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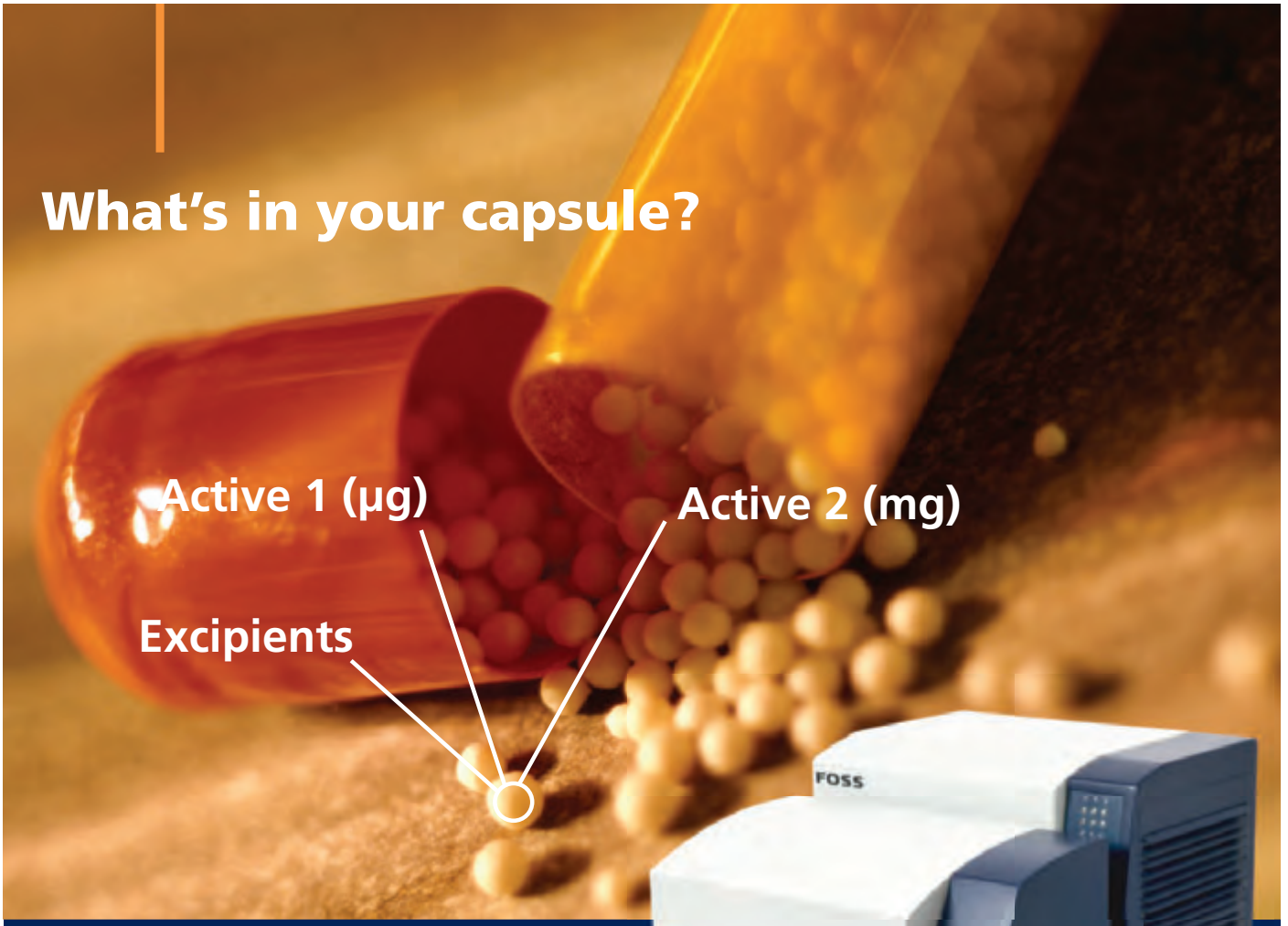

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NIRS IN AN INDUSTRIAL ENVIRONMENT

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Near infrared spectroscopy (NIRS) is a technique with wide and varied applications in the pharmaceutical industry. It is useful for identification, qualification and quantitative analysis of pharmaceutical raw materials, intermediate substances and finished products as well as for process control and diagnostics. It is regarded as one of the most important process analytical techniques enabling the pharmaceutical industry to move forward in adopting a 'continuous quality assurance' and it is an invaluable tool for the pursuit of the 'zero defect' target set by the industry.

The successful application of this technology depends on establishing an understanding of NIRS's abilities, its shortcomings and most importantly its sensitivity to external influence factors. To this effect, this short review will focus on the issues that affect the robustness of NIR and how that robustness is affected by the physical properties of the signal, the environmental factors and the way the signal is translated into a model. These three aspects should always be considered before an industrial method is developed. In the authors opinion, both NIR and its translation i.e. the chemometric analysis should be considered as one almost inseparable unit as each one individually can greatly influence the outcome of an analysis.

Near infrared light

Near infrared light is defined as the wavelength region from 730 to 2500 nanometres, in-between visible and the infrared light. The NIR region is characterised by overtone and combination bands of fundamental vibrations occurring in the mid infrared. These arise due to the anharmonic nature of molecular vibrations. All organic bonds have absorption bands in the NIR region, whereas minerals may only be detected in organic complexes and chelates or indirectly by their effect on hydrogen bonds[1]. Because of the light mass of the hydrogen atom, overtones and combination bands of hydrogen bearing functional groups (C-H, O-H and N-H) dominate the NIR spectra. These show broad and overlapping bands less suited for structural studies and microanalysis, having a low sensitivity for most constituents analysed. On the other hand, the NIR region offers some advantages for quantitative analysis of major elements. NIR instruments have a very high signal to noise ratio, which is typically 1000:1[1]. The spectral information is repeated through the successive overtones and combination tones, the intensity of the bands involved becoming each time weaker by an order of magnitude towards shorter wavelengths[2]. These lowered intensities in the NIR region mean that solid samples do not need to be diluted for diffuse reflectance measurements and non-linearity effects due to strong absorptions are less likely to occur. When monochromatic radiation interacts with a sample, it may be absorbed, transmitted or reflected. According to the Beer-Lambert law, the concentration of an absorber (c) is directly proportional to the sample absorbance (A): $c = A/\varepsilon L$, where ε is the molar absorptivity and L is the path length. This relationship is fundamental to quantitative absorption spectroscopy and it may be applied not only to transmission measurements, but also

to the diffuse reflectance of light scattering materials. The main difference is that the path length of radiation, which is maintained constant in absorption spectroscopy, is affected by light scattering. Scattering occurs when radiation transmitted through the surface and emerging after partial absorption is diffused by random reflections, refractions and diffractions at further interfaces inside the sample or undergoes further transmittance and absorption at other interfaces[3]. Scattering depends on the physical properties of the sample, the most important of which are particle size, moisture content and temperature. The relationship between concentration and absorbed energy is further disturbed by overlapping of spectral bands from different constituents present in a sample. As there is no mathematical law to describe the interaction of radiation with a scattering medium containing a heterogeneous distribution of absorbing species, NIR is an empirical or secondary technique requiring calibration using samples of known composition determined using standard chemical methods (primary techniques).

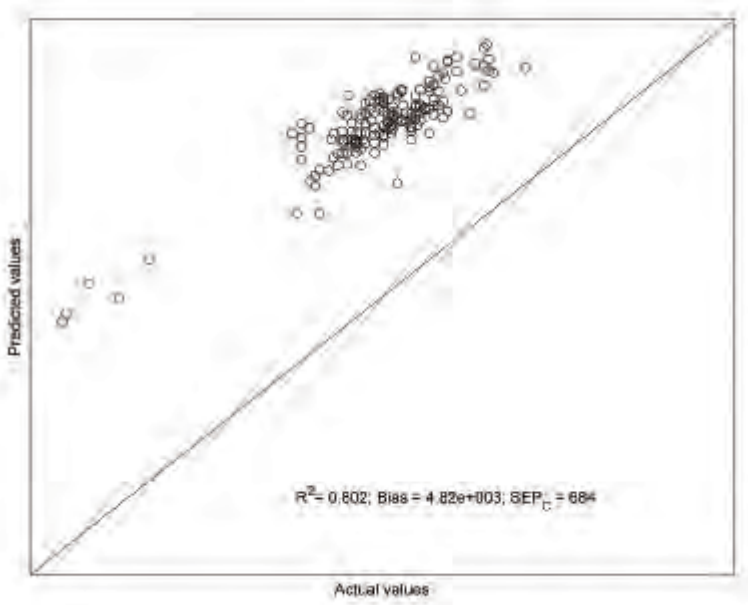

FIGURE 1 Effect of a constant influence on the translation of spectra

External influence factors and chemometrics

From an industrial perspective, the majority of the models generated are sensitive to external influence factors which are abundant in an industrial environment. These factors affect the robustness of these models and consequently can have a detrimental effect on the result of the analysis. Normally the conditions under which the method is developed are fairly controlled as the initial analysis occurs in a laboratory environment. Unfortunately, these external influences become more evident when the method is transferred to a manufacturing environment and most of the time, visual identification of the difference between spectra measured in the lab and spectra measured under industrial conditions is not possible. It is important to note here that these differences between laboratory and manufacturing conditions may not be evident immediately but become apparent further down the lifecycle of the method and therefore affect the robustness of the method at a later stage. Some of the most common factors that create these differences are product temperature, spectrometer temperature, stray light and wavelength shifts. Furthermore, these differences are not limited to instrumental variation but in addition, there are a multitude of factors that are sample related. These involve sample variations (recipe changes, differences in particle size, changes in the presentation of the sample to the NIR probe) and process variations (different manufacturing units, variability in unit conditions, process changes due to trouble-shooting other issues). All these changes can have an effect on the spectra and as a consequence the respective model used. These effects have a different manner of presenting themselves; for example when using a linear model such as PLS, the predicted values will have a bias if the influence of the external factor is constant during the measurement process. In other words if the alteration to the spectra is similar and regular for each measurement, then when the spectra are processed by the model, a similar and regular value will be added to the predictions. An example of this situation is presented in **Figure 1**.

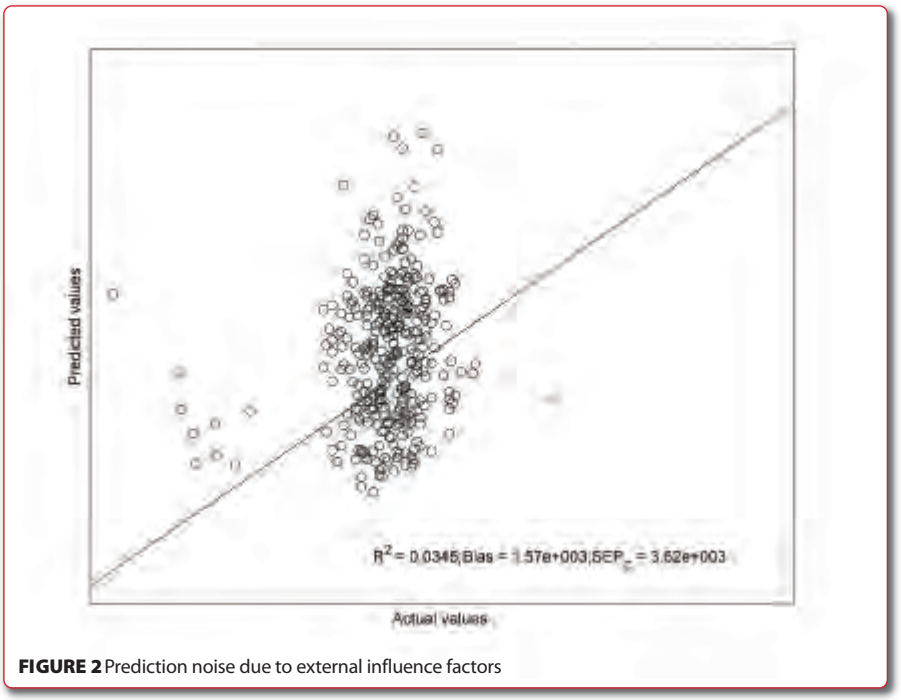

FIGURE 2 Prediction noise due to external influence factors

If the influence factor is directly related to the quality being predicted, then the regression line representing the best fit will have a slope that is different from the 'perfect regression'. On the other hand, if the external influence is not

stable during measurement (especially for process variations etc) then the model will translate this variation to 'prediction noise' i.e. higher variance and prediction errors and an irregular scattering of the prediction results around the regression line (**Figure 2** opposite).

In the authors opinion, the best way to approach this complication is by optically (NIR) understanding the matrix (sample and environment), identifying the variations of the matrix that are independent of the analyte of interest and by establishing how the respective spectra are affected by these external influences. Fundamental to achieving this understanding is the use of an extensive experimental design (e.g. Taguchi, response surface, nested, hierarchical or D-optimal design, factorial to name a few). Samples have to be analysed in order to identify the external factors that affect their spectral characteristics. By studying these influence factors through an experimental design it is possible to identify and measure their influence on the spectra; if the influence can be measured then it can also be removed. At this point, good use of chemometrics can come in handy as there are several methods available that deal with this exact problem. Obviously, one of the solutions to this problem is to re-measure every sample under the new conditions and construct a new model for the newly acquired spectra. This is not a practical solution to the problem since there is a substantial cost and time associated with building a robust calibration and it is not an efficient way of fixing a problem. An alternative is to apply chemometric techniques to correct for instrumental, sample to sample and environmental differences, thereby making the model resistant and avoiding full recalibration.

Several correction strategies have been implemented to cope with the influence of these external parameters. Optical methods aim at modifying the spectra collected under different conditions to match those collected before the influence was present. Direct and piecewise direct standardisation and the Shenk and Westerhaus patented algorithm are some examples of optical methods[4]. These techniques use a set of transfer samples to perform the spectral matching.

A second approach is to adapt predictions using a slope and an offset or a simple bias correction. These parameters are obtained by a linear regression between predictions made on the secondary unit and the reference values on a selected set of transfer samples by the same model. This is a widely used technique. Most, if not all, instrument firmware or software support these corrections. One of the problems with this approach though is that the corrected models are not robust to new changes or to a situation where the influence is not present anymore and the system reverts back to the original state.

Another possibility to achieving model robustness is to use orthogonal methods[4,5]. They are based on the theory that the column space of the spectral X matrix (all possible linear combinations of column vectors) is 'the sum of two subspaces, among which only one contains information useful for the model'. These methods are based on estimating the space of the external parameters and by removing it from the X matrix. External parameter orthogonalisation (EPO), independent interference reduction (IIR), transfer by orthogonal projection (TOP), dynamic orthogonal projection (DOP) and error removal by orthogonal subtraction (EROS) are methods that estimate interferences by using a set of samples measured in the different

conditions of interest to create a difference matrix representing external factors. The difference matrix between interfering and non-interfering conditions is decomposed in principal components and the first few loadings are removed from X. A calibration model is then developed with the new pre-processed X matrix.

The above methods are just a few of the methods available to deal with the issue of making spectra resistant to changes and they were selected because they represent different approaches to correcting the same problem but this is not an exhaustive list of solutions.

The importance of dealing with industrial effects on spectra has another impact on the 'process' of pharmaceutical manufacturing. When external influences are studied, measured and removed, improving method robustness is not the only benefit. If NIR spectra are well understood then they can also be used for process diagnostics, fault detection and process control activities. The majority of the current NIR applications are based on the use of a small wavelength range which is specific to the analyte of interest. Using the whole spectrum, on the other hand allows for a more detailed analysis on the changes to the signal that could be due to faults or incorrect process parameters for example. This is of great interest to the pharmaceutical industry as online detection and control of process deviations is paramount to achieving continuous verification. From this point of view, NIR can be a highly useful tool to a successful continuous verification which is a data driven form of manufacturing. Acquiring NIR signals and using them as signature profiles can not only be utilised quantitatively but also as a way of detecting deviations from normal operational conditions – especially when the data are combined with information from other sensors or chemical characteristics of the materials.

At the moment though this form of NIR implementation is at an embryonic stage; there are numerous applications which are reviewed in detail in the numerous publications to date which support the current belief that NIR is a success story for the pharmaceutical world but most of these applications are very specific and they serve single manufacturing units or have one single purpose (end point detections for drying, blending, tablet core assays etc). A holistic approach that will enable better process understanding and control still has a few hurdles (e.g. availability and structure of online data for real time analysis) to overcome but has started gaining momentum. In order though to achieve successful implementation of all the above, it is crucial to have a deep understanding of the spectral data involved and this entails the 'singular' approach i.e. the combination of the right use of NIR together with the understanding of the external factor influences and the right use of chemometrics.

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PHARMACEUTICAL ANALYSIS AND NIR

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Near Infrared (NIR) Spectroscopy has been used sporadically within the pharmaceutical industry for many years although it is one of the most common approaches for raw material identification. In the last five years or so, there has been a significant increase in the recognition of NIR as a viable tool for in-line and at-line process monitoring as well as its potential use to control manufacturing processes.

The early adoption of new technological advances (including NIR tools) by the pharmaceutical industry was driven by the regulators with the FDA publication of the industry guidance's; 'PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance'[1] and 'Process Validation: General Principles and Practices'[2], the EMA's draft guideline in 2009 on the use of NIR for industry[3] and their revision of 'Guideline on Real Time Release Testing' in 2010[4]. Correspondingly, there has been significant interest by pharmaceutical companies to identify tools that can aid in improving product quality through increased process understanding and enabling in-process control rather than solely relying on end-product testing. These controls are designed in a holistic manner by embodying the ICH Q8, 9 and 10 concepts[5-7], which incorporate risk analysis of product composition, and manufacturing processes with respect to criticality to the safety and efficacy of the product as well as quality by design (QbD) into the development program.

The implementation of a spectroscopic analytical method, such as NIR, requires an assessment of the capabilities of the tool to measure the required input or output material attribute(s) from a manufacturing process with the necessary level of accuracy, precision and robustness. Until recently, these attributes were not being measured in real-time and as a consequence many practitioners were unsure how to leverage the results to improve their process and this is still an ongoing area of interest, within both industry and academia. Once the criticalities of the attributes have been assessed and a measurement tool selected then the integration of the measurement into a regulatory submission should be straight-forward and many large Pharma companies have received regulatory acceptance of on-line and at-line NIR approaches. **Figure 1** on page 8 presents some common unit operations and examples of their respective critical quality attributes (CQAs).

In this article we have attempted to identify a handful of papers that show the recent advances in NIR spectroscopic measurements as they apply to pharmaceutical testing; both on-line and at-line. For a more in-depth review of the topic, the reader is directed to several excellent reviews on the use of NIR in the pharmaceutical industry from De Beer[8], Blanco Romia and Alcala Bernardez[9], Smith-Goettler[10], Rasanen and Sandler[11], Maurer and Leuenberger[12] and Reich[13].

Blending

Since the early introduction of on-line blend monitoring by NIR[14] there has been continued discussion regarding the merits of qualitative and quantitative approaches to evaluate blend uniformity[15,16]. Comparison of a 'reference' value using traditional thief sampling and traditional testing using HPLC to an on-line NIR value has been clearly demonstrated to be a significant challenge due to 1) appropriate sampling of the blend by the NIR tool[17], 2) sample size of NIR measurement 3) analytical sensitivity of the NIR method to changes in API concentration and 4) sample segregation and variability introduced by the traditional thief approach. The sample size with on-line NIR measurements is typically 1 to 100 milligrams depending upon the optics diameter and powder properties[18]. One should recognise that the powder is essentially static during typical measurement of blend sample (in a typical intermediate bulk

container IBC diffusion blender) and this has led to inaccurate sample mass calculations, which in turn results in inappropriately chosen moving averages. Moving block standard deviation (MBSD) appears to be the most common approach in the literature for evaluating uniformity, however this is probably because it is the easiest to apply. Without establishing the analytical sensitivity, e.g. %w/w analyte per absorbance unit change, it is very challenging to create acceptance limits for qualitative methods. The sensitivity question is clearly evident in the analysis of nicaldipine hydrochloride[19] where, as a result of a weak spectral response for nicaldipine, the blending profile shows very little change throughout the process. Consequently, the role of sensitivity should not be discounted and it should be linked in some manner to the quality attribute of interest. Puchert *et al.*[20] nicely discuss this challenge and introduced a novel approach; 'Principal Component Scores Distance Analysis' (PC-SDA). Puchert created a metric derived from the Euclidean distance of the score values from a target 'good blend' dataset. The blend monitoring was performed using a Hoteling's T^2 control chart. A second element from this paper was the adopted use of NIR chemical imaging as a reference method by which to measure powder uniformity using Symmetry Parameter Image Analysis (SPIA)[21]. Image analysis not only allows one to measure the active uniformity but potentially several other excipients within the same image, allowing a clearer link to the CQAs for the product. While these approaches do not directly tackle the sensitivity question, they clearly represent a step forward for implementing a qualitative method to monitor blend uniformity.

The application of blend monitoring has become largely accepted at this point although there are very few publications that clearly demonstrate the useful impact of the data. Sulub *et al.*[22] published results from 67 commercial batches conducted over three years using a quantitative multivariate model. Mining of this data led them to identify that different granulation conditions resulted in different blending kinetics, clearly recommending the need for on-line analytical measurements. The authors then leveraged this historical data to propose in process control of the blender. It was unclear however if this approach would meet regulatory scrutiny since there was no direct correlation between the NIR determined blend uniformity (BU) RSD and/or the tablet content uniformity (CU) RSD. Consequently, the RSD determined endpoint showed a weak correlation to product performance. Igne *et al.*[23] have presented a very elegant solution which leverages the error from the nominal target quality value (RMSNV); e.g. API concentration in blend. This is a significantly more sensitive metric than RSD from the mean since it factors in the difference between the mean and the target values.

Unit Operation	Critical Quality Attributes
Blend	Component Uniformity, flow, segregation propensity
Wet Granulation	Granule particle size distribution, flow, moisture content, granule porosity
Roller Compaction	Ribbon: density/tensile strength, Granule: particle size distribution, flow, compactability
Drying	Moisture, residual solvent, granule particle size/PSD
Tablet Compression	Hardness, friability, dissolution, disintegration, appearance
Coating	Dissolution, appearance, strength, thickness uniformity

FIGURE 1 Critical quality attributes for solid oral dosage manufacturing process

As the pharmaceutical industry looks to innovate their manufacturing processes it is clear that novel spectroscopic applications will be needed and NIR can play a significant role. As an example, advances in continuous mixers have increased the requirements for on-line measurements since it is now possible to directly affect the blending process and blend concentration using output from the NIR sensors. Vanarase *et al.*[24] demonstrated the approach using acetaminophen continuous blending where quantitative NIR methods directly measured the blender output in real time.

Wet granulation

Wet granulation is a complex process that for many years relied on the experience of the operator to consistently produce a wet granulated product. Early in the 1990s, pharmaceutical scientists recognised the need to implement in-line tools to gain insight into the process. As examples, List and Steffens[25] demonstrated the use of NIR for the in-line solvent content determination during granulation and Watano *et al.*[26] studied the relationship between the operational variables and the NIR measurements. On-line NIR data such as granule particle size distribution, water content and API solid state form (polymorphism), collected during wet granulation process has been well correlated to product quality or performance. These CQAs are directly affected by granulation process parameters such as water addition rate, impeller speed, and end-point of the granulation process[8-11], and the ability to monitor them on-line provides added knowledge which leads to more robust manufacturing process and sustainable product quality.

Rantanen *et al.*[27] studied the effect of particle size, composition and binder type on NIR at-line moisture measurements during granulation. Jørgensen *et al.*[28] related impeller torque measurements and NIR spectra to characterise the water addition phase. The baseline-corrected water absorbance obtained by NIR and the impeller torque showed similarities in following the water addition phase of wet granulation. In contrast to power consumption and temperature, Luukkonen *et al.*[29] demonstrated that in-line real-time NIR data was directly correlated to granule particle size, granule porosity and tablet hardness. Alcala *et al.*[30] developed a qualitative model using principal component analysis (PCA) to

identify and monitor each step of the granulation process and a quantitative PLS model to predict CQAs such as moisture, particle size and bulk density. It is important to note that NIR has struggled to become common-place for wet granulation monitoring and much of the recent literature points towards the use of Focal Beam Reflectance Measurements (FBRM)[31] for particle size analysis to inspect the growth phase and consolidation of the granules.

Drying

Water can negatively impact product quality. Moisture in APIs and excipients can impact drug product manufacturing unit operations such as granulation, conveyance, compaction, drying, etc. NIR spectroscopy has been extensively used for the timely monitoring of moisture content of APIs and materials during processing. Since NIR is a non-invasive technique that does not require sample preparation and provides real-time data, it has been selected as a tool of choice for drying control in many pharmaceutical applications[8-11,32-34]. NIR spectroscopy is well suited for the measurement of moisture because water shows strong NIR absorption bands; most prominent are the first overtone OH stretch at around 6800-7100 cm^{-1} (1470-1408 nanometres) and the combination band at around 5100-5300 cm^{-1} (1960-11887 nanometres).

On-line NIR has been used not only to determine water content but also for the simultaneous determination of other quality attributes during drying such as drying end-point, API assay, residual solvents, granule particle size, fluid-bed pellet coating and to visualise the different stages of the fluid bed drying process[35,36]. White[37] reported the use of NIR for on-line moisture end-point detection in a microwave dryer in the early 1990s. Harris and Walker[38] implemented the real-time quantification of organic solvents and water evaporating from a vacuum dryer. In-line NIR based control was implemented by Morris *et al*.[39] to accelerate the fluid bed drying process, demonstrating the ability to positively impact manufacturing processes.

During fluid bed drying, various drying end-point criteria based on temperature and humidity measurements have been used (e. g. inlet, bed and outlet temperatures). One accepted criteria is to establish a fixed temperature of the mass. However, when this criterion is used, finished granules with different moisture content can be obtained with varying inlet air humidity[40]. To reach a specific moisture content of the granules, an end-point criterion based on specific granule moisture content (determined in-line real-time) has proven to produce granules of consistent quality[40]. In this regard, NIR has been extensively used to determine the drying end point of a fluidised bed process. This was recently demonstrated by Peinado *et al*.[41] where they successfully validated an in-process method following ICH guidelines. NIR monitoring not only improved product quality but also reduced process cycle time and production costs. Hartung[42] linked the tablet characteristics to not only the residual moisture of the granules but also to the moisture profiles during the entire fluid bed granulation process.

Tableting

A large fraction of pharmaceutical products are prepared as tablets and consequently significant emphasis has been placed on understanding the manufacturing process and the CQAs pertaining to efficacy and performance of the product. These include individual tablet assay (average by potency and variation by content uniformity) and dissolution which have been extensively explored by NIR spectroscopy and imaging methods. A recent example of tablet potency determination by Boiret *et al*.[43] determined the content for 12.5 milligram Tianeptine coated tablets. The root mean square error of prediction was approximately two per cent, showing the excellent capability of NIR based methods. Additionally, to use this model with a second spectrometer in production, a piecewise direct standardisation (PDS) algorithm was used to facilitate calibration transfer. Similarly to the blending described

earlier, Puchert[21] applied the Symmetry Parameter Image Analysis (SPIA) to NIR chemical images for tablet homogeneity assessment. The next steps for the industry relates to the continued development of the relationship of how these statistics relate to product quality and efficacy.

An increasingly important area relates to supply chain integrity and product surety testing. NIR affords a significant advantage in that libraries of products can be readily developed and then implemented. Said *et al*.[44] demonstrated this nicely where Malaysian and UK paracetamol (acetaminophen) tablets were differentiated by their NIR spectra. With the development of handheld, lower costs spectrometers, such applications will be an important aspect for consumer safety.

Coating

Quality parameters of the coating process, such as coating layer thickness, uniformity and reproducibility, are often controlled by parametric means or are determined by indirectly using weight gain or tablet size increase. Such methods are typically inconvenient and may not provide sufficient information about the coating process. NIR spectroscopy has been applied quite extensively since the mid 1990s to investigate the coating process of tablets. Buchanan *et al*.[45] used offline NIR spectroscopy to quantitatively and qualitatively analyse API contained in the coating layer. Kirsch and Drennen[46,47] used off-line NIR to model the coating thickness and dissolution rate. The measurement of coating properties for sustained release products continues to be an important area for NIR applications. Tabasi *et al*., used at-line NIR spectroscopy to predict

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theophylline[48] and orbifloxacin[49] performances, not just for coating thickness but also to model the drug release of tablets coated as the blend of Eudragit copolymers changed.

More recently there has been interest in in-line measurements and one of the clear challenges to implementing inline NIR based coating measurements relates to the efficient preparation of calibration standards. Römer *et al.*[50] used a small-scale rotating plate coating system for collecting ex-situ in-line dynamic NIR data for calibration method development. Andersson *et al.*[51] monitored a fluid bed coating of pellets by in-line NIR for a thin coating of up to ~50 µm with a precision of ~ 2 µm, which clearly demonstrates the quality by which coating thickness can be measured. Interestingly the article discussed how wavelength errors produce clear bias in the measurements, highlighting the requirements for stability for in-process measurements. Gendre *et al.*[52] effectively used in-line NIR to predict the drug release profile during coating and incorporated an end-point control to demonstrate that quality was ensured. These advances in coating analyses highlight the power of NIR spectroscopy to help understand and effectively control the coating process.

BIOGRAPHY

Claudia C. Corredor is a Research Investigator II within the Analytical and Bioanalytical Development (ABD) division at Bristol-Myers Squibb (BMS), where she has worked for the last eight years. She has been responsible for the analysis of drug substances, process intermediates and final product by HPLC, GC, GC-MS and HPLC. Most recently, she is responsible for developing NIR and Raman methods to support PAT control strategies for drugs. Claudia received a BS in Pharmacy from the National University of Colombia, and PhD in Chemistry from the University of Central Florida (sponsored by BMS). Prior to joining BMS, Claudia was a validation manager at Aventis and a method development analyst at Merck KGaA. Her areas of interest include development of materials for non-linear optics, PAT, QbD, NIR, Raman and separations. She is the author of 15 publications.

BIOGRAPHY

Boyong Wan is currently a Research Investigator at Bristol-Myers Squibb Company. His work focuses on implementing vibrational spectroscopy and multivariate analysis tools for pharmaceutical product and process analysis. Boyong obtained his PhD in analytical chemistry from University of Iowa in 2007.

BIOGRAPHY

Gary McGeorge received his PhD in solid-state NMR spectroscopy (ssNMR) at Durham University for the analysis of polymorphic dyestuffs. He then held a Post Doctoral position at the University of Utah using ssNMR for the analysis of pharmaceutical and natural products. Currently, he is a Principal Scientist within the R&D organisation at Bristol-Myers Squibb, where he has worked for the last 13 years. During this time he has been responsible for the analysis of polymorphs within solid pharmaceuticals (both as isolated components and formulated products) using various spectroscopic tools (IR, NIR, Raman and ssNMR); identity testing of raw materials and finished product. Most recently, he is one of the technical leads for the designing and developing PAT control strategies for drugs within BMS. His research interests centre on using spectroscopy to understand and characterise key attributes of materials and how they determine the performance of a product. He is on the editorial advisory board for the Journal of Pharmaceutical Sciences and Spectroscopy magazine.

NEAR INFRARED LEADERS ROUNDTABLE

Matthew Montague
European Technical Sales Support for FTIR/FTNIR, ABB

Robert Mattes
Applications Scientist, FOSS NIRSystems Inc

Chris Moreland
NIR Product Manager, Thermo Fisher Scientific

Nutsima Schnell
Segment Manager NIR Pharma, Buchi Labortechnik AG

Moderator:
Yves Roggo, F. Hoffmann-La Roche

NIRS application in the food industry is wide. However, even if NIRS has a lot of advantages, its use in the pharmaceutical industry is limited. Could you explain this phenomenon?

Matthew Montague: The key difference between the pharmaceutical industry and other industries where NIR is used more widely such as food, but also from a PAT perspective petrochemicals, is the large regulatory framework it is forced to operate within. Introducing change and moving away from more established traditional methods is therefore viewed to have a comparatively greater potential risk within the pharmaceutical industry and presents a hurdle to implementation that is often not overcome. The economics of the pharmaceutical industry are also very different from other industries. In food and petrochemicals, production margins are an important driver for profitability, while in the pharmaceutical industry, production efficiency is less significant to overall profitability.

Robert Mattes: There are a wide range of NIR applications in the pharmaceutical industry. FOSS NIRSystems has been in the NIR market for over 45 years and has an impressive installed base of laboratory and process NIR analysers in this industry among others. FOSS NIR analysers are involved in the complete process, from incoming raw materials to finished products. Our proven digital dispersive NIR analysers, which are fast, accurate, and not affected by vibration, make it possible to perform quality control at very low levels.

Chris Moreland: While application of NIRS in the food industry has been more widely applied, there are several historical and technological explanations for this. Market reports estimate that the food industry is five times larger than the pharmaceutical industry, resulting in a larger install base. In addition, many food applications have been successfully developed on relatively low performance and low cost filter or dispersive technologies that have been readily available and used in the food industry for well over four decades. Conversely, the performance requirements in the pharmaceutical industry are much more stringent, due to tighter regulatory requirements, and as a result, wide

application of NIRS in the pharmaceutical sector was not developed until the introduction of dedicated FT-NIR analysers, with their higher spectral resolution and improved wavelength accuracy, over the last 15 years. Lastly, the aforementioned regulatory requirements have created a barrier to entry in the application of new technology for some manufacturers.

Nutsima Schnell: This is primarily due to the stringent regulations in the pharmaceutical industry compared to the food industry. The validation process necessary for the approval of the NIR method by the regulatory authorities is a long, expensive, labour intensive and demanding process. For that reason, pharmaceutical companies hesitate to introduce the changes in the current manufacturing process or quality control methods. Another reason is the fact that there is still lack of knowledge and experience in NIR. It took a long time for international regulatory authorities to harmonise their opinions and still there are a lot of opposite and confronting voices inside them (FDA, EMA, ICH).

Most pharmaceutical applications are very 'classical' like identification tests or water content determination. Why is the usage of NIRS not wider?

Chris Moreland: We question the premise of the question. The common parameters measured in food products are moisture, protein, carbohydrate and fat, while the measurements in the pharmaceutical industry can be much more challenging. It is not uncommon to see multi-component methods deployed for online process analysis that quantify for only a few per cent of an API in a complex matrix. In addition to the classical applications of NIRS in RMID and moisture analysis, NIRS has been deployed for fluid bed drying and emerging applications such as online analysis on cell cultures and hot melt extruders.

Nutsima Schnell: Near Infrared Spectroscopy, although present and known for quite a long period of time in scientific circles, is still not well understood and accepted by the current management milieu in the pharmaceutical companies. The other reason is the fact that the validation procedure could be complicated and requires highly experienced experts. The stringent regulations together with the lack of knowledge and experience in NIR spectroscopy slows down the process of implementing NIR as an alternative to the well-established traditional analytical methods.

Robert Mattes: The usage of NIR is much wider than that. NIR has been used for a long time for raw material inspection, but that is only a small part of the capabilities of NIR. It is used for quality control during the process at-line, in-line, on-line and finally for finished products. In the pharmaceutical, biotech and other industries, NIR process monitoring and control help to optimise extremely complex process parameters. NIR can measure multiple chemical and physical parameters from each spectrum.

Matthew Montague: Those are the most well-known applications but not the only ones. When the FDA triggered the pharmaceutical industry drive towards PAT, much of the focus was on moving the traditional laboratory quality tests on-line or at-line. This strategy appeared to offer the lowest risk as compendial tests were well understood. Focus is now more on process understanding and more applications have been implemented at different stages of drug manufacturing like crystallisation, granulation, extrusion, mixing, tablet content uniformity and coating. Further generalisation of NIR use in the pharmaceutical industry is underway as more chemometrics trainings and implementation guidelines are made available for end-users, and instrument vendors offer streamlined interfaces for method development and implementation.

The success of NIR spectroscopy in the pharmaceutical industry was linked with the Process Analytical Technology (PAT) initiative of the US Food and Drug Administration in 2003. Do you believe that NIR spectroscopy is one of the most powerful tools for PAT and why? Could you give us some examples of PAT projects using NIRS and explain the benefits for the pharmaceutical industry?

Nutsima Schnell: NIR spectroscopy is the most powerful tool for PAT due to the fact that the NIR spectrum carries information about both chemical (composition) and physical properties of the system. NIR spectrum is the fingerprint of the process. Every change in the composition of the reaction mixture and any change in the process parameters is reflected in the NIR spectrum. There are numerous examples of successful monitoring of granulation, drying, mixing, tableting and the coating process etc. using NIR spectroscopy. Such examples could be found in the scientific literature but also in numerous pharmaceutical companies. The benefits of implementing NIR spectroscopy as a PAT tool are numerous;

- in depth process understanding
- determination of the optimal process time and conditions
- possibility to fully control the production process
- real time release
- reduced number of rejected batches
- higher quality of the products
- saving resources
- possibility of continuous production

Matthew Montague: Over 60 per cent of implemented PAT applications involve NIR use due to multiple advantages: speed, non-invasiveness, non-destructiveness, multi-component analysis capability for physic-chemical properties, and support for remote sampling interfaces. It is therefore applicable to a wide range of applications across drug manufacturing unit operations. Recently we collaborated with major pharmaceutical companies to implement NIR monitoring on continuous processes. We implemented critical quality attributes control at two blending and two drying stages of drug production, using a single analyser fully integrated with control systems. In another case, the analyser allowed continuous verification of identity and content for three key materials in a formulation, whilst providing greater understanding of product behaviour during the continuous process.

Chris Moreland: The development of dedicated and rugged FT-NIR systems with matched optical components and fibre optic probes for in-process measurements has allowed analyses to be moved out of the QA/QC laboratory to the production line, making NIRS a useful and powerful PAT tool. Some examples of PAT applications are RMID, fluid bed drying, at-line tablet testing, and on-line blend analysis. The advantages to the pharmaceutical industry of applying online NIR analyses are improved process control, product quality and avoidance

of product waste. Ultimately, all of these benefits lead to improved profitability for the manufacturers.

Robert Mattes: NIR was a success long before PAT, but of course, the FDA PAT initiative encourages manufacturers to monitor processes before the final product stage. PAT has had an erratic start in the pharmaceutical industry due to the regulatory anxiety in GMP environments. However, many industries, including pharmaceutical, have implemented NIR at-line, on-line, and in-line analysis for quality monitoring and closed-loop feedback control. NIR is particularly well suited for process real-time analysis, because it can be utilised with no sample preparation, used with multiplexed fibre optic probes and is robust in industrial environments. Process NIR instruments are designed to be used in-line to measure multiple parameters, such as moisture and residual granulating liquid in fluid bed dryers or single-pot granulators. Mean particle size and polymorph conversion can also be monitored at the same time.

Good chemometrics solutions are needed for the development and the validation of NIR methods. What will be your solutions in term of software and new chemometric tools? Which new chemometrics will you implement in your software in the future?

Robert Mattes: The FOSS VisionTM software is simple to use and is a complete single package that includes data acquisition, qualitative and quantitative method development and routine analysis methods. Vision is 21 CFR Part 11 compliant and also linked to Unscrambler. In a global enterprise, global networking, instrument matching, and model transferability are important features within the Vision software.

Chris Moreland: We continue to explore solutions to make chemometric model development more accurate, robust and easier to transfer from one platform to another. For example, we have recently implemented improvements for calibration method transfer using variational standards. Variational standards are a set of samples which are collected over the range of variation that can be encountered in the sample population, to correct calibrations where more variation exists in the sample population than was accounted for in the initial calibration. These standards, for which it is not necessary to know primary chemical values, are used to correct existing calibrations for the additional variation encountered in the sample set. Variational standards are treated differently in our TQ Analyst Chemometric software package than calibration samples, so that it takes fewer variational standards to correct a model than conventional inoculation requires. We have also introduced the ability to create Principal Components 3D Scores plots which are interactive displays of three principal component scores, or principle component scores vs. component concentrations, to improve method development through population optimisation. In addition, we continue to support third party chemometric software packages such as GRAMS PLSplus/IQ and Camo's Unscrambler.

Nutsima Schnell: We would implement non-linear regression methods like support vector machines, artificial neural networks and locally weighted regression. Calibration transfer algorithms are not needed in the case of polarisation interferometer based FT-NIR spectrometers. Our software generates a lot of validation data that could help in the process of the method validation. There is still place for the improvement in the terms of automation and networking solutions although many already exist.

Matthew Montague: ABB has a long history in process control. We have both our NIR process software, FTSW100 and xPAT that offers the functionality to combine analytical and measurement inputs from multiple sources with control systems via process models and multivariate statistical process control approaches to fully enable closed loop process control. FTSW100 is not just compatible with our own chemometrics models, it also can incorporate models from third party specialist chemometric software, an area that we expect will grow in the future. To ease validation we will very soon implement additional tools in our Horizon software suite to greater automate the validation of NIR calibrations using additional validation samples.

What will be the major innovations in the NIRS in the future? Will new types of instruments be launched? What about NIR imaging, fast NIRS measurement or portable instruments? Do you plan to combine NIRS with other analytical tools?

Chris Moreland: With the recent acquisition of Polychromix by Thermo Fisher Scientific, we are pursuing projects that integrate handheld analysers and laboratory spectrometers in a field to lab to line strategy for qualitative and quantitative analysis. We are also investigating opportunities to integrate NIR technology with other platforms and techniques that will provide synergies to streamline workflows and improve product development.

Robert Mattes: As an industry leader, FOSS is continually investing in research and development of analytical instrumentation. FOSS produced the first commercial and then the first computerised near-infrared spectrophotometer. Unfortunately, we are unable to disclose the innovations we are working on at the moment.

Matthew Montague: NIR implementation can be expensive, particularly in a process environment. This is a problem not limited to the pharmaceutical industry. Much of the cost of an NIR solution arises not necessarily from the spectrometer itself but from the associated infrastructure and setup costs. ABB are developing our instruments with this in mind. We will continue to provide high performance FT-IR/FT-NIR instruments that can handle the most difficult applications. However, we will be introducing innovations to minimise the cost and complexity of both the implementation and on-going maintenance of our NIR solutions in the future.

Nutsima Schnell: NIR spectrometers, in line with the technology advancement, will become smaller, with better performance. Design will be very important as well as user friendly interface solutions. Hand-held analysers are becoming more and more popular although still with poorer performance compared to the bench-top instruments. 'Universal multipurpose analysers' are something that we can expect in the future.