

# Rapid Quality Screening of Intra-lot and Inter-lot Variability of Pentamidine Isethionate Using Near-Infrared Spectrometry

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## RAPID COMMUNICATION

### Abstract

Pentamidine for Injection, USP is a sterile, lyophilized antimicrobial agent supplied as a white to off-white powder in vials containing 300 mg for intravenous administration. The product is

reconstituted with sterile water for injection prior to administration, yielding a clear, colorless to slightly yellow solution.

Variability was detected both within a lot (where one vial from 8 vials was 18.4 SDs from the center of the cluster) and between lots of the drug, where spectra occupied distinct regions of hyperspace. Subcluster analysis confirmed statistically significant separation between lots ( $r_{tn} = 0.9635$ ,  $r_{ts} = 0.8898$ ,  $p = 0.02$ ). These results were derived using statistical analyses of the spectra that included principal component analysis (PCA) and the Bootstrap Error-Adjusted Single-sample Technique (BEST).

The variability detected suggests that pentamidine may have been manufactured while the production process was operating outside of a state of process control. These findings also highlight the utility of FT-NIR spectrometry in rapidly screening pharmaceutical products for quality.

## 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 (FT-NIR) 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

Pentamidine for Injection, USP is a sterile, lyophilized anti-infective agent intended for intravenous administration. It is supplied as a white to off-white powder, and each vial contains 300 mg of pentamidine isethionate equivalent to approximately 172.4 mg of pentamidine base.

Pentamidine is an aromatic diamidine with activity against a range of protozoal and fungal pathogens. It is primarily used in the prophylaxis and treatment of *Pneumocystis jirovecii* pneumonia (PJP), particularly in immunocompromised populations such as patients with HIV/AIDS or those undergoing immunosuppressive therapy. Pentamidine is also used in the treatment of leishmaniasis and African trypanosomiasis in certain clinical contexts.

[Figure 1](#) is a photo of the Seton Pharmaceuticals Pentamidine Isethionate product. The lot number is 10007045. [Figure 2](#) is a photo of Seton Pharmaceuticals lot number KZ5001A.



**Figure 1.** Pentamidine Isethionate 300 mg Seton Pharmaceuticals LLC Lot 10007045, exp. 11/2026. A total of 8 vials were scanned, which includes vial 5 rescanned twice (rescan 1 and rescan 2).



**Figure 2.** Pentamidine 300 mg Seton Pharmaceuticals LLC Lot KZ5001A, exp. 12/2026. A total of 6 vials from this lot were scanned.

## Background

Pentamidine isethionate is a long-established anti-infective agent whose clinical utility is defined by a significant duality: it serves as both a life-saving treatment for severe protozoal and fungal

infections and as a targeted prophylactic agent with a favorable safety profile, depending on its route of administration.

## Recent research and clinical trials involving pentamidine

Pentamidine isethionate is an aromatic diamidine, formulated as a sterile, nonpyrogenic, lyophilized white crystalline powder. It is soluble in water and glycerin but insoluble in ether, acetone, and chloroform. Its chemical designation is 4,4-[1,5-pentanediy]bis(oxy)]bis-benzenecarboximidamid ([FDA, 2019](#)).

The precise mechanism of its antiprotozoal and antifungal action is not fully understood, but it is known to be multifaceted ([FDA, 2025](#)). The primary mode of action is believed to be interference with microbial nuclear metabolism.

*In vitro* studies suggest that pentamidine binds to DNA and inhibits the synthesis of DNA, RNA, phospholipids, and proteins, thereby disrupting essential cellular processes in susceptible organisms like *Pneumocystis jirovecii* and *Leishmania* species ([NIH, 2024](#)). Further research indicates a broader range of effects, including antagonism of NMDA receptors and calmodulin, and inhibition of histone acetyltransferase, suggesting a complex interplay with multiple cellular targets that contributes to its therapeutic effects and its toxicity profile ([PubChem, 2004](#)).

### Established and Off-Label Therapeutic Indications

The clinical applications of pentamidine isethionate are distinctly separated by its formulation and route of administration, reflecting a strategic effort to balance efficacy with toxicity.

#### *FDA-Approved Indications*

The U.S. FDA has approved pentamidine for the treatment and prevention of *Pneumocystis jirovecii* pneumonia (PJP), a critical opportunistic infection, particularly in immunocompromised individuals ([PubChem, 2004](#)).

- Treatment of PJP: The injectable formulation of pentamidine isethionate (e.g., Pentam® 300) is approved for the treatment of active PJP infections ([Pentamidine, 2025](#)). Recognizing its importance for a rare and serious condition, it was granted Orphan Drug status for this indication on February 28, 1984, with subsequent marketing approval on October 16, 1984 ([FDA, 1984](#)).
- Prophylaxis of PJP: The inhaled, aerosolized formulation (e.g., NebuPent®) is approved for the prevention of PJP in high-risk, HIV-infected patients. This includes individuals with a history of one or more PJP episodes or a CD4+ T-lymphocyte count of 200 cells/mm<sup>3</sup> or less ([Pentamidine, 2025](#)). This prophylactic use also received an Orphan Drug Designation from the FDA, highlighting its targeted role in protecting a vulnerable patient population ([FDA, 1987](#)).

#### *Key Off-Label and Investigational Uses*

Beyond its FDA-approved indications, pentamidine isethionate is utilized for other serious protozoal diseases, often as a second-line agent.

- Leishmaniasis: It is an important therapeutic option for both cutaneous leishmaniasis (CL) and visceral leishmaniasis (VL), especially in cases that are resistant to first-line pentavalent antimonial drugs ([Pentamidine, 2025](#)). Its efficacy against specific *Leishmania* species, such as *L. guyanensis*, has made it a first-line treatment in certain endemic

regions.

- Human African Trypanosomiasis (HAT): Commonly known as sleeping sickness, pentamidine is considered a drug of choice for treating the first (hemolymphatic) stage of the disease caused by the parasite *Trypanosoma brucei gambiense* ([Pentamidine, 2025](#)).

### **Pharmacokinetics: Two Routes**

The pharmacokinetic profile of pentamidine isethionate is fundamentally different depending on whether it is administered parenterally or via inhalation. This distinction is central to its clinical use, as it dictates the balance between systemic therapeutic effect and systemic toxicity.

- **Parenteral (IV/IM) Administration:** When administered intravenously (IV) or intramuscularly (IM), pentamidine achieves significant systemic exposure necessary for treating disseminated infections like active PJP or leishmaniasis. Pharmacokinetic studies have reported a long terminal half-life ranging from 2.8 to 12 days, which is suggestive of drug accumulation in a deep peripheral tissue compartment ([Pentamidine Injection, 2025](#)). This is supported by findings in animal models showing that pentamidine concentrates heavily in organs such as the liver and kidneys, reaching levels 70 to 1,000 times higher than peak serum concentrations ([Pentamidine Injection, 2025](#)). While this tissue accumulation contributes to its sustained therapeutic effect, it is also directly linked to its potential for organ toxicity.
- **Inhaled (Aerosolized) Administration:** In stark contrast, the inhalation of aerosolized pentamidine results in minimal systemic absorption and consequently low plasma concentrations ([Label, 2025](#)). This route delivers the drug directly to the alveoli of the lungs, the primary site of PJP infection, thereby maximizing local drug concentration while minimizing the systemic side effects associated with parenteral use. This targeted delivery makes inhalation the preferred route for prophylaxis. However, this localized effect comes with a specific risk; because systemic levels are low, it offers little protection against extrapulmonary pneumocystosis, an infrequent but serious manifestation of the infection that has been reported in patients on aerosolized prophylaxis ([Label, 2025](#)).

This dual pharmacokinetic identity governs the drug's entire clinical strategy. The challenge for clinicians is not a question of whether pentamidine is effective, but rather how to manage its narrow therapeutic window. This fundamental paradox has driven decades of clinical practice and is the primary impetus for modern research into novel formulations and delivery systems that seek to replicate the targeted efficacy of inhalation without the systemic burden of injection.

### **Recalls**

The U.S. Food and Drug Administration (FDA) maintains strict oversight of drug manufacturing to ensure safety and efficacy ([Sterile Pentamidine Isethionate, 1992](#)). Recent actions related to pentamidine isethionate include a notable warning letter to a manufacturer other than Seton Pharmaceuticals.

#### **Warning Letter to Exela Pharma Sciences, LLC**

In July 2025, the FDA issued a warning letter to Exela Pharma Sciences, LLC, a manufacturer of various sterile drug products, including pentamidine isethionate for inhalation ([Exela Pharma Sciences, 2025](#)). The letter detailed significant violations of Current Good Manufacturing Practice (CGMP) regulations at their facility in Lenoir, North Carolina. The identified issues

included failures in media fill simulations intended to assess the sterility of their manufacturing process. The letter emphasized that these failures raised concerns about the sterility assurance of the drugs manufactured at the site. The FDA recommended that the company engage a qualified consultant to assist in remedying the violations and ensuring compliance with CGMP standards.

A comprehensive search of the FDA's drug recall database for the period of 2022 to the present did not identify any specific recalls for pentamidine isethionate. It is important to note that the absence of recalls does not preclude the possibility of localized product removals or other market actions not classified as a formal recall by the FDA.

## **Shortages**

The availability of critical medications like pentamidine isethionate is closely monitored by the FDA and organizations such as the American Society of Health-System Pharmacists (ASHP).

Based on a review of the FDA's official drug shortage database and information provided by the ASHP, there is no current widespread shortage of pentamidine isethionate in the United States.

Historically, pentamidine isethionate has experienced shortages. For instance, past shortages have been attributed to manufacturing delays and increases in demand. These past events highlight the importance of a robust and resilient pharmaceutical supply chain. The recent warning letter to a significant manufacturer underscores the potential for future supply disruptions if manufacturing issues are not adequately addressed. Both the FDA and ASHP provide platforms for reporting and monitoring drug shortages, which are crucial tools for healthcare providers in managing patient care during periods of limited availability.

Pentamidine isethionate remains a vital medication with an expanding research horizon. While its traditional uses are well-established, its potential as an anti-cancer agent is a promising area of ongoing investigation. The recent FDA warning letter to a key manufacturer serves as a reminder of the critical importance of stringent manufacturing standards to ensure patient safety and maintain a stable drug supply. Continuous monitoring of clinical trial outcomes, regulatory actions, and supply chain dynamics is essential for this important therapeutic agent.

## **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, 2024b](#)).

## 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, 1993](#)).

## 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-5](#) (OpenAI). AI can be used in a variety of ways, including to brainstorm, organize thoughts, develop arguments, and edit.

## Results and Analysis

### Intralot analysis

[Figure 3](#) presents the raw near-infrared spectra from lot 10007045, encompassing 6 vials and a total of 8 scans, including two rescans from vial 5. While a superficial visual inspection suggests similarity across all spectra, this inspection alone may not be adequate for discerning subtle variations or quality concerns.

[Figure 4](#) illustrates the principal component scores for pentamidine lot 10007045 samples, using the first three principal components (PC1, PC2, and PC3) to represent the spectral data from different vials within the same lot (intralot analysis). Vial 4 stands out significantly, located 18.4 standard deviations (SDs) away from the central cluster of the other vials. This substantial deviation suggests potential differences in the chemical properties of vial 4 compared to others in the lot. This variability could be due to manufacturing issues, contamination, or degradation.

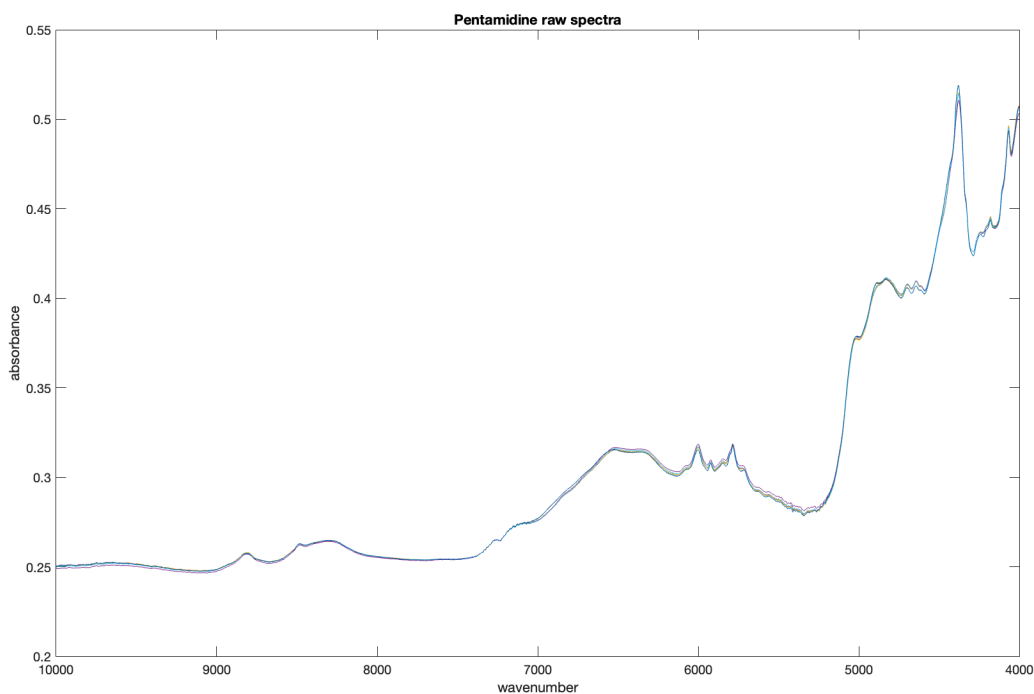


**Figure 3.** Pentamidine raw spectra lot 10007045 from a total 6 vials.

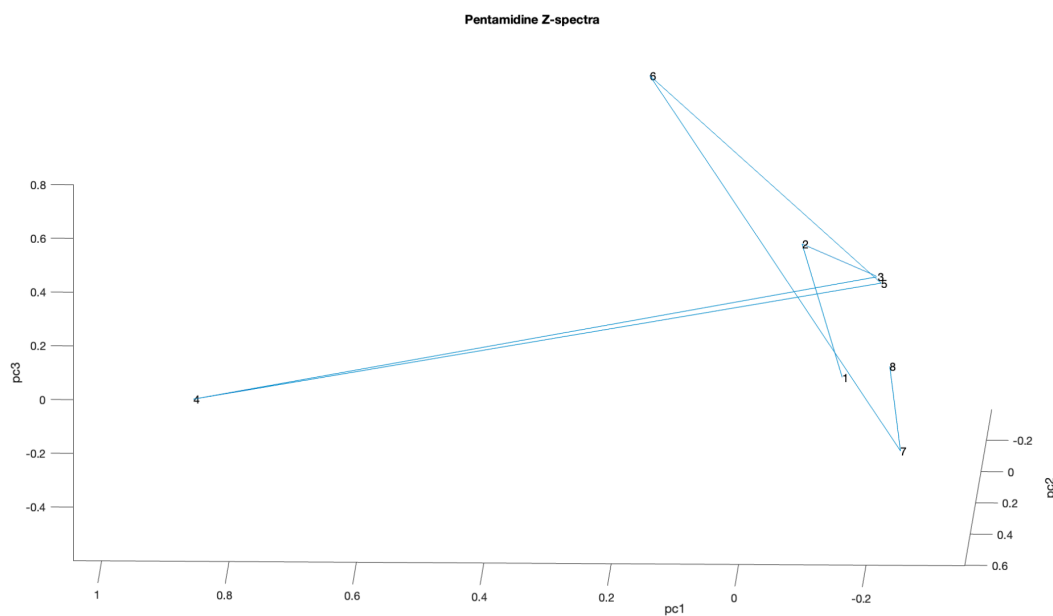


**Figure 4.** Vial 4 is 18.4 SDs from the center of the cluster of the other vials.

[Figure 5](#) suggests that there could be 2-3 groups within lot 10007045 based on the PC scatterplot.

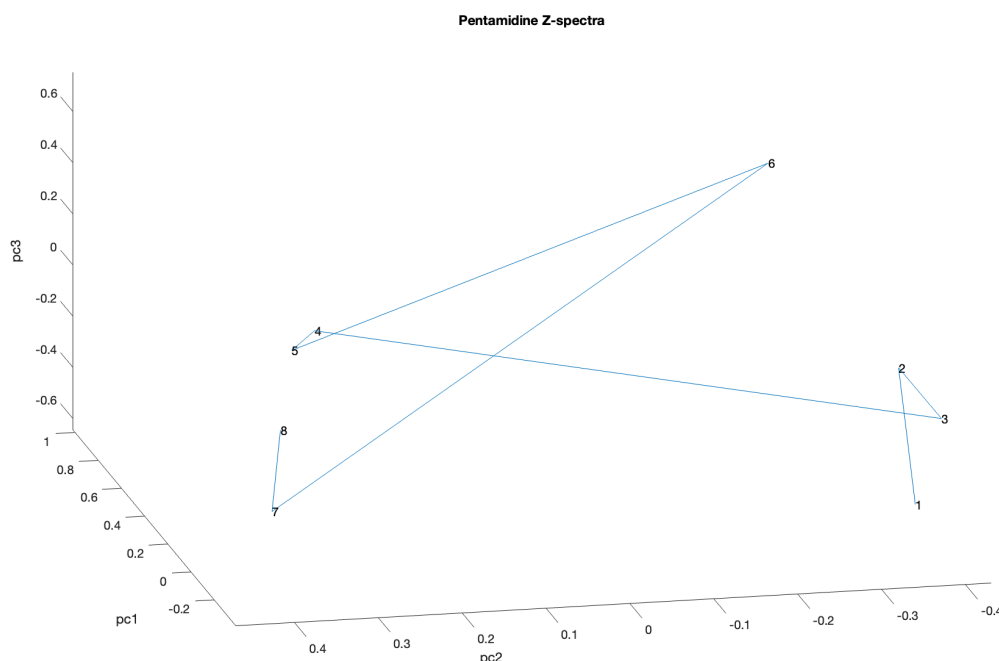


**Figure 5.** Vial 1 to 8 from lot 10007045 suggests there are more than 2 groups within the same lot vials.

## Interlot Analysis

[Figure 6](#) shows the 14 spectra of pentamidine vials sampled from two different lots (6 from lot KZ5001A and 8 from lot 10007045). The spectra from all 14 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 that could indicate manufacturing inconsistencies or quality control issues.

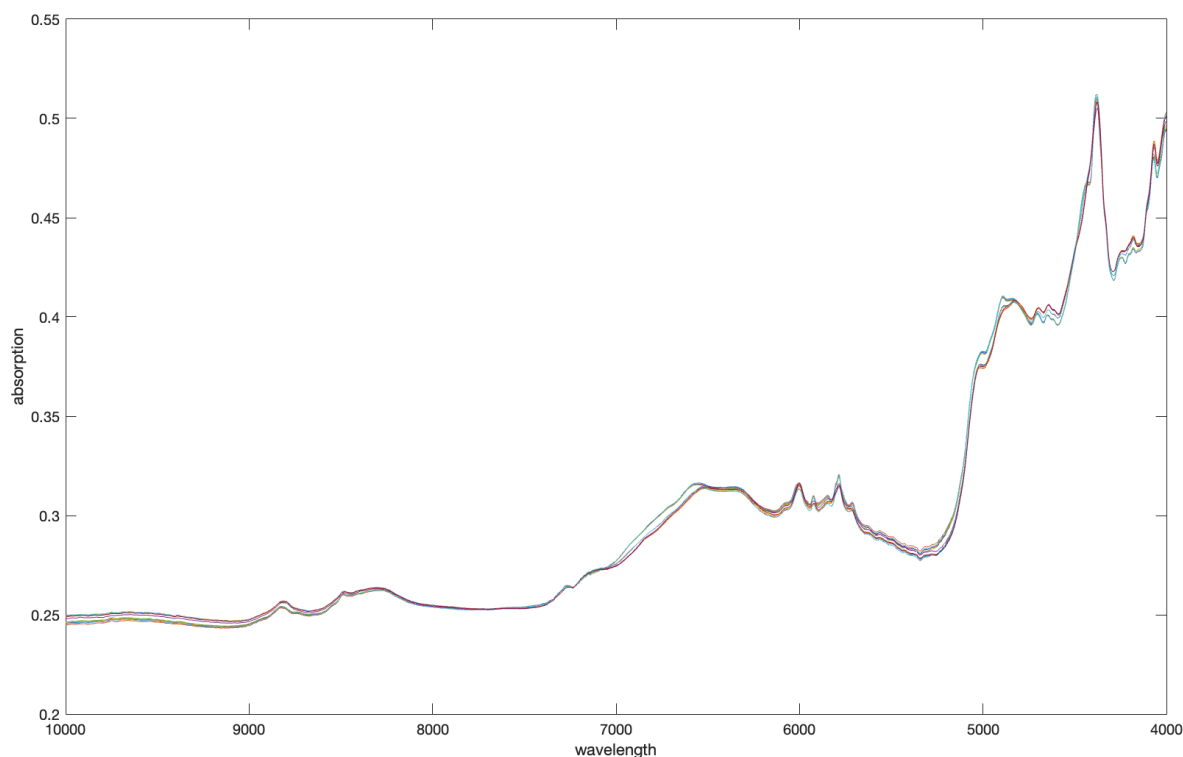


**Figure 6.** Spectra of all 14 of the pentamidine vials sampled from two different lots of the drug. The superficial similarity of the spectra shows the importance of computerized analysis of the data in order to detect differences between vials and estimate the probability that those differences arise from random noise. Two groups are apparent in the spectra.

[Figure 7](#) shows the principal component scatterplot for vials from the two different lots of pentamidine (lot 10007045 and lot KZ5001A). The figure emphasizes the effectiveness of NIR spectrometry 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.

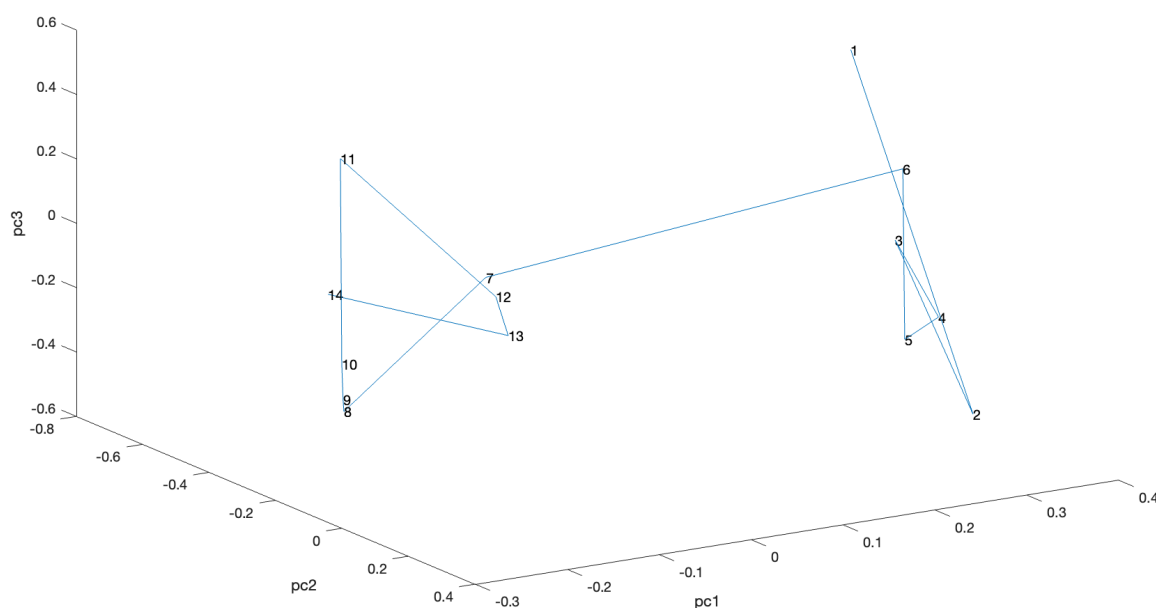


**Figure 7.** Vials 1 to 6 from lot K25001A and vials 7-14 are from lot 10007045.

A subcluster analysis was run on the spectra from the two lots. [Figure 8](#) shows the QQ plot from the subcluster detection test. The results were  $r_{tn}=0.9635$ ,  $r_{ts}=0.8898$ ,  $p=0.02$  and indicate that the two groups are located in different portions of hyperspace.

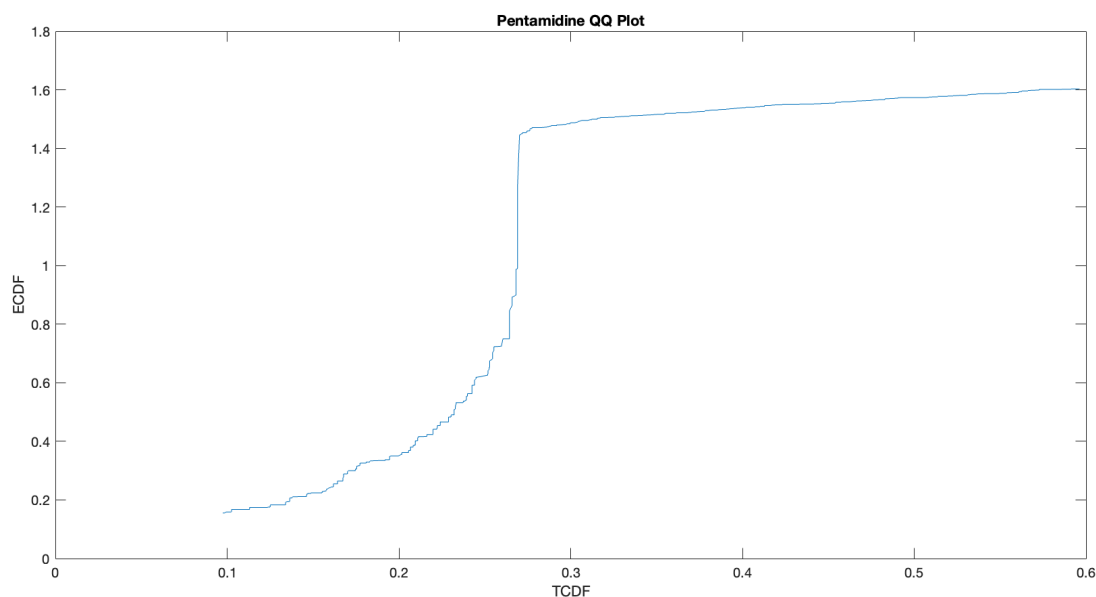


**Figure 8.** A QQ plot from the subcluster detection test showing 2 separate groups in hyperspace ( $r_{tn}=0.9635$ ,  $r_{ts}=0.8898$ ,  $p=0.02$ , one group corresponding to each lot of vials).

[Figure 9](#) displays the loadings spectrum for the first principal component (PC1) obtained from the pentamidine samples drawn from two production lots, 10007045 and KZ5001A. The plot highlights which wavenumber ranges exert the greatest influence on the overall variation represented by PC1. Peaks and troughs in the curve reveal the spectral features that either amplify or minimize differences seen between the sample sets. By interpreting this profile, analysts can target particular bands that explain both within-lot and between-lot variation, serving as a roadmap for deeper chemical examinations or for refining quality-assurance practices.

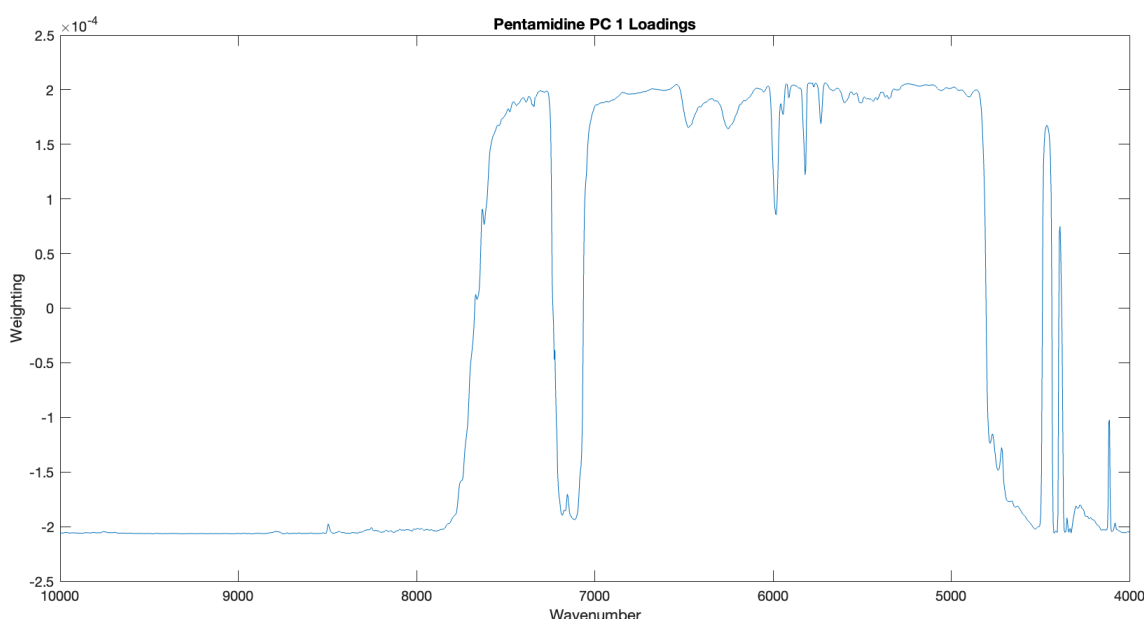


**Figure 9.** Pentamidine loadings for PC 1. The principal component loadings spectrum for the first principal component of the library of two lots of pentamidine is dominated by post-scatter-correction baseline variation of the spectra.

[Figure 10](#) presents the loadings spectrum for the second principal component (PC2) from the spectral study of two batches of pentamidine. Although the first principal component (PC1) explains the majority of the variation, PC2 reveals finer, less-obvious distinctions between the lots. These subtler features could stem from chemical changes or slight physical differences uncorrelated to the changes in PC1. Such regions might reflect minor shifts in formulation, processing, or incoming raw materials, possibly signaling small but meaningful inconsistencies during manufacture. Because PC2 carries its own significant signal, analysis combines it with techniques like BEST distances and multidimensional standard deviations instead of relying only on the eye or a single component. Treating PC2 as a separate source of evidence improves the chance of spotting outliers or delicate changes that otherwise go unnoticed. The significance of PC2 demonstrates the value of multivariate analytical techniques, such as principal component analysis (PCA), in pharmaceutical quality control. PCA allows the systematic identification and interpretation of multiple sources of variability, improving the robustness and sensitivity of quality assessments.

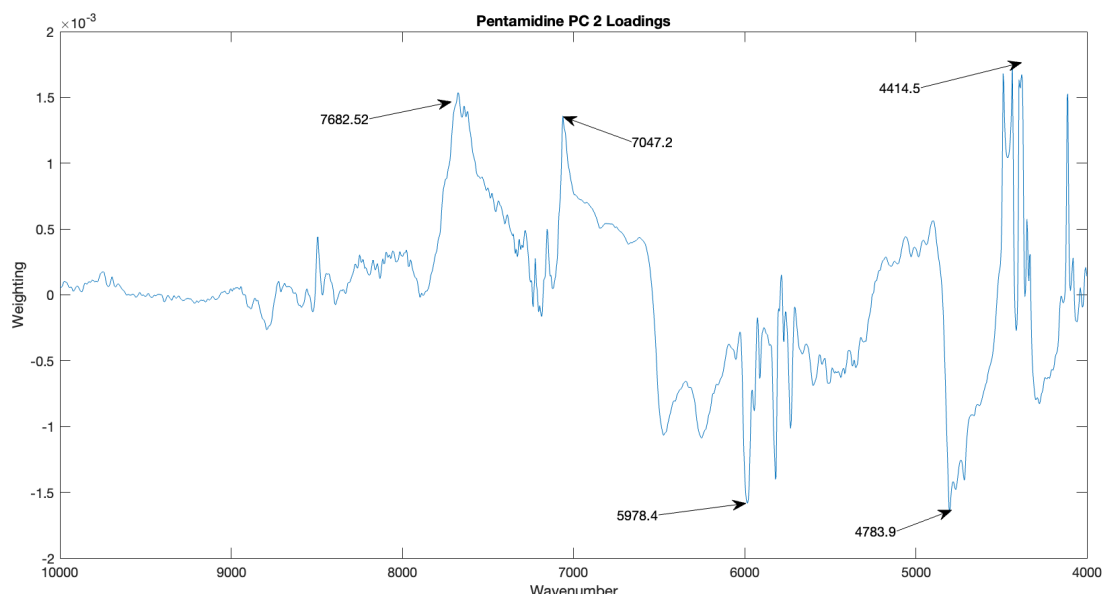


**Figure 10.** The principal component loadings spectrum for the second principal component of the library of two lots of pentamidine. Notable spectral features are marked at 4414, 4784, 5978, 7047, and 7683  $\text{cm}^{-1}$ .

[Figure 11](#) shows that PC3 revealed initial signs of variability, with moderate weighting across the NIR range suggesting emerging subgroup separation. This signal corresponds to minor spectral shifts likely related to lot-level manufacturing differences.

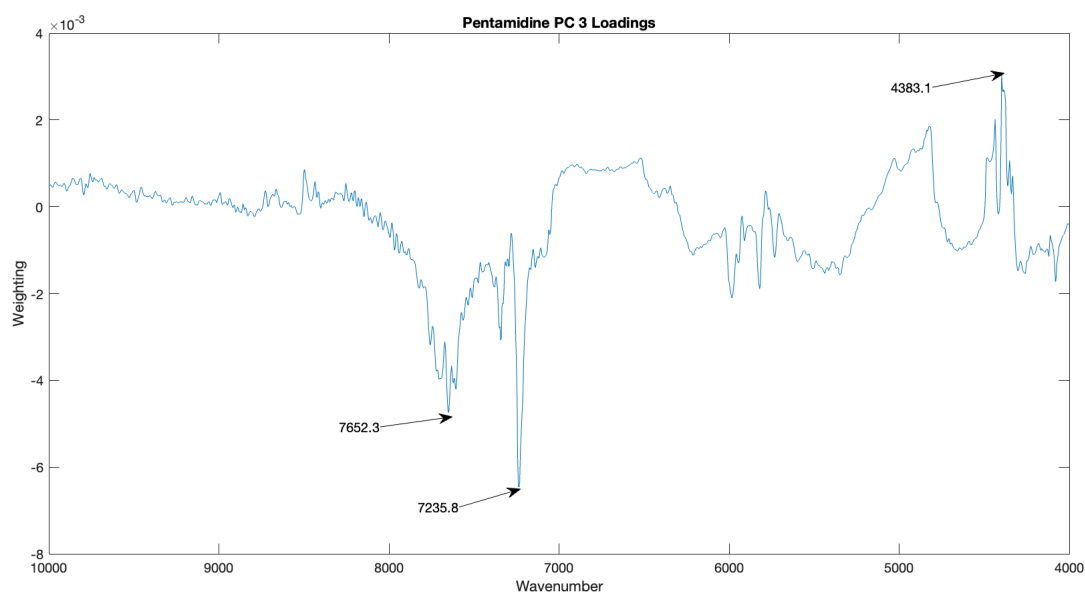


**Figure 11.** The principal component loadings spectrum for the third principal component of the library of two lots of pentamidine. Important spectral features appear at 4383, 7236, and 7652  $\text{cm}^{-1}$ .

[Figure 12](#) shows PC4 further emphasized small interlot distinctions, with structured features and more pronounced loading patterns, indicating divergence between multiple production lots.

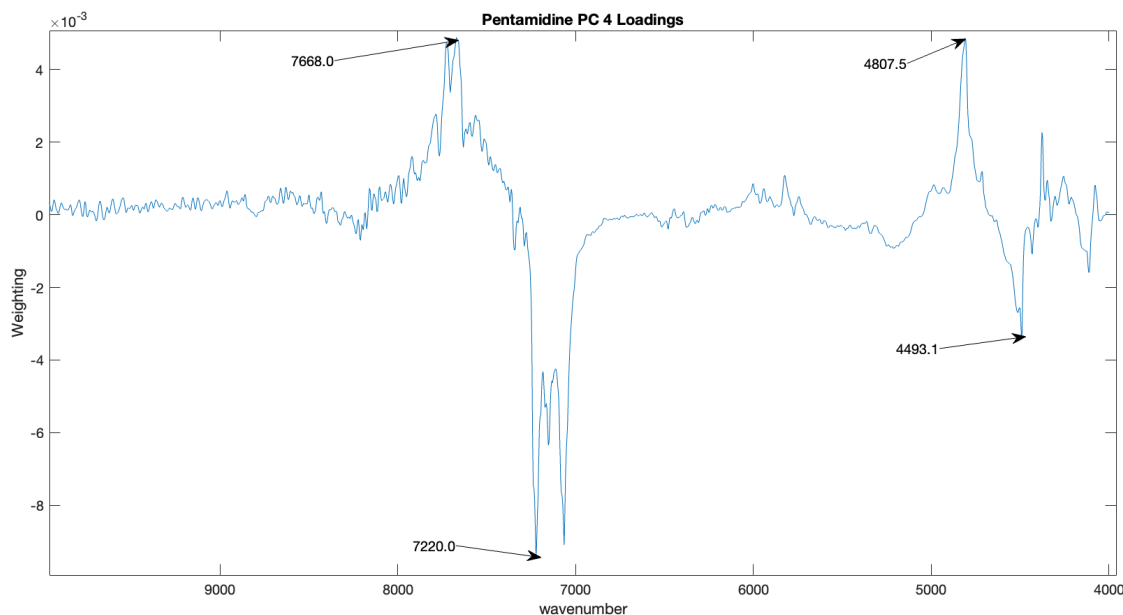


**Figure 12.** The principal component loadings spectrum for the fourth principal component of the library of two lots of pentamidine. Important spectral features are noted at 4493, 4808, 7220, and 7668  $\text{cm}^{-1}$ .

[Figure 13](#) shows PC5 exhibited higher weighting magnitudes and sharper spectral features, capturing more substantial variability. By PC5 considerable noise is beginning to creep into the spectrum from the high-energy side.

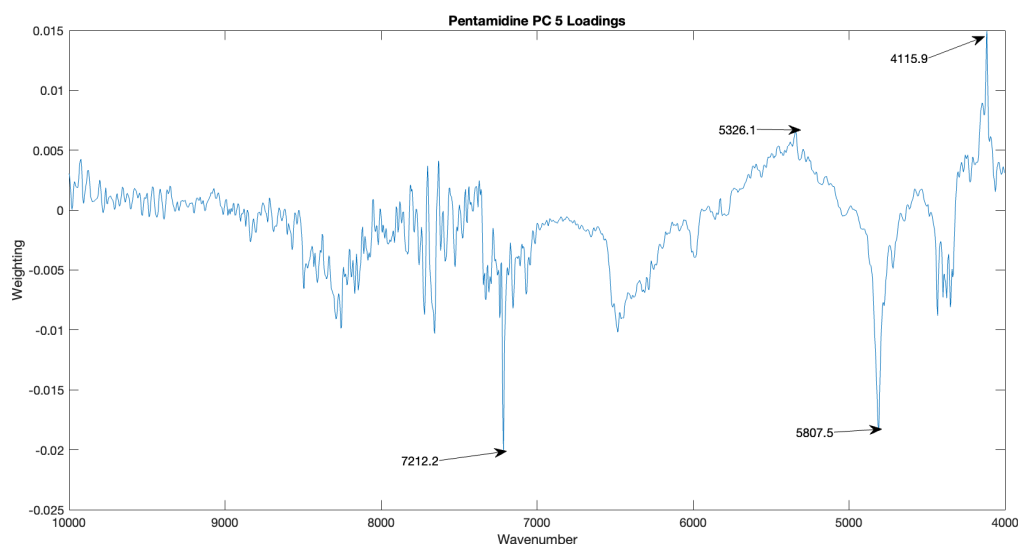


**Figure 13.** The principal component loadings spectrum for the fifth principal component of the library of two lots of pentamidine. Notable spectral features appear at 4116, 5808, 5326, and 7212  $\text{cm}^{-1}$ .

[Figure 14](#) the loadings for PC6 show the strongest peaks tightly around a small spectral region at the low wavenumber end of the spectrum.

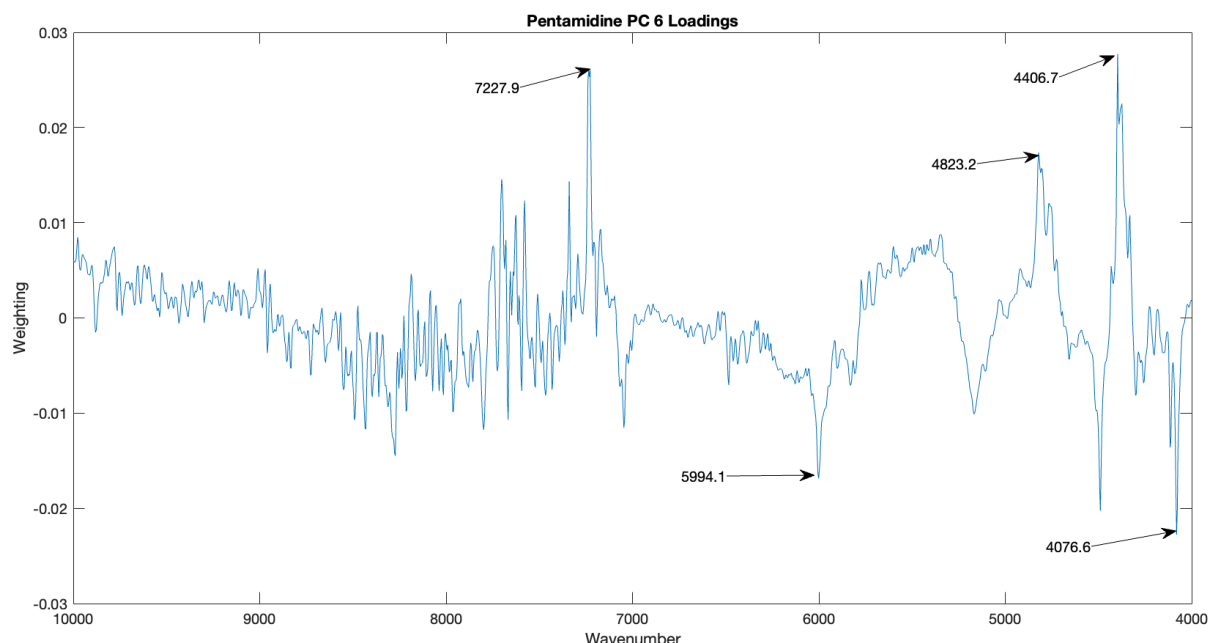


**Figure 14.** Pentamidine Principal Components 6. The principal component loadings spectrum for the sixth principal component of the library of two lots of pentamidine.

## Conclusion

Pentamidine for injection, USP is a sterile, lyophilized antimicrobial agent intended for intravenous or intramuscular administration. Each vial contains 300 mg of pentamidine isethionate, equivalent to approximately 172.4 mg of pentamidine base. The drug is reconstituted prior to use and administered in clinical settings for prophylaxis or treatment of select parasitic and fungal infections. Intra-lot variability was detected in the spectra of 8 vials of pentamidine sampled from the lot 10007045. One of the vials was more than 18.422 multidimensional SDs away from the center of the cluster of the other 7 vials, suggesting that the manufacturing process may not be in control. Inter-lot variability was detected in the two lots of pentamidine, 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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