

## A Comparison between Validating Laboratory and Process Near-Infrared Spectrophotometers

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*Greetings, dear readers. I trust your summers passed by with no major upsets.*

*Continuing in my series of Process Analytical Technologies (PAT) columns, I offer the following piece by Gary Ritchie as an example of the conundrum we face when validating process methods. We may have some guidelines for NIR applications, but they were written with lab methods in mind. Gary nicely touches on these concerns in the following piece about applying validation principles originally designed for lab instruments to process instruments.*

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Substantial progress is being made with the use of near-infrared (NIR) spectroscopy in the pharmaceutical industry — primarily due to increased understanding of what was once considered a “black box.” What change has removed this stigma? The foremost reason that NIR is being used both in the laboratory and in process streams is that, finally, considerable attention has been given to validation parameters that are required by the regulators of the industry to be used with these systems in current Good Manufacturing Practices (cGMP) mode. In this column, I will explore what those validation parameters are and how they may be applied differently, depending on whether the measurement is being made in the laboratory or at, in, or directly on a process.

During the past eight years, NIR has been given considerable

attention by several groups around the world interested in using it for the purposes of monitoring pharmaceutical manufacturing processes. In 1998, the U.S. Pharmacopeia (USP, Rockville, MD) published a proposal for a general chapter on NIR spectrophotometry (1). The primary focus of this proposal was to identify those validation parameters that could be useful for qualifying and verifying NIR instrumentation.

In 1997, the European Pharmacopoeia (Strasbourg, France) published its own monograph on NIR. Its focus was to provide validation parameters in order to establish an NIR spectral reference library (2). In 2001, two more publications emerged: one from the Pharmaceutical Analytical Sciences Group (PASG) NIR Sub-group (3) and one from the European Agency for the Evaluation of Medicinal Products (London, United

Kingdom) (4). Their intent was to provide users and regulators with a definitive guide to best practices for both qualitative and quantitative NIR method development, validation, and application, and to provide guidance to companies in the process of development, validation, and maintenance of an NIR method and the type of data to be submitted to the competent authorities for an NIR application, respectively.

In spring 2001, a meeting of the newly created Near-Infrared Validation Working Group (NIRVWoG) was held in Tarrytown, New York. NIRVWoG included members of the combined organizations of PASG, led by Kenneth Prebbles of GlaxoSmithKline; members of the Product Quality Research Institute (PQRI, Arlington, VA) Blend Uniformity Work Group, led by Joep Timmermans; and other interested pharmaceutical parties, led by myself, Emil Ciurczak, and Philip Palermo of Purdue Pharma LP (Stamford, CT), International Research & Development. A proposal for a final revision of the proposed USP 1998, 2000, and 2001 chapters, begun in that Tarrytown meeting, finally emerged in December 2002: *A Proposal For Stimulus To Revise USP Chapter <1119> Near-Infrared Spectro-*

*photometry* (5). The intent of this document was to provide final language for the USP general chapter for qualification and verification of NIR instruments and analytical method validation of NIR spectrophotometric measurements.

What emerged from this activity was very specific language to assist regulators and users worldwide in pinning

down what is required to have this technique comply with current regulatory International Conference on Harmonization (ICH) guidelines on analytical methodologies (6, 7). However, everyone now agrees that even this version of the USP chapter falls short on information to assist the regulators and users in the use of NIR in the process stream. Although we were cognizant of PAT

and potential NIR applications, they were not on the front burner when we moved to find appropriate and sufficient parameters to be able to validate NIR equipment and methods. We focused on laboratory applications primarily for expediency's sake to get a workable USP chapter. Nevertheless, leading PAT experts using NIR are addressing the issue of PAT applications, and we will explore some of these next.

The foremost issue for the manufacturers, as well as the U.S. Food and Drug Administration (FDA), is that most current regulations were not written for automated process control for pharmaceutical production. Some regulations do exist for computer-controlled devices and equipment, but they are not specifically aimed at process monitoring or control in the sense that we are discussing them here.

As many of you are aware, the U.S. pharmaceutical industry is probably the most regulated industry in the world. The price we pay for this is high, but the reward is that we have the safest, most efficacious medicines in the world. The current *modus operandi* for validation of our drugs is based on a paper-driven document-compliance operation called "quality assurance." Its main downside is that the product is tested after it is made. So new regulations and guidance will have to emerge to facilitate industry submissions of these new process methods and regulatory assessment of the submitted data to demonstrate compliance.

Currently, it is recommended that NIR equipment be calibrated by using current National Institute of Standards and Technology (NIST, Gaithersburg, MD) standards SRM1940 for wavelength accuracy in reflection mode and SRM2034 and SRM2035 for wavelength accuracy in transmission mode. Although suitable for laboratory instruments, it has been argued that their use would not be suitable for process instruments. The current revised <1119> chapter does provide for the use of other traceable standards. The primary question that is being raised regarding this proviso is: "Do we really need the process standards to be traceable?" We do need a "traceable" standard,

but traceable to whose standards? If we don't need new standards, what regulatory language exists now, or needs to be written, for guidance on what can be used to demonstrate suitability of the process analyzer?

## NIR is poised to become the workhorse of process analytics for the pharmaceutical industry

Another issue is whether or not it is appropriate for vendors to program software to test and report suitability of an instrument according to the prescribed USP specifications. The specifications, as written in (1119), apply to data obtained from the use of externally applied traceable standards. The intent here is to require users to demonstrate suitability of the instrument by first ap-

plying the appropriate standard, and then calculating the result externally to the vendor software. This calculated result is compared to the current standard value (and its current tolerance). Users then make a decision that the instrument has or has not met the specification. Having this procedure and calculation preprogrammed by vendors does not appear to be in compliance with cGMP, where users should demonstrate control over the instrument and reported result. This may be a matter of interpretation, however. If a vendor's USP reportable protocol is going to be relied on, then it appears that additional validation of the software would need to be performed by users to demonstrate that the algorithm and calculated result meet the cGMP and USP specifications. In either case, the agency would want to see either the appropriate validation documentation for the software generated by users or the instrument calibration (performance

qualification) documentation — that is, raw spectral data generated by users and the manually calculated results accompanying their reported pass/fail USP specifications and the user's decision. Electronically generated USP reporting should be acceptable, as long as users are willing to demonstrate the validity of that calibration scheme.

Despite these outstanding issues, NIR is poised to become the workhorse of process analytics for the pharmaceutical industry. You should be well aware of its use in other industrial areas. I have often wondered how it became so ubiquitous in these other areas and how the validation problems were solved.

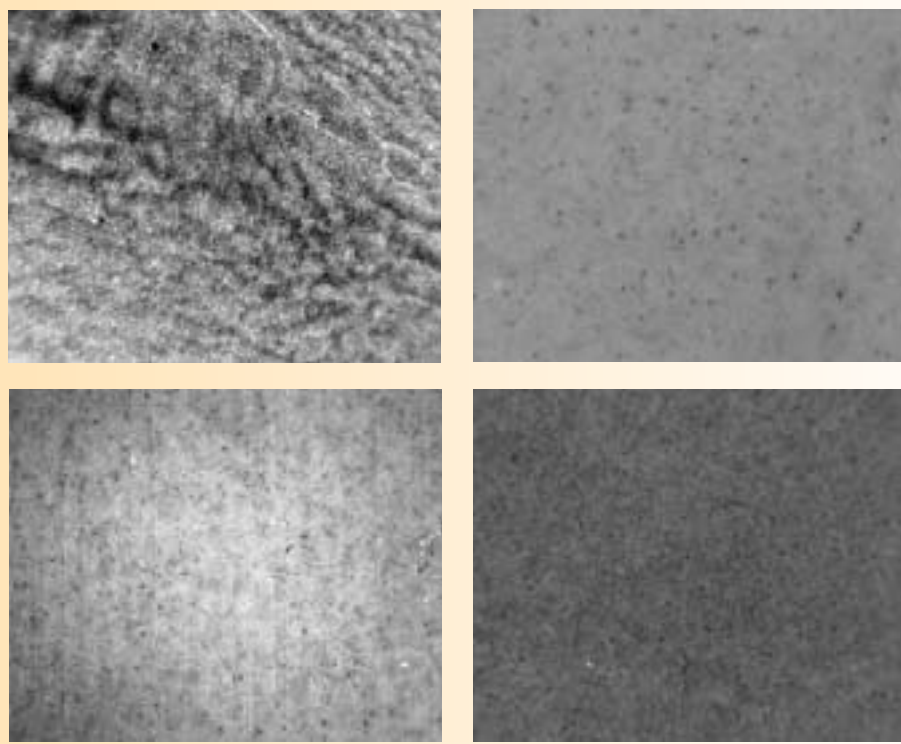
Validation — a requirement in the pharmaceutical industry — is essentially a documented verification of its systems, operations, and people in order to legally uphold the Food and Drug Act and ensure that manufacturers are producing products that are pure, safe, and efficacious. What this means is that a com-

**Figure 1 (upper left).** Surface of NIST standard 1920A for wavelength uncertainty at 1261 nm. Note the surface texture and homogeneity variations apparent at microscopic levels.

**Figure 2 (upper right).** 80% reflection sample at 1600 nm. Note the individual carbon black particles, distributed evenly throughout the material. While the “average” reflectance of the surface is sufficient for macro-systems, this nonhomogeneity makes imaging system calibration problematic.

**Figure 3 (lower left).** 60% reflection sample.

**Figure 4 (lower right).** 20% reflection sample.



**Table I. Comparison of Method Validation Parameters between Laboratory and Process Analyzers**

NIR method validation parameter	Laboratory analyzer	Process analyzer
Specificity	Challenges from similar compounds. The bands of the analyte of interest should be free from interference from other competing absorption bands.  Wavelengths, loadings, or factors can be inspected for corresponding analyte information.  Coefficients can be plotted and the regions of large coefficients compared with the spectrum of the analyte matrix. Variation can be used to assess effect on the corresponding analyte.	Not applicable.  Wavelengths, loadings, or factors can be inspected for corresponding analyte information.  Coefficients can be plotted and the regions of large coefficients compared with the spectrum of the analyte matrix. Variation can be used to assess effect on the corresponding analyte.
Linearity	A line plot for linearity, slope, intercept, and correlation coefficient is reported.	A line plot for linearity, slope, intercept, and correlation coefficient is reported.

*Table continues on page 40.*

pany has to unequivocally demonstrate to the FDA that these factors are in a state of control. Current validation requirements emphasize audit capabilities. For instance: Did you do what you said you did, and has it been documented? Signatures and countersignatures and dates and times verify this. If you go into electronic automated process mode, you will most likely be using electronic signatures. Auditing the acquired data will take on a whole new meaning. What is kept for the record, what is discarded, and even what is called data may have a whole new meaning.

NIR enjoys a head start in the shift from the current laboratory-based analytical testing to the future process-based testing in that it has its own USP General Chapter: <1119> Near-Infrared Spectrophotometry. This chapter is the culmination of seven years of industry's, and other interested parties' input into deciding the best validation practices for NIR. However, as things normally go, when this chapter was being written, process analytics was not on the minds of the creators, so this chapter will undergo revision to reflect validation best practices for laboratory as well as process-based usage.



**Table I. (Continued)**

NIR method

validation

parameter

Range

Laboratory analyzer

The range of analyte reference values in the validation set defines the range of the NIR method.

The range of analyte reference values also effectively defines the quantification limits for an NIR method.

A limited sample set does not preclude the use of an NIR method.

Accuracy

Accuracy may be indicated by how close the Standard Error of Prediction (SEP) is to the standard error of the reference method used for validation. The error of the reference method may be known based on historical data, or a measurement of the Standard Error of the Laboratory may be carried out.

Several statistical comparison methods can be applied to the NIR predicted values and reference values from the validation set samples to determine if there is any statistical difference between the results from the two methods, at a specified confidence limit (e.g. paired t-test, bias evaluation).

Process analyzer

May not have applicability for certain processes. In this case, the use of Conformity Index (CI), Mahalanobis Distance (MD) measurements, or other chemometrics to assess process variables spanning calibration space may be required.

Accuracy may be indicated by how close the SEP is to the standard error of the reference method used for validation. In lieu of specific reportable process endpoints, the use of CI or MD may be substituted.

New statistical approaches need to be developed to include chemical data as well as statistical outlier identification. Assuming more than 3000 assays per lot, at least one tablet could well be 50% or 150% of label claim. The efficacy and/or toxicity of the particular active pharmaceutical ingredient needs to be addressed in conjunction with the absolute number of outliers to determine pass/fail of the lot.

Precision

Repeatability: Statistical evaluation of a number of replicate measurements of the same sample without variation in sample position.

Statistical evaluation of multiple sample positioning or aliquots as appropriate.

Repeatability: Statistical evaluation of replicate measurements taken at the same and different times during the process and at different positions in the process stream is desirable.

Robustness

Analyst should demonstrate effects of environmental variation, sample presentation, and instrument variability.

Process statistical design to determine critical processing variables should be demonstrated.

Ruggedness

Not applicable.

The use of a bias correction to adjust the model if it is to be used by more than one instrument is recommended.

Slope adjustment between instruments is not usually performed and is not recommended.

Ongoing model evaluation

Ongoing monitoring of method accuracy, precision, or other suitable parameters.

Skip lot testing by primary methods performed on every N<sup>th</sup> batch verifies that the nominal endpoint value and the standard activity previously established still holds (8).

Model transfer

Transfer of electronic models to a second instrument requires that procedures and criteria must be applied to demonstrate that the model remains valid on subsequent instruments.

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Table I compares current calibration and validation best practices for laboratory and process NIR analyzers. The calibration parameters were the result of a designed collaborative study, while the validation parameters are modeled on the requirements for validation of an analytical method as prescribed by ICH Q2A and Q2B Guidelines. They are:

Calibration parameters:

- Wavelength uncertainty
- Photometric linearity
- Spectrophotometric noise
  - high-light flux
  - low-light flux.

Method validation parameters:

- Accuracy
- Intermediate precision
- Linearity
- Range
- Repeatability
- Robustness
- Specificity.

As they stand, these parameters are suitable to provide sufficient evidence for laboratory-based instrument performance (for diffuse reflection measurements) and laboratory-based method validations. They are suitable as guidelines for regulatory evaluation of laboratory-based NIR instruments and methods. However, they are deficient in certain elements necessary to support process measurements, especially those measurements made in transmission and “transflection” modes. It is even being argued that the guidelines are not suitable for some process measurements using diffuse reflection instruments. Although the revised (1119) does account for the use of NIST transmission standards, some process measurements applications may not be amenable to these standards. How are we to overcome these deficiencies?

If one has to choose whether or not to use traceable reference standard materials for calibrating process analyzers, it is argued that good science must prevail. It will be contingent on users to demonstrate the need to use or not use a reference standard or other suitable materials other than those recommended in (1119). In these cases, it is

always the choice of users, who must justify to the authorities their decision to proceed in a direction other than that given in the recommendations. I believe that it is also true that if the recommendations cannot accommodate all possible instrument configurations, then that should be stated also. For instance, not all of the (1119) recommendations can be applied to NIR imaging systems. Figure 1 shows the nonuniform surface of standard 1920A at the microscopic level. Although quite suitable for macro-NIR systems, the inconsistent micro-distribution of materials within the standard makes it not the standard of choice for imaging systems. It is certainly true that these recommendations were not written with NIR imaging systems in mind. However, the use of such systems is growing rapidly and they will play a major role in understanding what is occurring in a pharmaceutical process.

Figures 2 through 4 show the distribution of carbon black in various samples of sintered teflon used as percent reflection standards. The average reflectance values are very good for “normal” NIR systems, but a pixel-to-pixel application does not serve to calibrate a multidetector system. This does not imply that imaging equipment may not be validated; rather, only that there is no universal approach to validation of all equipment, both lab and process.

Thus, it is inappropriate to try to fit all of these recommendations, originally written with lab systems in mind, to these imaging systems word by word and specification by specification. Wide latitude should be given to circumstances like these and other similar situations, such as process analyzers. Common sense must prevail here and good science must be applied if the recommendations cannot be applied.

In addition to what is being recommended in the revised (1119), in a recently published paper by Ritchie, Mark, and Ciurczak (8), the authors examined the use of the Conformity Index (CI, described by Plugge et al. [9]) and the Mahalanobis Distance (MD, as described by Mark and Tunnell [10]). Plugge et al. introduced CI as a measure of the “degree of conformity” of a batch

with samples of standard quality. MDs have also been proposed as a means of assessing whether a sample is consistent with a set of data known to represent satisfactory product (11).

As has been mentioned, there is still room for developing the specification requirements for calibration and parameters for validation of NIR equipment and methods, respectively. We are, by no means, complete with respect to full regulatory compliance, and therefore the agency will have to be flexible in its approach to enforcing compliance with a still-fertile technique. Manufacturers using this technique must become more steadfast and confident in their abilities to be innovative in these uncharted waters. Hopefully there are those still willing to take educated risks with devising tests, materials, and specifications to demonstrate the validity of their approach.

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