Development and Submission of Near Infrared Analytical Procedures

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2021
Pharmaceutical Quality/CMC

Development and Submission of Near Infrared Analytical Procedures

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2021
Pharmaceutical Quality/CMC

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Development and Submission of Near Infrared Analytical Procedures Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations to applicants to aid the development, validation, and use of near infrared (NIR)-based analytical procedures in evaluating the identity, strength, quality, purity, and potency of drug substances and drug products. The recommendations apply to new drug applications (NDAs), abbreviated new drug applications (ANDAs), and supplemental NDAs and ANDAs for small molecule drugs. The principles in this guidance also apply to drug substances and drug products covered in Type II drug master files. FDA intends to issue recommendations specific to NIR methods used for biological products under biologics license applications in a future revision to this guidance. This guidance provides recommendations to applicants for applying the concepts described in the guidance for industry *PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance* (September 2004) (PAT guidance) and the International Council for Harmonisation (ICH) guidance for industry *Q2(R1) Validation of Analytical Procedures: Text and Methodology* (November 2005)[2] to NIR analytical procedures that use chemometric models.[3] This guidance also provides recommendations for submitting NIR documentation in applications.[4]

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

[2] In November 2005, the ICH incorporated both the ICH guidance for industry *Q2A Text on Validation of Analytical Procedures* and the ICH guidance for industry *Q2B Validation of Analytical Procedures: Methodology* into ICH Q2(R1). Although the FDA guidance web page separately lists ICH Q2A and ICH Q2B, any references to ICH Q2(R1) in this guidance, unless otherwise indicated, refer to both ICH Q2A and ICH Q2B.

[3] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[4] This guidance contains technical and scientific recommendations that may be useful during development of NIR-based analytical procedures for nonprescription drugs to which the application submission recommendations in this guidance do not apply.

Additionally, NIR implementation at commercial manufacturing sites must be in accordance with current good manufacturing practice (CGMP) regulations at 21 CFR parts 210 and 211 for drug products[5] and should be in accordance with the ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016) recommendations for drug substances.

This guidance pertains only to the development and validation of NIR analytical procedures and does not provide recommendations concerning the setup, qualification, maintenance, or calibration of NIR instruments. Although this guidance specifically addresses NIR spectroscopy, this guidance's concepts of validation can be applied to other process analytical technologies (PATs), including, for example, Raman, focused beam reflection measurement, particle imaging, and X-ray.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, 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.

II. BACKGROUND

NIR analytical procedures are increasingly being used in the pharmaceutical industry (1) for identification testing and assay measurements performed on pharmaceutical starting materials, intermediates, and finished products, and (2) for monitoring and controlling manufacturing processes. Therefore, to ensure the quality of pharmaceuticals, it is important for applicants who use these procedures to develop robust NIR analytical procedures and to understand both the factors that can affect the performance and suitability of these procedures and the approaches that can be used to validate them.

The PAT guidance and ICH Q2(R1) provide information about analytical procedures, such as those used for NIR. The PAT guidance explains the different 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 or Raman). ICH Q2(R1) provides:

- A "discussion of the characteristics that should be considered during the validation of analytical procedures"

[5] Although NIR procedures could be used in positron emission tomography drug production, it is not typical. Therefore, references to 21 CFR part 212, Current Good Manufacturing Practice for PET Drugs, are not included in this guidance.

- "[G]uidance and recommendations on how to consider the various validation characteristics for each analytical procedure"

- An "indication of the data that should be presented in a new drug application"[6]

Although many of the concepts described in ICH Q2(R1) can apply to a wide variety of analytical methodologies, ICH Q2(R1) does not address some characteristics unique to NIR analytical procedures.[7] NIR analytical procedures typically combine the following features:

- Instrumentation elements (e.g., an analyzer consisting of an NIR spectrophotometer, a reflectance or transmission probe, or spectral analysis software)

- Acquisition parameters

- A sample presentation (interface)

- A sampling scheme for process applications

- The composition of spectral datasets

- Spectral pretreatments

- Wavelength ranges

- A chemometric model

This guidance addresses the NIR-specific features listed above that are not addressed in ICH Q2(R1).

[6] See ICH Q2B, p. 1.

[7] At the time of this guidance's publication, the ICH Q2(R2)/Q14 expert working group planned to develop a new ICH quality guideline, ICH Q14, on analytical procedure development, and revise the ICH Q2(R1) guideline on validation of analytical procedures, with a view to potentially combine both documents into one, for simplification and clarity. See https://www.ich.org/page/quality-guidelines. ICH is a consensus-driven process that involves technical experts from regulatory authorities and industry parties in detailed technical and science-based harmonization work that results in the development of ICH guidelines. The commitment to consistent adoption of these consensus-based guidelines by regulators around the globe is critical to realizing the benefits of safe, effective, and high-quality drug products for patients as well as for industry. As a Founding Regulatory Member of ICH, FDA plays a major role in the development of each of the ICH guidelines, which FDA then adopts and issues as guidance to industry.

III. GENERAL MODES OF MEASUREMENT FOR NIR IMPLEMENTATION

For NIR-based process analyzers, the following modes of measurement are commonly used for process understanding, monitoring, and control:[8]

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

- At-line, where the sample is removed, isolated from, and analyzed in close proximity to the process stream or reactor (e.g., a measurement of a tablet assay or content uniformity by 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., a 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 subsections describe some specific features that applicants should consider during development when selecting the appropriate mode of measurement for NIR implementation.

A. Off-Line or At-Line

Generally, off-the-shelf NIR interfaces are used for off-line or at-line measurements. However, customized sample holders can be used when indicated for a specific application. Applicants should consider the following factors while developing off-line or at-line measurements:

- **Measurement.** NIR instruments typically allow for transmission measurements and for reflectance measurements, but selection of the appropriate measurement type should be based on both the optical properties of the sample and the intended application. For example, although a transmission measurement probes the bulk of the sample, a transmission measurement's useful spectral range is often more limited than a reflectance measurement's useful range, and a transmission measurement's spectra may contain more noise than a reflectance measurement's spectra. Similarly, although a reflectance measurement includes a surface signal component, that reflectance measurement typically produces less noise and a wider useful spectral range than a transmission measurement. Therefore, applicants should carefully choose the NIR instrument that balances these issues.

[8] When used for monitoring or control of the drug product during commercial manufacturing, each of these sample testing modes must satisfy existing CGMP requirements (see, for example, 21 CFR 211.110 and 21 CFR 211.165).

- **Spectral Acquisition Time.** A spectral acquisition time that simultaneously optimizes both the signal-to-noise ratio and the measurement duration for a given application should be selected.

- **Sampling.**[9] A sampling plan should be developed that ensures that the samples (1) represent the processed materials, (2) are based on rational criteria, and (3) accurately portray the material being sampled. Additionally, the sampling plan should involve time- and location-based sampling.

- **Sample Preparation.** Generally, there is no need to prepare (or change) the physical characteristics of the sample (e.g., through grinding) to make the sample more suitable for NIR analysis. However, if samples are prepared before spectral acquisition, the same sample preparation should be used both for calibrating and validating the sample and for analyzing the production batches.

B. On-Line or In-Line

Typically, on-line or in-line measurements use a custom-built interface to provide an acceptable signal-to-noise ratio and spectral acquisition time. Therefore, the following factors during the development of on-line or in-line measurements should be considered:

- **Interface.** First, 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., for measuring the solvent's content during drying), a probe connected to the analyzer by a fiber optic cable can be used. (However, an NIR signal transmitted through a fiber optic cable should be adequate for the intended measurement.) Second, the location of the interface (e.g., the interface's position, distance, and depth) should ensure that spectra that represent the properties of the entire processed materials are obtained. Finally, NIR interface consistency and cleanliness should be maintained throughout the entire data acquisition process to ensure data integrity.

- **Spectral Acquisition.** The interface should be designed to minimize the interference of spectral acquisition. To accurately monitor an operation unit, the interface should be exposed to the material being processed throughout the entire spectral acquisition time. For rotary blenders, spectral acquisition time and frequency should be adjusted so that sample spectra are obtained only while the interface is exposed to the material being blended or mixed. (For example, triggers based on chronometry or gravity should be used to synchronize the start or stop of spectral acquisition.) For liquid samples, the effect of bubble formation should be evaluated.

[9] When used for monitoring or control of the drug product during commercial manufacturing, each of these sampling approaches must satisfy existing CGMP requirements at 21 CFR 211.110, 21 CFR 211.160, and 21 CFR 211.165.

During development of the interface, it should be confirmed that the material does not stick or bind to the interface window. Additionally, applicants should understand and characterize the material properties within the unit operation to ensure that the material analyzed at interface is representative of the material as a whole.

- **Data Collection.** If wireless communication is used to transmit the NIR signal to the controller, hardware and software that ensures the robustness and integrity of the data transmission should be installed.

- **Sampling.** The assessment of an effective sample size is important for some applications (e.g., for a blend uniformity analysis). Applicants can determine if a sample size is effective for NIR measurements by evaluating the diameter of the NIR beam, the beam's depth of penetration, and the density of the sample. Generally, an effective sample size is small because the NIR beam would then illuminate a small sample volume. Specifically, for monitoring blend homogeneity, the effective sample size should be comparable to a unit dose of the finished drug product.

- **Reference Measurement.** Ideally, spectral acquisition and reference analysis should be performed on the same samples that will be used to develop the calibration model. It may be difficult, however, to use the same samples, particularly for in-line measurements. Therefore, when identical samples cannot be used, applicants should justify the pairing of the spectra with the reference results.

IV. DEVELOPMENT OF NIR MODELS

An NIR model is an integral part of an NIR procedure. NIR models can be categorized as either quantitative (e.g., for assay) or qualitative (e.g., for identification or for limit testing for the absence of polymorphs). Typically, the development of an NIR model is based on chemometrics and should involve the following steps.

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 the calibration samples. To create a robust model, applicants should build a calibration set with samples that: (1) include an appropriate concentration range for the component to be analyzed; (2) address potential sources of variability (e.g., a variation in the processes, the analyzer, the physical characteristics of the materials, the water content, or the temperature); and (3) cover the expected variations in process parameters (e.g., in-design space parameters) that have a potential to influence the spectral response.

Calibration samples should mimic as closely as possible the samples that are expected to be representative of the commercial process; calibration samples from batches that are either produced at the intended commercial scale or representative of the commercial process are ideal because they generally exhibit the expected process variability. If the samples obtained from the

process do not provide a sufficient range of variability, additional samples can be prepared under laboratory conditions. When preparing calibration samples, applicants should consider the following factors, including, but not limited to:

- Variations from sample preparations (e.g., lack of batch homogeneity) can affect the calibration results.

- The physical attributes of the prepared samples should ensure a spectral response similar to the response of materials manufactured with the use of a commercial process. For example, tablets prepared in a laboratory should have physical characteristics equivalent to tablets prepared with a commercial process.

- Spectral preprocessing should adequately minimize the influence of the difference in physical attributes for the laboratory-prepared and production samples on the measured spectra.

- To capture the expected material variabilities calibration samples of qualified materials from multiple vendors or from different manufacturing lots should be used.

- For quantitative NIR models, concentrations of the analyte of interest should span a range that is wider than the acceptable specification limit to ensure that the model can characterize nonconforming materials.

- When the NIR procedure is intended to simultaneously characterize multiple analytes, the design of the experiment methodology can be used to select the optimum combination of the concentrations of analytes in the calibration samples.

- Any potential variability from the 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 introduce a significant source of variability. This variability can be lowered by activating standardization options, which are often available in the software associated with NIR instruments. The design of calibration sets to support this standardization can facilitate future extension of the calibration model to new instruments or to new sites.

B. Presentation of Samples

For both qualitative and quantitative analyses, the presentation of samples to the NIR instrument can influence the instrument's spectral quality, which would therefore affect the performance of the NIR analytical procedure. A typical NIR analyzer offers multiple options for the presentation of samples (e.g., diverse reflectance and transmission measurements, single and multiple sample holders, different probe window sizes, and a variety of individual fibers in a fiber cable); applicants should decide which option best fits the requirements of the NIR procedure to their processes and properties of interest. In addition, applicants should:

- Use an equivalent interface and sample presentation to obtain calibration and routine production sample spectra

- Ensure that, if sample holders are used that provide for multiple positions (e.g., tablet wheels or trays), the location of their samples in those holders does not affect the obtained spectra

- Ensure that, if the obtained spectra depend on which side of a tablet is presented to the spectrometer, the same side of the tablet is presented to the spectrometer for each scan

- Include replicate scans of the same materials if hand-held probes are used

- Perform a replicate scanning of the samples that are placed in vials if those samples are scanned through the vial to reduce the interference of vial variability

C. Development of Chemometric Models

For NIR analytical procedures, chemometric models are usually built upon predictor variables that are either wavelength-dependent spectral intensities or the linear combinations of those wavelength-dependent spectral intensities. Chemometric models are usually developed using common chemometric algorithms such as principal component analysis, partial least square, and principal component regression, which are all typically included with commercially available chemometric software.

Applicants should consider the following factors 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; therefore, model performance should be tested rigorously using both narrow and full ranges.

- Usually, raw NIR spectra should be pretreated to reduce their variability and to enhance spectral effects related to chemical composition. For example, impact of particle size or compression force on the intensity of scattered light can be significantly reduced 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 underfitting or overfitting 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 fitting parameters can lower the robustness of the model and lead to poor predictive performance of the calibration model.

- Potential outliers in the calibration set (e.g., samples with high leverages or high residuals or atypical NIR spectra or reference results), which can often be identified either by visual inspection of the data or during internal validation, should be investigated. Most software programs contain outlier and model diagnostics during prediction. Data resulting from spectral acquisition or reference analysis errors should be considered *confirmed outliers* and therefore rejected. Any inclusion or exclusion of outliers should be justified.

- To increase the accuracy of the NIR measurement of the active ingredient content of a tablet, the calibration model should be developed using reference assay values from individual tablets based on the matched weight and concentration for each tablet. Conversely, during a routine analysis of the model, the NIR concentration result from each tablet should be corrected for the weight of that tablet to obtain the assay value. If weight correction is not feasible, an alternative approach should be justified.

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

D. Internal Validation of Identification Libraries

Identification libraries based on the chemometric models should be internally validated (1) to verify the proper assignment of spectra, (2) to ensure that there are no conflicts among library products, and (3) to confirm that the library threshold is appropriately set. This internal validation should be performed by treating each spectrum in the library as an unknown and by determining whether each spectrum is correctly and uniquely identified by the library.

E. Internal Validation of Quantitative Calibration Models

Two common approaches for internally validating quantitative calibration models include (1) cross-validation using the calibration set, and (2) validation using an internal validation set.

(1) **Cross-Validation Using the Calibration Set.** The cross-validation process involves the following steps:

(a) Removing one or more spectra from the calibration set
(b) Creating a model based on the remaining spectra
(c) Applying that model to the spectra that have been removed
(d) Calculating the differences between the known reference values and the values predicted by the model (i.e., the residuals)

These steps should be sequentially applied to the entire calibration set, and the resulting residuals can be used to calculate the root mean square error of cross-validation.

(2) **Validation Using an Internal Validation Set.** Validation using an internal validation set involves applying one or more of the models that were 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 root mean square error of cross-validation or SEP can be used as one criterion for model optimization. The optimum model for the analytical procedure usually exhibits an acceptable error but minimizes the sensitivity of the error to small variations in either sample characteristics or model parameters.

At the end of the optimization process, the standard error of calibration (SEC) should ensure that the measurement is performed with the accuracy necessary for the intended purpose of the analytical procedure, such that the accuracy of the NIR method is comparable to that of the reference method.

F. Development of Rate-of-Change Models

Typically, rate-of-change models are used to monitor and detect the endpoint of dynamic processes (e.g., blending or mixing).[10] If these models are used, the endpoint usually will coincide with the measured rate of change reaching a predefined threshold that indicates that the process is complete. These models can be based on a change in the (1) concentration of the active ingredient or other component, or (2) spectral magnitude related to the component of interest.

Applicants should consider the following when developing rate-of-change models:

- The endpoint criteria should provide assurance that the detected endpoint is not a transient phenomenon. For example, applicants can specify that the rate of change remains below the endpoint value for a predetermined time or number of blender revolutions.

[10] When used for monitoring or control of the drug product during commercial manufacturing, the implementation of the processing endpoint must satisfy the CGMP requirements (see, for example, 21 CFR 211.110) and be validated (see 21 CFR 211.100 and 21 CFR 211.160).

- For endpoint criteria that are based on statistical considerations (e.g., the 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 a low concentration, risk exists that the endpoint represents a uniformity of the major components. For these blends, the endpoint criteria should indicate a uniform distribution of the low-level component of interest.

- If a rate-of-change model for blend uniformity (e.g., blending or mixing) is based on a quantitative model for either the active ingredient or another component, the rate-of-change model and the quantitative model should separately be developed and validated to ensure an accurate and reliable endpoint detection.

V. EXTERNAL VALIDATION OF NIR ANALYTICAL PROCEDURES

Applicants should perform validation after their chemometric models are developed. This validation is sometimes referred to as *external validation*. Internal validation of the chemometric model is not considered a substitute for external validation.

The samples used by applicants for external validation should: (1) span a suitable range of operating conditions (including the range expected during commercial production); (2) be independent from the calibration and internal validation samples used during the development of the NIR models; (3) be of a sufficiently large number to provide statistically meaningful results; and (4) either be produced at the intended commercial scale or represent the commercial process. Also, results should be acquired either (1) from the NIR and reference analytical procedures using the same sample when feasible, or (2) by using representative samples and providing a justification for those samples.

Qualitative analytical, quantitative analytical, and rate-of-change procedures should be validated as follows.

A. Qualitative Analytical Procedures

Qualitative NIR procedures based on identification libraries should be validated for specificity and robustness. Specificity normally involves demonstrating that positive and negative controls yield the correct pass or fail results. Positive controls usually comprise samples of known identity, and acceptance of the sample's quality should be confirmed by independent reference testing. Placebos or other samples that show spectral similarities to the tested material can be used as negative controls.

B. Quantitative Analytical Procedures

Applicants should validate quantitative procedures for accuracy, precision, specificity, linearity, range, detection and quantitation limits, and robustness.[11]

- **Accuracy.** The accuracy of the NIR procedure should be determined by comparing the results from the NIR analytical procedure using external validation samples with the results from a suitable reference analytical procedure.

  The SEP can be calculated as a measure of accuracy relative to the external validation set. Significant differences between the SEC and SEP, as well as significant biases, could indicate either differences between the calibration samples and the validation samples or an inadequately optimized calibration model, both of which should be appropriately investigated and rectified.

  The independent validation set used to determine the accuracy of the NIR procedure 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 measurements should cover the expected range of sample variation. Multiple measurements should be made of each sample. If possible, the sample should be repositioned in the sample holder or on the sample presentation module after each measurement. Intermediate precision, which involves different analysts or different days, should also be determined.

- **Specificity.** Specificity is conventionally considered to be verified if the main features of the loadings plots correspond to the loadings plots of the NIR spectrum of the analyte of interest. The NIR spectrum should be pretreated in the same way as spectra used in the model. Another element of specificity is the ability of the method to reject outliers (e.g., samples with high leverages or high residuals).

- **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. If the resulting values are plotted over a suitable range, a correlation coefficient close to 1 and, where applicable, a y-intercept close to 0 indicate an 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, detection limit and quantitation limit should be determined by, for example, analyzing minor components or detecting the endpoint for drying.

[11] See ICH Q2(R1).

- **Robustness.** Robustness can be addressed during the calibration model's development by including anticipated sources of variability (e.g., raw materials and operating and environmental conditions). Robustness can be confirmed during validation by using validation samples that include sources of variability that may occur during commercial production.

C. Rate-of-Change Procedures

To validate rate-of-change procedures (e.g., blending or mixing), manufacturers should demonstrate both the adequacy of the NIR endpoint criteria and the specificity of the NIR procedure for components of interest. First, the adequacy of the endpoint criteria should be confirmed with an appropriate reference methodology (e.g., a traditional blend uniformity analysis). During the validation of the rate-of-change procedure (e.g., blending or mixing), the procedure should be stopped as soon as the endpoint criteria are achieved; otherwise, misleading results may occur. Second, specificity can be demonstrated by showing that the wavelength region used for the NIR procedure included major bands of the components of interest.

VI. IMPLEMENTING AND MAINTAINING NIR ANALYTICAL PROCEDURES

Applicants must ensure that NIR analytical procedures are appropriately followed, maintained, and updated as needed throughout the drug product's life cycle in accordance with CGMP requirements.[12] The CGMP regulations for finished pharmaceuticals require that drug product manufacturers establish procedures to:

- Appropriately maintain hardware (by, for example, conducting reliability testing to estimate the mean time to failure and the mean time between failure, performing suitability testing, and creating and following a maintenance and repair schedule)[13]

- Monitor calibration model predictions and model diagnostics to detect changes, including trends and shifts;[14] continual monitoring is recommended to ensure rapid detection and timely intervention to prevent product failure

- Recognize circumstances, such as the following, that may warrant revision of the calibration model:[15]

[12] When used for monitoring or control of the drug product during commercial manufacturing, CGMP requirements at, for example, 21 CFR 211.110, 21 CFR 211.68, and 21 CFR 211.160 apply.

[13] 21 CFR 211.68

[14] 21 CFR 211.100(b); 21 CFR 211.110; 21 CFR 211.160(b)(4)

[15] 21 CFR 211.68; 21 CFR 211.160(b)(4)

  - 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[16]

The extent of the model's maintenance (e.g., periodic verification) should be dependent on the effect of the model on the drug product's quality. Retention of development and maintenance of NIR analytical procedures and calibration model must be consistent with record retention requirements in the regulations.[17] The calibration model should be retained in a knowledge management system for as long as the information is useful in evaluating the model's performance and history of use that is relevant to any product released using this model.[18]

Applicants should consider developing contingency procedures to follow if their NIR equipment fails before or in the middle of measurements or ongoing operations. This could reduce the need to reject drug material and limit production delays. These contingency procedures are particularly important for the on-line or in-line implementation of an NIR analytical procedure when the measurement is to be used to satisfy a CGMP requirement.

VII. INFORMATION SUBMITTED IN AN APPLICATION

An applicant must provide information about every NIR analytical procedure that is included in its commercial control strategy,[19] as well as information about the development and validation of these procedures (as detailed in sections VII.A. through VII.C.).[20] Additionally, applicants should provide high-level summaries of their plans for the life cycle maintenance of models associated with NIR analytical procedures. Detailed life cycle maintenance plans, as well as records of any changes in software versions over the life cycle, must be maintained at the manufacturing site as part of the manufacturing site's quality systems risk and knowledge management programs and available for inspection.[21] Information about the NIR procedures

[16] 21 CFR 211.68; 21 CFR 211.180(e)

[17] 21 CFR 211.68; 21 CFR 211.180. NIR model information should be retained for active pharmaceutical ingredients consistent with ICH Q7 and as described here.

[18] See the ICH guidance for industry *Q10 Pharmaceutical Quality System* (April 2009) about knowledge management.

[19] 21 CFR 314.50(d)

[20] See ICH Q2(R1).

[21] 21 CFR 211.180

used only for developmental or informational purposes does not need to be included in the application.

If NIR and another equivalent method are both submitted, the applicant should indicate the role of each method to provide clarity for decisions concerning in-process/intermediate material and finished batch disposition. Specifically, the applicant should indicate which method will be used for the routine release and, if applicable, which will be considered the alternate method per 21 CFR 314.50(d)(1)(i) (for drug substances) and 21 CFR 314.50(d)(1)(ii)(a) (for drug products).

A. Procedural Information

For NIR analytical procedures, applicants should provide at least the following information:

- The purpose of the procedure, including:
  - The location within the process (i.e., which unit operation)
  - The mode of measurement (i.e., in-line, on-line, at-line, or off-line)
  - The property or attribute of interest to be measured
  - The intended use (e.g., for in-process or end-product release testing)
- The analyzer and software specifications, such as:
  - The instrument manufacturer, model, and type (e.g., dispersive or Fourier Transform)
  - Whether custom-made software will be used for spectral acquisition, model development, and routine prediction
  - Data acquisition, including the measurement principles (e.g., the transmission or reflectance mode), the acquisition times, the number of spectra averaged, the number of scans, the number of replicates, and the wavelength ranges, among others
  - The sampling accessories
  - The sample's orientation (e.g., random, with indentation up or down) if a specialized sample holder is used
- The steps for the sample's analysis, including, when relevant:
  - The reference (background) spectrum collection
  - The sample presentation
  - The sample preparation or conditioning

- A system suitability description
- The tablet weight measurement for assay and content uniformity

For in-line or on-line methods, applicants should also provide information, as applicable, regarding:

- How the NIR instrument is interfaced to the process
- The system or procedure followed to ensure that the interface remains clean and free of adherent material
- For on-line blending or mixing, the system used to trigger spectral acquisition to ensure that the interface window remains covered by the blend throughout the acquisition
- The endpoint criteria of a process, such as blending or mixing
- Any contingency plan that addresses both a potential failure of the NIR analyzer and a potential failure of an in-process NIR procedure to detect the pre-established endpoint

B. Development Information

For the development of NIR analytical procedures, applicants should provide at least the following information:

- For calibration and internal validation sets:
  - The associated batches, including the number of batches, the batch size, and the number of samples from each batch that were used to create the calibration set
  - If an internal validation set is used, the method used for distinguishing the calibration set from the internal validation spectra
  - For quantitative procedures, the distribution of the reference values in the calibration and internal validation sets (which can also be shown in the form of predicted versus reference results or in residual plots)
  - If some samples are prepared in small batches to represent a known concentration of the analyte, any differences in appearance (such as in shape, size, dimension, or indentation) between the small batch samples and the production samples
  - Any sources of variation included in the calibration set and how these variations relate to potential variations in the raw materials and process parameters expected during commercial production

- For chemometric models:
  - A rationale for using a particular wavelength range, spectral pretreatment,[22] algorithm, and threshold
  - For quantitative methods, the internal model validation conducted to justify the number of latent variables, including a predicted residual error sum of squares (PRESS) plot or other diagnostic to demonstrate that the model is not overfit
  - For a qualitative model (identification library), the positive predictive value used, such as the distances (match values) between all library products for small libraries or a graphical representation for large libraries
  - The applicant's handling of outliers
  - Raw and pretreated spectra, including pure component spectra, if available
- For in-line or on-line methods, as applicable:
  - Data that demonstrate the suitability of the probe window location
  - Data that support a contingency plan for the potential failure of the in-process NIR method to detect the pre-established endpoint even after prolonged processing
- For on-line and in-line methods for blending or mixing, as applicable:
  - An estimation of and a rationale for the effective sample size, including the applicant's consideration of the sample's potential movement during spectral acquisition
  - A justification for using a rate-of-change-based method, as well as any data supporting the endpoint criteria of the blending or mixing process

C. Validation Information

For the validation of NIR analytical procedures, applicants should provide at least the following information:

- The external validation set, including:
  - The associated batches, including the number of batches, the batch size, and the number of samples from each batch that were used to create the external validation set

[22] For spectral pretreatments, applicants should also provide information about the order that the processing was applied.

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

- The specificity, linearity, accuracy, precision, and robustness of the quantitative procedures used, as appropriate[23]

- A validation of the qualitative method used, including testing for specificity of that method

- The reference analytical procedure and its standard error

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

- The procedure's maintenance over the drug product's life cycle, which can be written as a high-level summary and include, for example:

  - The frequency of, methods for, and acceptance criteria for periodic model verification

  - Any possible triggers for method verification to be conducted outside of the regular schedule

For in-line blending or mixing, applicants should also provide validation information about their sampling strategies for the reference analytical procedure and the test results used to verify the blend uniformity as determined by NIR.

For measuring assay and content uniformity, applicants should also, when feasible, provide validation information comparing their NIR results (including any tablet weight correction) with the reference analytical procedure results for the same samples. This comparison should be performed on a statistically significant number of individual samples from commercial-scale batches.

VIII. LIFE CYCLE MANAGEMENT

This section provides recommendations to applicants for the life cycle management of their qualitative and quantitative NIR analytical procedures. Because of the unique characteristics and complexity of NIR procedures, as compared to conventional analytical procedures, FDA's recommendations for reporting postapproval changes to NIR procedures are detailed.

After an applicant successfully validates and implements its NIR procedure, it should periodically evaluate the procedure during the life cycle of the drug product to continually ensure

[23] See section V.B. of this guidance.

that the procedure remains fit for its intended purpose. This periodic evaluation is particularly important because NIR procedures (1) are highly sensitive to the manufacturing process and to the incoming material's attributes, and (2) offer only limited availability of real-time reference standards.

Changes to NIR procedures used for commercial manufacturing must be handled in accordance with CGMP[24] and should be managed under the manufacturing site's pharmaceutical quality system (PQS).[25]

An applicant should determine an appropriate mechanism for reporting each postapproval change to its NIR procedure based on the potential impact the change has on:

- The performance of the procedure (e.g., the procedure's accuracy or specificity)
- The identity, strength, quality, purity, or potency of the drug substance and drug product

The significance of that impact (i.e., low, medium, or high) depends on the role of the procedure in the applicant's overall control strategy. For example, a failure of the procedure used for the real-time release testing (RTRT)[26] of a finished drug product can have a high impact on drug product quality.

The following table is a schematic representation of how applicants can evaluate the potential impact of a change to the NIR procedure and the appropriate corresponding reporting mechanism (i.e., managed solely under the manufacturing site's PQS, an annual report (AR), a changes being effected in 30 days supplement (CBE-30), or a prior approval supplement (PAS)). The reporting categories suggested in this table apply when the corresponding supportive criteria are met as exemplified in section VIII.A. through D. of this guidance.

Table: Levels of Changes and Reporting Mechanisms

		Potential Impact of a Change on the Procedure's Performance		
		Low	**Medium**	**High**
Potential Impact of a Change on the Product's Quality[1]	Low	Minimal change (PQS[2])	Minor change (AR)	Moderate change (CBE-30)
	High	Minor change (AR)	Moderate change (CBE-30)	Major change (PAS)

[1] This potential impact depends on the role of the procedure in the applicant's overall control strategy.
[2] This implies that no regulatory reporting (AR, CBE, PAS) is needed.

[24] 21 CFR 211.22(c); 21 CFR 211.100(b); 21 CFR 211.166(a)

[25] See ICH Q10.

[26] See the ICH guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009).

The following subsections describe types of postapproval changes and provide recommendations for appropriate reporting mechanisms. These recommendations are written to be generally appropriate for any applicant and are not intended to address all possible scenarios for managing postapproval changes. If applicants implement a postapproval change not mentioned below, they can either use a strategy similar to the ones listed to determine the appropriate filing mechanism or, for special cases, request additional guidance from the relevant FDA review division. Applicants can also choose to use tools outlined in the ICH guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (May 2021), such as established conditions and comparability protocols (referred to in ICH Q12 as postapproval change management plans),[27] which can leverage increased product and process knowledge to support alternate approaches to identifying postapproval changes that require reporting along with the associated reporting categories.

A. Major Changes

Major changes to an NIR procedure could potentially have a high impact on the procedure's performance and on the quality of the drug substance or drug product. For example, FDA would expect the following changes to NIR analytical procedures to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, and potency of drug products:

- The addition of a new NIR analytical procedure that will be used for the RTRT of drug substances or drug products.

- The replacement of an analyzer or a sample interface that will necessitate a new spectral set and a new calibration model for the NIR analytical procedure that is used for the RTRT of drug substances or drug products. (When the acceptance criteria for validation of the updated procedure are equivalent to those of the approved procedure, a reduced reporting category could be considered.)

- Significant changes to the in-process procedures used for the RTRT of drug substances or drug products where the acceptance criteria for validation of the revised procedure are not equivalent to those of the approved procedure.

Major changes, as described in the examples above, must be reported in a PAS.[28]

B. Moderate Changes

Moderate changes to an NIR procedure could potentially elicit either (1) a high impact on the procedure's performance but a low impact on the drug product's quality, or (2) a medium impact on the procedure's performance but a high impact on the drug product's quality. For example, FDA would expect the following change to an NIR analytical procedure to have a moderate

[27] See also the draft guidance for industry *Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information* (April 2016). When final, this guidance will represent FDA's current thinking on this topic).

[28] 21 CFR 314.70(b)

potential to have an adverse effect on the identity, strength, quality, purity, and potency of drug products:

- The establishment of a new chemometric model resulting from a new calibration set for an NIR analytical procedure that will be used for testing raw materials, in-process materials, or intermediates for a drug substance or a drug product

Such changes must be reported in a CBE-30 supplement.[29]

C. Minor Changes

Minor changes to an NIR procedure could potentially elicit (1) a medium impact on the procedure's performance but a low impact on the drug product's quality, or (2) a low impact on the procedure's performance but potentially a high impact on the drug product's quality. For example, FDA would expect the following changes to NIR analytical procedures to have a minimal potential to have an adverse effect on the identity strength, quality, purity, and potency of drug products:

- The addition of a new product (material) to a validated identification library, provided that the acceptance criteria are identical to the criteria used in the validation of the original procedure

- A minor change to the NIR procedure used for RTRT of the drug substance or drug product (e.g., addition or subtraction of few spectra, small change in a wavelength range) providing the following conditions are met:

  - The size, composition, distribution, and variation of the calibration and validation sets are equivalent to those used for the originally approved procedure

  - The spectral data are pretreated using the same method that was used for the original procedure

  - The number of factors is established using an approach that is the same (or similar) to the approach that was used in the original procedure

  - The validation of a revised NIR procedure covers at a minimum the same attributes with the same or improved acceptance limits as those used in the original procedure

Such changes must be reported in an AR.[30]

[29] 21 CFR 314.70(c)

[30] 21 CFR 314.70(d)

D. Other Minimal Changes

Minimal changes to an NIR procedure are those that have no or a low potential to impact the procedure's performance and the drug product quality. These changes would not require any regulatory notification; however, all changes should be managed and documented within the PQS[31] and must be approved by the site's quality unit.[32] For example, FDA would expect the following changes to NIR analytical procedures to have no potential adverse impact on the identity strength, quality, purity, and potency of drug products:

- Addition of a few spectra to augment variation in the calibration set, when major calibration parameters and scope of validation remains the same as in the original calibration model

- Repairs to an existing NIR instrument(s) when there is no change in the calibration model

- Update to existing software associated with the NIR procedure when verification shows there are no changes in the predictive performance of the method

[31] See ICH Q10.

[32] 21 CFR 211.22, 21 CFR 211.100, and 21 CFR 211.160.

GLOSSARY

Accuracy: As defined in ICH Q2(R1), "[t]he accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found."[33] For NIR procedures, the accepted reference value is usually obtained from a reference procedure.

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

Calibration Set: A set of spectra with corresponding physical characteristics and known concentrations.

Chemometric Models: Multivariate models that describe the relationship between the spectral variation in the calibration set and the sample's characteristics (e.g., the sample's drug concentration and identity).

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

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: For quantitative models, external validation involves confirming the NIR calibration model's performance with an independent (or naïve) dataset. For identification libraries, external validation involves analyzing samples (challenges) not represented in the library to demonstrate the discriminative ability of the library model.

External Validation Set: A set of spectra and the related reference values that are (1) separate from the calibration set and internal validation set, and (2) 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.

Identification Test: A qualitative implementation of NIR spectroscopy for NIR procedures 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. Internal validation 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. Although this guidance uses the term *internal validation*, other publications might use the terms *internal model testing* or *model optimization* instead, in particular when referring to multivariate methods in general.

[33] See ICH Q2A, p. A-1.

Internal Validation Set: A set of spectra with corresponding physical characteristics and known concentrations obtained from samples that have physical and chemical characteristics that span a range of variabilities similar to the samples used to construct the calibration set. Note that this guidance uses the term *internal validation set* for consistency; however, the equivalent terms *test set* or *internal test set* can be found in other publications.[34]

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

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

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

Predicted Residual Error Sum of Squares (PRESS) Plot: 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.

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

Rate-of-Change Model: An NIR procedure based on observed changes in (1) the concentration of the active ingredient, (2) the other ingredients (i.e., the ingredients of primary interest), or (3) the spectral magnitude. This model 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 (RTRT): The ability to evaluate and ensure the quality of the 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., a high-performance liquid chromatography test) to obtain the reference values of the calibration and validation samples.

Reference Values: Numerical results obtained from a reference method.

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

[34] See, for example, United States Pharmacopeia General Chapter <1039> *Chemometrics*.

Specificity: The ability to unequivocally assess the analyte in the presence of components that may be expected to be present (e.g., impurities, degradants, or matrices).[35]

Spectral Acquisition Time: The period during which a specified number of scans are averaged into a sample spectrum.

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

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

Where Y_c = NIR predicted value obtained from a calibration set sample; y_c = reference value from the same calibration set sample; n = number of samples; and p = number of coefficients in the model (e.g., wavelength (such as multiple linear regression), principle components (such as principal component analysis or principal component regression), or factors (such as partial least square)).

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

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

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

[35] See ICH Q2A, p. A-1.