Quality Variations in Thyrotropin Alfa

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RAPID COMMUNICATION

Abstract

Thyrotropin alfa is a heterodimeric glycoprotein containing human thyroid stimulating hormone (TSH). It is used as an adjunctive diagnostic tool for serum thyroglobulin (Tg) testing with or without radioiodine imaging in the follow-up of patients with well-differentiated thyroid cancer who have previously undergone thyroidectomy.

Inter-lot variability in the Fourier transform near-infrared spectra of 30 samples obtained from four separate lots of Thyrogen® was detected in the Drug Quality Study (DQS). The vials fell into two distinct groups (r_{tst} = 0.90, r_{lim}= 0.98, p=0.02). In addition, one vial of the 30 (3%) appeared 4.7 multidimensional SDs from all of the other vials, suggesting that it also represents a different material.

Introduction

The University of Kentucky's (UK) Drug Quality Study was established in August of 2019 to engage in consumer-level quality assurance screening for drugs used within UK HealthCare's pharmacies (Isaacs, 2023a). DQS 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, DQS has assembled a spectral library containing medications typically

used in a health system setting. Statistical analyses using DQS' spectral library are performed to identify potential intra-lot and inter-lot variability in medications under review. Using Medwatch and publications in the scientific literature, DQS reports its findings in an effort to hold manufacturers accountable for GMP requirements and to improve patient outcomes by providing information on quality to augment the information on price that is already available. The increasing transparency is designed to improve the pharmaceutical supply chain.

Drug Product

Thyrotropin alfa for injection (Thyrogen®, Sanofi Genzyme) is supplied as a sterile, non-pyrogenic, white to off-white lyophilized product, intended for intramuscular (IM) administration after reconstitution with Sterile Water for Injection, USP. Each vial of Thyrogen contains 1.1 mg thyrotropin alfa, 36 mg mannitol, 5.1 mg sodium phosphate, and 2.4 mg sodium chloride. After reconstitution with 1.2 mL of Sterile Water for Injection, USP, the thyrotropin alfa concentration is 0.9 mg/mL. The pH of the reconstituted solution is approximately 7.0. Figure 1 is a photo of the drug product. (Thyrogen package insert, 2023)

The lot numbers making up the spectral library were OY0272, BY0349, BY0351, and BY0484.

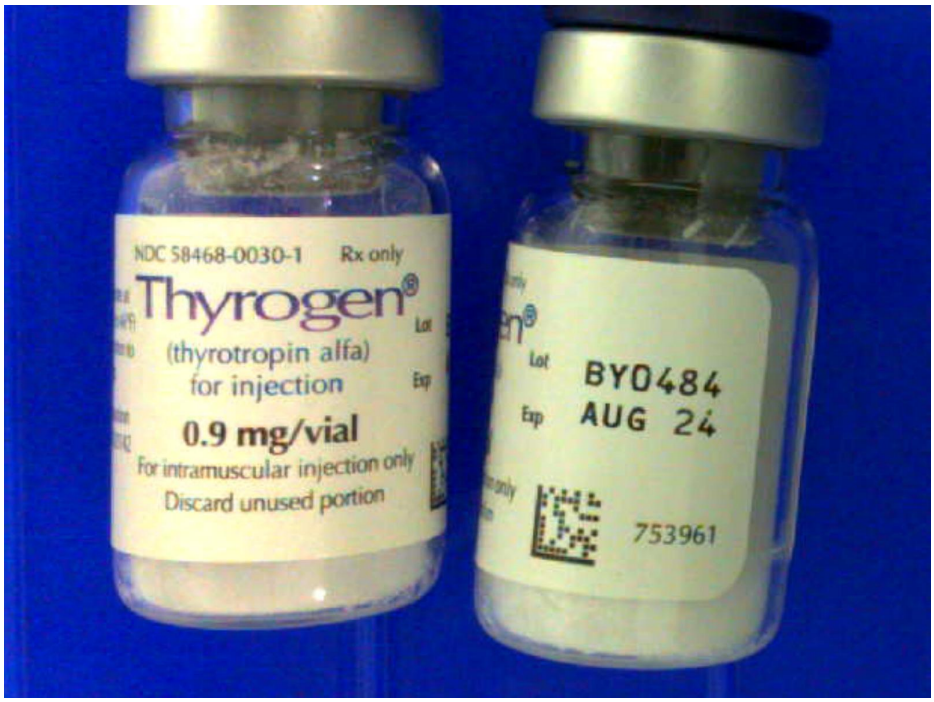

Figure 1. Vials of thyrotropin alfa for injection from lot BY0484. The drug appears as a white freeze-dried powder.

Background

A recent study (Kawamoto, 2023a) discussed the long-term clinical outcomes and prognostic factors for patients with papillary thyroid carcinoma (PTC) with other organ invasions after adjuvant radioactive iodine (RAI). In the study, the patients were administered thyrotropin alfa via intramuscular injection (0.9 mg) 2 days before RAI to stimulate the release of TSH. PTC is the most common endocrine malignancy. The standard management for high-risk PTC patients includes thyroidectomy and adjuvant radioactive iodine (RAI). A fixed administered activity of RAI is recommended, and increasing the dosage may not improve clinical outcomes for patients without evidence of persistent disease. Some cases of locally advanced PTC may not be amenable to resection, and locoregional disease progression can significantly affect quality of life. The prognostic factors for locoregional recurrence-free survival in patients with PTC and other organ invasions who underwent surgery and adjuvant RAI were metastatic lymph node size, resection margin status, and post-RAI suppressed thyroglobulin level. However, the work does not mention prognostic factors for distant metastasis.

Another study (Kawamoto, 2023b) by the same team examined the benefits of adjuvant external-beam radiotherapy (EBRT) in patients with papillary thyroid carcinoma (PTC) with other organ invasions. In this study, the patients were also administered thyrotropin alfa via intramuscular injection (0.9 mg) 2 days before RAI to stimulate the release of TSH. The study used propensity score matching to reduce heterogeneity and evaluated survival outcomes and toxicities associated with EBRT. The results showed that adjuvant EBRT plus radioactive iodine (RAI) improved locoregional recurrence-free survival and recurrence-free survival compared to RAI alone. EBRT was well-tolerated and exhibited acceptable toxicity. The study concludes that adjuvant EBRT plus RAI is beneficial for PTC patients with other organ invasions.

Two recalls of Genzyme Corporation's thyroid medication, thyrotropin alfa for injection (Thyrogen) 0.9 mg/mL, were launched after the presence of glass particulate matter was discovered after reconstitution (Vaccaro, 2016). The recalled products included 4,669 cartons in 4 lots, and 2 lots with one containing cartons and one containing vials.

There have been reports of a shortage of thyrotropin alfa. A shortage was reported in Canada and initially was expected to last until at least May 23, 2023 (Drug Shortages Canada, 2022). However, the shortage was resolved on Feb. 7, 2022. The drug was also on the Drug Shortage Quantity Restrictions List in the United States for a time, with a limited supply available. Some health organizations monitored the shortage and worked on solutions, but availability was sometimes affected.

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 belonging to 4 lots as part of routine medication quality screening. A representative sample of 30 individual vials were selected for screening from lots 0Y0272, BY0349, BY0351, and BY0484 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, 2023)(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 dusters can vary significantly in shape and size due to variation in sample packings, particle-size distributions, component concentrations, and drift with time. These factors, when combined with discriminant analysis using simple distance metrics, produce a test in which a result that places a particular point inside a particular cluster does not necessarily mean that the point is actually a member of the cluster. Instead, the point may be a member of a new, slightly different cluster that overlaps the first. A new cluster can be created by factors like low-level contamination, moisture uptake, or instrumental drift. An extension added to part of the BEST, called FSOB (Fast Son of BEST) can be used to set nonparametric probability-density contours inside spectral clusters as well as outside (Lodder, 1988), and when multiple points begin to appear in a certain region of cluster-hyperspace the perturbation of these density contours can be detected at an assigned significance level using r values, and visualized using quantile-quantile (QQ) plots. The detection of unusual samples both within and beyond 3 SDs of the center of the training set is possible with this method. Within the ordinary 3 SD limit, however, multiple instances are needed to detect unusual samples with statistical significance.

Artificial Intelligence Tools

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

Results and Discussion

Interlot analysis

It is common to see different lots of a drug cluster on slightly different regions of the near-IR spectral hyperspace. The composition of the drug can end up slightly modified because of a small drift in the manufacturing process from batch to batch, yet still represent the approved product. This drift would consequently be reflected in the spectra.

It's uncommon, however, for spectra of drugs from the same drug number to vary dramatically. A process that is in control generally produces the same drug repeatedly, and as a result, the spectra are very similar.

An intralot analysis was not performed for the thyrotropin alfa because there were not many samples from any one lot. Figure 2 shows the spectra of 30 vials from the 4 lots from 4150 cm^{-1} to 4900 cm^{-1}.

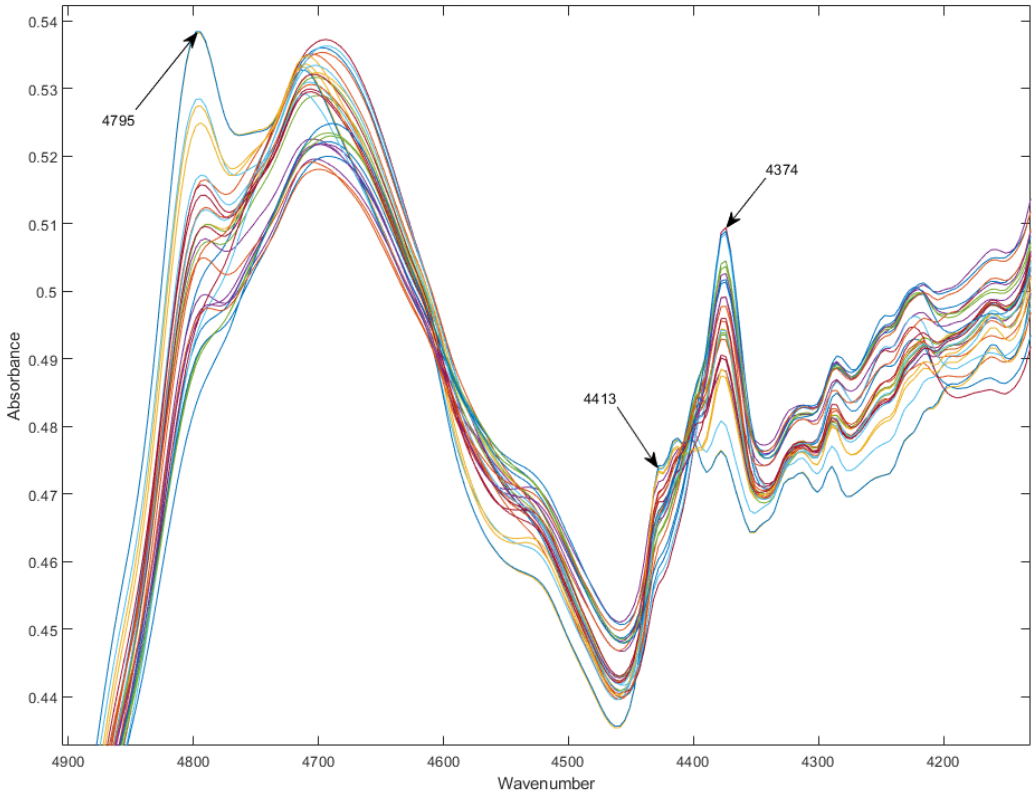

Figure 2. Spectra of 30 vials from lots OY0272, BY0349, BY0351, and BY0484 from 4100-4900 cm^{-1}.

In the spectral region covered by Figure 2, as the peaks at 4795 and 4374 cm^{-1} grow, the peak at 4374 cm^{-1} is reduced. There are also peak differences around 4150, 4225, 4530 and 4710 cm^{-1}.

Figure 3 shows another region of the spectrum of the same 30 vials shown in Figure 2. Major peak variations occur at 6628 cm^{-1} and 6249 to 6300 cm^{-1}. There are also peak variations between the vials at 5900 cm^{-1} and about 5930 cm^{-1}, and at 5870 cm^{-1}.

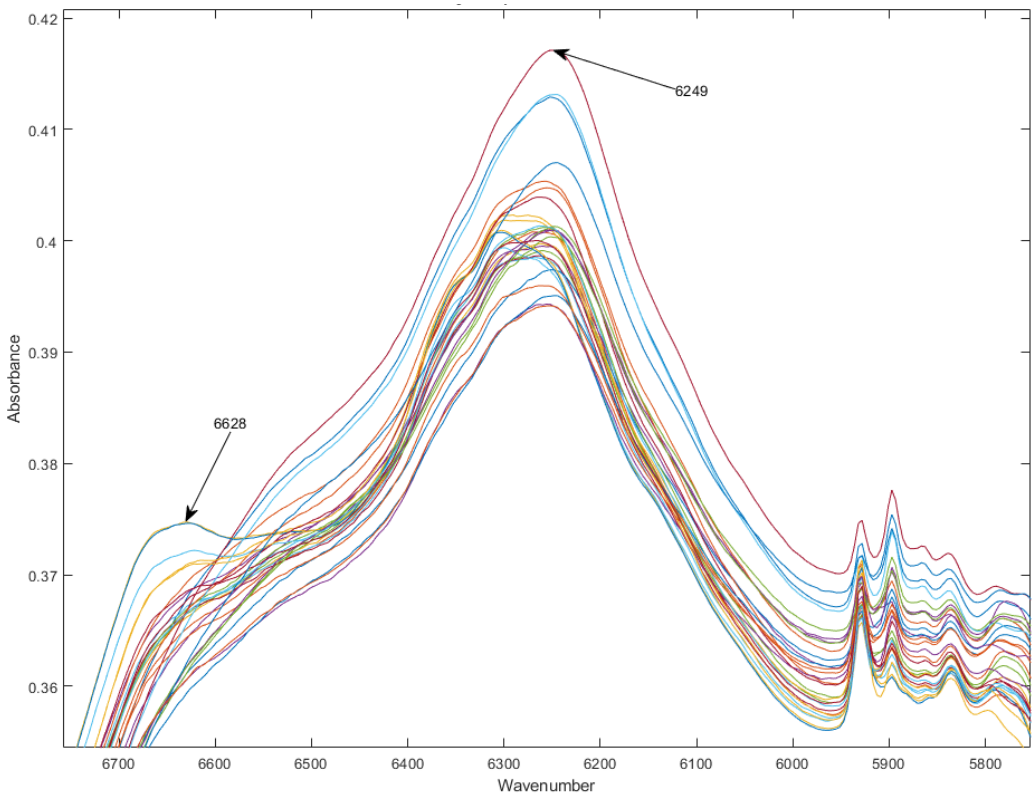

Figure 3. Spectra of 30 vials from lots 0Y0272, BY0349, BY0351, and BY0484 from 5750-6750 cm^{-1}.

The spectral variation accounted for by each of the first six principal components, as well as the cumulative variation of the first six principal components, is given in Table 1.

Table 1: Variation accounted for by each of the principal components of the spectra of lot BY0484

PC Number	Variation in this PC	Cumulative PC Variation
1	0.3044	0.3044
2	0.2247	0.5291
3	0.1646	0.6937
4	0.0973	0.7910
5	0.0372	0.8282
6	0.0256	0.8539

Of note, the spectral variation accounted for by the first principal component is not particularly large.

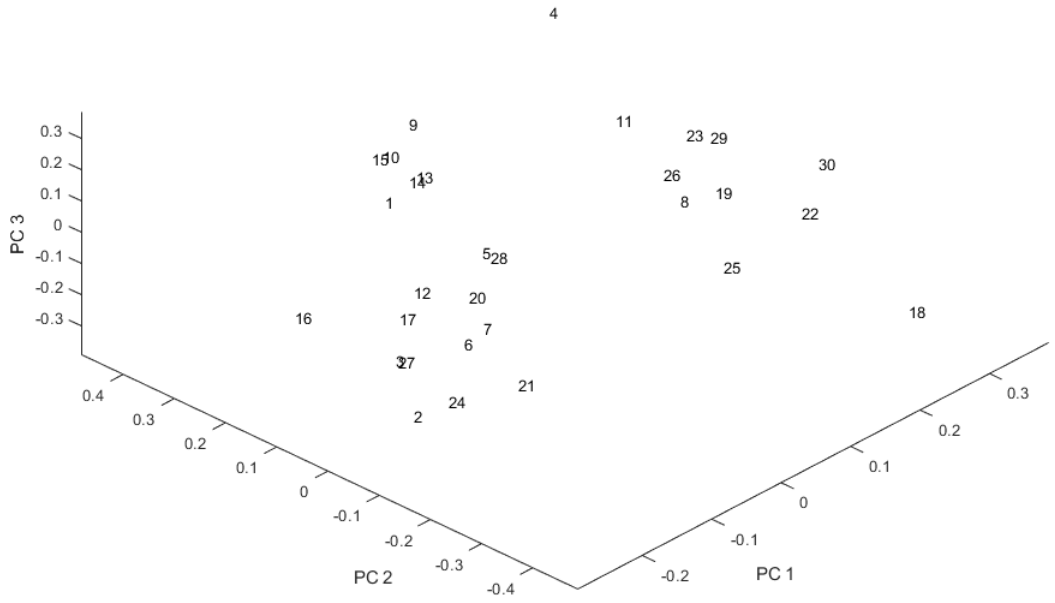

Figure 4. Spectra of 30 vials from lots 0Y0272, BY0349, BY0351, and BY0484 cluster into 2 groups. The groups are significantly different according to the subcluster detection test (r_{tst} = 0.90, r_{lim}= 0.98, p=0.02).

Figure 4 is a PC plot of the first 3 PCs of the spectra of 30 vials in lots 0Y0272, BY0349, BY0351, and BY0484. The spectra cluster in 2 groups that are 31.7 SDs apart based on the subcluster detection test.

Figure 5 adds a blue line to the data in Figure 4.The blue line connects the vials and lots in Figure 4 in order. The blue line crosses between the two groups 13 times because both groups contain vials from all of the lots. In other words, whatever issue causes the vials to separate into two groups exists across all four lots of vials examined.

The next smaller PCs, 4, 5, and 6, were also checked (see Figure 6). In these PCs, vial 2 was displaced 4.6 standard deviations from the other 29 vials. The other 29 miles formed a homogeneous group.

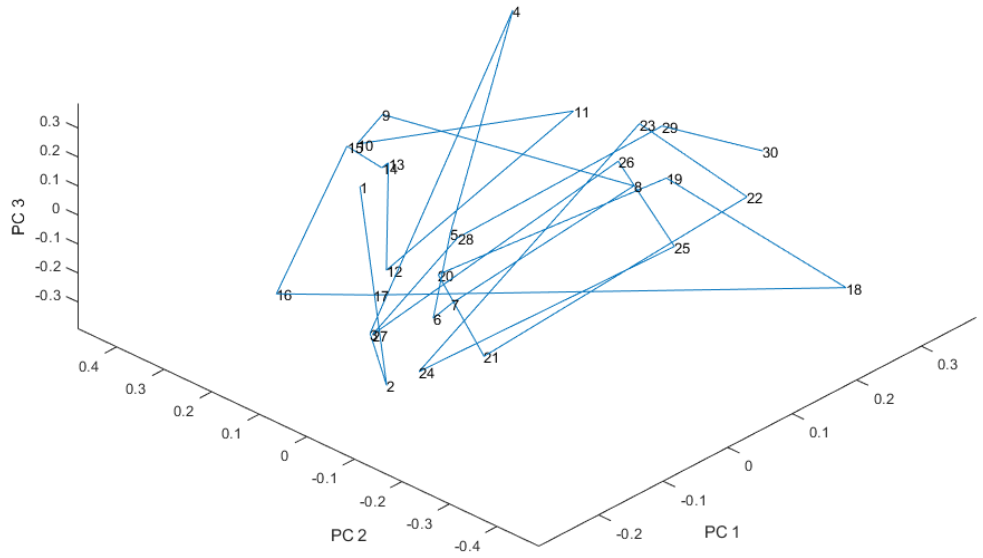

Figure 5. The blue line connects the vials and lots in Figure 4 in order. The blue line crosses between the two groups 13 times because both groups contain vials from all of the lots.

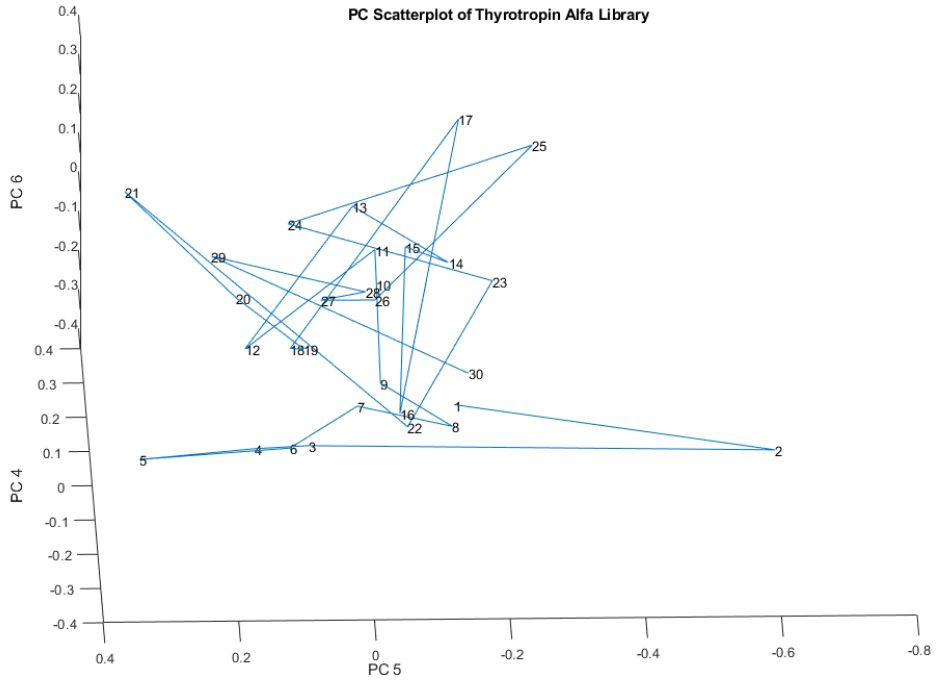

Figure 6. On the next 4 PCs (4, 5 and 6) for the 4 lots, only one vial appears unusual. Vial 2 is displaced 4.6 standard deviations from the other 29 vials.

Figure 7 shows the principal component loadings of the thyrotropin alfa library composed of spectra of the four lots (0Y0272, BY0349, BY0351, and BY0484). Notable peaks appear at 4412, 4759, 5555, 6359, and 6709 cm^{-1}.

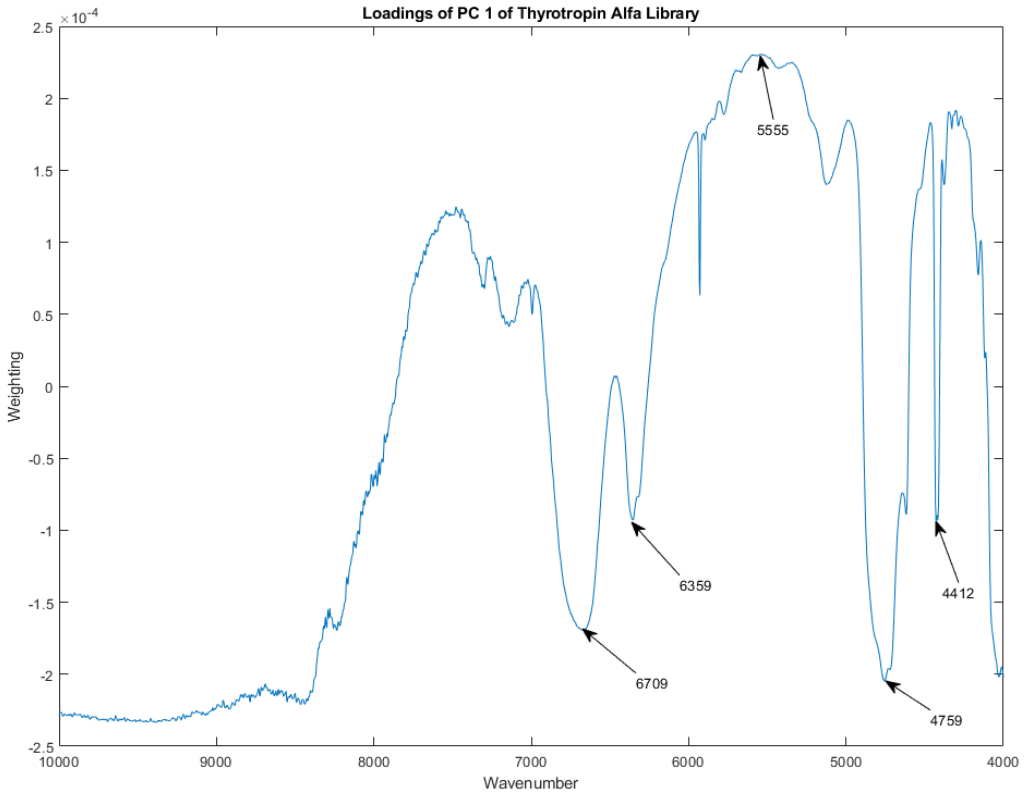

Figure 7. PC loadings of the thyrotropin alfa library composed of spectra of the four lots (0Y0272, BY0349, BY0351, and BY0484).

Figure 8 depicts the loadings of the second PC of the spectral library. Major peaks appear at 4087, 4440, 4676, 6546, 7010, and 7918 cm^{-1}.

Figure 9 shows the loadings of the third principal component of the spectral library. Major peaks are pointed out on the spectrum at 4378, 4419, 4827, 6214, and 6872 cm^{-1}. A little noise begins to appear toward the visible light region of the spectrum. Progressing from PCs 4 to 6 results in increasing noise in the visible light region of the spectrum (Figures 10-12).

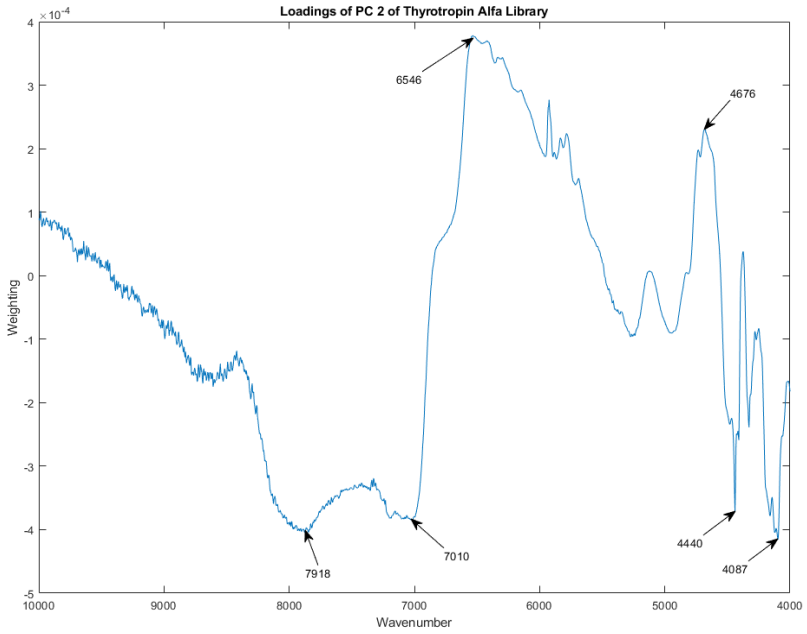

Figure 8. Loadings of the second PC of the spectral library. Major peaks appear at 4087, 4440, 4676, 6546, 7010, and 7918 cm^{-1}.

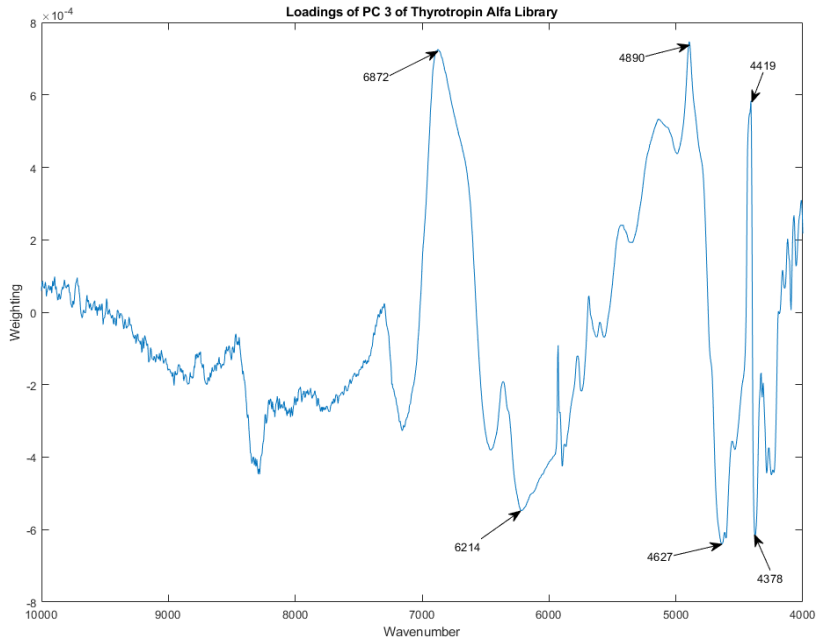

Figure 9. Loadings of the third PC of the spectral library. Major peaks are noted on the graph.

Figure 10 and Figure 11 show the loadings for PC 4 and 5, respectively.

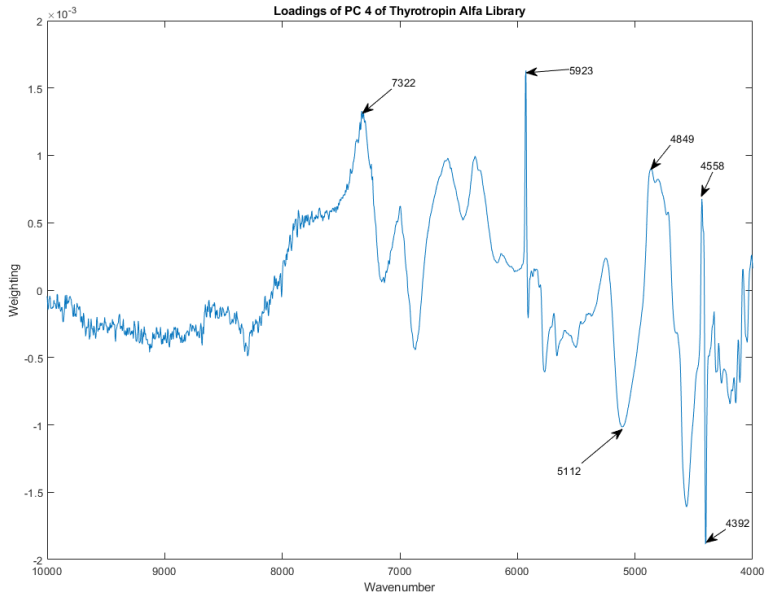

Figure 10. Loadings of the fourth PC of the spectral library. Major peaks are noted on the spectrum.

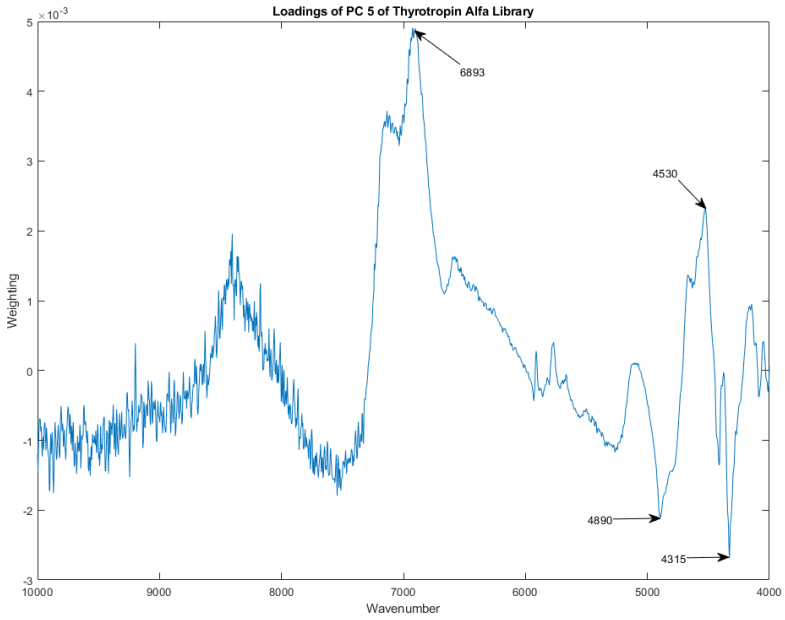

Figure 11. Loadings of the fifth PC of the spectral library. Major peaks are noted on the graph.

Figure 12 depicts the loadings of the sixth PC of the spectral library. The major peaks of note are at 4398, 4890, 5223, 5937, 6872, and 7052 cm^{-1}.

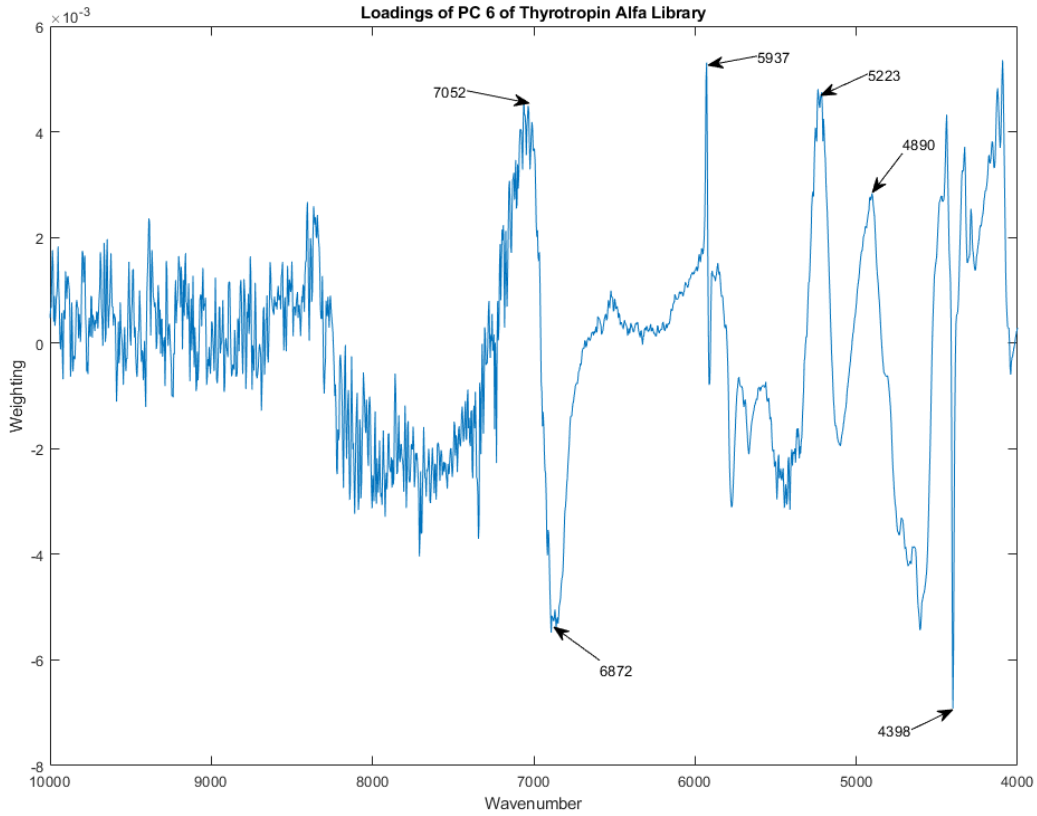

Figure 12. Loadings of the sixth PC of the spectral library. Major peaks are noted on the graph.

Conclusion

Thyrotropin alfa is used as an adjunctive diagnostic tool for serum thyroglobulin (Tg) testing with or without radioiodine imaging in the follow-up of patients with well-differentiated thyroid cancer who have previously undergone thyroidectomy (FDA, 2020).

Inter-lot variability in the Fourier transform near-infrared spectra of 30 samples obtained from four separate lots of Thyrogen® was detected in the Drug Quality Study (DQS). The vials fell into two groups (r_{tst} = 0.90, r_{lim}= 0.98, p=0.02), suggesting that the groups contain at least slightly different material. In addition, one vial of the 30 (3%) appeared 4.7 multidimensional SDs from all of the other vials, suggesting that it also might represent a different material at a lower concentration.

These FTNIR results do not prove an excess level of impurities or adulteration. However, they suggest that the manufacturing process may have been operating outside of a state of process control. Additional investigation is needed.

Acknowledgements

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