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Validation of a near-infrared transmission spectroscopic procedure
Part B: Application to alternate content uniformity and release assay methods for pharmaceutical solid dosage forms

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Abstract

NIR analytical methods can be validated to meet the requirement of demonstrating that it is suitable for the analysis of the materials for which it is being used. Applying previously described protocols for NIR methods to the analysis of two types of pharmaceutical products shows that for these products, NIR is suitable as an alternate analytical method for assay and for content uniformity. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Validation; Near-infrared transmission spectroscopy; Release assay; Content uniformity; Film-coated tablets; Capsules; Chemometrics

1. Introduction

The benefits to be gained from the use of NIR analysis [1] are not being ignored. Perusal of the bibliography in almost any recent issue of NIR News [2] shows worldwide activity and interest in the application of this analytical tool to pharmaceutical analysis. For the most part, however, since they are done in the absence of specific controlling regulations, these analyses are being validated on almost an ad-hoc basis.

When developing and validating analytical methods for pharmaceutical analysis, guidelines from the FDA and the International Conference on Harmonization (ICH) are available [3,4]. While these guidelines were originally developed with analytical techniques such as titrations and chromatography in mind, they specify those aspects of an analytical method that must be characterized in order to meet the fundamental requirement that every analytical technique must be shown to be suitable for its intended purpose

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([3], section 1) and that the characterization of the method must be supported by a laboratory study demonstrating its validity [5]. Documentation of the successful completion of such as study is therefore a basic requirement for determining whether any new analytical method is suitable for its intended purpose.

More recently, the pharmacopoeia has proposed guidelines for NIR analysis [6] which, although currently under revision as of this writing, contain much useful information relating to how to implement good NIR practice for pharmaceutical analysis. The recent paper by Moffat et al. [7] also contains more useful information and advice for implementing an NIR method in a regulatory environment.

The authors of this article represent two different working groups. These two groups each independently decided to develop and validate an NIR analytical method for a solid pharmaceutical dosage form, and in so doing, followed the guidelines of the ICH. In so doing they independently developed an almost identical validation protocol, which is described in the companion paper [1]. One group developed an analytical NIR method for tablets, the other for capsules; therefore the two methods will be identified, when distinguishing them is necessary, by the nature of the product being analyzed.

The purpose of this paper is to describe the application of the protocol described in the companion paper to the validation of the NIR analytical methods developed for the two pharmaceutical product types. For the tablet product, the goal of the development of the NIR method was to use it as an alternate assay method for product release. For the capsule product the goal was an alternate method to assess content uniformity.

2. Experimental

2.1. Instrumentation

A FOSS-NIRSystems® model 6500 NIR spectrometer equipped with an *Intact*™ tablet analyzer module was used to collect NIR transmission spectra. Transmittance measurements were deemed more appropriate than diffuse reflectance measurements because when transmittance measurements are performed, there is assurance that the radiation traverses, and therefore interacts with, the entire sample. When diffuse reflectance measurements are performed, the reflected radiation measured has interacted preferentially with layers of the sample at or near the surface of the sample.

The instrument manufacturer also designed a dosage-specific product mask for each product. The masks served multiple functions: they minimized leakage of light past the samples, held the sample in a fixed position with respect to the instrument and the optical beam, and ensured reproducible positioning of the sample, whenever a sample was removed and another one inserted.

For each sample, 32 scans were measured, the spectra averaged and ratioed against air as a reference reading.

2.2. Validation of instrument operation

The European Pharmacopoeia currently provides a procedure for calibrating the instrument hardware and verifying proper operation [8]. The United States Pharmacopoeial Forum has also published proposed procedures for calibrating NIR spectrometers [9]. Both of these sets of recommendations are effectively equivalent to the procedure recommended by the American Society for Testing and Materials (ASTM) [10]. While these procedures are couched in the context of reflectance measurements, the tests for wavelength accuracy, photometric precision and accuracy and noise are suitable for use with transmittance measurements as well. These tests are routine quality control tests of the instrument performance and as such were performed at the prescribed intervals to verify correct instrument performance but are not considered part of the current study.

2.3. Sample sets

For the tablet product, 138 tablets representing five lots of samples were available. Three of the lots were process lots containing tablets with as-

say values from 95 to 100% of the target value for the analyte. Two of the lots were development lots, manufactured in a pilot plant to extend the range of analyte to 80–120% of the target value for the product, this being the required range for test sets of samples needed to validate a method for assay according to the ICH guidelines [4]. Of the 138 tablets, 96 were selected at random for inclusion in the calibration set, the remaining 42 tablets were reserved for use as a test set for independently testing the calibration model developed.

In addition to the above samples, 60 tablets representing six lots of tablets were obtained and reserved as a second independent set of validation samples. These samples represented three process lots (different than the three process lots used to provide the calibration samples) and three scale-up lots.

For the capsules, 70 samples representing seven lots covering the range of 70–130% of the target analyte value were prepared by the technical services group following the normal production process. The range 70–130% is also specified by the ICH [4] as the required range for a content uniformity analytical method. An additional set of samples representing 21 actual production lots were obtained to provide validation samples. Ten capsules from each production lot were selected at random and analyzed by both the NIR and high-pressure liquid chromatography (HPLC) methods. A second set of validation samples were not available for the capsules.

2.4. Reference analyses

As described in the companion article [1], a reference method is needed to provide the values used both for the calibration calculations. Reference values are also needed to compare with the values measured using the NIR method, in order to determine the accuracy of the NIR method. For both sample types, the reference method used for these purposes was the appropriate validated HPLC method described by the submitted USP monograph for the corresponding dosage form.

3. Results

3.1. Calibration

After measuring the spectra of the samples and their reference values, all as described above, separate calibration models were calculated for the two product types. Table 1 summarizes the properties of the data sets and the nature of the calibration models achieved.

3.2. Validation

The protocols for validation are described in the companion article [1]. Here we present the results from those protocols, following that order of presentation. The companion article should be consulted for the details.

3.3. Accuracy

Accuracy is evaluated by the statistical quantities SEC (also called SEE) and SEP. Both of these statistics describe in quantitative terms the agreement between the NIR values and the values from the reference method from the same samples, in accordance with the ICH guidelines [4] and using the calculations recommended by the ASTM [10]. The difference between the SEC and SEP is that the samples used for the calculation of SEC are those used to obtain the calibration model, while the calculation of SEP uses data from samples not included in the calibration calculations. Table 2 presents these statistics for both sample types. It also presents the average difference between the NIR and HPLC methods (the bias) for the validation samples used to calculate the SEP.

3.4. Repeatability

Thirteen repeat readings for tablets at each of three levels (80, 100 and 120% of the target value for the analyte concentration) and 10 readings for capsules are listed in Table 3, along with summary statistics. The ICH guidelines [4]: require either a minimum of six readings at 100% of the target value or a minimum of three readings at each of three levels of analyte concentration. Therefore,

Table 1
Summary of properties of the data sets used and parameters for calibration models

	Tablets	Capsules
Number of calibration samples	96	70
Number of validation samples	42 (process + development samples); 60 (second set: process samples only)	210
Mean analyte value in calibration set (HPLC)	190.4	150.2
Mean analyte value in validation set (HPLC)	195.0	150.3
SD of analyte values in calibration set (HPLC)	21.4	30.0
SD of analyte values in validation set (HPLC)	1.9	2.3
Range of analyte values in calibration set (HPLC)	Maximum = 238.7; Minimum = 155.1	Maximum = 195.8; Minimum = 102.7
Range of analyte values in validation set (HPLC)	Maximum = 198.0; Minimum = 189.3	Maximum = 156.5; Minimum = 144.4
Data transform applied to spectra	Multiplicative scatter correction followed by first derivative ($dA/d\lambda$)	Second derivative ($d^2A/d\lambda^2$)
Derivative parameters	Segment = 10; gap = 0; spacing = 6	Segment = 10; gap = 0; spacing = (NA)
Calibration algorithm	MLR	PLS
Wavelengths/wavelength regions (nm)	1192 1292 1508 1644	730–756 812–856 1000–1116 1200–1340

the results presented in Table 3 more than satisfy both of these criteria, instead of only the one required.

3.5. Intermediate precision

In accordance with the description in the companion article [1], tablets at 80, 100 and 120% of the target value were obtained. Thirteen readings of each were measured by one analyst on the 1st day without moving the sample during the series of measurements ('original' orientation). After having been measured in place, each tablet was then removed from the holder 10 times and then replaced ('alternate' orientation), and a measurement was performed after each removal/replacement. The same procedure was followed by a different analyst on a different day, thus including the potential effects of analysts and days in the experimental design.

Table 4A presents the summary statistics for tablets. Each set of summary statistics is the result of readings similar to those shown for repeatability in Table 3. Since this test was performed with the tablets in both the original and the alternate orientation, the results of different analysts and different days are shown for both orientations. Indeed, the summary results from Table 3 constitute the values for the original orientation from the first analyst on the 1st day.

Table 2
Accuracy results for both types of samples used in this study

	Tablets	Capsules
SEC	2.4	1.89
SEP	2.22	2.51
Average difference of validation samples (bias)	−0.79	0.51
SEP for second validation set	1.93	na
Bias from second validation set	0.39	na

Table 3
Repeatability results for 10 repeat readings of each of the two sample types: (A) shows the individual data are for samples at 100% of target; (B) presents the summary results for tablets and capsules

Data for samples at 100% of target	Tablets	Capsules
Reading #1	196.86	151.36
Reading #2	195.9	151.53
Reading #3	195.99	151.46
Reading #4	195.73	151.18
Reading #5	195.5	151.21
Reading #6	195.48	151.21
Reading #7	195.53	151.07
Reading #8	195.43	151.92
Reading #9	195.42	151.92
Reading #10	195.37	151.96
Reading #11	195.54	
Reading #12	194.85	
Reading #13	195.39	
Mean	195.61	151.18
SD	0.48	0.21
RSD	0.24	0.14

Summary statistics for sample repeatability	Tablets in original orientation	Capsules in original orientation
80% *of target*		
Mean	159.99	
SD	0.19	
RSD	0.12	
100% *of target*		
Mean	195.61	151.18
SD	0.48	0.22
RSD	0.24	0.14
120% *of target*		
Mean	236.70	
SD	0.58	
RSD	0.25	

The tablet results comprise data from one tablet at each of the three levels used in the study: 80, 100 and 120% of the target value for analyte concentration.

For the capsule product, 10 capsules were selected at random from each of 21 production lots. Each capsule was measured one time. The summary results are presented in Table 4B.

3.6. Range

As discussed in the section describing the sample sets, for both sample types the sample set for calibration was comprised of production samples augmented with development samples. Each set was designed to cover the range appropriate to the intended application. Thus, for the calibration set for assay of tablets, the total range was 155.1–238.7 mg, corresponding to $\pm$20% of the target value of 200 mg. The validation set covered the range 157.7–238.4 mg. The second validation set consisted entirely of process samples, and covered the range 189.3–198.0 mg.

For the calibration set for content uniformity of capsules, the total range was 102.7–195.5 mg, corresponding to $\pm$30% of the target value of 150 mg. The validation set of process samples covered the range 144.4–156.5 mg.

3.7. Linearity

The ICH guidelines [4] require graphically presenting the results comparing the analytical method under test to the known values. For the NIR methods under consideration here, the known values are the values obtained from the validated HPLC analyses of the same samples. Fig. 1 presents the graphs for the tablets and capsules. Table 5 presents the various statistics prescribed by the ICH guidelines for evaluating linearity through the use of a linear regression relating the NIR to the HPLC values. The ICH guidelines require calculation of the correlation coefficient, Y-intercept, slope of the regression line and residual sum of squares. In addition to those, Table 5 includes the values of the Durbin–Watson statistic, calculated from the residuals of the calibration data and validation data for both product types.

3.8. Qualification

The two data sets corresponding to the two products were each subjected to Principal Component Analysis [11,12]. The first three of the resulting Principal Component scores are plotted along the three Cartesian axes of a mathematical space

defined by these Principal Components in Fig. 2. This figure shows, for the two types of samples, that the data indeed cluster together in multidimensional mathematical space. Each of the small clusters in each of Fig. 2A and B corresponds to one of the subsets of samples used to form the calibration data set. Each of the sample subsets, both the production samples and development samples, contained only a small range of constituent concentrations. Therefore, the small clusters appear separated because of the small range of constituent values in each of the sample subsets. Each data set taken as a whole occupies a well-defined region of space. Other samples can then be verified as being of the proper type if they fall within the region of this mathematical space occupied by the calibration samples. If they fall outside the region of space occupied by the calibration samples then they are not the type of samples for which the calibration model was developed.

3.9. Specificity

Fig. 3 presents the second derivative spectra ($d^2A/d\lambda^2$) for the two sample types. The second derivative data transform minimizes the physical effects (scatter, etc.) superimposed on the data. The seven bands of spectra correspond to the seven levels of constituent concentration in each of the calibration data sets. The wavelengths of these bands correspond to wavelengths of corre-

Table 4
Intermediate precision results: (A) results from tablets representing two analysts with measurements on 2 days; (B) intermediate precision results for 21 lots of capsules

	Tablets: first analyst, 1st day		Tablets: second analyst, 2nd day		Capsules: pooled results from 21 lots	
	Mean	SD	Mean	SD	Mean	SD
80% of target	159.99	0.19	160.48	0.14		
100% of target	195.61	0.48	196.48	0.12	149.16	1.42
120% of target	236.70	0.58	240.62	0.19		
Lot number	Means of 10 capsules		SD of 10 capsules			
1	150.04		1.55			
2	148.79		1.51			
3	147.49		0.94			
4	151.39		2.75			
5	150.64		1.72			
6	151.47		1.12			
7	152.45		2.26			
8	147.72		1.07			
9	149.22		1.60			
10	149.52		1.43			
11	146.25		0.95			
12	146.02		1.47			
13	147.79		1.06			
14	150.02		0.94			
15	146.69		1.52			
16	147.47		1.05			
17	149.53		0.99			
18	150.14		1.15			
19	152.33		1.36			
20	148.08		1.01			
21	149.42		0.84			

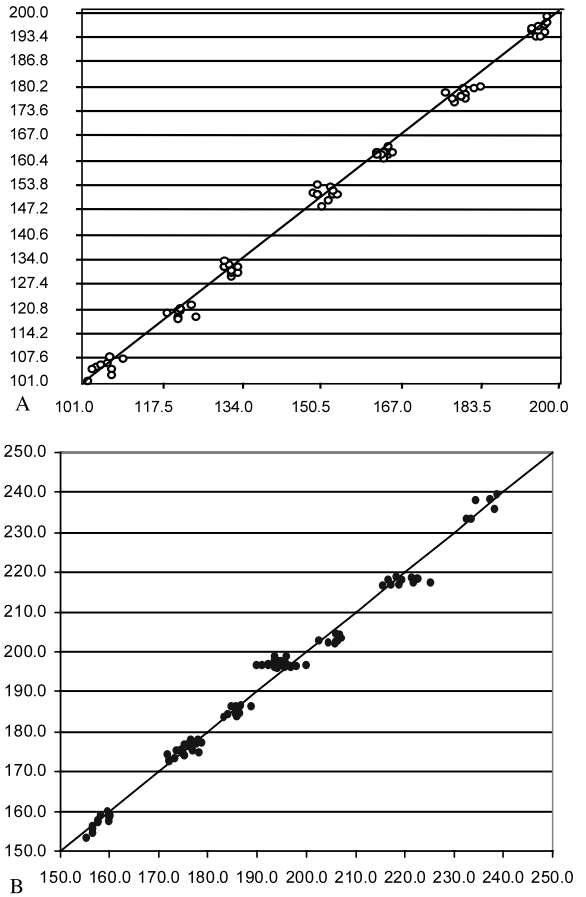

Fig. 1. Plot of NIR values versus HPLC values for testing linearity. (A) Plot for capsules. (B) Plot for tablets.

sponding second derivative bands in the pure analytes.

3.10. Robustness

Table 6 presents the results of measurements on both sample types when the samples were removed from the holder and replaced in a different orientation. Tablets were measured multiple times at three different concentrations of analyte. For each reading, the tablet was removed from the holder and replaced.

Capsules were measured 10 times at one concentration level, each time being removed and replaced in the holder in similar fashion to the tablets.

4. Discussion

4.1. Validation

All the parameters required for evaluation of an analytical method by the ICH have a corresponding implementation appropriate to evaluating an NIR method. Some of the NIR parameters are the same, or closely analogous to the methods used for HPLC, which are the methods implicitly envisaged by the ICH guidelines. In contrast, some of them differ considerably, usually in ways that are beneficial. An example is the calculation of accuracy. Standard statistics normally used are applied to this calculation, but the ease and simplicity of performing an NIR measurement allows the calculation to be performed on a far larger number of samples than is required by the ICH guidelines.

Another example is the use of the Durbin–Watson statistic for evaluating linearity. This statistic augments the subjective visual evaluation of a data plot with a mathematical calculation that can be used to perform objective statistical hypothesis tests.

4.2. Accuracy

The standard error for the tablet product is roughly 2.1 mg. At the target value level of 200 mg per tablet, this corresponds to a relative error of 1% at the 1 standard deviation (SD) point, or 2% at the 2 SD point. This compares favorably

Table 5
Statistics for evaluating linearity: ICH requirements, also the Durbin–Watson statistic

	Tablets	Capsules
Correlation coefficient	0.993	0.998
Y-intercept	−0.000031	0.60
Slope of calibration line	1.000	0.996
Residual sum of squares	550.011	242.05
Durbin–Watson statistic (calibration data)	1.40	1.84
Durbin–Watson statistic (validation data)	1.17	1.25

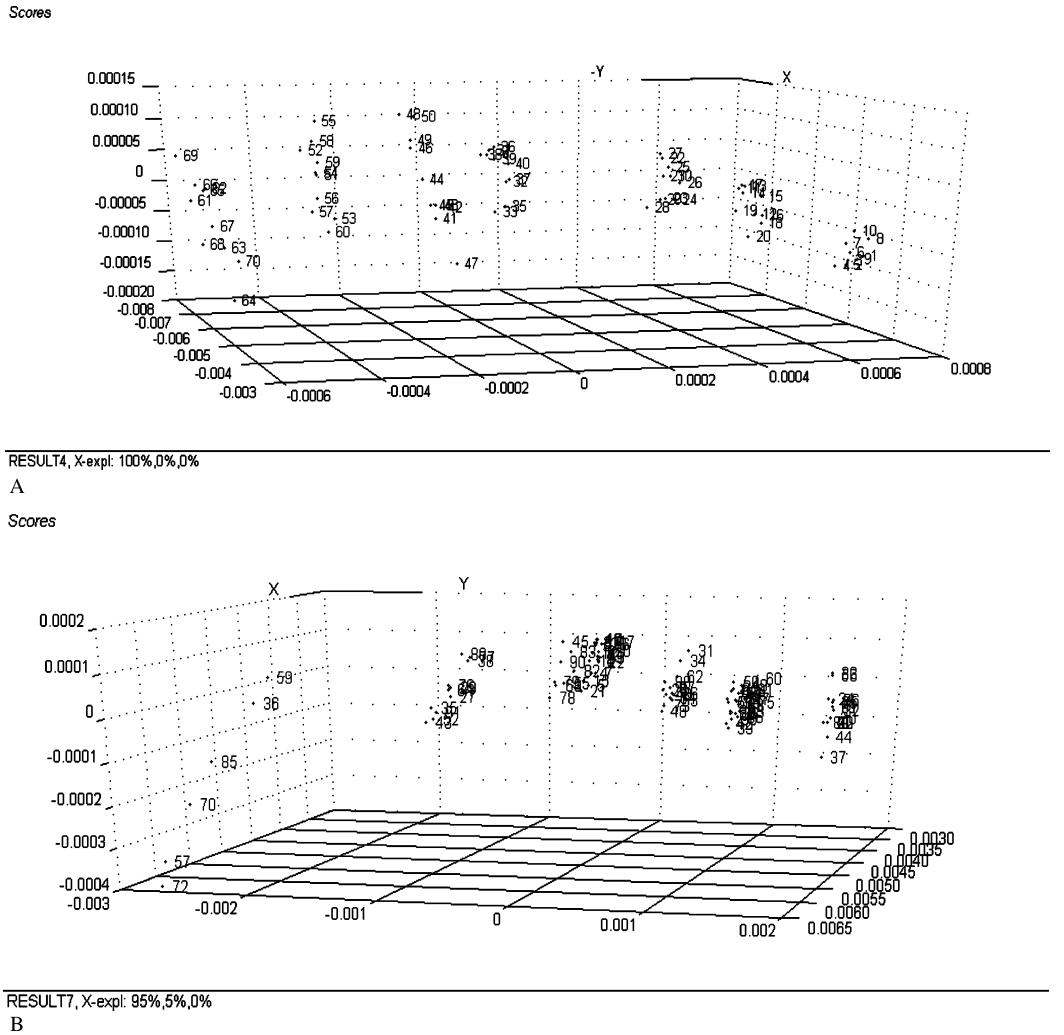

Fig. 2. Scores plots resulting from the Principal Component Analysis of their calibration samples for capsules (A) and tablets (B): for both parts of the figure, the axes represent: *X*-axis, first Principal Component; *Y*-axis, second Principal Component; *Z*-axis (vertical, not marked), third Principal Component.

with the allowed error for the reference HPLC method, which is also 2% for the maximum allowed error.

The reference method accuracy for the capsule product is 1.5%, which corresponds to 2.2 mg at the target value level of the analyte in the capsules. The NIR accuracy results for the capsules are again comparable to the accuracy results for the reference HPLC method.

4.3. Repeatability

The pooled SDs from the three levels of analyte concentration for tablets give an overall value of 0.44 for repeatability of tablets, and the repeatability for the capsule product is 0.14 mg. These values are far smaller, in both absolute and relative terms, than the corresponding values for the reference HPLC methods.

4.4. Intermediate precision

For the tablet product, the results in Table 4 are summarized in Table 7, which shows the average difference to be −0.47 mg. For comparison, the pooled SD of the readings from Table 4 is 0.335. A two-way ANOVA could be done from Table 7, but is hardly necessary. The row differences, since they are due to the known difference of the tablets prepared at different levels of concentration, are statistically significant, and this is expected. From the pooled SD,

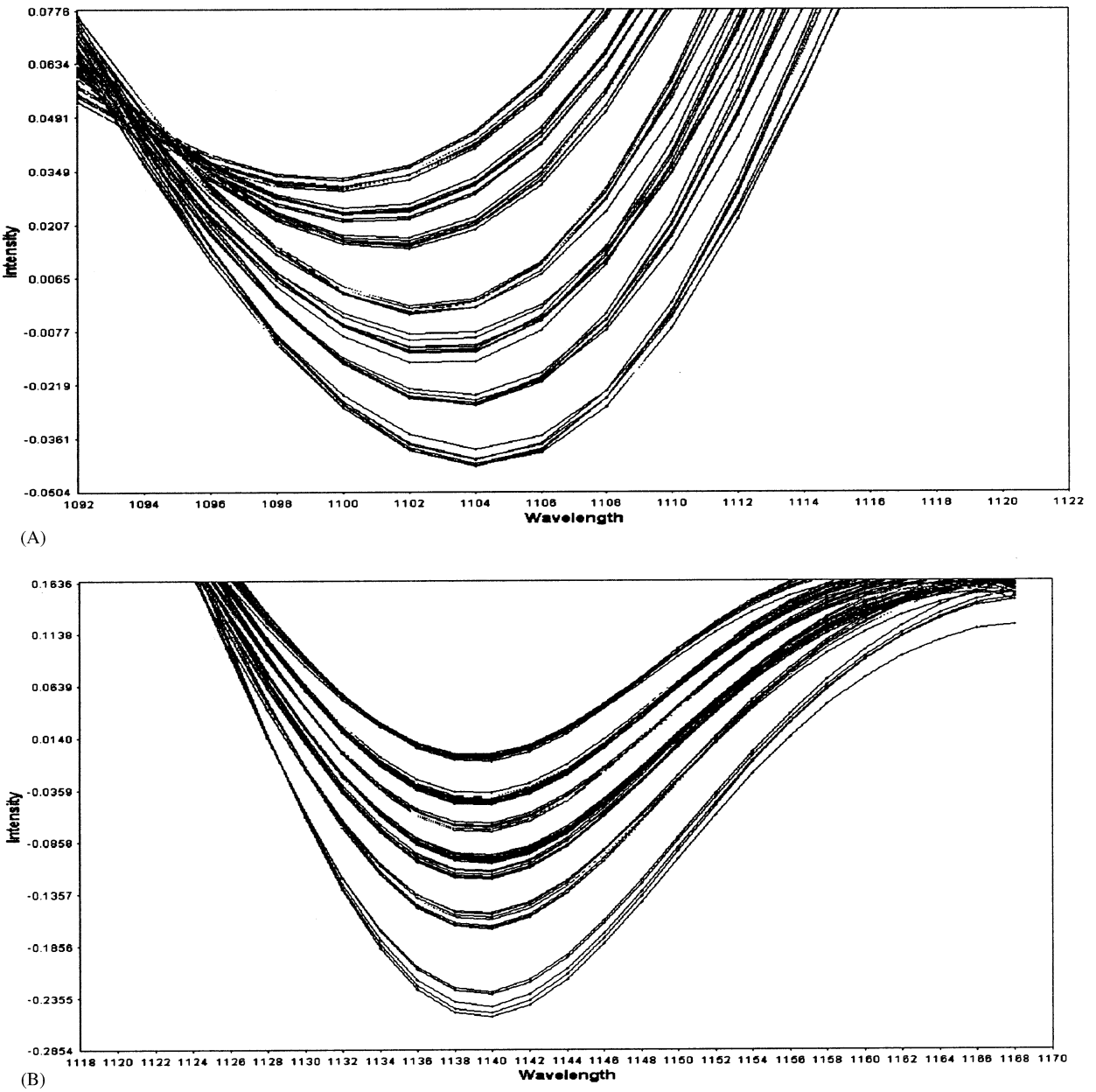

Fig. 3. Second derivative spectra ($d^2A/d\lambda^2$) of calibration samples for capsules (A) and tablets (B).

Table 6
Robustness results for measurements of samples in different orientations

	Original orientation		Alternate orientation		Capsules, original orientation		Capsules, alternate orientation	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Original analyst, 1st day, 80% of target	159.99	0.19	159.91	0.15	151.18	0.22	151.92	0.81
Original analyst, 1st day, 100% of target	195.61	0.48	195.12	0.43				
Original analyst, 1st day, 120% of target	236.70	0.58	238.54	0.24				
Second analyst, 2nd day, 80% of target	160.48	0.14	159.92	0.09				
Second analyst, 2nd day, 100% of target	196.48	0.12	196.37	0.32				
Second analyst, 2nd day, 120% of target	240.62	0.19	239.76	0.26				

Part of this table comprises Table 4 as well.

the column difference of 1.7 mg can be tested using a t-test:

$$t = \frac{\overline{Y_1} - \overline{Y_2}}{s_p \times \sqrt{(1/n_1) + (1/n_2)}}. \quad (1)$$

Substituting the numbers we calculate the value of $t = 20.4$ which is also statistically significant. Inspecting Table 7, we observe that the vast majority of the contribution to the difference between the columns is due to the almost 4 mg difference between the two analysts for the sample at 120% of target, indicating an interaction between concentration of analyte and analyst/day. Since the effects of analysts and days cannot be separated in these data, we cannot take the analysis of these results any further.

For capsules, the pooled SDs of readings for the 21 lots is 1.42 mg. Again, this is smaller than the accuracy of the reference method. We compare the intermediate precision values for the capsule product (which we find from Table 4A equals 1.42 with 189 degrees of freedom) with the repeatability value (which we find from Table 3B equals 0.22 with 9 degrees of freedom) using an F-test:

F (experimental) $= 1.42/0.22 = 6.45$,

$F(0.95, 189, 9) = 2.7$.

We note that the critical F value is correct for numerator degrees of freedom from 120 to ∞. We therefore conclude that there is a statistically significant increase for intermediate precision over the repeatability value.

4.5. Range

The companion paper [1] contains a discussion of the effects of the limitations of production samples on the range and the associated statistics. As expected from this discussion, the validation sample sets consisting of only production samples cover only a relatively small range, even though the calibration data sets include the full range of constituent concentrations specified by the ICH guidelines because the production samples were augmented with development samples. For the tablet product, one validation set was also augmented with development samples, and therefore this sample set also covers the range of concentrations specified in the ICH guidelines.

4.6. Linearity

The plots of the NIR versus HPLC results presented in Fig. 1 show no visible evidence of non-linearity.

According to Draper and Smith ([13], pp. 184), the value of the Durbin–Watson statistic for the calibration data from tablets (shown in Table 5) is inconclusive. The value for calibration data of capsules show no serial correlation.

The value for the validation data from tablets reveals serial correlation. Inspecting the plot of residuals versus NIR values for the tablet validation data (not shown) reveals that this serial correlation is a linear serial correlation, indicating a possible departure from unity slope. This can occur for validation data even though it cannot occur for calibration data. A t-test was performed against the null hypothesis:

Ho: $b = 1$,

where b is the slope of the regression of the NIR versus HPLC values for the validation data. The result, $t = 0.16$, indicates that the departure from unity slope was not statistically significant.

Therefore, there is no evidence from either the calibration data or validation data that either product type departs from a linear relationship between the NIR and HPLC values.

4.7. Qualification

From the clustering of the data shown in Fig. 2, we clearly see that samples not matching the spectral characteristics of the calibration samples will not fall into the region occupied by the calibration data. Samples not from the calibration population can be identified by this means as not belonging to the same population as the calibration data and conversely, samples filling within this region are identified as valid samples, since they belong to the correct population.

Principal Component Analysis was used to compress the spectral data into the abstract variables that comprise the three axes of the plots in Fig. 2. This compression ensures that spectral information at all wavelengths contributes to the qualification process, strengthening the results over what might be concluded from other means.

4.8. Specificity

The correspondence of the wavelengths of the bands shown in Fig. 3 to those of pure analyte, combined with the monotonic variation of the strength of those bands with analyte concentration, demonstrate that the NIR method is indeed sensitive to the concentration of analyte. The possibility still exists, however, that other materials may have a similar absorption band. The ICH guidelines allow for the use of confirmatory tests, as evidenced by the following quotes:

> "Lack of specificity of an individual analytical procedure may be compensated by other supporting analytical procedure(s)." [3]

> "It is not always possible to demonstrate that an analytical procedure is specific for a particular analyte (complete discrimination). In this case, a combination of two or more analytical procedures is recommended to achieve the necessary level of discrimination." [4]

Therefore, we recommend that confirmatory tests using an alternate method also be performed. By following the procedure outlined in the companion article for combining results from more than one analytical procedure (as recommended by the ICH guidelines), this can be accomplished without introducing any extra delay or requiring any extra effort.

Table 7
Summary of intermediate precision results from Table 4

	Mean reading: first analyst, 1st day	Mean reading: second analyst, 2nd day	Row mean
80% of target	159.99	160.48	160.23
100% of target	195.61	196.48	196.04
120% of target	236.70	240.62	238.66
Column mean	197.43	199.19	Grand mean = 198.56

Table 8
Summary of robustness results from Table 6: (A) summary results for tablets; (B) summary results for capsules

	Means, original orientation	Means, alternate orientation	Row means
First day, original analyst			
80% of target	159.99	159.91	
100% of target	195.61	195.12	
120% of target	236.70	238.54	
First day means	197.43	199.19	198.56
Second analyst, 2nd day			
80% of target	160.48	159.92	
100% of target	196.48	196.37	
120% of target	240.62	239.76	
Second day means	199.19	198.68	198.94

	Capsules, original orientation		Capsules, alternate orientation		Mean difference
	Mean	SD	Mean	SD	
Original analyst, 1st day, 80% of target	151.18	0.22	151.92	0.81	0.74

4.9. Robustness

From Table 6, we find that the pooled SD from all the tablet data is 0.305. This differs slightly from the value found for the pooled SD using the intermediate precision data because of the contribution from the alternate orientations of the tablets, which have slightly smaller SDs overall than from the original orientation.

From Table 8a, we find that the difference between orientations for tablets is 0.38 mg. Given the large number of degrees of freedom for this difference (60), we find that this difference is statistically significant. Draper and Smith, however, draw a clear distinction between 'statistically significant' and 'useful' ([13], p. 243–248), or what we might reasonably think of as 'practically significant.' The implications here is that the difference between orientations is of no practical consequence, given that it is smaller than other measurable sources of variation and of essentially the same magnitude as the pure random error.

From the results given in Table 6, the pooled SD of the capsule data is 0.717 mg. From Table 8B, the difference between orientations is 0.74 mg. Again, this difference is statistically significant, but not practically significant.

5. Conclusions

The protocols defined in the companion paper can be implemented in a practical way, to provide validation results that conform to the FDA and ICH guidelines. The auxiliary statistical results produced by common NIR data analysis software, and which are recommended by ASTM, implicitly provide the values needed for some of the required parameters, such as accuracy.

Other parameters, such as repeatability and intermediate precision are calculated in the same manner as for any other analytical method. The physical variables that are changed to provide the data corresponding to different conditions are determined by the intended application of the method, and could reasonably be chosen the same way if a non-NIR method were being validated.

The new statistic introduced, the Durbin–Watson statistic, showed that there was no non-linearity of tablet or capsule analysis, although it did reveal an expected linear serial correlation in validation results.

The results from this study show that for both product types studied, NIR analysis provides analytical results suited to the purpose of being an alternate assay method for the tablet product and also suited to the purpose of being an alternate product uniformity method for the capsule product.

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