Development and Submission of Near Infrared Analytical Procedures

Guidance for Industry

DRAFT GUIDANCE

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I. INTRODUCTION

This guidance provides recommendations to applicants of new drug applications (NDAs), abbreviated new drug applications (ANDAs) and drug master file (DMF) holders regarding the development and submission of near infrared (NIR) analytical procedures used during the manufacture and analysis of pharmaceuticals (including raw materials, in-process materials and intermediates, and finished products). It also provides recommendations regarding how the concepts described in the International Conference on Harmonization (ICH) guidance for industry Q2(R1) *Validation of Analytical Procedures: Text and Methodology* (ICH Q2(R1)) and *PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*[2] can be applied to the development, validation, and submission of NIR analytical procedures.

This guidance only pertains to the development and validation of NIR analytical procedures and does not provide recommendations concerning the set-up and qualification of NIR instruments or their maintenance and calibration. While this guidance is written specifically for NIR, the fundamental concepts of validation can be applied to other PAT technologies including Raman, focused beam reflection measurement, particle imaging, X-ray, among other techniques.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This draft guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

II. BACKGROUND

NIR analytical procedures are increasingly being used in the pharmaceutical industry for the identification and assay of pharmaceutical starting materials, intermediates, and finished products. They are also used to monitor and control manufacturing processes. The development and validation of NIR analytical procedures are therefore important for ensuring the quality of pharmaceuticals. It is important for manufacturers who use such procedures to understand the factors that can affect the performance and suitability of the procedures and the approaches that can be used to validate them.

ICH Q2(R1) provides a discussion of the "characteristics that should be considered during the validation of analytical procedures," "guidance and recommendations on how to consider the various validation characteristics for each analytical procedure," and "an indication of the data that should be presented in a registration application." Although many of the concepts described in ICH Q2(R1) can apply in general to a wide variety of analytical methodologies, the ICH guidance does not address some unique characteristics of NIR analytical procedures.

NIR analytical procedures typically combine the following: (1) elements of instrumentation (analyzer consisting of a NIR spectrophotometer, reflectance or transmission probe, spectral analysis software, etc.), (2) acquisition parameters, (3) sample presentation (interface) and sampling, (4) composition of spectral data sets, (5) spectral pretreatment, (6) wavelength range(s), and (7) a chemometric model, and can therefore be considered more complicated than the types of analytical procedures for which ICH Q2(R1) was written. This guidance is intended to discuss how the concepts described in ICH Q2(R1) can be applied to NIR analytical procedures that use chemometric models and to describe CDER's current thinking about other issues related to the development and validation of NIR analytical procedures. This guidance is also intended to describe the type of information that should be submitted about NIR analytical procedures in applications.

III. MODES OF MEASUREMENT FOR NIR IMPLEMENTATION

The guidance describing a regulatory framework for process analytical technology (PAT)[3] differentiates between the modes of measurement that can be used by a process analyzer during the manufacturing process to measure a chemical or physical property-of-interest based on vibrational spectroscopy (e.g., NIR, Raman). For NIR-based process analyzers, the following modes of measurement are commonly used for process understanding, monitoring, and control:

- Off-line, where the sample is analyzed away from the process stream or reactor (e.g., identity testing of raw material samples by NIR in the quality control (QC) lab).

- At-line, where the sample is removed, isolated from, and analyzed in close proximity to the process stream or reactor (e.g., measurement of tablet assay or content uniformity by

[3] Guidance for Industry *PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*.

NIR, where the NIR analyzer is located next to the tablet press and fed manually or automatically).

- On-line, where the sample is diverted to a side stream off the main manufacturing process, and may be returned to the process stream or reactor (e.g., measurement of cell density in an anaerobic fermentation process using a flow through cell).

- In-line, where the sample is not removed from the process stream or reactor (e.g., an in-line monitoring of blend uniformity by NIR, where the NIR analyzer is interfaced with the blender through a window and takes continuous spectra measurements).

The following section describes some specific considerations for different modes of NIR implementation:

A. At-line or Off-line

Generally, off-the-shelf NIR interfaces are used for at-line or off-line applications. When called for by a specific application, customized sample holders can be used. The following factors should be considered during the development of at-line or off-line measurements.

- Measurement

  Typical NIR instruments allow transmission and reflectance measurements. Transmission measurement allows probing of the bulk of the sample, but the useful spectral range is often limited and the spectra may contain more noise. Reflectance measurement is dominated by surface signal, but typically has lower noise and a wider useful spectral range. Transmission measurement offers advantages over reflectance measurement when sample homogeneity cannot be assured independently. Selection of an appropriate measurement type should be based on the optical properties of the sample and the intended application.

- Spectral Acquisition Time

  Spectral acquisition time is the period during which a specified number of scans are averaged into a sample spectrum. The spectral acquisition time should be selected to simultaneously optimize both the signal-to-noise ratio and the measurement duration for a given application.

- Sampling

  A sampling plan should be developed to ensure that the samples represent the process. Samples should be drawn based on rational criteria and intended to ensure that the samples accurately portray the material being sampled. Additionally, this can involve time- and location-based sampling.

- Sample Preparation

  Sample preparation (i.e., changing the physical characteristics of the sample to make it more suitable for NIR analysis (e.g., grinding)) is normally not necessary. However, in situations when sample preparation is performed before spectral acquisition, the sample preparation used for calibration and validation samples should be the same as that used for batch samples before measurement during routine operations.

B. In-line or On-line

This implementation typically utilizes a specialized analyzer and custom built interface to provide an acceptable signal-to-noise ratio and spectral acquisition time. The following factors should be considered during the development of in-line or on-line measurements.

- Interface

  The appropriate measurement interface depends on the application. For example, to monitor blending in a rotary blender or mixer, a sapphire window is often built into the blender or mixer wall or lid with an analyzer bolted outside the mixer to ensure that the analyzer will not be dislodged by the rotary motion of the equipment.

  For other types of measurements (e.g., measuring solvent content during drying), a probe connected to the analyzer by fiber optic cable can be used. The NIR signal transmitted through fiber optic cable should be adequate for the intended measurement. The location of the interface (e.g., position, distance, depth) should ensure that representative spectra are obtained. NIR interface consistency and cleanliness should be maintained throughout the entire data acquisition to ensure data integrity. For some applications, multiple interfaces may be used to ensure representative measurement.

- Spectral Acquisition

  To accurately monitor a blending/mixing operation, the interface should be exposed to the material being blended or mixed throughout the entire spectral acquisition time. For rotary blenders, spectral acquisition time and frequency are typically adjusted so that sample spectra are obtained only while the interface is exposed to the material being blended or mixed (e.g., triggers based on chronometry or gravity are used to synchronize the start or stop of spectral acquisition).

  Before the process is implemented, manufacturers should confirm that material does not stick or bind to the interface window during rotation. Additionally, the fluid dynamic properties (i.e., granular flow) of material within the blender should be understood and characterized to ensure that the material analyzed through the interface represents the blended material as a whole and will not segregate during spectral acquisition.

- Data Collection

  For rotary blenders, if wireless communication is used to transmit the NIR signal to the controller, installed hardware and software should be adequate to ensure the robustness and integrity of the data transmission.

- Sampling

  Assessment of the effective sample size is important for some applications (e.g., blend uniformity analysis). The effective sample size during NIR measurements can be evaluated from the diameter of the NIR beam, its depth of penetration, and the density of material. The effective sample size is generally small because the NIR beam illuminates a small sample volume illuminated by the NIR beam. For blend uniformity analysis, the effective sample size should be comparable to a unit dose.

- Reference Measurement

  Ideally, spectral acquisition and reference analysis are performed on identical samples and subsequently used to develop the calibration model. This may be difficult to achieve, particularly for in-line measurements. When identical samples cannot be used, the pairing of the spectra with the reference results should be justified.

IV. DEVELOPMENT OF NIR MODELS

An NIR model, which is an integral part of the NIR procedure, is a mathematical expression that describes how the NIR spectral data are related to the analyte property-of-interest. The development of an NIR model is usually based on chemometrics. NIR models can be categorized as quantitative (e.g., for assay) or qualitative (e.g., for identification). Another type of model involves a rate of change of the process (e.g., blending). Typical steps to develop NIR models are described below.

A. Construction of a Calibration Set

An essential part of developing an NIR model is the construction of a calibration set. The spectra that comprise the calibration set are acquired from calibration samples. To create a robust model, the variation built into the calibration samples should include an appropriate concentration range for the component to be analyzed and other possible sources of variability (e.g., process, analyzer, variation in physical characteristics of materials). Additionally, expected variation in process parameters (e.g. design space parameters) that have a potential to influence spectral response should be built into the calibration samples.

- Calibration Samples

  Calibration samples should mimic as closely as possible the samples that are expected from the commercial process. Samples from batches produced at the intended

commercial scale or representative of the commercial process are ideal because they generally exhibit the expected process variability. If these calibration samples alone do not provide a sufficient range of variability, additional samples can be prepared under laboratory conditions. When preparing calibration samples, the manufacturer should consider several factors, including, but not limited to, the following:

- Potential for variation from the sample preparation (e.g., intra-batch inhomogeneity) that could affect the calibration results.

- Physical attributes of prepared samples that ensure spectral response similar to that of material manufactured using the commercial process (e.g., lab-prepared tablets have physical characteristics equivalent to tablets from the commercial process).

- Spectral preprocessing that adequately minimizes the undesired influence of physical attributes of both lab-prepared and production samples on measured spectra.

- When qualitative NIR models are used to identify pharmaceutical materials, calibration samples that represent the expected variability from each material should be included. For example, calibration samples can use qualified materials from multiple vendors or different manufacturing lots

- For quantitative NIR models, inclusion of concentrations of the analyte of interest that span a range that is wider than acceptable limits to ensure that the model can characterize non-conforming materials.

- When the NIR procedure is intended to simultaneously characterize multiple analytes, design of experiment methodology that aids selection of the optimal combination of concentrations of components in calibration samples.

Other sources of variability that can influence the calibration set include sample presentation, environmental conditions, and the use of different instruments. Additional factors for consideration during calibration include:

- Potential variability from sample presentation should be built into the calibration set.

- Environmental variability can be addressed either by measuring spectra under different environmental conditions, or by maintaining constant environmental conditions during sample acquisition and spectral measurement.

- Inclusion of spectra from multiple instruments of the same type can facilitate future extensions of the calibration to a new instrument or to a new site.

- Instrument characteristics may constitute a significant source of variability. This can be lowered by activating standardization option, often available in the software associated with NIR instrument. Design of calibration sets to support standardization can facilitate future extension of the calibration model to new instrument or to new sites.

B. Sample Presentation

For both qualitative and quantitative analyses, the presentation of samples to the NIR instrument can influence the spectral quality, which affects the performance of the NIR analytical procedure. A typical NIR analyzer offers various options for sample presentation (e.g., reflectance versus transmission measurement, single versus multiple sample holders, acquisition window size, number of individual fibers in a fiber cable). Manufacturers should decide which option will provide the most useful data.

Equivalent sample presentation conditions should be used for obtaining calibration and routine production sample spectra. If sample holders are used that provide for multiple positions (e.g., tablet wheels or trays), manufacturers should ensure that the location of a sample in the holder does not affect the obtained spectra. Similarly, if the spectra depend on which side of a tablet is presented to the spectrometer, the procedure should ensure that the same side of the tablet is presented to the spectrometer for each scan. When hand-held probes are used, replicate scans of the same material should be included. Similarly, when samples are placed in vials and scanned through the vial bottom, replicate scanning to reduce the interference of vial variability should be performed.

C. Development of Chemometric Models

Chemometric models are multivariate models that describe the relationship between spectral variation in the calibration set and sample characteristics (e.g., drug substance concentration, sample identity). For NIR analytical procedures, the multivariate models are usually built upon predictor variables that are wavelength dependent spectral intensities or their linear combinations. The models are usually developed using common chemometric algorithms such as principal component analysis (PCA), partial least square (PLS), or principal component regression (PCR), which are typically included with the commercially available chemometric software.

The following factors should be considered by the manufacturer when developing chemometric models:

- The wavelength range of the spectral data used to construct the chemometric model does not need to include the full range of the analyzer. However, restricting the calibration wavelength range to cover only narrow regions around an analyte peak can compromise the model’s robustness and model performance should be tested rigorously using both narrow and full ranges.

- Raw NIR spectra should usually be pretreated to reduce variability and enhance spectral features related to chemical composition (e.g., effects such as particle size or compression forces on the intensity of scattered light can be removed through spectral pretreatment). However, inappropriate pretreatments can introduce artifacts or reduce the signal-to-noise ratio.

- The appropriate number of factors or latent variables should be chosen to avoid under- or over-fitting of the model. Most chemometric software packages include statistical tools to help determine the optimal number of factors. Establishing the number of factors based on the number of components in the analyte sample is not considered to be a suitable substitute for the use of these tools. Overfitting the data with too many fit parameters can lower robustness and lead to poor predictive performance of the calibration model.

- Potential outliers in the calibration set (e.g., samples with high leverage or high residuals, or atypical NIR spectra or reference results) can often be identified by visual inspection of the data or during internal validation and should be investigated. Additionally, most software programs contain outlier diagnostics. Those data resulting from spectral acquisition or reference analysis errors should be considered confirmed outliers and should be rejected. Otherwise, these samples should be retained in the calibration set.

- When using an NIR procedure for measuring the active ingredient content of the tablet, the calibration model should be developed using assay values from individual tablets, based on the matched weight and concentration for each tablet. Conversely, during routine analysis, the NIR concentration result from each tablet should be corrected for the weight of the same tablet to obtain the assay value.

- The preprocessing regimen, spectral range, and the number of latent variables can be optimized to improve model performance and robustness through internal validation.

D. Internal Validation for Quantitative Calibration Models

The following are two common approaches to internal validation: (1) cross-validation using the calibration set and (2) validation using an internal validation set.

- Cross-Validation

  This validation process involves removing one or more spectra from the calibration set, creating a model based on the remaining spectra, applying the model to the spectra that have been removed, and calculating the differences between the known reference values and the values predicted by the model (i.e., residuals). These steps are applied sequentially to the entire calibration set and the resulting residuals can be used to calculate the root mean squared error of cross-validation (RMSECV).

- Validation Using an Internal Validation Set

  This validation process involves applying one or more models obtained from the calibration set to the internal validation set. The resulting residuals can be used to calculate the standard error of prediction (SEP).

The RMSECV or SEP can be used as one criterion for model optimization. The optimum model for the intended purpose of the analytical procedure usually exhibits acceptable error while minimizing the sensitivity of the error to small variations in sample characteristics or model parameters.

At the end of the optimization process, the standard error of calibration (SEC) should be comparable to the standard error of the reference procedure.

E. Internal Validation of Identification Libraries

Identification libraries should be internally validated to check proper assignment of spectra to ensure there are no conflicts among library product and confirm that the library threshold is appropriately set. Internal validation is performed by treating each spectrum in the library as an unknown and determining whether each spectrum is correctly and uniquely identified by the library.

F. Development of Rate of Change Models

Rate-of-change models are typically used to monitor and detect the end-point of dynamic processes (e.g., blending or mixing). The end-point usually coincides with the measured rate of change falling below a predefined threshold which indicates that the process is sufficiently close to completion. These models can be based on a change of concentration of active ingredient or other component or a change in spectral magnitude related to the component-of-interest.

Manufacturers should consider the following when developing the rate of change models:

- The end-point criteria should provide assurance that the detected end-point is not a transient phenomenon (e.g., specifying that the rate of change remains below the end point value for a pre-determined time or number of blender revolutions).

- For end-point criteria that are based on statistical considerations (e.g., F-value between consecutive blocks of spectra), any underlying assumptions (e.g., data normality) should be met.

- For blends in which a component-of-interest is present in low concentration, risk exists that the endpoint represents uniformity of major components. In such cases, the end point criteria should be demonstrated to be indicative of uniform distribution of the low-level component of interest.

- For models that are based on a change of concentration of active ingredient or other component, the quantitative NIR model for the component should be separately developed and validated to ensure accurate and reliable end point detection.

V. EXTERNAL VALIDATION OF NIR ANALYTICAL PROCEDURES

Validation should be performed after the chemometric model underlying the NIR analytical procedure is developed. This is sometimes referred to as "external validation." Internal validation of the chemometric model is not considered a substitute for external validation.

The samples used for external validation should span a suitable range of operating conditions (i.e., ranges expected during commercial production) and should be obtained independently from the calibration and internal validation samples used during the development of the NIR models. These samples should be produced at the intended commercial scale or represent the commercial process. The number of samples analyzed during validation should be sufficiently large to provide statistically meaningful results. Results from the NIR and reference analytical procedures should be acquired using the same samples.

A. Qualitative Analytical Procedures

Qualitative NIR procedures based on identification libraries should be validated for specificity. Specificity is defined by ICH Q2(R1) as "the ability to assess unequivocally the analyte in the presence of components which may be expected to be present." This normally involves demonstrating that positive and negative controls yield the correct pass or fail results. Positive controls are usually comprised of samples of known identity and acceptable quality as confirmed by independent reference testing. Placebo or other samples that show spectral similarities to the tested material can be used as negative controls.

B. Quantitative Analytical Procedures

Quantitative procedures should be validated for accuracy, precision, specificity, linearity, and range.[4]

- Accuracy

  The accuracy of the NIR procedure should be determined by a comparison of the results from the NIR analytical procedure using external validation samples with the results from a suitable reference analytical procedure. The standard error of prediction (SEP) can be calculated as a measure of accuracy relative to the external validation set. Significant differences between SEC and SEP could indicate differences between the calibration samples and validation samples or an inadequately optimized calibration model and should be investigated and rectified appropriately. The

[4] ICH Q2(R1).

independent validation set used to determine accuracy should span a suitable range of sample concentrations.

- Precision

  The standard deviation of repeat measurements (i.e., repeatability) can be a useful measure of precision. Samples for repeatability measurement should cover the expected range of sample variation. Multiple measurements should be made on each sample. After each measurement, the sample should be repositioned in the sample holder or on the sample presentation module. Intermediate precision, involving different analysts or different days, should also be determined.

- Specificity

  Specificity is normally considered to be verified if the main features of the plot of the regression coefficients correspond to those of the NIR spectrum of the analyte of interest. The spectrum should be pretreated in the same way as spectra used in the model.

- Linearity

  To evaluate linearity, analytical results for the external validation samples obtained using the NIR analytical procedure should be compared to the results obtained using the reference analytical procedure. When the values are plotted over a suitable range, a correlation coefficient close to 1 and a y-intercept close to 0 indicate acceptable linearity.

- Range

  As recommended in ICH Q2(R1), the appropriate range for validation studies should depend on the attribute being evaluated.

- Detection and Quantitation Limits

  If the NIR analytical procedure will be used near the limit of its detection capability, LOQ or LOD should be determined. Examples include the analysis of minor components or drying end-point detection.

- Robustness

  To evaluate robustness during validation, validation samples should include anticipated sources of variability during commercial production (e.g., raw materials, operating and environmental conditions).

C. Rate of Change Procedures

For rate of change procedures (e.g., blending or mixing), the validation should demonstrate the adequacy of the NIR end-point criteria and the specificity of the NIR procedure for components-of-interest. The adequacy of the end-point criteria should be confirmed with an appropriate reference methodology (e.g., traditional blend uniformity analysis or an alternative downstream determination of uniformity). During validation, the blending/mixing operation should be stopped as soon as the end-point criteria are achieved. Continuing to blend after the end-point criteria are achieved can produce misleading results. Specificity can be demonstrated by showing that the wavelength region used for the NIR procedure includes major bands of the components-of-interest.

VI. IMPLEMENTING AND MAINTAINING NIR ANALYTICAL PROCEDURES

The quality management system should ensure that NIR analytical procedures are appropriately followed, maintained, and revised as needed throughout the product life cycle. To accomplish this, manufacturers should establish appropriate hardware maintenance procedures (e.g., reliability testing to estimate the mean time to failure (MTTF) and mean time between failure (MTBF), suitability testing, maintenance schedule, repair). In addition, the manufacturer should establish procedures to:

- Continually monitor calibration model predictions to detect changes, including trends and shifts.

- Recognize circumstances that might warrant revision of the calibration model. Examples of such circumstances may include the following:

    - Significant changes of materials, equipment, and/or manufacturing processes.
    - Unusual or erroneous NIR results.
    - Failure to meet routine method verification criteria.
    - Transfer of the NIR analytical procedure.
    - Major repair of the analyzer.

- Revise and revalidate the calibration model.

Such procedures should maintain the model over the product life cycle and may be documented in the manufacturer's internal quality system.

When implementing NIR procedures, a manufacturer should consider developing contingency procedures to follow if NIR equipment fails before or in the middle of measurements or ongoing operations. This is particularly important for in-line or on-line implementation of an NIR analytical procedure.

VII. INFORMATION SUBMITTED IN AN APPLICATION

The applicant should provide information about all NIR analytical procedures that are included in the control strategy. Information should be provided related to the following: (1) NIR analytical procedure, (2) development of the NIR analytical procedure, and (3) validation of the NIR analytical procedure. Additionally, the applicant should provide a high level summary of the plans for life cycle maintenance of models associated with NIR analytical procedures. Information for NIR procedures used only for development or information purposes during commercial manufacturing does not need to be submitted.

If NIR and another equivalent method are both submitted, the applicant should indicate the role of each method to provide clarity for decisions concerning batch disposition. Specifically, the applicant should indicate which method would be used for routine release and which would be considered the alternate method in accordance with 314.50(d)(1)(i) (for drug substance) and 314.50(d)(1)(ii)(a) (for drug product).

A. PROCEDURAL INFORMATION

The following basic information should be provided for NIR analytical procedures:

- Purpose of the procedure.
    - Location within the process (i.e., which unit operation).
    - Mode of measurement (in-line, on-line, at-line, off-line).
    - Property or attribute-of-interest to be measured.
    - Intended use (e.g., in-process, end-product release testing).
- Analyzer and software information.
    - Instrument manufacturer, model, and type (e.g., dispersive or Fourier Transform).
    - Name and version number of the software used for spectral acquisition, model development, and routine prediction. Indicate if the software is custom-made.
    - Data acquisition information including measurement principle (e.g. transmission or reflectance mode), acquisition time, number of spectra averaged, number of scans, number of replicates, wavelength ranges, etc.
    - Information on sampling accessory. If a specialized sample holder is used, information on sample orientation (e.g., random, with indentation up or down).
- Description of the steps for the sample analysis. It should include, when relevant:
    - Reference (background) spectrum collection.
    - Sample presentation.

- Sample preparation or conditioning.
- System suitability description.
- For assay and content uniformity the tablet weight measurement.

For in-line or on-line methods, the following additional information should be provided:

- Information on how the NIR instrument is interfaced to the process.

- A description of the system or procedure followed to ensure that the interface remains clean and free of adherent material.

- For on-line blending or mixing, a description of the system used to trigger spectral acquisition that ensures the interface window remains covered by the blend throughout the acquisition.

- End-point criteria of a process, such as blending or mixing.

- A contingency plan addressing a failure of the NIR analyzer and situations when an in-process NIR procedure fails to detect the pre-established end-point, as applicable.

B. DEVELOPMENT INFORMATION

The following basic information should be provided about the development of NIR analytical procedures:

- Calibration and internal validation sets:

  - Information about the respective batches including, batch number, batch size, and number of samples from each batch used to create the calibration set.

  - If an internal validation set is used, the method of separating calibration and internal validation spectra.

  - For quantitative procedures, distribution of the reference values in the calibration and internal validation sets (it can also be shown in the form of predicted vs. reference results or residual plots).

  - If some samples are prepared in small batches to represent a known concentration of the analyte, indication of differences in appearance (shape, size dimensions, indentation) from the production samples.

  - Information on sources of variation included in the calibration set and how they relate to the potential variations in raw materials and process parameters expected during commercial production.

- Chemometric model:
    - Rationale for the selection of wavelength ranges, spectral pretreatments, algorithms and thresholds used. For spectral pretreatments the order that the processing was applied should be reported
    - For quantitative methods, internal model validation to support the number of latent variables, including PRESS (predicted residual error sum of squares) plot or other diagnostics to demonstrate that the model is not over-fit
    - For a qualitative model (identification library), some measure of positive predictive value should be provided. This could include the distances (match values) between all library products for small libraries or graphical representation for large libraries.
    - Description of outlier handling.
    - Examples of spectra, raw and pre-treated, including pure component spectra, if available.

For in-line or on-line methods, the following additional development information should be provided:

- Estimation and rationale for the effective sample size for blending or mixing.
- Data demonstrating that the interface is covered with sample and that the sample remains stationary during spectral acquisition.
- Data demonstrating suitability of probe window location
- Justification with data supporting end-point criteria of a process such as blending/mixing.
- Data supporting contingency plans for a situation when the in-process NIR method does not indicate end-point even after prolonged processing, as appropriate.

C. VALIDATION INFORMATION

Basic information that should be provided about the validation of NIR analytical procedures includes:

- Information on the external validation set:
    - Information about the respective batches, including batch number, batch size, and number of samples from each batch used to create the external validation set.

- For quantitative procedures, distribution of the reference values in the external validation set (it can also be shown in the form of predicted versus reference results or residual plots).

- Validation of a quantitative procedure, including specificity, linearity, accuracy, precision, and robustness, as appropriate (see section V).

- Validation of a qualitative method, including specificity.

- Information on the reference analytical procedure and its standard error.

- Data to demonstrate that the model is valid at commercial scale (e.g., use of commercial scale data during procedure development).

- High level summary of how the procedure will be maintained over the product's life cycle.

For in-line blending or mixing, validation information should also include sampling strategy for the reference analytical procedure and test results used to verify blend uniformity determined by NIR.

For measuring assay and content uniformity, validation information should also include a comparison of NIR results (including tablet weight correction) with reference analytical procedure results for the same tablet. The comparison should be performed on statistically significant number of individual tablets from commercial scale batches.

VIII. POSTAPPROVAL CHANGES

This section provides recommendations for the reporting category for postapproval changes related to NIR analytical procedures. It is not intended to describe what information should be provided by the applicant regarding the assessment of the effect of a change on the identity, strength, quality, purity, or potency of a drug product.

In general, the appropriate reporting categories for postapproval changes to NIR procedures depend on the following conditions:

- Probability that the change to the NIR procedure could compromise the performance of the procedure (e.g., accuracy, specificity).

- Potential impact on product quality and its severity if the analytical procedure is compromised, which depends on the role of the procedure in the control strategy (e.g., failure of a procedure used for the release of the final product can have a high impact on product quality).

The table below is a schematic representation of how applicants can use these considerations to determine the type of change and appropriate reporting mechanism:

Types of Changes and Reporting Categories				
		Potential impact of change on procedure performance		
		Low	Medium	High
Potential impact of failure on product quality (depends on the role of the procedure in the control strategy)	Low	Minor Change (Annual report)	Minor Change (Annual report)	Moderate Change (CBE[5] 30)
	High	Minor Change (Annual report)	Moderate Change (CBE 30)	Major Change (PAS)[6]

A. Major Changes (Prior Approval Supplement)

Shown below are examples of changes related to NIR analytical procedures that FDA considers to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product and should be submitted as a prior approval supplement. These changes are expected to have a high potential impact on both the procedure performance and product quality.

- The addition of a new NIR analytical procedure (or replacement of a traditional analytical procedure) used for release or stability testing of drug product or drug substance, or in-process procedures used for real time release testing (RTRT).

- A change to a principle of operation of an NIR analytical procedure (e.g., reflectance to transmission) used for release or stability testing of drug product or drug substance, or in-process procedures used for RTRT.

- A replacement of an analyzer, software or sample interface that requires a new calibration model (e.g. totally new spectral set) resulting from a new calibration set for an NIR analytical procedure used for release or stability testing of drug product or drug substance, or in-process procedures used for RTRT.

B. Moderate Changes (Changes Being Effected in 30 Days Supplement)

The following is a list of changes related to NIR analytical procedures that FDA considers to have a moderate potential to have an adverse effect on the identity strength, quality, purity, or potency of the drug product. These should be submitted as a CBE 30 supplement. These changes are expected to have the following: (1) a high potential impact procedure performance but a low potential to impact product quality, or (2) a medium potential impact procedure performance and a high potential to impact product quality.

[5] Changes being effected.
[6] Prior approval supplement.

- Examples of changes to an NIR analytical procedure that is used for release or stability testing of a drug product, a drug substance or in-process procedures used for RTRT:

    - Addition of a significant number of new spectra to the original calibration set provided that the procedure is validated using acceptance limits equivalent to those used for the original procedure.

    - Transfer of an NIR procedure when the procedure is validated using acceptance limits equivalent to those used for the original procedure.

- Addition of a new NIR analytical procedure (or replacement of a traditional analytical procedure) used for testing raw materials, in-process materials or intermediates for drug substance and drug product

- Establishing a new chemometric model resulting from a new calibration set for an NIR analytical procedure used for testing raw materials, in-process material, or intermediates for a drug substance and a drug product.

C. Minor Changes (Annual Report)

The following is a list of changes related to NIR analytical procedures that FDA considers to have a minimal potential to have an adverse effect on the identity strength, quality, purity, or potency of the drug product. These should be submitted in the annual report. These changes are expected to have the following: (1) a low potential to impact both procedure performance and product quality, (2) a medium potential impact procedure performance and a low potential to impact product quality, or (3) a low potential impact procedure performance but a high potential to impact product quality.

- Examples of changes to an NIR analytical procedure that are used for testing raw materials and in-process material or intermediates:

    - Addition of a significant number of new spectra to the original calibration set provided that the procedure is validated using acceptance limits equivalent to those used for the original procedure.

    - Transfer of NIR procedure provided that the procedure is validated using acceptance limits equivalent to those used for the original procedure.

    - Addition of a few new spectra to the original calibration set for an NIR procedure used for release or stability testing of a drug product or a drug substance, including in-process procedures used for RTRT, provided the NIR procedure is validated using acceptance limits equivalent to those used for the original procedure.

- A replacement of an analyzer, or sample interface that does not result in recalibration as demonstrated by successful verification of the existing procedure on the new hardware.

Note that changes not mentioned in the above three categories, can use a similar approach to determine appropriate filing strategy. If unclear about selection of an appropriate regulatory notification pathway, the applicant can contact appropriate review division.

IX. GLOSSARY

Accuracy: As defined in ICH Q2(R1), the accuracy of an analytical procedure expresses the closeness of agreement between the value that is accepted either as a conventional true value or an accepted reference value and the value found. For NIR procedures, the accepted reference value is usually obtained from a reference procedure.

NIR Model: A mathematical expression that describes how the NIR spectral data are related to the analyte property-of-interest.

Chemometrics: Multivariate methods to analyze, extract, or compare data from chemical systems.

Calibration Model: A model used to predict characteristics or properties of unknown samples.

Calibration Set: A set of spectra with corresponding known sample concentrations or physical characteristics of interest.

Detection Limit: The lowest amount of analyte in a sample that can be detected at a specified confidence level but not necessarily quantitated with suitable precision and accuracy.

External Validation: In the context of quantitative models, refers to confirmation of NIR calibration model performance with an independent (or naïve) data set. For identification libraries, external validation involves analysis of samples not represented in the library (challenges) to demonstrate discriminative ability of the library model.

External Validation Set: A set of spectra and related reference values that is separate from the calibration set and internal validation set and is used to give an independent assessment of the performance of the calibration model. Ideally, the range of the validation set should be similar to that of the calibration set.

Quantitation Limit: The lowest amount of analyte in a sample that can be quantitatively determined with suitable precision and accuracy.

Identification Test: For NIR procedures, a qualitative implementation of NIR spectroscopy where an unknown sample spectrum is compared to one or more spectra representing materials of known identity included in a spectral library.

Internal Validation: A part of the model optimization process that involves a comparison of NIR predictions with corresponding reference values. This can be accomplished using an internal validation set (test set) or the calibration data by cross validation. Internal validation is not a substitute for the external validation of the model.

Internal Validation Set: A set of spectra obtained from samples that have physical and chemical characteristics that span a range of variability similar to the samples used to construct the calibration set.

Linearity: The ability of the procedure (within a given range) to achieve predictions that are proportional to the concentration of analyte in the sample (i.e., the reference concentration).

Precision: The closeness of agreement between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision is determined by three factors: (1) repeatability (intra-assay precision), (2) intermediate precision (within laboratory), and (3) reproducibility (between laboratories).

PRESS Plot: A plot of predicted residual error sum of squares (PRESS) as a function of the number of latent variables. PRESS values decrease initially with an increasing number of latent variables, reach a minimum, and then increase again or remain stable. PRESS plots are used to estimate an optimal number of latent variables to avoid overfitting.

Rate of Change Models: An NIR procedure based on the observation of changes of concentration of active ingredient, other ingredient (i.e., the ingredient of primary interest), or spectral magnitude. This approach is typically used for blending monitoring where the endpoint is often related to the rate of change falling below a certain threshold.

Real Time Release Testing: The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls.

Reference Method: An analytical procedure (e.g., an HPLC test) that is used to obtain reference values of calibration and validation samples.

Reference Values: Numerical results obtained using a reference method.

Robustness: The capacity of NIR model predictions to remain unaffected by small variations in manufacturing and environmental conditions. It indicates the procedure's reliability during normal usage.

Specificity: The ability to unequivocally assess the analyte in the presence of components or other compounds that may be expected to be present (e.g., impurities, degradants, matrix etc.).

Standard Error of Calibration (SEC): A measure of the difference between NIR values and reference values of the same calibration set. SEC is given by the following equation:

$$SEC = \sqrt{\frac{\sum_{i=1}^{n}\left(y_{C,i} - Y_{C,i}\right)^2}{n - p - 1}}$$

Where: Yc = NIR predicted value obtained from a calibration set sample; yc= referencevalue from the same calibration set sample; n = number of samples; p = number of coefficients in the model (e.g., wavelength (MLR), principle components (PCA or PCR), factors (PLS)).

Standard Error of Prediction (SEP): A measure of the difference between NIR values and reference values of validation set. SEP is given by the following equation:

$$SEP = \sqrt{\frac{\sum_{i=1}^{n}\left(y_{V,i} - Y_{V,i}\right)^2}{n}}$$

Where: Yv = NIR predicted value from a validation set sample obtained using the established NIR calibration model; yv= reference value of the same validation set sample; n = number of samples.