Journal of Pharmaceutical and Biomedical Analysis 54 (2011) 1001–1006

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Detection of diethylene glycol adulteration in propylene glycol—Method validation through a multi-instrument collaborative study☆

Xiang Li[a,b], Sergey Arzhantsev[a], John F. Kauffman[a], John A. Spencer[a,*]

[a] Division of Pharmaceutical Analysis, Center for Drug Evaluation and Research, US Food and Drug Administration, 1114 Market St, Room 1002, Saint Louis, MO 63101, USA
[b] The Pennsylvania State University, University Park, PA 16802, USA

ARTICLE INFO

Article history:
Received 2 August 2010
Received in revised form 1 November 2010
Accepted 27 November 2010
Available online 8 December 2010

Keywords:
Near infrared transmission
Propylene glycol
Diethylene glycol
Partial least squares
Hand-held instruments

ABSTRACT

Four portable NIR instruments from the same manufacturer that were nominally identical were programmed with a PLS model for the detection of diethylene glycol (DEG) contamination in propylene glycol (PG)–water mixtures. The model was developed on one spectrometer and used on other units after a calibration transfer procedure that used piecewise direct standardization. Although quantitative results were produced, in practice the instrument interface was programmed to report in Pass/Fail mode. The Pass/Fail determinations were made within 10 s and were based on a threshold that passed a blank sample with 95% confidence. The detection limit was then established as the concentration at which a sample would fail with 95% confidence. For a 1% DEG threshold one false negative (Type II) and eight false positive (Type I) errors were found in over 500 samples measured. A representative test set produced standard errors of less than 2%. Since the range of diethylene glycol for economically motivated adulteration (EMA) is expected to be above 1%, the sensitivity of field calibrated portable NIR instruments is sufficient to rapidly screen out potentially problematic materials. Following method development, the instruments were shipped to different sites around the country for a collaborative study with a fixed protocol to be carried out by different analysts. NIR spectra of replicate sets of calibration transfer, system suitability and test samples were all processed with the same chemometric model on multiple instruments to determine the overall analytical precision of the method. The combined results collected for all participants were statistically analyzed to determine a limit of detection (2.0% DEG) and limit of quantitation (6.5%) that can be expected for a method distributed to multiple field laboratories.

Published by Elsevier B.V.

1. Introduction

Propylene glycol (PG) is included in the FDA Inactive Ingredients Database [1] and is widely used in the pharmaceutical industry as an excipient [2]. It is a clear, colorless, viscous liquid with sweet taste. Recent findings of PG contamination with diethylene glycol (DEG) cause significant concern for the safety of consumers and pharmaceutical products [3–5]. With an increasing number of overseas suppliers of pharmaceutical raw materials, the best way to prevent economically motivated adulterated materials from entering the US market is to drastically increase the number of samples to inspect for quality control [6–8]. Therefore, it is important to develop rapid analytical methods that are suitable to identify toxic impurities and contaminants [9–13]. The USP [14] and other methods [15] of identifying diethylene glycol in propylene glycol use gas chromatography, which can only be done in the laboratory and are time consuming. Near infrared (NIR) absorbance spectroscopy coupled with chemometrics is a powerful tool in analytical chemistry to identify pure chemicals and components in mixtures [9]. Both propylene glycol and diethylene glycol have strong absorption bands in the NIR spectral region that can be used to create a quantitative chemometric model. Evidence from field surveillance suggested that economically motivated adulteration (EMA) would occur in the range of 5–15 wt% [7]. To intercept such adulterated materials we have suggested deploying portable spectrometers with chemometric models capable of detecting DEG as an impurity in propylene glycol–water mixtures down to the 1–2% level.

Typically, analytical instruments are used for one application at a time. Individual instruments are calibrated and validated for each particular task. This is not the case for field regulatory surveillance, as well as many PAT applications. Multiple copies of the same basic instruments are used by a variety of people in a range of environments. Even instruments of the same model may differ in wavelength calibration and photometric sensitivity. A means to standardize multiple instruments so that a model developed on

☆ The findings and conclusions in this article have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any Agency determination or policy.

* Corresponding author. Tel.: +1 314 539 3859; fax: +1 314 539 2113.
E-mail address: john.spencer@fda.hhs.gov (J.A. Spencer).

0731-7085/$ – see front matter. Published by Elsevier B.V.
doi:10.1016/j.jpba.2010.11.042

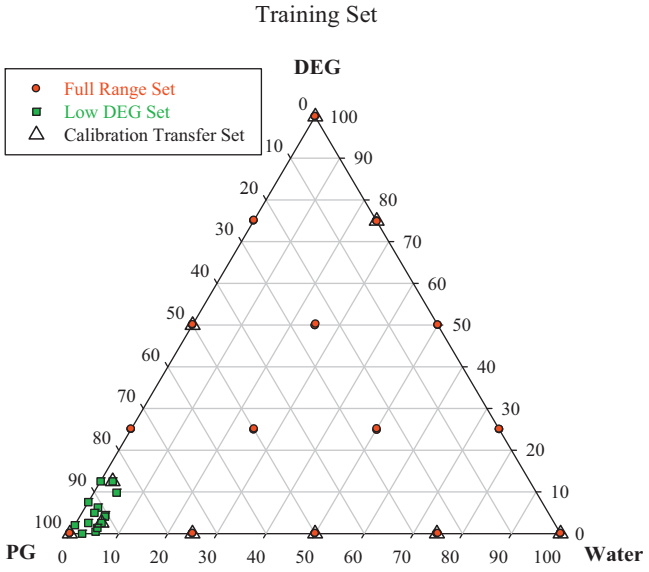

Fig. 1. Ternary diagram of training set sample compositions used in the PLS model.

one master instrument can be used on many similar secondary instruments is required. Though the specific problem at hand was the detection of diethylene glycol in propylene glycol, this work also evaluated the transfer of calibration models to multiple instruments using an optimized set of calibration transfer samples and piecewise direct standardization. Such a technique allows any instrument in the group to produce the same result as would be found on the master instrument.

In this work we used a multi-site, multi-instrument collaborative study to analyze the variations inherent in four "identical" near infrared spectrometers. Our objective is to develop an intermediate measure of the precision that accounts for different users, secondary instruments and locations. The spectrometers were used to quantitatively measure the composition of a ternary mixture (PG–DEG–water) using a chemometric model (PLS) developed on one master instrument. Water was included because USP grade PG allows variable water content and the DEG calibration model must therefore be insensitive to water composition. Detection and quantitation limits were determined for the entire group of secondary instruments and compared to the results typical for any single instrument.

2. Materials and methods

2.1. Materials

USP grade propylene glycol and reagent grade DEG were purchased from Fisher Scientific (Fair Lawn, NJ, USA). The water contents of as-received PG and DEG were determined by Karl–Fischer titration to be 0.03% and 0.05%, respectively. Disposable dual pathlength plastic CVD-UV cuvettes (Plastibrand®, Ocean Optics, Dunedin, FL, USA) were sealed with polyethylene caps and Parafilm 'M'®. The sample pathlength was 0.5 cm.

2.2. Design of experiment

JMP 5.1 software [16] was used to generate an optimum ternary array of training samples, see Fig. 1. The training set had 29 samples chosen in such a way that the first fifteen samples encompassed the full ternary range while the remaining fourteen simulated more realistic adulterated propylene glycol (over 85% propylene glycol–water mixtures with up to 15% diethylene glycol). Thirty-

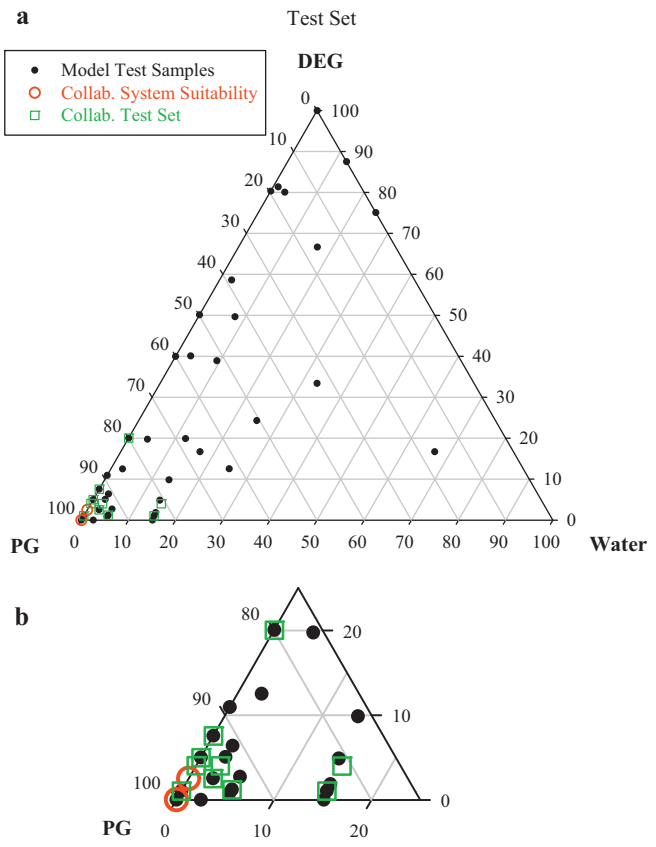

Fig. 2. (a) PLS model test set. (b) Close-up of low DEG, low water region of system suitability (circles) and test samples (squares) used in the collaborative study.

nine test samples were made up to cover the same overall range (Fig. 2a), again with emphasis on lower levels of adulteration (see Fig. 2b). All samples were made in bulk by weight (nominally 50 g total weight basis). Karl–Fischer water determinations for PG and DEG were taken into account in the formulation. All were mixed for 30 min on a Turbula® orbital mixer.

2.3. Near infrared spectra

NIR transmission measurements were made on a B&W Tek, Inc., *i-Spec* BWS025 that uses a 5 W incandescent source and a cooled 256 element InGaAs CCD array detector in the range 1100–2200 nm. The sample cuvettes were placed in a fiber-optic coupled sample holder. Spectra were measured using an integration time of about 5 ms. 300 spectra were co-added before calculating optical density. An empty cell was scanned initially as a reference. The overall time required to analyze one sample was less than 2 s.

Four portable NIR spectrometers of the same model (referred to as NIR01, NIR02, NIR03 and NIR04) were characterized in-house and one was selected based on stability, reproducibility and low noise to be a 'Master' instrument on which the chemometric model was constructed and to which the others were mathematically matched using a 'calibration transfer' method. All instrument operation, subsequent chemometric calculations and report generation were handled by Visual BASIC for Applications (VBA) program running in Excel and Word.

A printed and illustrated step-by-step protocol, along with a video and the sample set was distributed to four collaborating FDA field laboratories (referred to as 1, 2, 3 and 4). The sample set was measured at least three times (twice on battery and once on AC

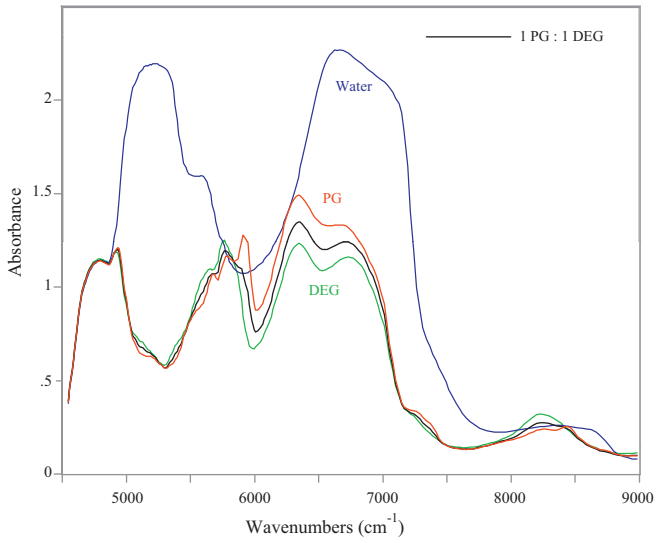

Fig. 3. NIR spectra of the three components along with the spectrum of a 50–50 mixture of propylene glycol–diethylene glycol.

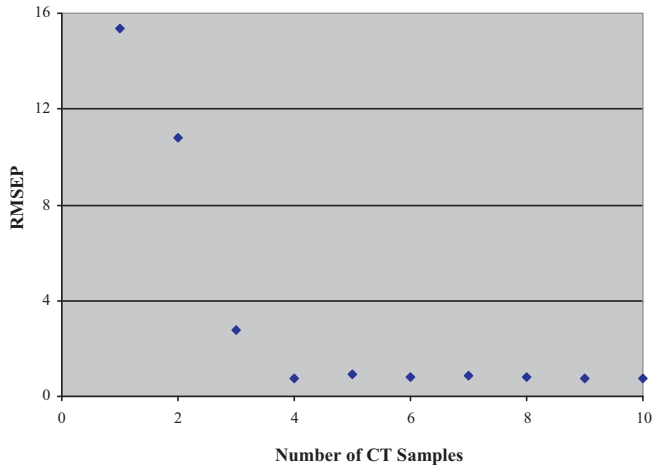

Fig. 4. Change in RMSEP values as the number of calibration transfer samples increases.

power) by an assigned analyst. None of the participants had prior experience with portable NIR instruments.

2.4. Chemometrics

Partial least squares (PLS) model development and testing were done using Pirouette® 4.0 [17]. The resulting optimized model was then called from an Excel-based VBA user interface that controlled the spectrometer, collected the data, invoked the chemometric prediction engine (Infometrix InStep™ 3.0) and created a text report using MS Word. This software program used the PLS model developed on the master instrument to quantitate the three components on the secondary instruments. Threshold values (>85% PG, <1% DEG and <5% water) were used to establish a Pass or Fail status for each of the three components. A Pass/Fail was reported to the analyst and in the event of a failure the percent composition that exceeded the threshold was also shown on the screen. All the spectra and quantitative predictions were saved for post-study analysis of the collective performance of the four instruments.

3. Results and discussion

3.1. NIR spectra and model

Fig. 3 shows NIR spectra of pure components, PG, DEG and water and a mixture of 50% PG and 50% DEG as observed on one of the study instruments. There are measurable differences between the spectra of all three components. The strongest NIR absorber among the components is water which when present even in relatively small amounts tends to dominate the overall spectrum. Under these circumstances simple univariate models are not useful. A partial least squared (PLS) regression chemometrics approach was shown to be capable of predicting quantitative concentrations of all the components including water.

The PLS model was constructed on the master instrument using 58 spectra (29 training samples measured in duplicate). All spectra were mean-centered and no spectral preprocessing was required. Adding two Orthogonal Signal Correction (OSC) components substantially improved the model root mean squared errors of prediction of the test sample set (RMSEPs) and yielded the most stabile predictions for the 12 sample test set used in the collaborative study. The orthogonal loadings for PG and DEG on OSC1 show a close correlation to the NIR spectrum of water which suggests that it is compensating for a water contribution common to all three components. The resulting model had 3 factors for PG, 6 for DEG and 3 for water. The leave-one-out crossvalidated model gives RMSECV of ~0.3% for DEG. Evaluation of the quality of the PLS model was based on prediction of the test sample set. The RMSEPs were found to be ±1.2%, ±0.7% and ±0.4%, respectively, for the PG, DEG and water.

Prior to generating a final PLS model for distribution, we evaluated the performance of all four spectrometers by scanning the training and test sets, creating models and comparing multiple RMSEP values. Detection limits as low as 0.7% were achieved on test sets measured on a single instrument using instrument-specific PLS models where the training and test sets were measured by the same analyst on the same day. For the collaborative study, the model developed on the master instrument was used and calibration transfer was applied in order to distribute the model. This approach was selected to evaluate the capability of a model that could be implemented on several distributed instruments without developing PLS models on each individual instrument. Each contributing laboratory made at least three complete runs – two using battery and one on AC power.

3.2. Calibration transfer

A set of calibration transfer (CT) samples was used to transfer a model from the master instrument to a secondary spectrometer. These CT samples comprise a subset of the original training set that must be measured on each spectrometer before applying the PLS model for sample predictions. CT samples were selected from the training set by ranking all of the training set spectra according to the Kennard–Stone [18] algorithm and selecting the top ten for the standardization procedure. The piecewise direct standardization algorithm with a 3 point window was used for calibration transfer. The CT samples were scanned on the secondary instrument prior to all other measurements. The software then uses these spectra and the spectra of identical samples measured on the master instrument during model development to standardize the spectra on the secondary instrument. The ten CT samples used are depicted with triangles in Fig. 1. During the course of this study we examined the sensitivity of the calibration transfer procedure to the number of CT samples used for standardization. Fig. 4 shows how the precision of the test sample predictions improves as more CT samples up to 10 are included in the PLS model. Fig. 4 suggests the number of CT samples could be limited to as few as four as this method is

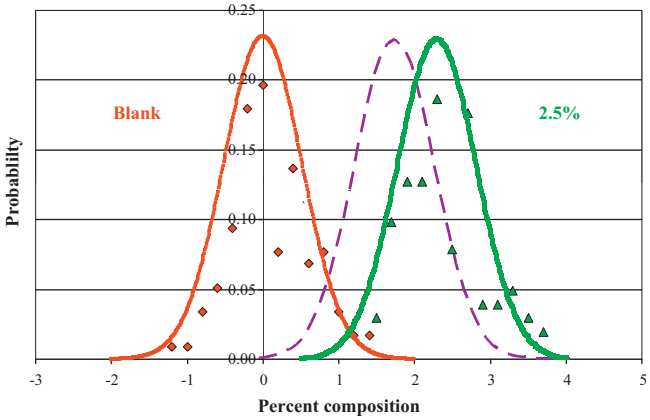

Fig. 5. Distribution of system suitability sample measurements before the collaborative study (117 blank and 102 2.5% samples). Dashed line has a mean value of 1.7%, corresponding to a critical limit (CL) of 0.86.

deployed in the future, but all ten CT samples were used for the collaborative study.

3.3. Critical level and limit of detection

Two system suitability samples were measured after the CT samples. These consisted of a PG blank (A) and a sample containing 2.5% DEG(B) representing a composition near the anticipated lower detection limit. Spectra of each of these two samples were measured ten times prior to each run in order to provide meaningful statistics for their predicted values. During model development, these samples were used to determine the critical level (CL), which is the Pass/Fail decision threshold for the predicted concentration. A test sample passes if its concentration is predicted to be below the CL and fails if its predicted concentration is above the CL. The CL is determined from a statistical analysis of predictions on the blank sample as the upper limit of a one sided confidence interval at the 95% level. Typically a normal distribution is assumed, and the CL is computed as the mean predicted blank concentration plus 1.65 blank standard deviations. The limit of detection (LD) is then defined as the predicted concentration at which a sample will fail with 95% confidence. Assuming a normal distribution, the LD is computed as the CL plus 1.65 standard deviations, so that the CL is the lower limit of a one sided confidence interval at the 95% level, and the mean value of this distribution is the LD. The low level sample (B) is used to estimate the standard deviation of a sample at the limit of detection. These concepts have been thoroughly established by Currie [19] and are illustrated in Fig. 5 as discussed below. In the collaborative studies, the system suitability samples served to assure the analyst that the measurement system was working properly by comparing the means and standard deviations of the predictions on these samples to values that were deemed acceptable. These predicted values were also available following the collaborative study to assess the overall variability of the method by examining the standard deviations of all blank predictions (A) and all low level predictions (B).

Table 1 collects the mean and standard deviation values for DEG in the blank sample (A) and low level (2.5%) sample (B). This table includes the measurements made on the master instrument, those made on all four instruments during the model development phase and the individual determinations made by the collaborating laboratories. The reported results from the participating laboratories were collected and reanalyzed to determine an aggregate LD and limit of quantitation (LQ) for the measurements as shown in Table 1. The LQ is determined as the blank mean plus 10 low level sample standard deviations. Values from the development stage measurements mainly describe the variability between instruments while results from the collaborative study are a measure of intermediate precision. The aggregated standard deviation of prediction for samples A and B in both development and collaborative studies describes the overall performance of the instruments. This includes stability of the light source and detector, between-instrument variability, robustness of PLS model, variability due to site differences and variability due to different operators. Table 1 shows that the standard deviation of sample A predictions is very similar to that for sample B predictions. The histograms of the predictions for samples A and B measured on all four instruments during model development are shown in Fig. 5. Histograms for both samples are consistent with normal distributions, and justify the use of the normal distribution for establishing the CL, LD and LQ. These results were used to establish the CL for the collaborative study. The dashed line in Fig. 5 is a normal curve whose mean value (1.7%) is equal to the LD. This distribution centered on the LD crosses the CL at the location where the blank distribution crosses the CL. The area of the dashed curve below the CL is 5% of the distribution, and the area of the blank distribution that exceeds the CL is 5% of the blank distribution. Thus when the CL is used as the Pass/Fail decision threshold, the blank is expected to fail at a rate of 5%, and a sample at the LD is expected to pass at a rate of 5%. The combined results for samples A and B in the collaborative study were also found to be normally distributed. Low level sample B had an overall standard deviation of ±0.73%, which is statistically identical to the RMSEP (±0.7%) of the original PLS model, and is a good indication that the PLS model represents mainly spectral data and not noise. The overall LD for all collaborating laboratories was 2% and the LQ was 7%, which compare favorably with the development study LD of 1.7% and LQ of 5.2%.

As one can see from Table 1, the mean values of blank sample (A) from the various collaborative study labs and overall are shifted relative to the value found in the development work, and the prediction of sample B was shifted by about the same amount. We attribute these shifts to the degradation of the calibration transfer samples used for instrument standardization over the course of the collaborative study. A follow-up investigation verified that moisture absorption in the CT samples was the source of the shifts in means in Table 1. Since both PG and DEG are extremely hygroscopic, variable moisture absorption into all the samples, particularly the calibration transfer samples, slightly degraded the

Table 1
Statistics for the system suitability samples measured prior to distribution, for individual collaborating laboratories and overall. Ten A (DEG = 0%) and ten B (DEG = 2.5%) samples per run. Means and standard deviations, critical level, limit of detection and limit of quantitation for DEG.

Lab	Instrument	Runs (samples)	Mean A	$\pm\sigma_A$	Mean B	$\pm\sigma_B$	CL	LD	LQ
Development	NIR01, 2, 3, 4	24 (219)	0.00	0.52	2.29	0.52	0.86	1.73	5.20
1	NIR01	3 (60)	−0.06	0.40	2.41	0.46	0.60	1.37	4.54
2	NIR02	4 (80)	−1.15	0.24	1.35	0.22	−0.76	−0.39	1.05
3	NIR03	5 (100)	−0.55	0.33	1.78	0.47	0.00	0.79	4.11
4	NIR04	3 (60)	0.49	0.50	2.79	0.76	1.32	2.59	8.09
Collaborative	NIR01, 2, 3, 4	15 (300)	−0.40	0.69	1.99	0.73	0.73	1.95	6.87
All data	NIR01, 2, 3, 4	39 (519)	−0.23	0.65	2.11	0.67	0.85	1.97	6.44

Table 2
Number of false positive and negative determinations of DEG in PG for the system suitability samples measured on four instruments deployed in the field. DEG threshold set at1.0% for pass/fail during collaborative study.

Lab	Instrument	Runs (samples)	False positive	False negative
Development	NIR01, 2, 3, 4	24 (219)	4	0
1	NIR01	3 (60)	0	0
2	NIR02	4 (80)	0	0
3	NIR03	5(100)	0	1
4	NIR04	3 (60)	4	0
Collaborative	NIR01, 2, 3, 4	15 (300)	4 (1.3%)	1 (0.3%)
All data	NIR01, 2, 3, 4	39 (519)	8 (1.5%)	1 (0.2%)

Table 3
Statistics for DEG in the test sets measured by the four collaborating laboratories (12 test samples C-N measured in triplicate). Test F-N columns omit the low DEG test samples.

Lab	Instrument	Runs	All test samples (C-N)		Test F-N	
			Samples	RMSEP	Samples	RMSEP
1	NIR01	3	108	0.82	81	0.81
2	NIR02	3	108	1.47	81	1.58
3	NIR03	5	60	0.89	45	0.90
4	NIR04	3	108	1.70	81	1.72
Combined	NIR01, 2, 3, 4	14	384	1.32	288	1.35

Table 4
False positive and negative Pass/Fail statistics for the four collaborating laboratories.

Lab	Instrument	Runs	All test samples (C-N)			Test F-N		
			Samples	False positive	False negative	Samples	False positive	False negative
1	NIR01	3	108	0	13	81	0	0
2	NIR02	4	118	0	22	88	0	2
3	NIR03	5	60	0	11	45	0	1
4	NIR04	3	108	0	10	81	0	0
Combined	NIR01, 2, 3, 4	15	394	0 (0%)	56 (14%)	295	0 (0%)	3 (1.0%)

model predictions. This experience emphasizes the critical importance of maintaining the integrity of calibration transfer samples if they are to be used to recalibrate instruments over an extended time period. In our lab this issue has been addressed by sealing the lids to the cuvettes with impermeable glue and establishing a sample shelf life.

3.4. Pass/Fail

Upon return of the instruments, the Pass/Fail status of all system suitability measurements was collated and evaluated for Type I and Type II errors. The Pass/Fail decision is made by comparing the quantitative predictions with the CL threshold values for each of the three components. The 1% threshold for DEG is rounded up from the aggregate critical limit (0.86) found in the development phase (Table 1). The results of this analysis for DEG are shown in Table 2. From the perspective of hypothesis testing, our null hypothesis is that a sample contains no DEG. A Type I error, an incorrect rejection of the null hypothesis, occurs when a blank sample fails and is also known as a false positive. Of most concern to the user is the rate of Type II error, an incorrect acceptance of the null hypothesis, also known as a false negative. These are samples that should fail due to the presence of more than 1% DEG but are reported to pass. In this study a single 2.5% sample out of 519 scans failed to meet the 1% threshold. A false negative rate of less than 1% compares favorably to the 5% expected rate for a sample at the LD at the 95% confidence level. The eight Type I errors constitute less than 2% of the samples screened and are all attributed to blank samples predicted between 1 and 2%.

Test samples A and B, (0.0 and 2.5% DEG), though used here to measure the LD, also serve as a system suitability test. In the field, an instrument would be expected to be able to pass 9 of 10 of the blank and fail 9 of 10 of the 2.5% (B) samples to be deemed suitable for the intended purpose.

3.5. Quantitative analysis – test samples

Following the LD measurements, a set of twelve test samples (labeled C-N) were measured in triplicate. The concentrations of samples comprising the test set are shown as squares in Fig. 2a and b. Note that the choice of concentrations is constrained to the expected range for adulterated and/or wet (>0.2% water) PG. Table 3 contains the RMSEP values found for each of the laboratories. Table 4 displays the corresponding Pass/Fail determinations for the test set. Notice a much higher Type II error rate occurs when the first three samples (C, D and E) are included in the analysis. These samples contained 1.02, 1.20 and 1.04% DEG and 0, 5 and 15% water, respectively. Samples C, D and E are below the predicted limit of detection and so are expected to pass at a rate exceeding 5%. They account for essentially all the error in the Pass/Fail determinations as demonstrated by the 1% false negative (Type II) rate for the subset using only samples F-N. Elimination of these samples does not significantly influence the RMSEPs shown in Table 3, indicating that the variability in predictions for samples below the LD is similar to the variability for predictions of samples above the LD.

4. Conclusions

The present work demonstrates that individually calibrated portable NIR instruments using a PLS model are able to detect DEG at or below the 1% level. When a calibration model developed on a single master instrument was transferred to four secondary instruments with a 10 sample calibration transfer set, the collective

detection limit of the four secondary units was 1.7% for DEG. The quantitative performance for individual instruments for a system suitability set (0 and 2.5% DEG) demonstrated that the predictions conform to a normal distribution. Comparison of predicted compositions for the system suitability samples by the four collaborating laboratories deviated somewhat from the values observed during model development (Table 1) due to moisture corruption of the Calibration Transfer standards. In spite of this, the overall limit of detection that can be expected for a group of instruments deployed in the field was found to be ~2%. The prediction error for 12 independent test samples (Table 3) ranged from ±0.8 to ±1.7%.

The Pass/Fail performance is consistent with the quantitative results which are based on a statistical determination of the critical limit. With a 1% critical level for DEG, only a single false negative (Type II) error out of 500 predictions of a 2.5% system suitability sample was observed. The false positive (Type I) error rate was shown to be 1.5% for the blank sample. With the exclusion of samples formulated below the DEG detection limit, the application of the Pass/Fail criterion described above produced a 1% rate of Type II error for the test set.

We have demonstrated that portable diode array NIR instruments can be field standardized using a PLS model employing piecewise direct standardization calibration transfer. A simple instrument qualification for any given model can be developed by defining a maximum tolerable number of Pass/Fail results for multiple scans of blank and low level system suitability samples following the calibration transfer scans. Detection limits in the field using a field standardized secondary instrument will necessarily be less than what can be achieved on an individual instrument using a purposely constructed PLS model. Finally, a reliable Pass/Fail determination can be made using a PLS model in spite of some degradation of the transfer calibration standard set.

Acknowledgments

We recognize the valuable contribution made by a group of dedicated analysts in the FDA Office of Regulatory Affairs field laboratories as well as within the Division of Pharmaceutical Analysis.

References

[1] U.S. FDA, Inactive Ingredients Database, U.S. FDA, 2010.
[2] A. Wade, P.J. Weller, Handbook of Pharmaceutical Excipients (1994) 407–408.
[3] Fatalities associated with ingestion of diethylene glycol-contaminated glycerin used to manufacture acetaminophen syrup – Haiti, November 1995–June 1996, MMWR Morb. Mortal Wkly. Rep. 45 (1996) 649–650.
[4] Diethylene glycol poisoning associated with paracetamol liquid formulations, Adverse Drug React. Toxicol. Rev. 17 (1998) 207–208.
[5] C.A. Brown, S.A. Brown, Food and pharmaceuticals: lessons learned from global contaminations with melamine/cyanuric acid and diethylene glycol, Vet. Pathol. 47 (2010) 45–52.
[6] B. Roehr, FDA looks afresh at adulteration of products, Br. Med. J. 338 (2009), b1851-1851.
[7] R.W. Lutter, HHS (Ed.), Economically Motivated Adulteration, Public Meeting, Request for Comment, 2009.
[8] G. Lavine, Am. Soc. Health Syst. Pharm. (2010).
[9] N.W. Broad, R.D. Jee, A.C. Moffat, M.J. Eaves, W.C. Mann, W. Dziki, Non-invasive determination of ethanol, propylene glycol and water in a multi-component pharmaceutical oral liquid by direct measurement through amber plastic bottles using Fourier transform near-infrared spectroscopy, Analyst 125 (2000) 2054–2058.
[10] C.M. Gryniewicz, J.A. Spencer, M. Hankins, J.F. Kauffman, Spectroscopic methods for rapid determination of diethylene glycol in glycerin, Am. Pharm. Rev. 10 (2007) 24–30.
[11] J.F. Kauffman, C.M. Gryniewicz-Ruzicka, S. Arzhantsev, J.D. Dunn, J.A. Spencer, S. Wolfgang, X. Li, L.N. Pelster, B.J. Westenberger, L.F. Buhse, Pharmaceutical surveillance with rapid spectroscopic screening technologies, Am. Pharm. Rev. 13 (2010), 58–62, 64.
[12] A.J. O'Neal, R.D. Jee, G. Lee, A. Charvill, A.C. Moffat, Use of portable near infrared spectrometer for authentication of tablets and the detection of counterfeit versions, J. Near Infrared Spectrosc. 16 (2008) 327–333.
[13] R. Kalyanaraman, G. Dobler, R. Rubick, Portable spectrometers for pharmaceutical counterfeit detection, Am. Pharm. Rev. 13 (2010) 38–45.
[14] U.S. Pharmacopoeia, USP 32 – NF 27, Propylene Glycol. 2009.
[15] G. Holloway, R. Maheswaran, A. Leeks, S. Bradby, S. Wahab, Screening method for ethylene glycol and diethylene glycol in glycerin-containing products, J. Pharm. Biomed. Anal. 51 (2010) 507–511.
[16] JMP 5.1.1, SAS Institute, Cary, NC, 2004.
[17] Pirouette 4.0 Rev. 1, Infometrix, Bothell, WA, 2007.
[18] R.W. Kennard, L.A. Stone, Technometrics 11 (1969) 137.
[19] L.A. Currie, Limits for qualitative detection and quantitative determination, Anal. Chem. 40 (1968) 586–593.