Rapid Quality Assessment of Ceftriaxone Using Near-Infrared Spectroscopy

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RAPID COMMUNICATION

Abstract

Ceftriaxone for injection, USP is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration. Ceftriaxone sodium is a white to yellowish crystalline powder which is readily soluble in water, sparingly soluble in methanol and very slightly soluble in ethanol. The color of ceftriaxone sodium solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used. Each vial contains ceftriaxone sodium equivalent to 250 mg, 500 mg, 1 gram or 2 grams of ceftriaxone activity. Ceftriaxone sodium contains approximately 83 mg (3.6 mEq) of sodium per gram of ceftriaxone activity.

Intra-lot variability was detected in the spectra of 6 vials of ceftriaxone sampled from one lot. One of the vials was more than 8.3 multidimensional SDs away from the center of the cluster of

the other 5 vials from the same lot, suggesting that the manufacturing process may not be in a state of control. Interlot variability was detected between two lots of the drug using a subcluster detection test (r_{tn}=0.9629, r_{ts}=0.9148, p=0.02).

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, 2023a). 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

Ceftriaxone for injection, USP is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration (FDA, 2013). Ceftriaxone sodium is a white to yellowish crystalline powder which is readily soluble in water, sparingly soluble in methanol and very slightly soluble in ethanol. The pH of a 1% aqueous solution is approximately 6.7. The color of ceftriaxone sodium solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used. Each vial contains ceftriaxone sodium equivalent to 250 mg, 500 mg, 1 gram or 2 grams of ceftriaxone activity. Ceftriaxone sodium contains approximately 83 mg (3.6 mEq) of sodium per gram of ceftriaxone activity.

Figure 1 is a photo of the Hikma drug product. The lot number was C1240321.

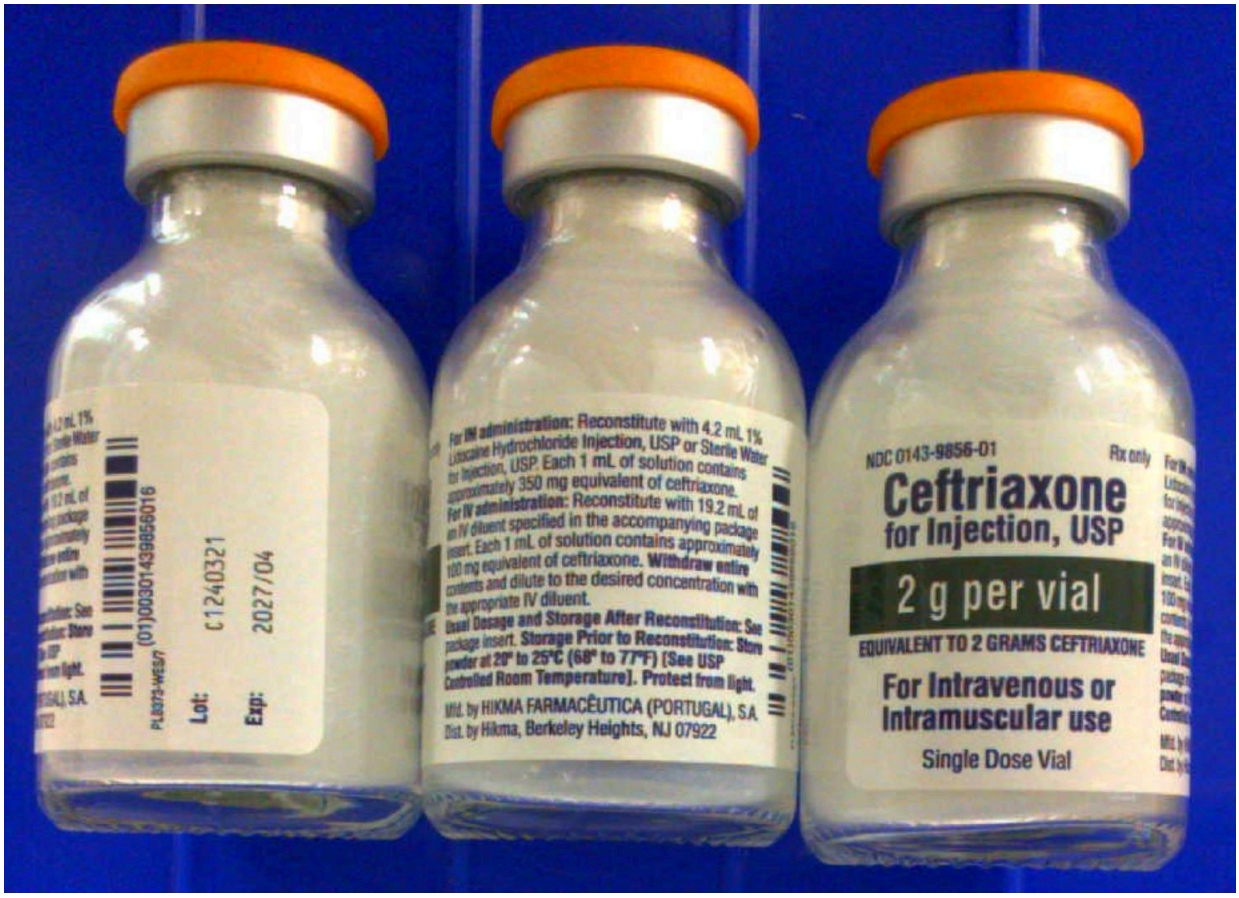

Figure 1. Vials of ceftriaxone drug product from lot C1240321.

Background

Recent Research and Clinical Trials Involving Ceftriaxone

Ceftriaxone is a widely used third-generation cephalosporin antibiotic with a broad spectrum of activity against Gram-positive and Gram-negative bacteria (Shirin, 2020). It is commonly used to treat various infections, including pneumonia, meningitis, gonorrhea, and infections caused by multidrug-resistant Enterobacteriaceae (Richards, 1984). Recent scientific research and clinical trials have explored new potential applications for ceftriaxone and provided further insights into its efficacy and safety.

One area of research has focused on the use of ceftriaxone for the treatment of methicillin-susceptible *Staphylococcus aureus* (MSSA) bloodstream infections (BSI). A systematic review and meta-analysis (Alsowaida, 2022) investigated the effectiveness and safety of ceftriaxone compared to the standard of care for MSSA BSI. The analysis included seven studies with a total of 235 patients in the ceftriaxone arms and 427 patients in the

standard of care arms. The results indicated that ceftriaxone could be a viable alternative treatment for MSSA BSI, particularly in acute care and outpatient parenteral antimicrobial therapy (OPAT) settings.

A study evaluated the appropriateness of ceftriaxone use in medical and emergency wards of a hospital in Ethiopia. The study involved reviewing patient records and assessing ceftriaxone prescriptions against established guidelines. The findings revealed that ceftriaxone was often used inappropriately, with the most common reasons being unnecessary frequency of administration (e.g., prescribing it every 12 hours when once daily would suffice), absence of a culture and sensitivity test to confirm the bacterial infection, and prolonged duration of therapy, exceeding the recommended treatment period. This highlights the need for more judicious use of ceftriaxone to minimize the risk of developing antibiotic resistance and ensure optimal patient outcomes.

Ceftriaxone has demonstrated efficacy in treating various infections, including complicated and uncomplicated urinary tract infections, lower respiratory tract infections, skin and soft tissue infections, bone and joint infections, bacteremia, septicemia, and pediatric meningitis caused by susceptible organisms . These findings underscore the broad clinical utility of ceftriaxone in managing a wide range of bacterial infections (Richards, 1984).

In addition to its antibacterial properties, ceftriaxone has shown potential antitumor activity. A research paper reported that ceftriaxone suppressed lung cancer growth by targeting Aurora B kinase, a protein involved in cell division. This finding suggests that ceftriaxone could be repurposed as an anticancer agent, particularly for lung cancer treatment. This is a significant finding as it highlights the potential for drug repositioning, where existing drugs are explored for new therapeutic applications. This approach can accelerate the development of new treatments and reduce costs compared to developing novel drugs from scratch. Another example of drug repositioning is Orlistat, a drug used to treat obesity, which is also being investigated for its anticancer properties (Li, 2012)(Li, 2017).

Clinical trials have also investigated the use of ceftriaxone for various conditions. One trial evaluated the efficacy and safety of ceftriaxone in patients with amyotrophic lateral sclerosis (ALS). The trial involved 513 participants who received either ceftriaxone or a placebo. Unfortunately, the results showed that ceftriaxone did not significantly slow the progression of ALS or improve survival. (Rosenfeld, 2014)

Another clinical trial explored the use of ceftriaxone pulse dosing for post-treatment Lyme disease syndrome. This syndrome refers to persistent symptoms experienced by some individuals after completing standard Lyme disease treatment. The trial aimed to determine if intermittent ceftriaxone administration could alleviate these symptoms (CenterWatch, 2024).

A clinical trial compared the clinical effectiveness and safety of gentamicin and ceftriaxone in treating gonorrhea. This trial is crucial due to the emergence of ceftriaxone-resistant strains of *Neisseria gonorrhoeae*, the bacteria that causes gonorrhea. The trial assessed the clinical cure

rates and safety profiles of both antibiotics to determine the optimal treatment strategy for gonorrhea (EU Clinical Trials Register, 2024).

Another clinical trial investigated the effectiveness of different antibiotic regimens for acute pyelonephritis in children aged 1 month to 3 years. The trial compared a 3-day intravenous antibiotic treatment with a 3-day intravenous treatment followed by a 7-day oral antibiotic treatment. This research aimed to identify the most effective and convenient treatment approach for acute pyelonephritis in young children (EU Clinical Trials Register, 2024).

Recalls

Ceftriaxone is a widely used antibiotic that is effective against a broad range of bacterial infections. It is a third-generation cephalosporin antibiotic that is administered intravenously or intramuscularly. Like all medications, Ceftriaxone can be subject to recalls if there are concerns about its safety, quality, or efficacy. Drug recalls are actions taken to remove a drug from the market because it may be defective or potentially harmful. Recalls are typically initiated by the manufacturer or by regulatory agencies like the Food and Drug Administration (FDA).

In January 2019, Lupin Pharmaceuticals, Inc. issued a voluntary recall of 42 lots of Ceftriaxone for Injection, USP, in 250mg, 500mg, 1g, and 2g doses (Contemporary Clinic, 2019). The recall was initiated after the discovery of visual grey particulate matter in reconstituted vials (FDA, 2019). Further investigation revealed that the particulate matter was rubber from the vial stopper, likely dislodged when a needle with a gauge larger than 21 was used during reconstitution. If injected, the rubber particles could irritate the vein or cause inflammation (phlebitis). In more serious cases, it could even block an artery in the lungs (pulmonary embolism). This could lead to long-term health problems or damage to organs. The recall was a precautionary measure to prevent potential harm to patients, and no adverse events related to this issue were reported.

Lupin Pharmaceuticals, Inc. advised hospitals and physicians to stop using and return the recalled products to Genco Pharmaceuticals Services. The FDA classified the recall as Class II, indicating a situation where the use of or exposure to a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote (FDA, 2024). The FDA published the company's recall announcement as a public service. It is important to note that Lupin has discontinued these Ceftriaxone presentations, which may be related to the recall and could have implications for the availability of Ceftriaxone in the market.

In February 2024, Becton Dickinson & Co. initiated a recall of BD BBL Sensi Disc Ceftriaxone due to potential issues with the reproducibility, accuracy, and quality control of antibiotic susceptibility testing (AST) for *H. influenzae*. This recall specifically affected catalog numbers 231634 and 231635, with numerous lot numbers impacted (FDA, 2024).

To address this recall, Becton Dickinson & Co. issued URGENT Medical Device Product Correction letters to customers on January 8, 2024, instructing them to stop using the affected products and destroy any remaining inventory. They also implemented labeling changes for future lots to warn against using the product for AST of *H. influenzae*.

Shortages

Drug shortages are a significant concern in healthcare, impacting patient care and increasing the burden on healthcare providers. Ceftriaxone, a widely used broad-spectrum cephalosporin antibiotic, is among the drugs that have experienced shortages. The American Society of Health-System Pharmacists (ASHP) tracked a record 323 active drug shortages during the first quarter of 2024, surpassing the previous record of 320 shortages in 2014. The Federal Food, Drug, and Cosmetic Act defines a drug shortage as a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug. This article explores the causes and impact of ceftriaxone shortages and discusses potential solutions to address this issue. On 11/13/2019 Hikma reported a shortage of ceftriaxone due to “manufacturing delay.” At the same time, Wockhardt and Lupin had discontinued their ceftriaxone presentations, Pfizer had ceftriaxone injection on shortage due to increased demand and manufacturing delays, and Fresenius Kabi stated the reason for their shortage was increased demand (ASHP, 2019).

Ceftriaxone shortages can arise from various factors, often stemming from manufacturing and supply chain issues. Some of the key contributors include:

- **Manufacturing Delays:** Production delays due to equipment malfunction, quality control issues, or insufficient manufacturing capacity can significantly impact ceftriaxone supply. The U.S. Food and Drug Administration (FDA) halted inspections during COVID-19, and now that they have resumed, factories that haven't been inspected in five or six years are experiencing delays as they address any issues found. These fixes can take anywhere from 6 to 18 months for production to get fully back on schedule.
- **Discontinuation by Manufacturers:** Some manufacturers may discontinue specific ceftriaxone presentations due to business decisions or other factors, further reducing available options . For example, Lupin has discontinued their ceftriaxone presentations .

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, 2023b).

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 (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 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, 2023c)(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

Intra-lot variability was detected in the spectra of 6 vials of ceftriaxone sampled from lot C1240321. One of the vials in lot C1240321 stood out from the rest (vial 4, 8.3 SDs), prompting a closer examination of the available vials. The distances of the vials from the center are given in Table 1.

Table 1 shows the intra-lot variability detected in the spectra of ceftriaxone vials sampled from one specific lot (lot C1240321). The table specifically lists the vial numbers and their

corresponding distances (measured in multidimensional standard deviations, SDs) from the center of the spectral cluster.

The important findings from Table 1 are:

- Significant intra-lot variability was detected among the vials analyzed.
- One vial (vial number 3) exhibited a notably large deviation (8.3 SDs away from the cluster center), indicating it was significantly different from the other vials in the same lot.
- This substantial deviation (8.3 SDs) triggered further investigation and analysis of an additional lot (lot C1240371).

The importance of Table 1 lies in its identification of potential quality control issues within a single manufacturing lot. The presence of a vial significantly distant from the rest suggests that the manufacturing process may not be adequately controlled, potentially indicating contamination, formulation inconsistencies, or other manufacturing irregularities. This finding underscores the necessity for rigorous quality monitoring and highlights the value of using advanced analytical techniques, such as near-infrared spectroscopy combined with statistical analysis, to detect subtle but critical differences that might not be visually apparent.

Table 1. Distances in Multidimensional SDs of Vials from the Center of Lot C1240321

Vial Number	Distance (SDs)
1	1.7
2	0.8
3	8.3
4	1.2
5	0.1
6	1.0

Figure 2 shows the spectra of all 12 ceftriaxone vials sampled from two different lots (6 vials from lot C1240321 and 6 vials from lot C1240371). The figure visually illustrates the spectral data collected from these vials using near-infrared spectroscopy. The spectra from all 12 vials appear superficially similar, indicating that visual inspection alone may not be sufficient to detect subtle differences or quality issues. Despite this superficial similarity, statistical analysis revealed significant intra-lot variability using the BEST metric, highlighting the importance of advanced analytical methods to detect subtle but potentially critical differences. The figure also emphasizes the necessity of using advanced analytical techniques (such as near-infrared spectroscopy combined with statistical methods) to reliably detect and quantify variability

within and between lots, which could indicate manufacturing inconsistencies or quality control issues.

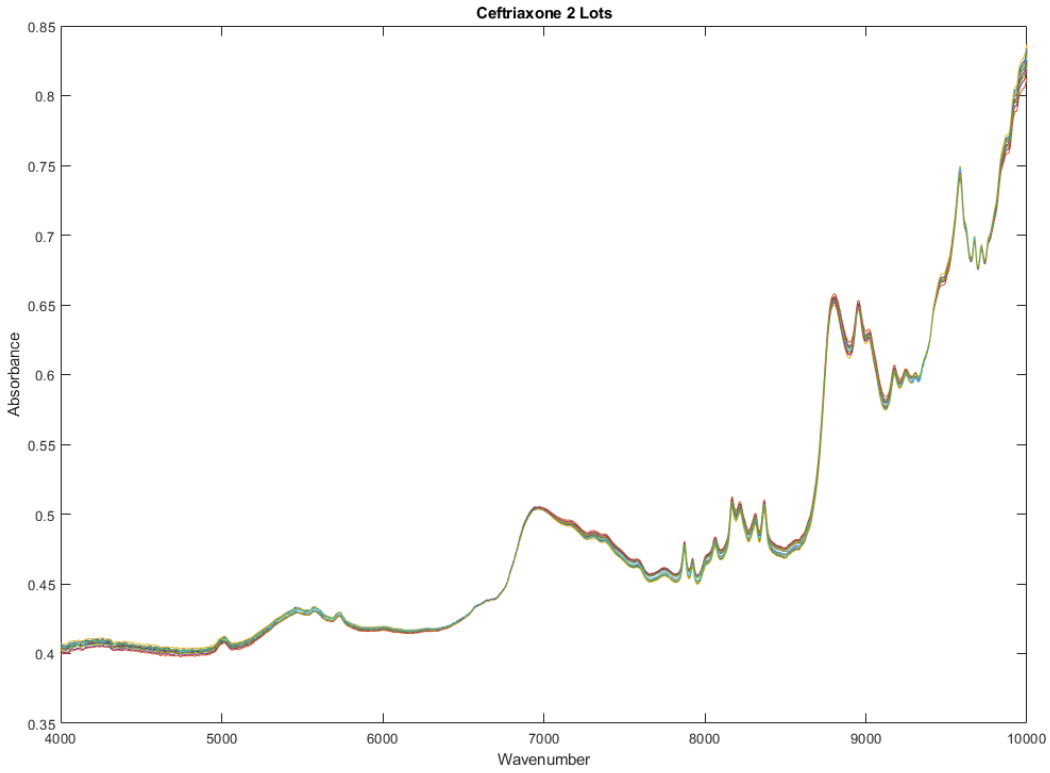

Figure 2. Spectra of all 12 of the ceftriaxone vials sampled from both lots of the drug. The superficial similarity of the spectra shows the importance of computerized analysis of the data in order to detect differences between vials and measure the probability that those differences arise from random noise.

Figure 3 shows the spectral analysis results for vials from two different lots of ceftriaxone (lot C1240321 and lot C1240371). Specifically, it visually illustrates the spectral variability among vials within lot C1240321 (vials 1 to 6), highlighting that one vial (vial number 3) is significantly different from the others, being located 8.3 standard deviations (SDs) away from the cluster center. This substantial deviation prompted further investigation into an additional lot (lot C1240371). The significant deviation of vial 3 prompted further investigation into another lot (C1240371) to assess whether this variability was isolated or indicative of broader manufacturing inconsistencies. The figure emphasizes the effectiveness of spectral analysis combined with statistical methods (such as principal component analysis and multidimensional distance metrics) in detecting subtle but critical differences among pharmaceutical samples that might not be visually apparent.

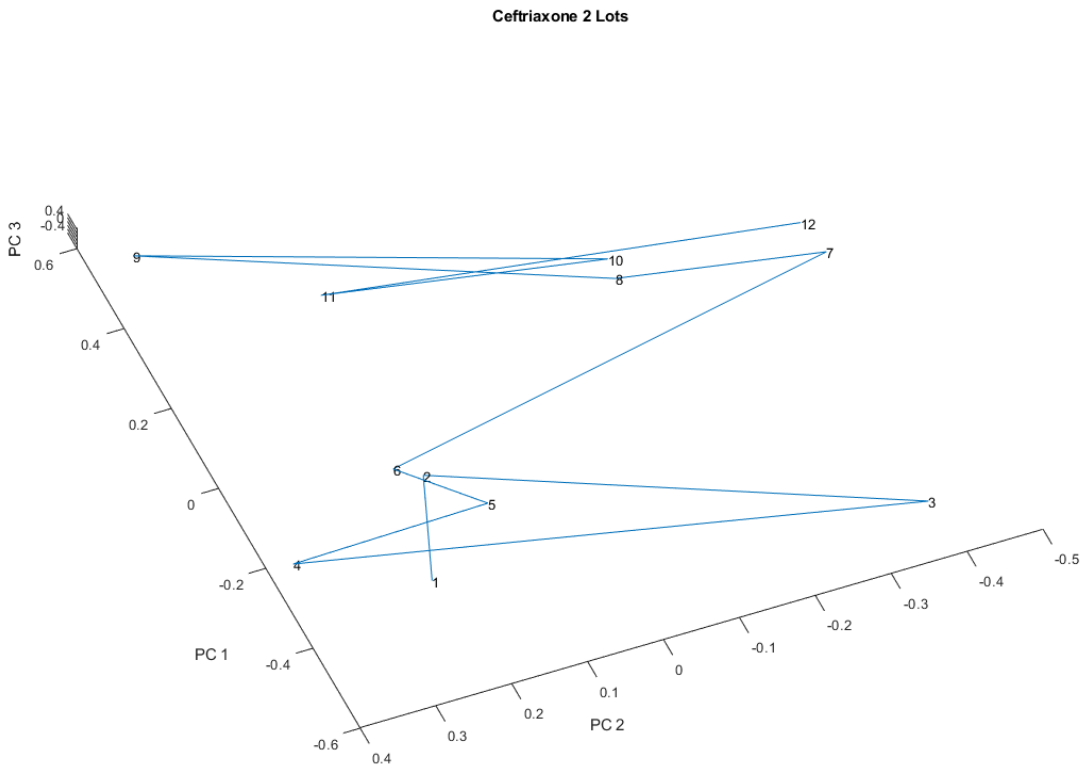

Figure 3. Vials 1 to 6 are from lot C1240321 and vials 7-12 are from lot C1240371. Vial 3 is 8.3 SDs from the center of lot C1240321. It was this distance for vial 3 that triggered the examination of the second lot, lot C1240371.

Figure 4 provides another view after rotation of the first three principal components (PCs) for the ceftriaxone vials from two different lots (lot C1240321 and lot C1240371). The figure visually illustrates how the relative positions of samples in principal component space can change depending on the rotation or perspective of the coordinate system. The important points shown by Figure 4 are that different rotations or views of the principal component space can alter the apparent relationships among samples, making different vials appear as outliers depending on the perspective. In this particular rotation, vial 4 appears more like an outlier than vial 3, despite vial 3 previously being identified numerically as the most significant outlier (8.3 SDs away from the cluster center). This observation reinforces the importance of using numerical, objective methods (such as multidimensional distance metrics like BEST) rather than relying solely on visual inspection of principal component plots to identify outliers.

It also highlights the necessity of examining multiple rotations or perspectives of the data to fully understand the relationships among samples and to ensure accurate identification of outliers.

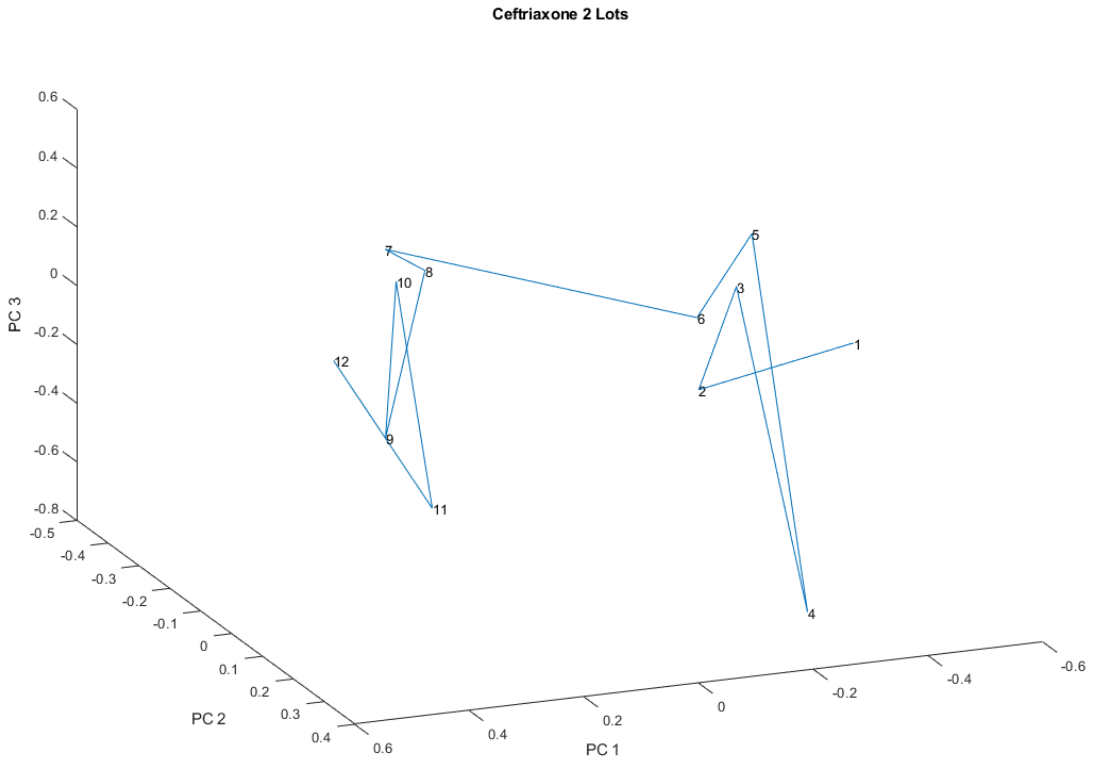

Figure 4. Another view of the first 3 PCs for both lots. Vials 1 to 6 are from lot #C1240321 and vials 7-12 are from lot #C1240371.

Interlot analysis

Table 2 in the provided document shows the variation accounted for by each of the principal components (PCs) in the spectral analysis of ceftriaxone samples. Specifically, it indicates how much of the total variability in the spectral data is explained by each principal component (PC). The table reveals that the first principal component (PC1) accounts for the majority of the variation (and approximately 99.49% of the cumulative variation is accounted for by the sixth component), indicating that most of the spectral differences among the ceftriaxone samples can be explained by the first few principal components. Subsequent principal components (PC2 through PC6) account for progressively smaller amounts of variation, with the second component accounting for a smaller but still meaningful portion, and the contributions rapidly decreasing thereafter. This information is important because it highlights that the spectral variability among ceftriaxone samples is primarily captured by the first few principal

components, suggesting that these components are sufficient for detecting significant differences between lots or within a lot. This analysis is crucial for identifying potential quality control issues, such as intra-lot variability or deviations in the manufacturing process.

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

PC Number	Variation in this PC	Cumulative PC Variation
1	0.8944	0.8944
2	0.0549	0.9493
3	0.0218	0.9711
4	0.0166	0.9876
5	0.0049	0.9925
6	0.0024	0.9949

Figure 5 shows the principal component loadings spectrum for the first principal component (PC1) derived from the spectral analysis of ceftriaxone samples from two different lots (C1240321 and C1240371). Figure 5 identifies the specific spectral regions (wavenumbers) that contribute most significantly to the variability captured by the first principal component. Peaks and valleys in the loadings spectrum indicate wavenumbers that contribute strongly to the variability among the ceftriaxone samples. These spectral regions are likely associated with chemical or physical differences between samples. By examining the loadings spectrum, researchers can pinpoint specific spectral features responsible for the observed intra-lot and inter-lot variability, potentially guiding further chemical analysis or quality control investigations.

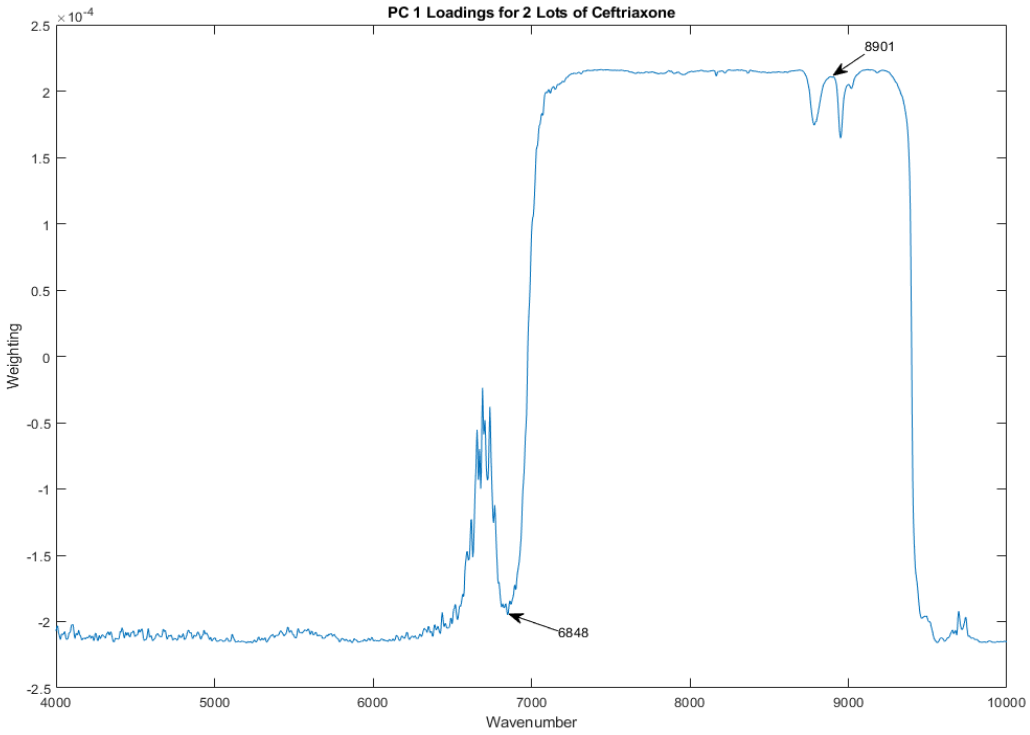

Figure 5. The principal component loadings spectrum for the first principal component of the library of two lots of ceftriaxone.

Figure 6 shows the principal component loadings spectrum for the second principal component (PC2) derived from the spectral analysis of two lots of ceftriaxone. While the first principal component (PC1) captures the largest portion of spectral variability, the second principal component (PC2) highlights additional, subtler differences among the samples. These differences may represent secondary chemical or physical variations that are not captured by PC1.The peaks and valleys in the PC2 loadings spectrum indicate specific wavelengths that contribute significantly to the secondary variability among the ceftriaxone samples. These spectral regions may correspond to chemical constituents or physical properties that differ between samples or lots, potentially indicating subtle manufacturing inconsistencies or variations in raw materials. The presence of meaningful variability in PC2 underscores the importance of using numerical, statistical methods (such as BEST distances and multidimensional standard deviations) rather than relying solely on visual inspection or a single principal component. PC2 provides additional dimensions of information that can help detect outliers or subtle differences that might otherwise be overlooked. The significance of PC2 demonstrates the value of multivariate analytical techniques, such as principal component analysis (PCA), in pharmaceutical quality control. PCA allows researchers to systematically identify and interpret multiple sources of variability, improving the robustness and sensitivity of quality assessments.

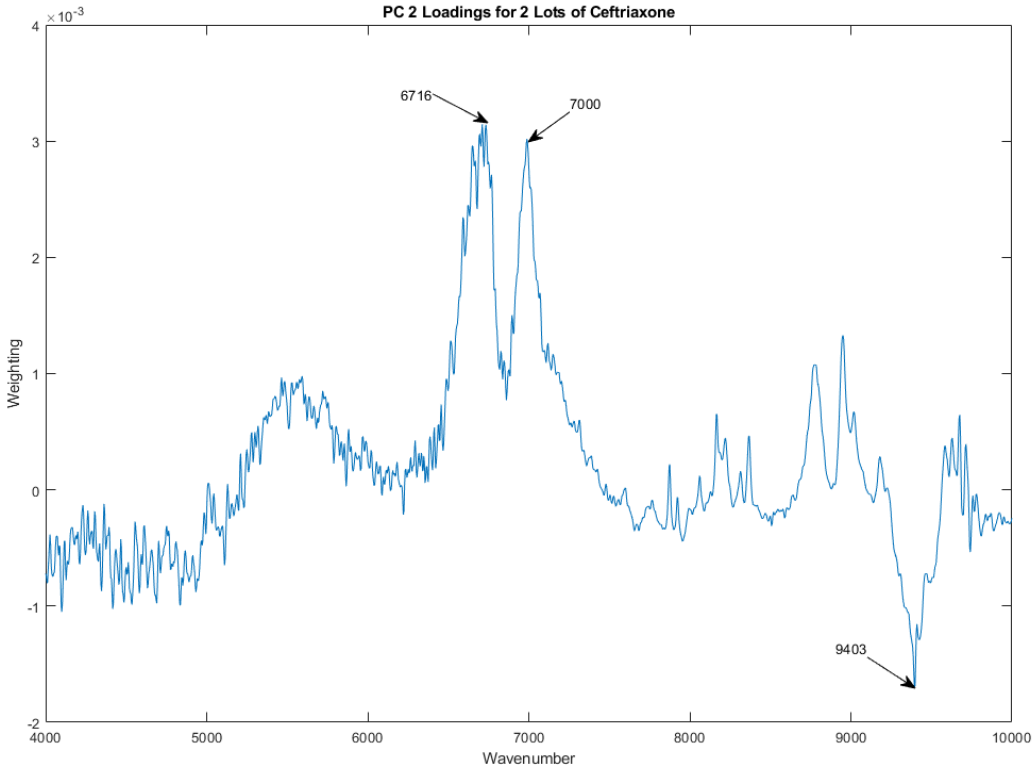

Figure 6. The principal component loadings spectrum for the second principal component of the library of two lots of ceftriaxone.

A subcluster analysis was run on the spectra from the two lots. Figure 7 shows the QQ plot from the subcluster detection test. The results were r_{tn}=0.9629, r_{ts}=0.9148, *p*=0.02 and indicate that the two groups are located in different portions of hyperspace.

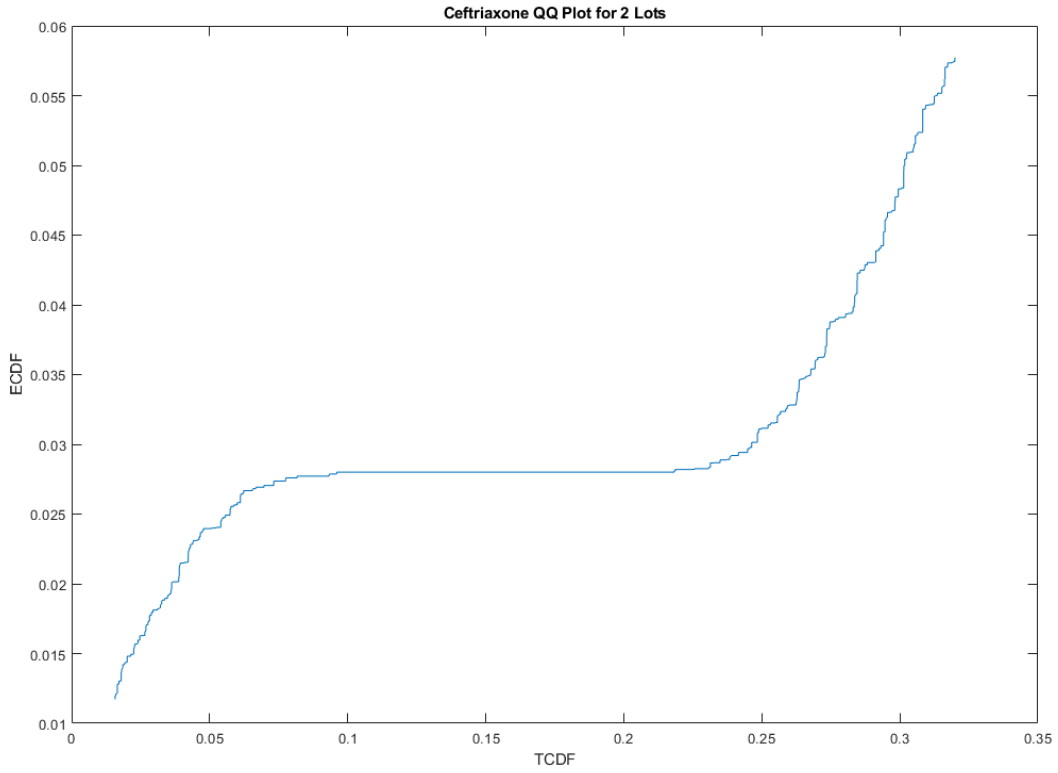

Figure 7. A QQ plot from the subcluster detection test showing 2 separate groups in hyperspace (r_{tn}=0.9629, r_{ts}=0.9148, *p*=0.02), one group corresponding to each lot of vials.

Conclusion

Ceftriaxone for injection, USP is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration. Ceftriaxone sodium is a white to yellowish crystalline powder which is readily soluble in water, sparingly soluble in methanol and very slightly soluble in ethanol. The color of ceftriaxone sodium solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used. Each vial contains ceftriaxone sodium equivalent to 250 mg, 500 mg, 1 gram or 2 grams of ceftriaxone activity. Ceftriaxone sodium contains approximately 83 mg (3.6 mEq) of sodium per gram of ceftriaxone activity.

Intra-lot variability was detected in the spectra of 6 vials of ceftriaxone sampled from the lot C1240321. One of the vials was more than 8.3 multidimensional SDs away from the center of the cluster of the other 5 vials, suggesting that the manufacturing process may not be in control.

Inter-lot variability was detected in the two lots of ceftriaxone, which did not fall in the same volume of hyperspace. However, it is possible that both of these clusters fall inside the “box” that's defined as the drug product in the NDA.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 vials from new lots and further investigation are needed.

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