Application Note 52624

Direct Transfer of a Quantitative Model between Antaris FT-NIR Instruments

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Key Words
Antaris, Method Transfer, Near-infrared, Quantitative Models

Introduction

Near-infrared (NIR) spectroscopy is used by the pharmaceutical industry for a wide variety of applications including drug substance identification, drug product identification, raw materials identification, tablet assay, uniformity of content, water content, solid state form and process analytical technologies (PATs). It has the advantages of being rapid, high throughput, non-destructive and suitable for use by non-specialist operators. It is suitable for good manufacturing practice (GMP) analysis and has regulatory acceptance. However, the disadvantage of NIR spectroscopy is that methods often require the use of complex multivariate models and large libraries of standard spectra, particularly for quantitative or product methods. There is also a requirement to carry out periodic maintenance to ensure the continued suitability of the models.

Historically it has not been possible to directly transfer quantitative models from one instrument to another without the use of correction standards or algorithms to account for instrument-to-instrument differences. Instead quantitative models are traditionally transferred by re-building of the calibration libraries on the new instrument, possibly requiring new standards to be prepared. However, advances in instrument technology now mean that direct transfers are feasible in certain cases. This application note discusses how AstraZeneca® was able to perform a direct transfer of a quantitative model for a minor polymorphic form in a drug product between two Thermo Scientific™ Antaris™ Method Development System (MDS) NIR analyzers without the need for a correction algorithm. In addition, this transfer was completed between two instruments of very different ages and with slightly different electronics – the donor instrument being an Antaris I system in excess of ten years of age and the receiving instrument being a new Antaris II system.

Thermo Scientific™
Antaris™ II FT-NIR Analyzer

Method Background

Quantification of a minor polymorphic form within a formulation is technically very challenging as analysis must be carried out in the solid state. In this example, it was necessary to develop and validate a method to rapidly and accurately detect and quantify a minor polymorphic form of the active pharmaceutical ingredient (API) within a capsule formulation. Even with a drug loading of only 10% w/w, and a significant spectral contribution from the excipients, NIR was shown to be highly sensitive to the polymorphic form of the API within this formulation. This is illustrated in Figure 1 in which the area of spectral discrimination between the desired polymorph A and the unwanted polymorph B is highlighted.

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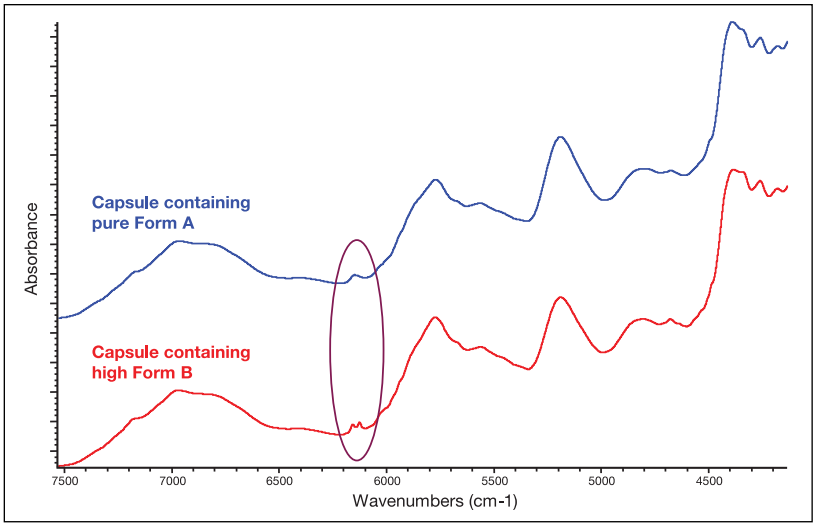

Figure 1: NIR spectra of capsules containing the desired polymorphic Form A and the unwanted polymorph B

Based on this strong spectral discrimination for the two forms, it was decided to develop a reflectance NIR method for quantification of Form B. An Antaris I MDS NIR analyzer with the integrating sphere accessory was employed for this purpose. Fifteen separate batches of capsules were manufactured, each spiked with a different level of polymorph B, for the development and validation of this model. These fifteen batches were divided into three sets, a calibration set, a model test set and a fully independent validation set. The validation set was prepared with different lots of active pharmaceutical ingredient, excipients and capsule shells to the other two sample sets. The large size and non-circular shape of this capsule meant that it was not possible to sample an entire capsule in a single reflectance measurement. Each capsule was therefore sampled by acquiring three individual reflectance measurements, each in a different orientation. These individual measurements were then averaged to provide a single mean spectrum for each capsule as illustrated in Figure 2 and Figure 3.

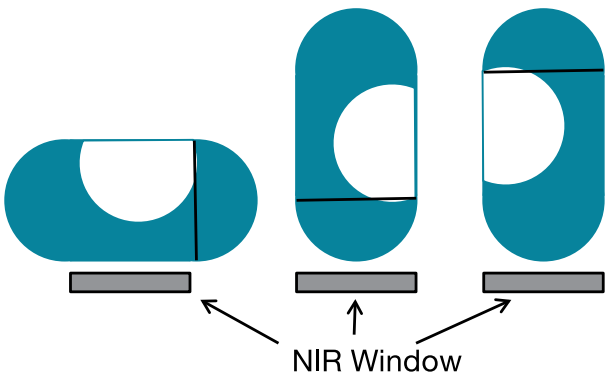

Figure 2: Schematic of NIR sampling regime

Figure 3: Capsule sampling using the integrating sphere accessory

A partial least squares (PLS) calibration model was built using the Thermo Scientific™ TQ Analyst™ software package, to predict the Form B content in new samples. Spectral pre-processing, including taking a second derivative, standard normal variate (SNV) and mean centering, was applied to remove background and physical effects and to normalize the data. The model range was limited to the area showing the greatest differentiation between the two forms, 5800 cm^{-1} to 6252 cm^{-1}. Overlaid processed spectra of the calibration standards clearly show the spectral dependence on Form B concentration as illustrated in Figure 4. The calibration data gave a standard error of calibration (SEC) of 1.11%. This model was validated using the independently prepared set of validation standards, also spiked with known concentrations of Form B. These independent validation samples gave a standard error of prediction (SEP) of 1.47%.

Typically, NIR models for drug product would employ large spectral libraries designed to contain all expected product variability. As no primary reference method exists to accurately quantify the level of Form B within a given capsule, this was not achievable and the method was therefore calibrated and validated using artificially prepared spiked capsules that cannot contain the desired natural product variation.

In order to ensure the validity and accuracy of this method for independent samples, it was necessary to apply strict outlier limits. An outlier screening was developed utilizing a classification model generated within the TQ Analyst software. The discriminant analysis classification technique was used to determine whether an unknown spectrum matched the defined calibration spectra by computing the unknown's distance from the center of each class of standards in Mahalanobis distance units. The limits for the Mahalanobis distance value check were defined based on the distance values obtained for the calibration and validation samples and set to ensure that only samples that gave similar spectra to the calibration standards were quantified by the model. Using this criterion, a Mahalanobis distance value of <1.8 was required to give a pass result.

Transfer of the Method between Instruments

The original method for detection and quantification of Form B in capsules was built and validated on a single development instrument, an Antaris I MDS NIR analyzer. As the project progressed through development it became necessary to transfer this method to a new Antaris II MDS NIR analyzer. It was decided to investigate whether this could be achieved by direct model transfer. Spectra of calibration standards were transferred to the new instrument together with the TQ Analyst methods for both outlier detection and quantification.

Validation of the transferred model was performed using the independently prepared validation standards, spiked with known levels of Form B, which were used to validate the original model. Six capsules from each validation batch were analyzed on both the donor and the receiving instrument. The capsules were numbered and separated such that each capsule could be directly compared, for example, the result labeled 12% Form B replicate 1 applied to the same capsule on both donor and receiving instrument. A comparison of the validation data from the two instruments is presented in Table 1.

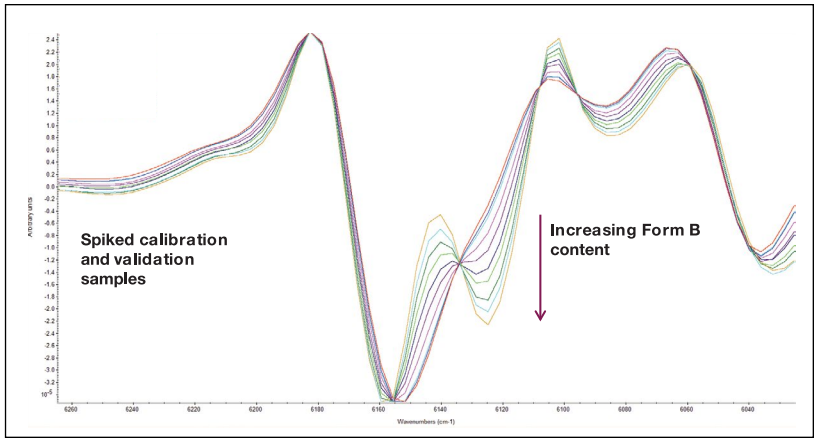

Figure 4: NIR spectra (second derivative) of spiked calibration and validation capsules demonstrating the dependence on polymorphic form

Independent Validation Standards	%B Donor Instrument	%B Receiving Instrument	Error	Square Error
4% Form B replicate 1	2.63	3.79	1.15	1.33
4% Form B replicate 2	3.43	3.55	0.12	0.01
4% Form B replicate 3	3.79	3.18	-0.62	0.38
4% Form B replicate 4	3.52	3.20	-0.31	0.10
4% Form B replicate 5	3.31	3.90	0.59	0.35
4% Form B replicate 6	3.60	3.71	0.11	0.01
12% Form B replicate 1	11.34	11.79	0.45	0.20
12% Form B replicate 2	11.96	11.90	-0.06	0.00
12% Form B replicate 3	11.59	11.64	0.05	0.00
12% Form B replicate 4	11.94	11.89	-0.05	0.00
12% Form B replicate 5	11.98	12.02	0.04	0.00
12% Form B replicate 6	11.41	11.55	0.15	0.02
21% Form B replicate 1	20.56	22.11	1.55	2.41
21% Form B replicate 2	20.26	21.46	1.20	1.44
21% Form B replicate 3	20.44	21.97	1.54	2.36
21% Form B replicate 4	22.70	21.65	-1.05	1.11
21% Form B replicate 5	23.34	22.60	-0.74	0.55
21% Form B replicate 6	22.08	22.43	0.36	0.13
29% Form B replicate 1	28.76	28.64	-0.12	0.01
29% Form B replicate 2	29.25	29.79	0.54	0.29
29% Form B replicate 3	30.28	30.26	-0.02	0.00
29% Form B replicate 4	30.59	32.07	1.47	2.17
29% Form B replicate 5	31.80	33.00	1.21	1.46
29% Form B replicate 6	33.27	33.13	-0.14	0.02
37% Form B replicate 1	40.34	39.37	-0.97	0.94
37% Form B replicate 2	38.40	37.23	-1.17	1.36
37% Form B replicate 3	41.09	42.93	1.84	3.38
37% Form B replicate 4	39.23	39.29	0.06	0.00
37% Form B replicate 5	39.06	37.40	-1.66	2.74
37% Form B replicate 6	40.88	42.44	1.56	2.43
			Mean	**0.84**
			RMSEP	**0.92**

Table 1: Comparison of predicted Form B content for each of the validation samples on both the donor and receiving instruments

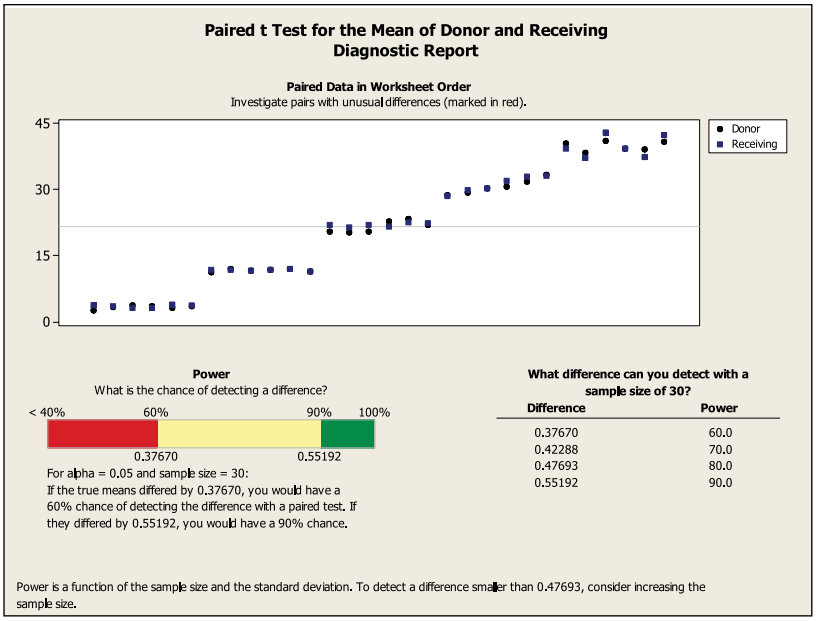

Figure 5: Paired t test for mean of donor and receiving instruments

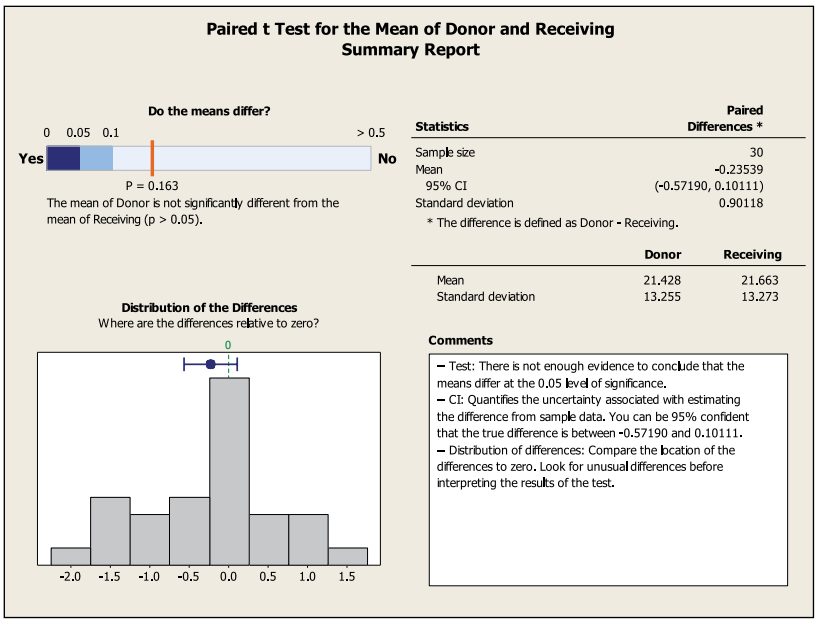

Figure 6: Paired t test for mean of donor and receiving instruments summary

The Root-Mean-Square Error of Prediction (RMSEP) between the two data sets was 0.92%, this was significantly less than the SEP of the method 1.47%. The difference between the two values obtained for each capsule fell within expected prediction errors and there was no trend between the two data sets. These data demonstrated that there was no significant difference between the results obtained using the donor instrument and the results obtained using the receiving instrument.

A statistical evaluation of instrument bias was carried out using a paired t test for the mean of the donor and receiving instruments. A summary of the t test results is presented in Figure 5 and Figure 6. The results demonstrate that the mean of the donor instrument is not significantly different to the mean of the receiving instrument at the 95% confidence level.

Including the level of Form B as a factor in the model accounted for both the differences between instruments and the levels in the standards, a summary of this statistical evaluation is presented in Figure 7.

Using this approach the confidence interval for the difference in instrument means was (-0.29 to +0.76) % Form B. This met the internal AstraZeneca acceptance criteria that the difference in instrument means was not more than 1% and that the confidence interval for the difference in instrument means included the ideal value of zero.

The classification model for outlier detection was used to demonstrate that the spectra of all validation samples, acquired using the receiving instrument, were a good fit for the calibration model. All samples generated a Mahalanobis distance value of <1.8 and were therefore shown to fall within the model space. In order to provide a visual assessment of instrument bias, a PCA model was generated for the calibration samples using the standard model pre-processing and spectral range. The spectra from both the donor and receiving instruments were projected onto the Hotellings T^2 95% confidence limits for principal components 1 and 2. In this model, principal component 1 was dominated by the level of Form B and principal component 2 was dominated by sampling variability. The scores plot is presented in Figure 8. The plot demonstrated that within each Form B level there was a spread of physical or sampling variation in PC2, however, the data points for the two instruments were completely overlapped and there was no bias or offset between the two data sets.

Comparison of instruments at different Form B levels

General Linear Model: Amount versus Level, Method

Factor	Type	Levels	Values
Level	Fixed	5	4%, 12%, 21%, 29%, 37%
Instrument	Fixed	2	Donor, Receiving

Analysis of Variance for Amount, using Adjusted SS for Tests

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Level	4	10125.1	10125.1	2531.3	1735.59	0.000
Instr	1	0.8	0.8	0.8	0.57	0.454
Error	54	78.8	78.8	1.5		
Total	59	10204.7				

S = 1.20767 R-Sq = 99.23% R-Sq(adj) = 99.16%#

The results indicate a good model and a non-significant difference between instruments (*p* - value >> 0.10).

Grouping Information Using Tukey Method and 90.0% Confidence

Method	N	Mean	Grouping
Receiving	30	21.66	A
Donor	30	21.43	A

Means that do not share a letter are significantly different.

Tukey 90.0% Simultaneous Confidence Intervals

Response Variable Amount

All Pairwise Comparisons among Levels of Method

Method = Donor subtracted from:

Method	Lower	Centre	Upper
Receiving	-0.2865	0.2354	0.7572

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+---------+---------+---------+------
(-----------------*----------------)
+---------+---------+---------+------
-0.30      0.00      0.30      0.60
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Figure 7: Comparison of instruments at different Form B levels

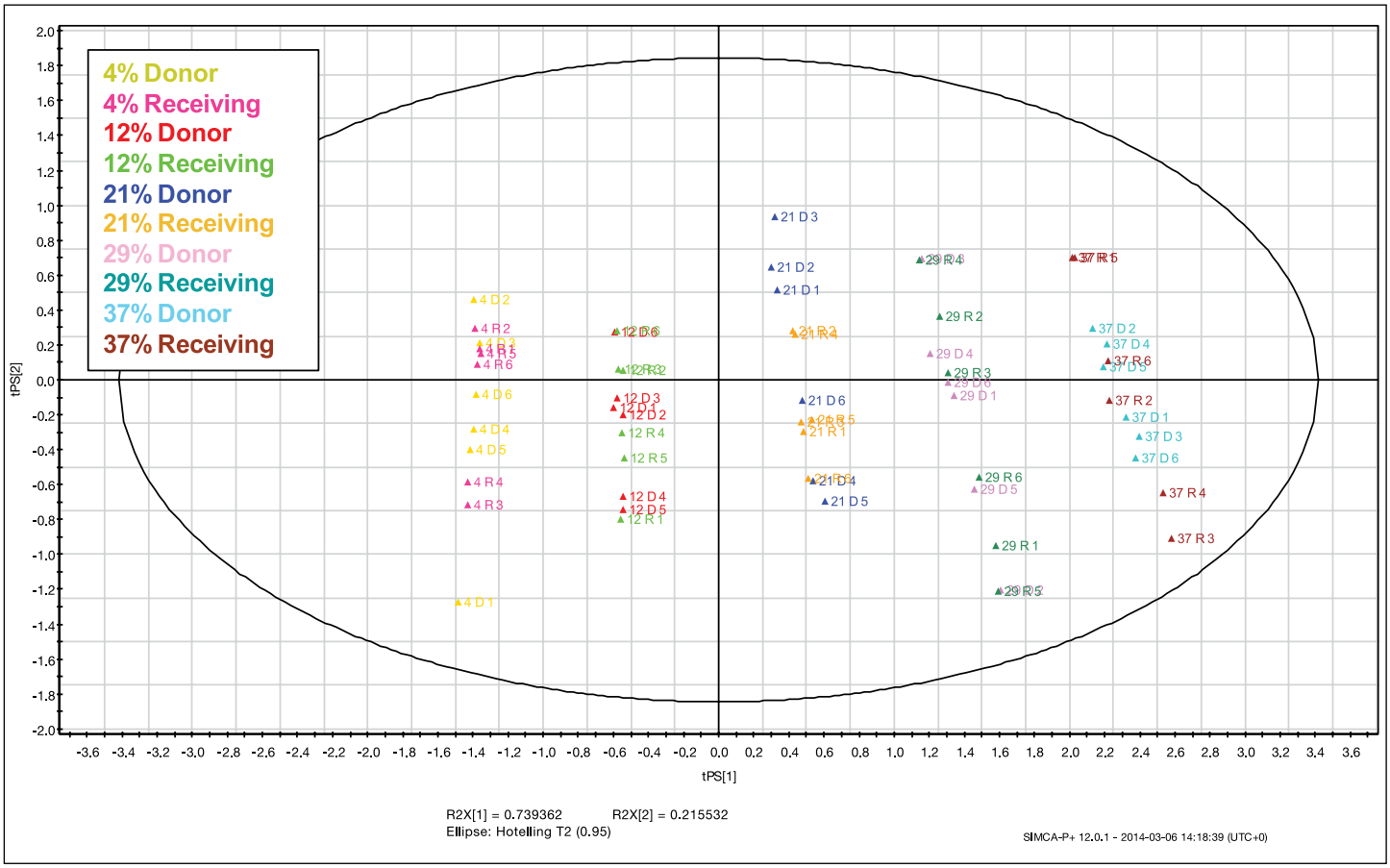

Figure 8: Scores plot showing the relative positions of data acquired using the donor and receiving instruments within the model space

Conclusions

Advances in instrument technology now mean that, in certain circumstances, direct transfer of complex, multivariate, quantitative NIR models between instruments is achievable.

In the case study discussed in this report, a method to quantify a minor polymorphic form of an active pharmaceutical ingredient, within a complex capsule formulation, was successfully transferred between an Antaris I MDS NIR analyzer and an Antaris II MDS NIR analyzer. Statistical tests were used to show that the same models on both the donor and receiving instruments gave equivalent results without the need for corrective algorithms or correction standards. The ability to perform a direct transfer has greatly simplified the transfer process for this GMP method and also saved considerable time and expense in the preparation of new calibration and validation standards.

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