analysis performed on the spectral library of 222 cefepime vials. It lists nine PCs and details the amount of spectral variation accounted for by each individual component and the cumulative total.

The table is structured into three columns: PC Number, Variation in this PC, and Cumulative PC Variation. PC 1 captures the largest portion of the spectral variation at 42.69%. PC 2 accounts for 27.13% of the variation, and PC 3 accounts for 18.01%. The amount of variation captured decreases significantly with each successive component, with PC 4 at 6.99% and dropping to 0.11% by PC 9.

By the third principal component, 87.83% of the total spectral variation is explained, and by PC 9, 99.30% of the variation is accounted for.

[Table 2](#) is critical for understanding the mathematical foundation of the interlot analysis for several reasons. The table shows dimensionality reduction, and it demonstrates that the vast majority of the complex spectroscopic data (87.83%) can be compressed into just the first three dimensions. These data justify the use of 3D scatterplots (such as [Figure 8](#) and [Figure 9](#)) to represent the entire spectral library, as the first three PCs capture most of the relevant information.

By identifying that significant variation exists across multiple PCs (rather than just one), the table suggests that the differences between lots are multi-factorial and not due to a single spectroscopic or chemical change. The distribution of variation across multiple components provides a statistical framework for the conclusion that the manufacturing processes across different lots exhibit notable differences.

Table 2: Variation accounted for by each of the principal components of the library spectra

PC Number	Variation in this PC	Cumulative PC Variation
1	0.4269	0.4269
2	0.2713	0.6982
3	0.1801	0.8783
4	0.0699	0.9482
5	0.0216	0.9698
6	0.0126	0.9823
7	0.0061	0.9884
8	0.0035	0.9919
9	0.0011	0.9930

[Figure 12](#) displays a plot of the loadings for the first principal component (PC 1) of the spectral library, which accounts for 42.69% of the total variation. The x-axis represents the wavenumber in cm^{-1} across a wide range from 4000 to 10000, while the y-axis shows the weighting, or the

relative contribution, of each wavelength to the first principal component. Key features in this loading plot are highlighted with arrows at several wavenumbers, including 8918, 7872, 6587, 5566, and 4481 cm^{-1} . These specific peaks and troughs indicate which spectral regions are most responsible for the primary differences observed between the 222 cefepime vials in the library. In near-infrared spectrometry, multiplicative scatter correction is used as a normalization technique to correct for physical variations in light scattering by adjusting the scale and offset of spectra relative to a reference mean. Despite this correction, residual baseline shifts often appear predominantly in PC 1 because principal component analysis is designed to capture the direction of maximum variance in a dataset. Baseline shifts, which are characterized by a broad, consistent displacement of the signal across a wide range of wavelengths, frequently represent the largest source of mathematical variation remaining after normalization. Because these shifts affect the entire spectrum simultaneously rather than individual narrow chemical bands, the PCA algorithm identifies them as a primary trend, grouping this variation into the first principal component to maximize the explained variance.

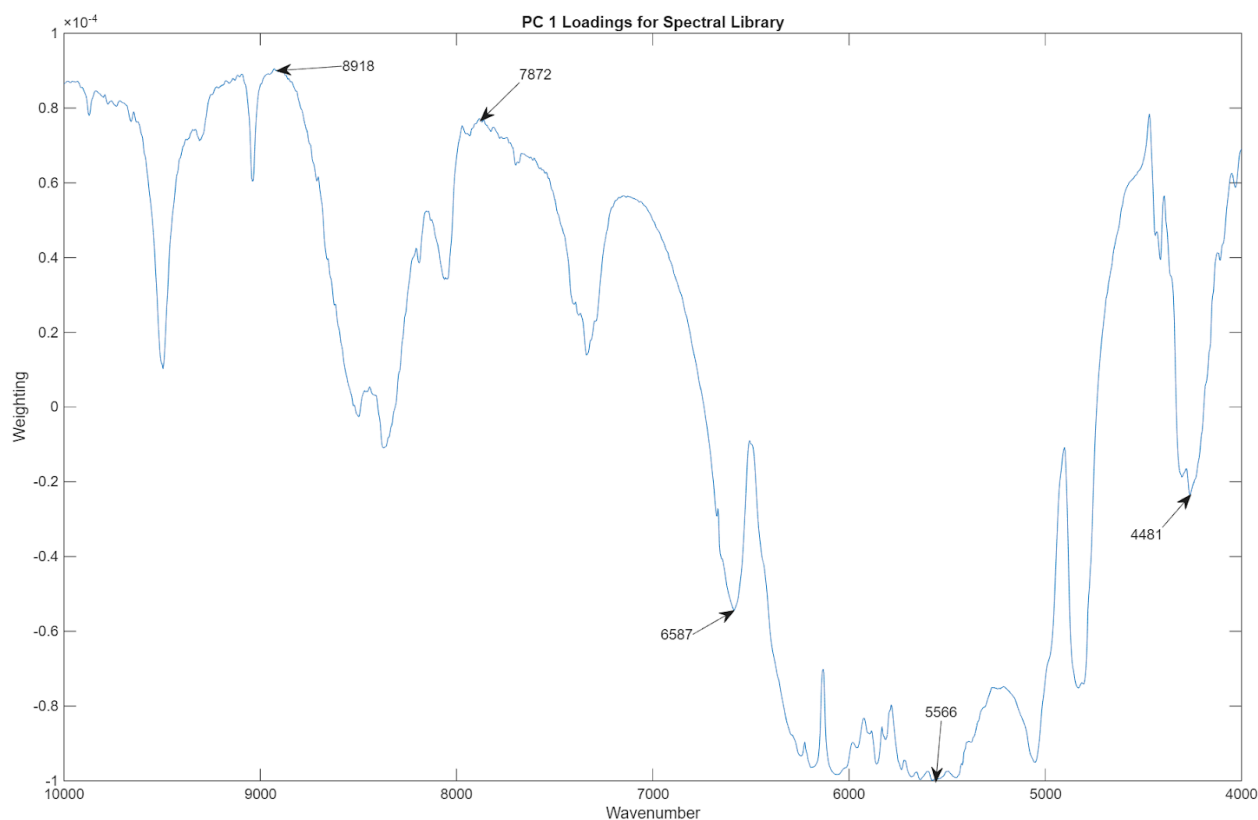


Figure 12. Plot of the loadings for PC1 of the library spectra.

[Figure 13](#) presents a plot of the loadings for the second principal component (PC 2) of the cefepime spectral library. This principal component accounts for 27.13% of the total spectral variation found among the 222 vials across 17 manufacturing lots. The y-axis, labeled as "Weighting," indicates the relative importance or contribution of each wavenumber to this specific component, while the x-axis displays the wavenumber in cm^{-1} . The figure highlights five specific wavenumbers with arrows to identify the most significant features of the loading curve: 8393, 7472, 6700, 4586, and 4286 cm^{-1} . These loadings are important because they provide a mathematical "fingerprint" of the secondary largest source of diversity within the spectral library. While the first principal component often captures dominant baseline variations, the specific peaks and troughs in the PC 2 loadings frequently correspond to variations in chemical composition or specific physical attributes like moisture uptake and particle-size distributions. By analyzing these specific spectral regions, researchers can investigate the chemical or physical causes behind why certain vials or lots cluster separately from others in the multidimensional scatterplots.

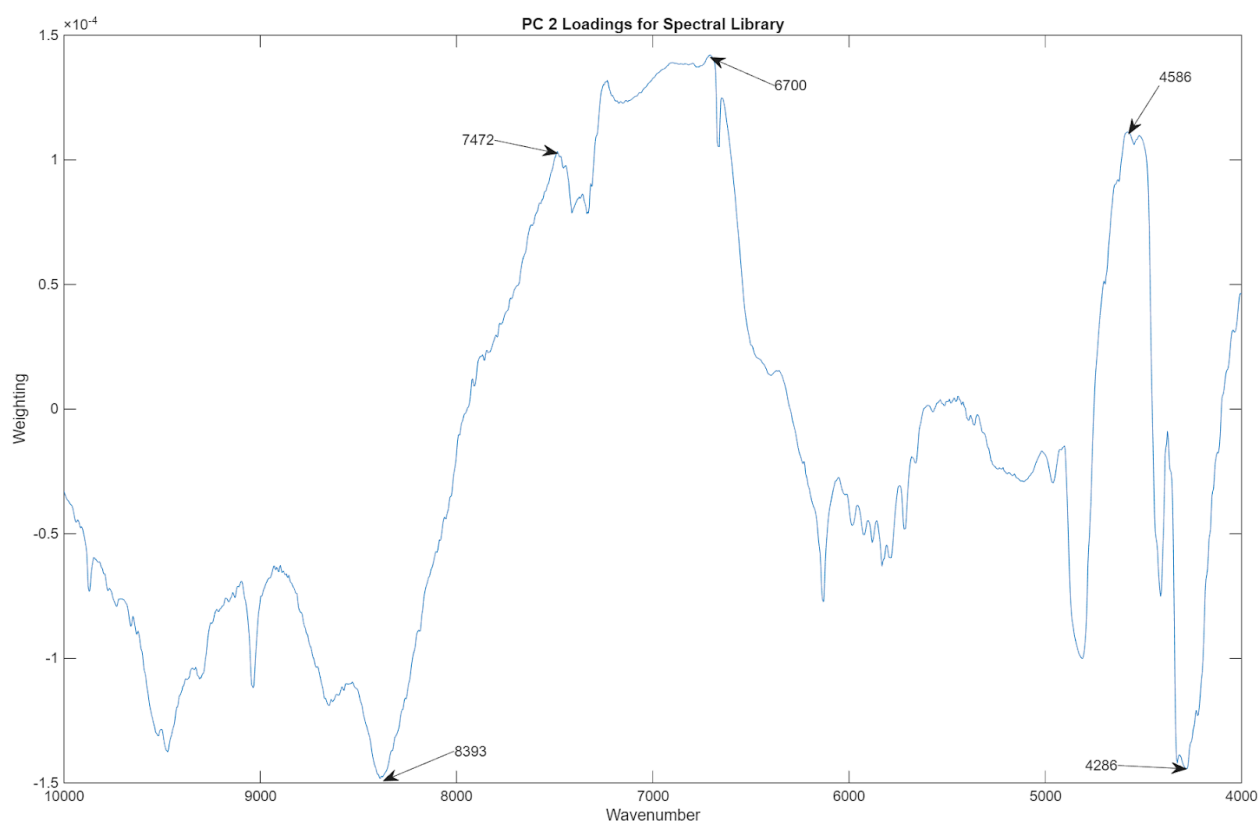


Figure 13. Plot of PC2 loadings of library spectra.

[Figure 14](#) displays the loadings for the third principal component (PC 3) of the spectral library, which accounts for 18.01% of the total variation. This plot reveals how each wavenumber

across the near-infrared spectrum contributes specifically to the variation captured by PC 3. Arrows on the graph highlight key features and peak weightings at wavenumbers 8032, 6473, 4913, and 4747 cm^{-1} . These particular wavenumbers indicate the specific molecular vibrations or physical characteristics that are responsible for the third most significant set of differences among the 222 cefepime vials. The importance of this figure lies in its ability to pinpoint the chemical or structural origins of the variability that causes vials to separate along the Z-axis in the 3D scatterplots shown in [Figure 8](#) and [Figure 9](#). While PC 1 and PC 2 capture broader trends like baseline shifts and major component variations, PC 3 often identifies more subtle chemical differences, such as slight changes in hydration states or minor variations in the crystalline structure of the cefepime powder. By examining the specific peaks highlighted in these loadings, researchers can better understand the underlying causes of the inter-lot variability and determine if the manufacturing process is maintaining a consistent "state of control" for these more nuanced product attributes.

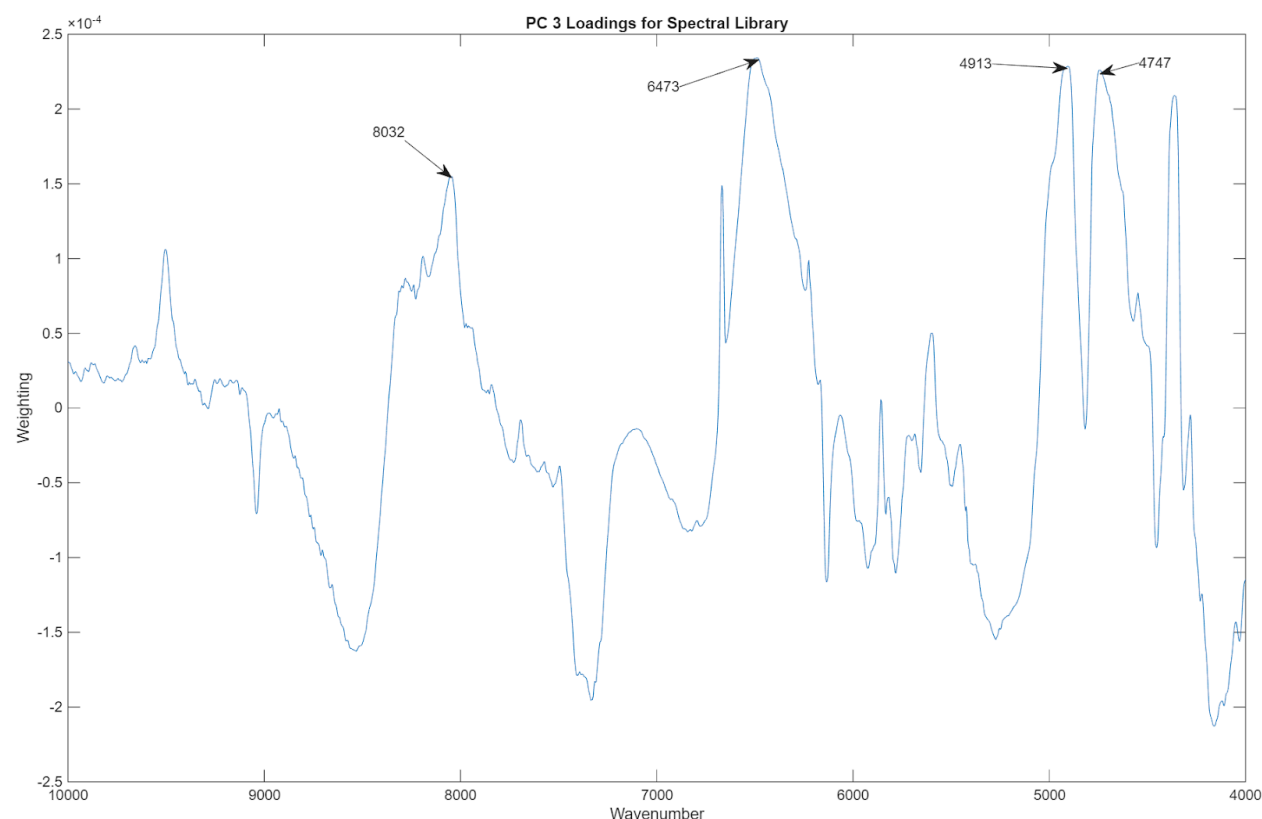


Figure 14. Plot of the loadings for PC3 of the library spectra.

[Figure 15](#) presents the loadings for the fourth principal component (PC 4) of the cefepime spectral library. This component accounts for approximately 6.99% of the total spectral variation observed across the 222 vials in the library. The plot illustrates the weighting or contribution of

specific wavenumbers to the variance captured by PC 4 across the range of 4000 to 10000 cm^{-1} . Arrows on the graph identify several significant features and extrema at wavenumbers 7699, 7150, 4591, and 4330 cm^{-1} . This figure is important because it begins to characterize the more subtle, low-level variations that remain after the primary data structures (PCs 1-3) have been extracted. While accounting for a relatively small percentage of total variation, these loadings help identify specific chemical or physical attributes that may be deviating from the norm in only a subset of the manufacturing lots. By pinpointing these precise spectral markers, researchers can investigate more granular issues such as minor instrumental artifacts or specific chemical inconsistencies that might otherwise be masked by larger global variations in the dataset.

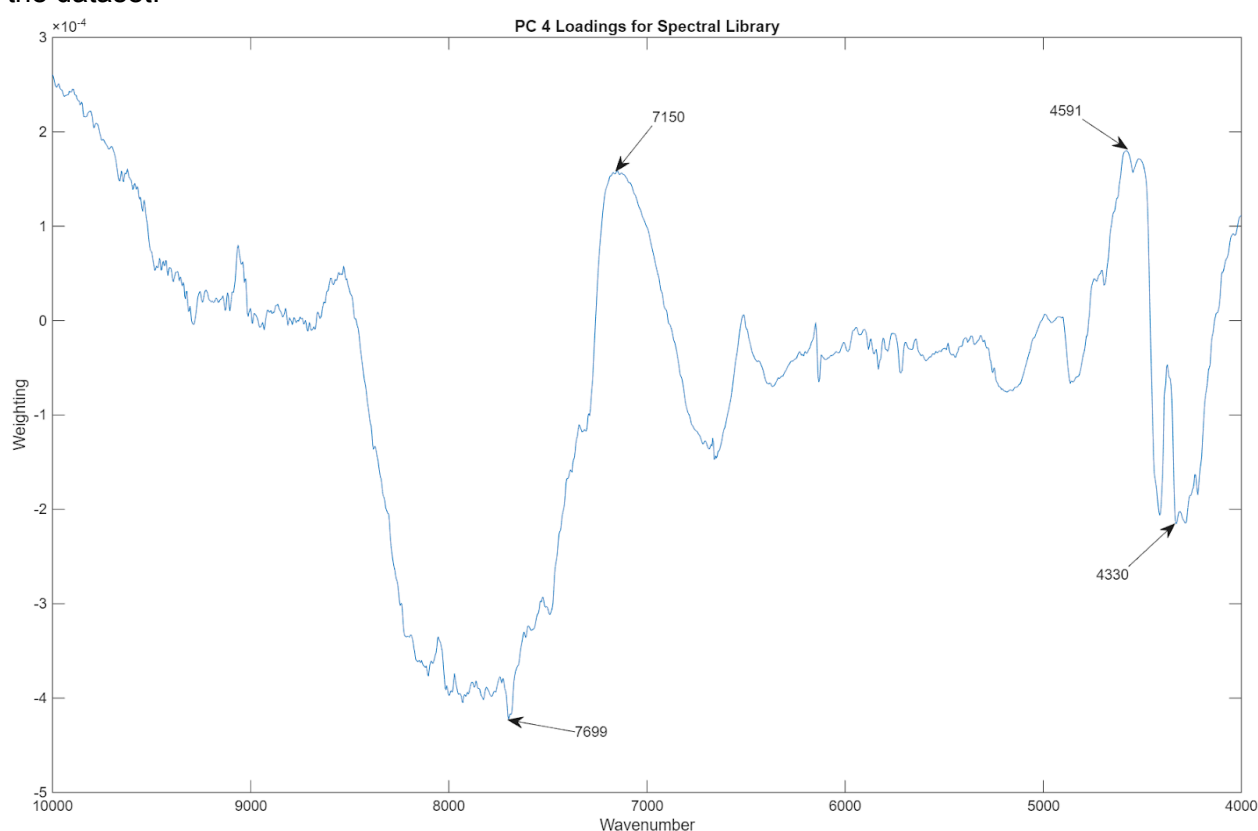


Figure 15. Plot of the loadings for PC4 of the library spectra.

[Figure 16](#) illustrates the loadings for the fifth principal component (PC 5) of the cefepime spectral library. This principal component captures a small but distinct portion of the total spectral diversity, accounting for approximately 2.16% of the variation across the library of 222 vials. The plot shows the weighting assigned to each wavenumber across the near-infrared spectrum, indicating which specific regions contribute to this particular dimension of variability. Arrows on the loading curve highlight five critical spectral features located at wavenumbers 9498, 8032, 7527, 4774, and 4414 cm^{-1} . This figure is important because it

identifies the specific molecular vibrations or physical phenomena that represent the fifth largest source of inconsistency between the various manufacturing lots. While the percentage of variation is low, the sharp and defined nature of these loading peaks suggests that they may correspond to very specific chemical signatures, such as the presence of minor degradants, specific solvates, or subtle changes in the hydration state of the drug product.

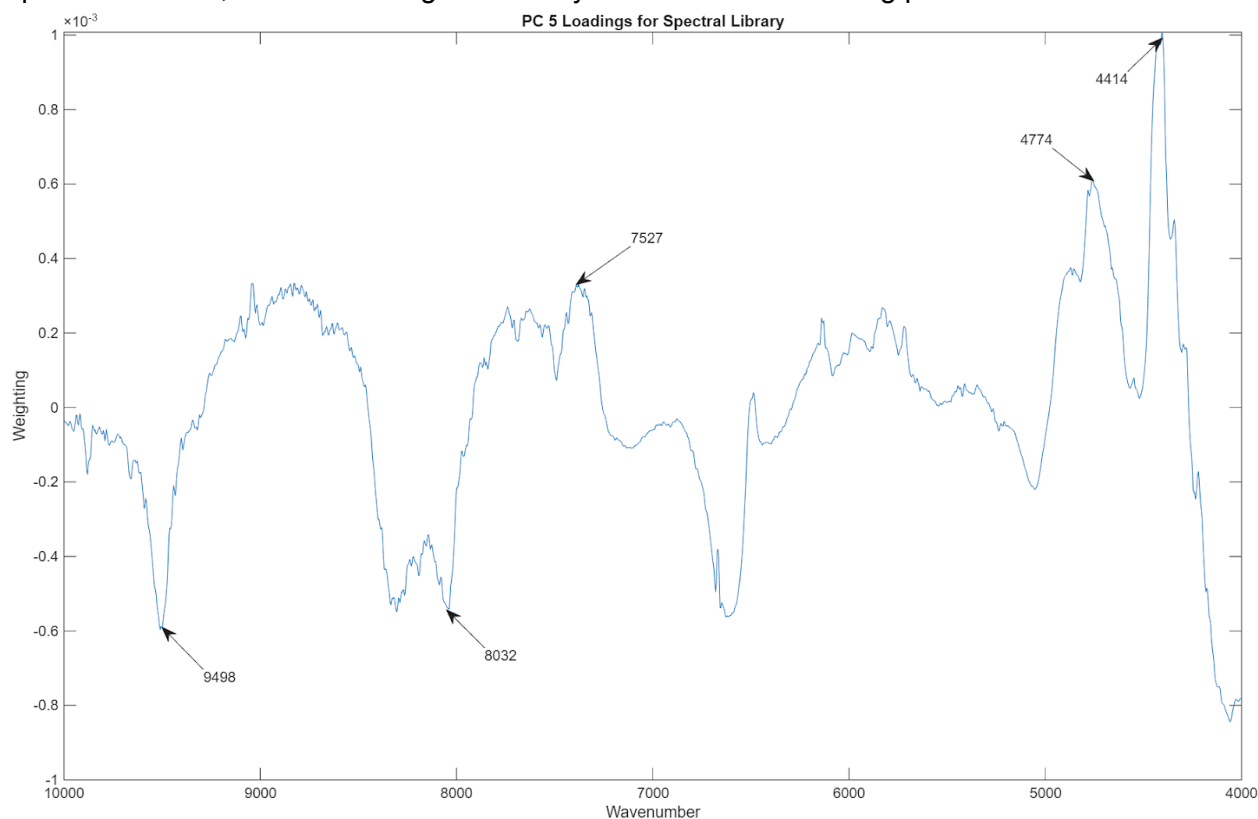


Figure 16. Plot of the loadings for PC5 of the library spectra.

[Figure 17](#) displays the loadings for the sixth principal component (PC 6) of the cefepime spectral library, illustrating how different wavenumbers contribute to this specific dimension of variability. This component accounts for approximately 1.26% of the total spectral variation across the library of 222 vials. The plot maps the weighting of each wavenumber from 4000 to 10000 cm^{-1} , with arrows identifying the most significant features and peak weightings at 6745, 6217, 5118, and 4452 cm^{-1} . This figure is important because it pinpoints the molecular vibrations and physical characteristics responsible for the sixth-largest source of diversity within the dataset. Although it represents a small fraction of the total variation, the sharp peaks in these loadings help researchers identify subtle chemical signatures or physical inconsistencies that might be overlooked in higher-order components. By analyzing these minute details, the Drug Quality Task Force can detect very specific deviations from the expected chemical profile, providing

further evidence that a manufacturing process may be operating outside of a state of process control.

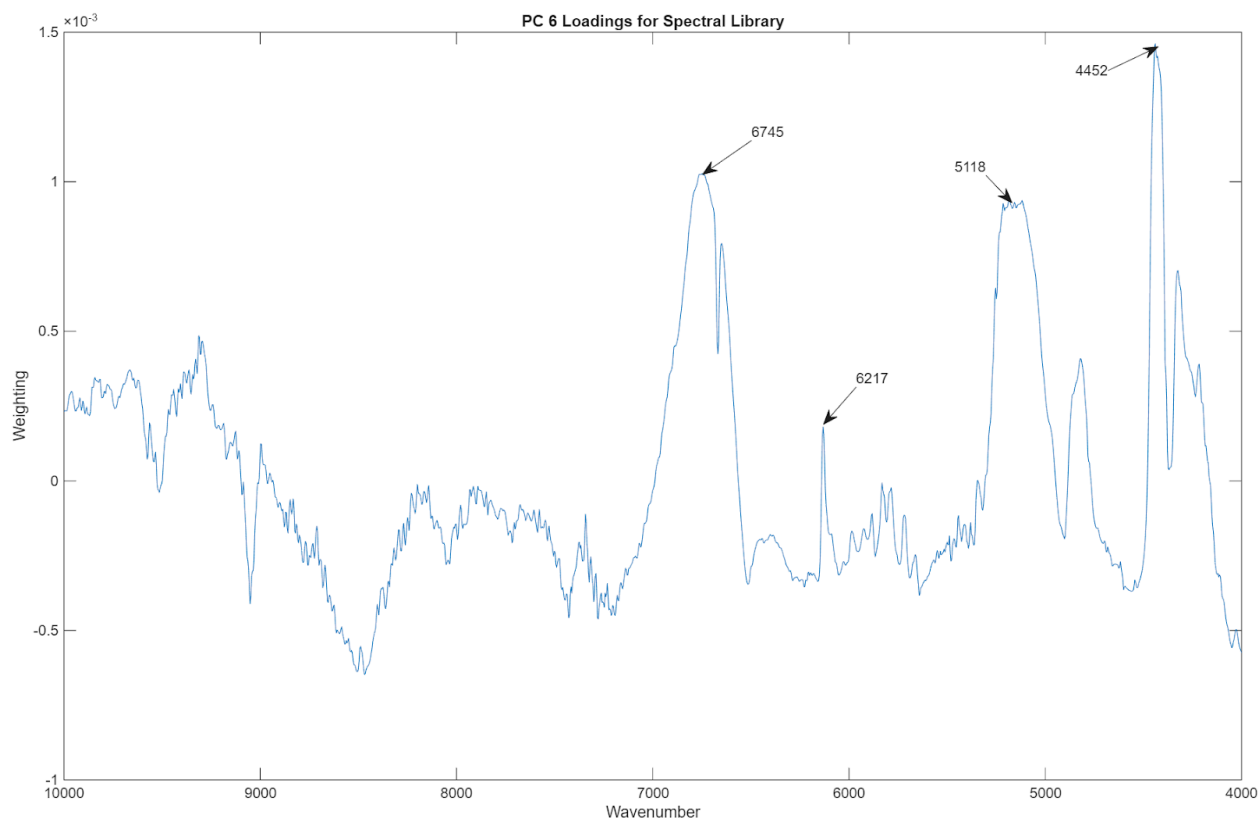


Figure 17. Plot of the loadings for PC6 of the library spectra.

[Figure 18](#) displays the loadings for the seventh principal component (PC 7) of the cefepime spectral library, mapping the weightings of wavenumbers across the near-infrared spectrum from 4000 to 10000 cm^{-1} . This component represents an extremely small fraction of the total spectral variation, accounting for only 0.61% of the diversity found within the 222-vial library. Arrows on the plot identify the most significant spectral features contributing to this component at wavenumbers 6517, 5002, and 4458 cm^{-1} . The importance of [Figure 18](#) lies in its ability to isolate and visualize very minute spectroscopic differences that are otherwise masked by the much larger variances captured in the primary principal components. Note that thermal noise is beginning to creep into the spectrum from the high wavenumber end of the spectrum.

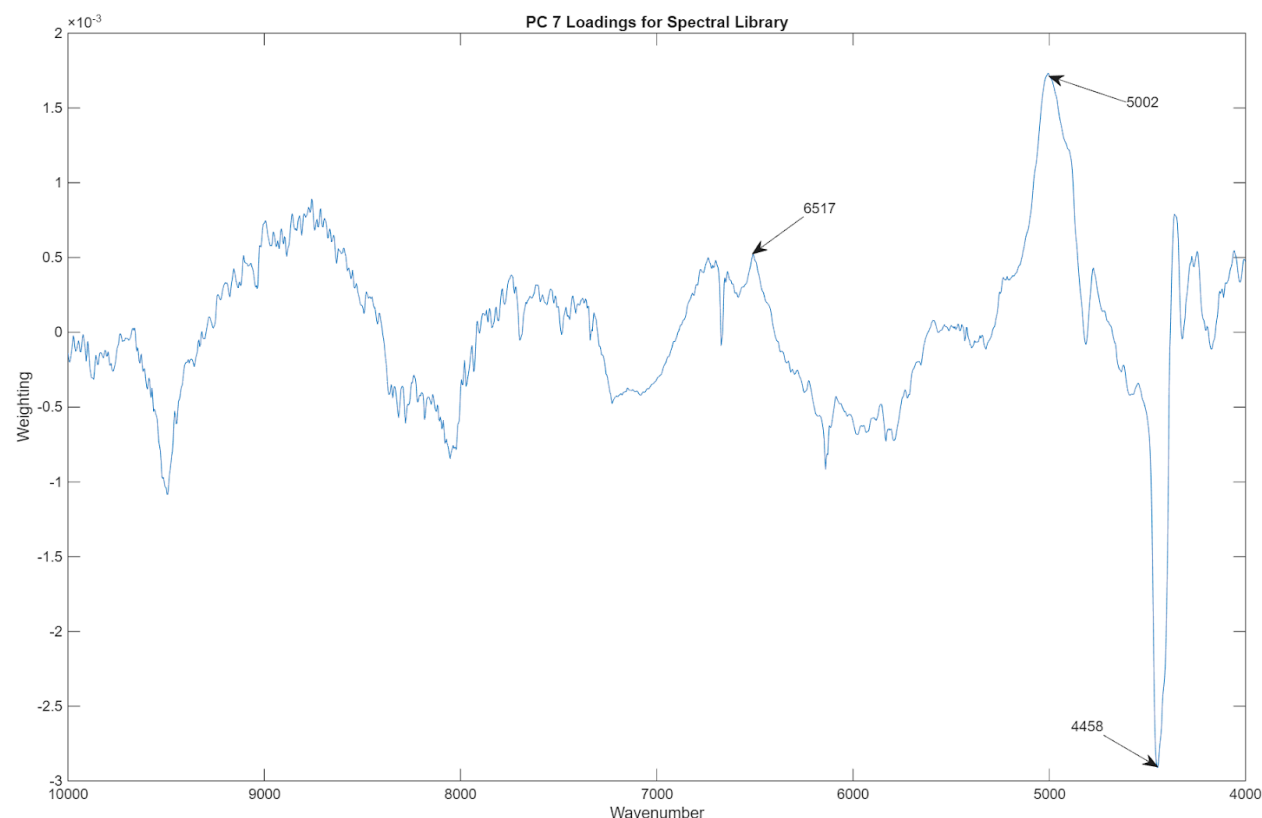


Figure 18. Plot of PC7 loadings of library spectra.

[Figure 19](#) presents the loadings for the eighth principal component (PC 8) of the cefepime spectral library. This component explains a very small portion of the total spectral variation, specifically 0.35%. The graph plots the weighting of each wavenumber across the near-infrared spectrum, indicating which specific regions are responsible for this particular dimension of variability. Several prominent spectral features are identified with arrows at wavenumbers 8377, 7872, 6795, 5363, and 4397 cm^{-1} .

[Figure 20](#) displays the loadings for the ninth principal component (PC 9) of the cefepime spectral library¹. This component accounts for approximately 0.11% of the total spectral variation found within the library of 222 vials. The plot illustrates the weighting or contribution of each wavenumber across the range of 4000 to 10000 cm^{-1} , with specific spectral features and extrema identified by arrows at 6606, 6123, 5340, 4808, and 4391 cm^{-1} . This figure is important because it represents the threshold where the analysis begins to encounter the limits of useful spectral information before transitioning primarily into random noise.

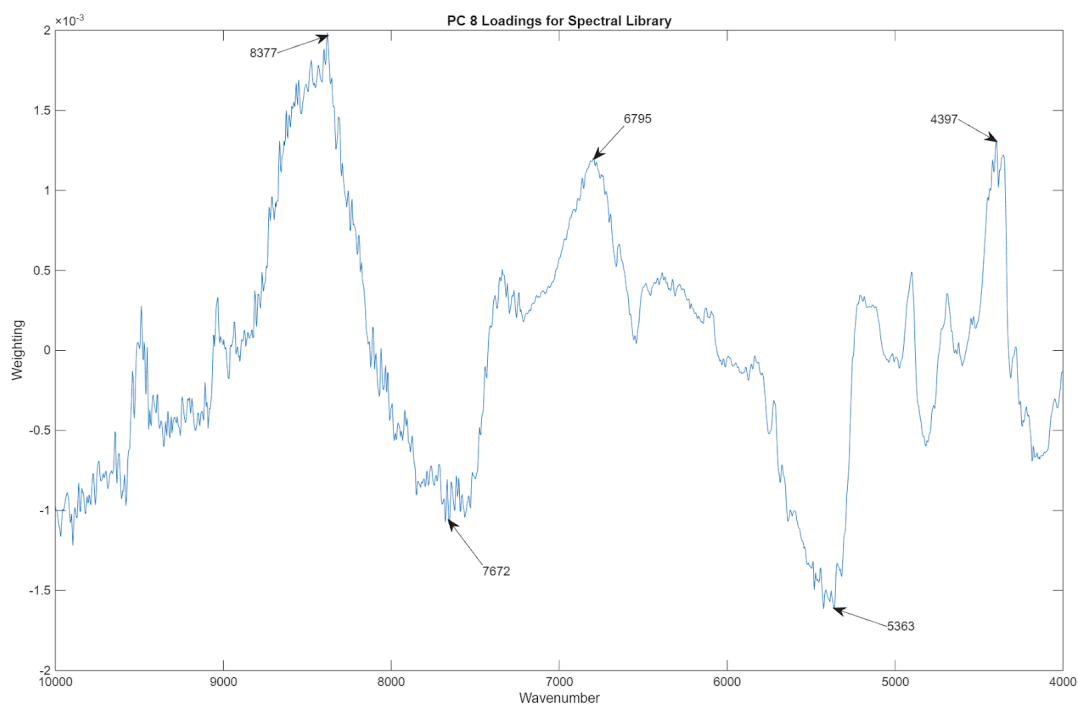


Figure 19. Plot of the loadings for PC8 of the library spectra.

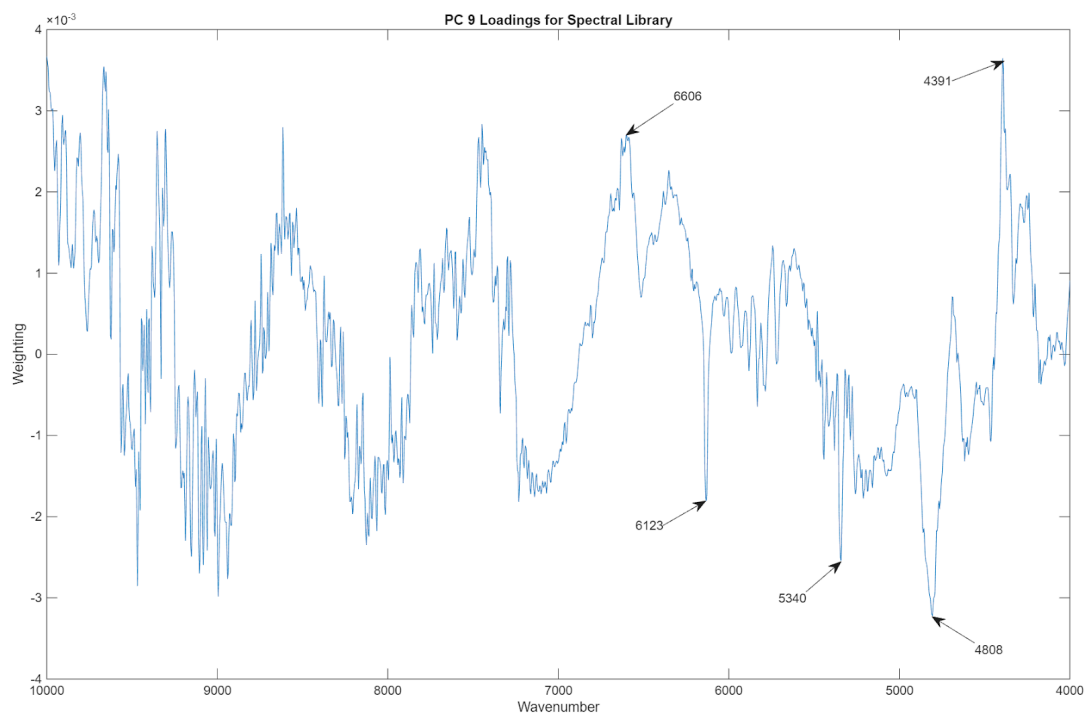


Figure 20. Plot of PC9 loadings of library spectra.

[Table 2](#) provides a detailed breakdown of the mathematical structure of the spectral library, which consists of 222 cefepime vials from 17 different manufacturing lots. It reveals how the total spectral variation is distributed across the first nine principal components (PCs):

PC 1: Captures the largest single portion of the data's variability, accounting for 42.69% of the total variation.

PC 2: Explains 27.13% of the variation.

PC 3: Accounts for 18.01%.

The amount of variation explained by each individual component drops off significantly after the first three, with PC 4 accounting for 6.99% and PC 9 explaining only 0.11%.

The table is particularly significant because it shows that the first three principal components collectively account for 87.83% of the total cumulative PC variation. This reveals that the vast majority of the complex spectroscopic information can be condensed into just three dimensions while still preserving nearly 88% of the original data. This mathematical compression justifies the use of the three-dimensional scatterplots seen in [Figure 8](#) and [Figure 9](#) to visually map the relationships and clusters among the 222 vials.

Furthermore, by the ninth principal component, 99.30% of the total variation is explained, indicating that nearly all relevant spectroscopic differences between the various lots are captured within these nine dimensions.

Table 2: Variation accounted for by each of the principal components of the spectral library

PC Number	Variation in this PC	Cumulative PC Variation
1	0.4269	0.4269
2	0.2713	0.6982
3	0.1801	0.8783
4	0.0699	0.9482
5	0.0216	0.9698
6	0.0126	0.9823
7	0.0061	0.9884
8	0.0035	0.9919
9	0.0011	0.9930

Drug Tracing

There are two specific facilities in China that may have manufactured the cefepime drug product based on a search using [ProPublica Rx Inspector](#) ([Rx Inspector, 2026](#)). The first facility is Qilu Pharmaceutical Co., Ltd. (High Tech Zone Site) located in Jinan, Shandong, China. The most

recent FDA action for this site occurred on January 14, 2025, where an inspector documented issues at the facility during the inspection.

The second facility identified is Qilu Antibiotics Pharmaceutical Co., Ltd., also located in Jinan, Shandong, China. The last FDA action for this facility was recorded on May 30, 2023. In that instance, the FDA found issues but determined that the facility could correct them voluntarily.

It is important to note that manufacturing challenges have been faced by Apotex, a partner associated with these products. While no direct recall was named for "Apotex Cefepime for Injection" at the time of the report's submission, the company received a serious FDA Warning Letter on October 31, 2025, for its Richmond Hill, Ontario facility. This warning cited significant violations in sterile manufacturing, such as failure to investigate container leaks and visible damage to critical sterile equipment like glove barriers. Consequently, Apotex suspended manufacturing of sterile solutions from that site, and there were confirmed shortages of APO-CEFEPIME in Canada as of September 2025.

Conclusion

Cefepime for Injection is a cephalosporin antibacterial indicated for the treatment of the following infections caused by susceptible strains of designated microorganisms: pneumonia; empiric therapy for febrile neutropenic patients; uncomplicated and complicated urinary tract infections (including pyelonephritis); uncomplicated skin and skin structure infections; complicated intra-abdominal infections (used in combination with metronidazole) in adults ([Cefepime package insert, 2021](#)).

Cefepime for Injection remains a critical broad-spectrum antibacterial agent for treating serious conditions such as pneumonia, febrile neutropenia, and complicated urinary tract or intra-abdominal infections. This study utilized FTNIR spectrometry and multivariate statistical analysis to evaluate the quality of current drug inventory. The findings demonstrate significant intralot variability within lot 5056KFPDL1, where subcluster analysis identified two statistically distinct groups of vials ($p=0.02$). Furthermore, the interlot analysis of 222 vials across 17 manufacturing lots revealed substantial spectroscopic differences, with the first three principal components accounting for only 87.83% of the total variation and mapping the vials into several distinct clusters in spectral hyperspace. While these spectroscopic variations do not definitively prove the presence of impurities or adulteration, they strongly suggest that the manufacturing process may be operating outside of a state of process control. Given the recent FDA Warning Letter issued to Apotex regarding sterile manufacturing violations and subsequent product shortages, these findings highlight the need for increased transparency and rigorous consumer-level quality assurance screening. These spectrometric 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.

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