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5 **Guideline on the use of Near Infrared Spectroscopy
6 (NIRS) by the pharmaceutical industry and the data
7 requirements for new submissions and variations**

8 Draft

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9
10 This guideline replaces the Note for Guidance on the Use of Near Infrared Spectroscopy by the
11 Pharmaceutical Industry and the Data Requirements for New Submissions and Variations,
12 CPMP/QWP/3309/01 and EMEA/CVMP/961/01

13
14 Comments should be provided using this [template](#) to QWP@ema.europa.eu

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15 **Guideline on the use of Near Infrared Spectroscopy**
16 **(NIRS) by the pharmaceutical industry and the data**
17 **requirements for new submissions and variations**

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84 **EXECUTIVE SUMMARY**

85 Near Infrared Spectroscopy (NIRS) is a technique, usually requiring tandem chemometric statistics,
86 with a wide and varied use in pharmaceutical, chemical, physical and process analysis. This includes
87 identification, qualification and assay of pharmaceutical starting materials, intermediates and finished
88 products and verification of physicochemical properties.

89 NIRS also constitutes one of the major techniques in Process Analytical Technology (PAT) and may also
90 be used as part of a Real Time Release Testing (RTRT) strategy. When used as such, NIRS is
91 underpinned by the principles of Quality by Design (QbD).

92 The suitability of an NIRS procedure is dependent upon many factors, including the instrumentation
93 and applied chemometrics, as well as the sound understanding of the physicochemical basis of the
94 measurement. This document provides guidance on the development, calibration, validation and
95 maintenance of NIRS procedures, when used with chemometric statistics and when used for direct
96 process monitoring.

97 The development and implementation of an NIRS procedure, with its interdependent stages, is
98 iterative and ongoing, and is amenable to the application of lifecycle concepts, which allow good
99 change control practice. Guidance on change control (whether or not within the remit of GMP), taking
100 into account the defined scope of the NIRS procedure, is provided.

101 The terminology used to describe NIRS reflects its wide and varied use, both within and outside the
102 pharmaceutical arena. A comprehensive glossary is therefore provided to support this guideline.

103 **1. Introduction**

104 To aid the narrative of this guidance, the following key terms are used:

105 NIRS method: describes the key elements, principally within the NIRS apparatus, which enable NIRS
106 measurement of the analyte of interest

107 NIRS model: describes how the NIRS spectral data measured using the NIRS method are related to the
108 analyte of interest, generally employing chemometric software.

109 NIRS procedure: describes how the NIRS method and model are used for the intended purpose, within
110 its defined scope (see section 4.1.1)

111 NIRS allows for fast, direct measurement of materials with little or no sample preparation, usually
112 generating complex spectra, which can only be interpreted easily by the use of chemometric models.
113 These are developed using carefully selected and representative samples, which have in turn been
114 qualified by a reference analytical method, using analytical reference standards. Consequently, NIRS is
115 not generally used as a 'primary' analytical method.

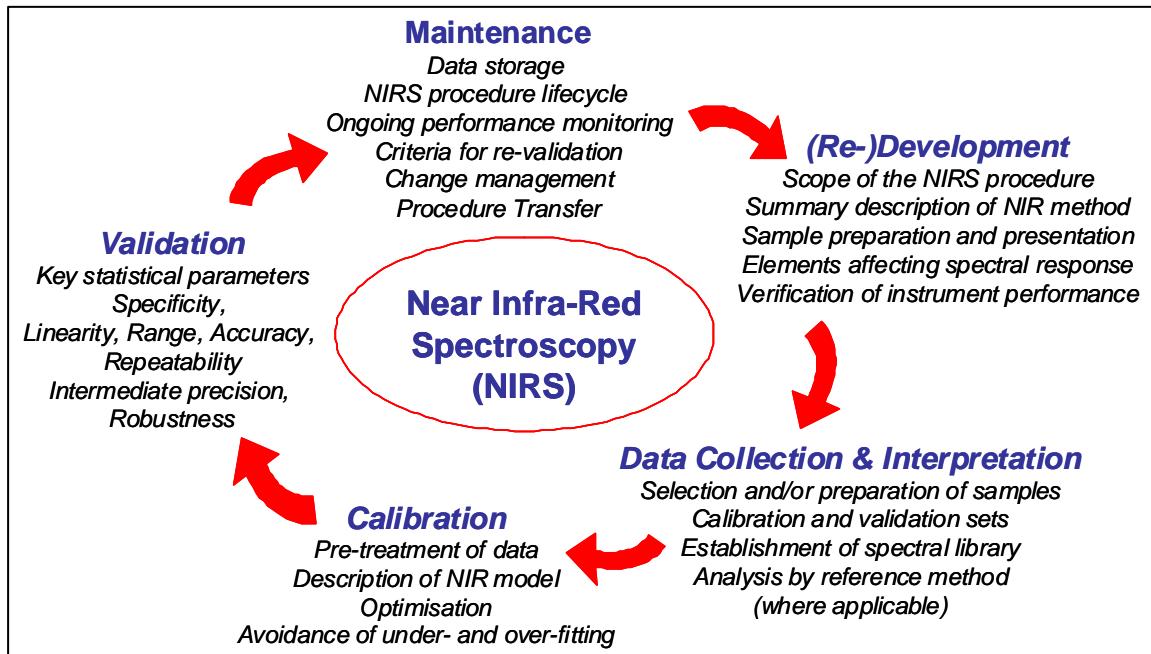
116 In general, NIRS procedures used for the release testing of drug substances or drug products need to
117 be developed and validated in conjunction with the reference methods. As NIRS procedures cannot be
118 repeated easily by official control laboratories, the reference methods and corresponding specifications
119 should remain in the authorised specifications, with an indication that these methods would not be
120 used for routine batch release.

121 For PAT NIRS procedures, e.g. dynamic process monitoring of a powder blend, it may not be possible
122 to refer to a conventional reference method, if this is unavailable for justified reasons e.g. the potential
123 for sampling errors.

124 It is recognised that the development and implementation of an NIRS procedure is iterative and that
125 the stages are interdependent. The main stages in developing and establishing NIRS procedures are
126 summarised in Figure 1. Some of these stages may not be necessary for all procedures such as
127 variations or PAT applications, for which the absence of information for these stages may then be
128 justified.

129 It is possible to update calibration models of NIRS procedures as new data become available following
130 the purchase or production of new analyte batches. This is considered good practice and is
131 recommended. For guidance on the implementation of changes, see Section 7.

132 Figure 1. The iterative nature of NIRS



143 2. Scope

144 This guideline describes the regulatory requirements for marketing authorisation applications and
145 variation applications submitted for medicinal products for human or veterinary use, which include the
146 use of NIRS.

147 NIRS differs from conventional analytical techniques such as HPLC or GC because chemometric
148 techniques are generally (although not exclusively) required for interpretation of the analyte signal.

149 NIRS is described in the European Pharmacopoeia; however a single reference to the Ph.Eur. general
150 chapter on NIR spectroscopy (Ph.Eur. 2.2.40) as a sole description for the NIRS procedure is
151 insufficient to support the use of such a procedure in marketing authorisation applications or variation
152 submissions.

153 This guideline outlines the requirements for applications in which NIRS is used for qualitative and
154 quantitative analysis or where it is used as a process analytical technology (PAT) for monitoring and
155 controlling drug substance synthesis and finished product manufacturing processes. Approaches other
156 than those described in this guidance may be used, if appropriately explained and justified.

157 The chemometric principles described within this guideline may also be applicable to other analytical
158 techniques.

159 **3. Legal basis**

160 This guideline should be read in conjunction with Directive 2001/82/EC, as amended and Directive
161 2001/83/EC, as amended.

162 This guideline should be read in conjunction with:

- 163 • Ph. Eur. Monograph 2.2.40.
- 164 • ICH Q2(R1) Guideline on Validation of Analytical Procedures (CPMP/ICH/381/95)
- 165 • VICH Guidelines GL1 & GL2 on Validation of Analytical Procedures (CVMP/VICH/590/98 &
166 CVMP/VICH/591/98)
- 167 • CHMP and CVMP Notes for Guidance on Process Validation (CPMP/QWP/848/96 &
168 EMEA/CVMP/598/99)
- 169 • ICH Q8: Guideline on Pharmaceutical Development
- 170 • ICH Q9: Guideline on Quality Risk Management
- 171 • ICH Q10: Guideline on Pharmaceutical Quality System
- 172 • ICH Guideline Q8, Q9 and Q10 - questions and answers (CHMP/ICH/265145/2009)

173 **4. General requirements**

174 **4.1. Development**

175 **4.1.1. Establishing the scope of the NIRS procedure**

176 The scope of the NIRS procedure (i.e. how the NIRS method and NIRS model are to be used for the
177 intended purpose) should be clearly identified in any application in which NIRS is used. The scope of
178 the NIRS procedure should include details of the NIRS method (i.e. the key elements that enable NIRS
179 measurement), the NIRS model (e.g. how the NIR spectral data are related to the analyte or property
180 of interest) as well as any limitations of the method (e.g. operating range of validity with respect to
181 analyte concentration, probe position, wavelength range, chemometric algorithm used etc). The
182 definition of the scope of the NIRS procedure is particularly important for the consideration of how
183 future changes to the procedure may be implemented from a regulatory perspective (see Section 7).

184 NIRS has a wide range of qualitative and quantitative applications and its use requires a sound
185 understanding of the physicochemical basis on which its measurements rely and of the instrumental
186 and chemometric principles involved. The applicant should identify any assumptions made during
187 procedure development.

188 The NIRS signal may be directly attributed to the analyte of interest or may be an indirect
189 measurement correlated with light scattering effects. The applicant should discuss the scope and
190 purpose of the NIRS procedure and show it to be relevant to the analyte or property under
191 consideration.

192 The NIRS procedure should, as a pre-condition, be able to reject samples that are outside of its
193 defined scope (e.g. out of range, compositionally incorrect).

194 The complex informative content of the NIRS signal often requires chemometric techniques to visualise
195 and extract relevant information from the spectra, or to show that the spectra are correlated to a
196 signal measured with the reference method. Chemometric data analysis and modelling are usually
197 performed using statistical software packages. In general, these work by correlating the variance in
198 the NIRS signal to a number of latent variables or factors, constrained by a set of calibration reference
199 data. There is always a risk that the correlations identified by the software are due to chance only and
200 not to changes in the analyte; therefore chemometric models should always be validated with an
201 independent set of samples.

202 **4.1.2. Summary description of the NIRS method**

203 Summary details of the NIRS method should be provided, including the instrument measurement
204 mode (e.g. reflectance, transmission, transreflectance), the principle of the monochromator (e.g.
205 grating, FT-IR), the wavelength (wavenumber) range used, the detector type (e.g. silicon, lead
206 sulphide), the optical bandwidth, the spectral resolution, wavelength accuracy and precision, the signal
207 to noise ratio, a description of any sampling devices and details of any other additional components or
208 controls considered necessary for the proposed procedure. The means of data collection, analysis and
209 associated software packages should also be described.

210 **4.1.3. Feasibility study**

211 The feasibility of using NIRS should be considered in the development of new procedures to
212 demonstrate that it is suitable for the intended purpose. Such a feasibility study may include (but is
213 not limited to), the determination of a suitable NIR response, investigations into specificity and matrix
214 interference and the examination of the effects of sample handling and preparation.

215 **4.1.4. Variables affecting spectral response**

216 Background physical and chemical variables, which may affect the spectral response, may be present.
217 It is not possible to list all possible variables, but these may include the environment in which
218 measurement takes place; sample temperature; residual moisture and solvents; sample thickness;
219 sample optical properties; optical quality of the glassware; polymorphism; particle size; homogeneity
220 and the age of the samples. Time of measurement and instrumental drift should also be considered.
221 Each known potential variable that may affect the spectral response should be considered and
222 discussed in turn and either shown to be insignificant or controlled satisfactorily (supported by
223 appropriate data).

224 **4.2. Data collection**

225 **4.2.1. Sample preparation and presentation**

226 Details of sample preparation, if any, should be provided and justified.
227 The interface between the sample and the NIRS detector should be described. The impact of possible
228 variations of the presentation on the NIRS response should be discussed, supported by appropriate
229 data, and, if shown to be significant, demonstrated to be controlled satisfactorily.

230 Before any NIRS measurement takes place, it is important to optimise the presentation of the sample
231 to the NIRS instrument. Examples of variables that should be optimised are sample orientation,
232 sample size, optical quality of glassware and environmental conditions.

233 The spectral range employed and the number of scans recorded per sample should be stated and
234 justified.

235 **4.2.2. Sample population**

236 Samples should be independent. The applicant should define what they understand to be a 'sample'
237 and their definition of an 'independent sample'. These definitions should be justified with respect to
238 the parameter that the intended model is proposed to predict.

239 Samples for NIRS analysis should be representative of the production process and should be collected
240 according to acceptable procedures for sampling. Samples that are representative of the commercial
241 process, which were obtained during development and pilot scale production may also be utilised.
242 Justification should be given to support the choice of samples.

243 The sample population for a qualitative or a quantitative procedure should cover all potential variation
244 that may be encountered in routine production. Such variation may include for example:

- 245 • concentration of the analyte of interest
- 246 • particle size
- 247 • material suppliers
- 248 • water content
- 249 • residual solvent content
- 250 • qualitative and / or quantitative variations in the matrix (e.g. excipient grade, formulation)
- 251 • process variation (e.g. samples collected over an extended period)
- 252 • sample age
- 253 • temperature

254 **4.2.3. Pre-treatment of data**

255 Given that NIR spectra are affected by physical parameters such as particle size and sample
256 presentation, raw NIR spectra are often treated mathematically prior to development and testing of
257 the calibration model. Such treatments include (but are not limited to) normalisation and derivation,
258 which are performed in order to remove unwanted sources of variation from the data prior to
259 treatment and to enhance spectral features.

260 Caution must be exercised when performing any pre-treatments because artefacts can be introduced
261 or essential information lost. Any pre-treatment of data should be documented and justified.

262 **4.2.4. Analysis by the reference method (when applicable)**

263 For NIRS procedures for which a reference analytical method is used, the samples used for NIRS
264 calibration and validation require authentication or quantitative values to be assigned by the reference

265 method. Ideally, reference measurements should take place at around the same time as NIR
266 scanning.

267 When a reference method is used, data to support the choice of reference method should be provided
268 and should include:

269 • a description of the analytical procedure according to Module 3.2.P.5.21 data requirements.

270 • details of the validation of the analytical procedure according to the Module 3.2.P.5.31 data
271 requirements and the ICH Q2(R1) Guideline on Validation of Analytical Procedures
272 (CPMP/ICH/381/95). For Veterinary applications reference is made to the VICH Guidelines GL1 &
273 GL2 Validation of Analytical Procedures (CVMP/VICH/590/98 & CVMP/VICH/591/98).

274 • details of relevant reference standards and materials according to the Module 3.2.P.6.1 data
275 requirements.

276 **4.2.5. Establishment of a spectral reference library**

277 The composition of the spectral reference library should cover the scope of the NIRS procedure and
278 should be subject to a change management system (subject to GMP inspection).

279 Batches should be representative of the marketed materials or products and laid down in a list of batch
280 numbers.

281 For qualitative analysis, where the spectral reference library may be very large or diverse, it may be
282 useful to divide the library into appropriate 'sub-libraries' to avoid calibration models becoming too
283 complex. The choice of subsets and the number of sub-libraries should be described and justified.
284 Measures should be taken to avoid using the wrong library. The use of only one library can avoid the
285 possible error of using the wrong library.

286 **4.3. Data interpretation**

287 **4.3.1. Description of the NIRS model**

288 The NIRS chemometric model (if used) should be described fully. Further information in relation to the
289 model is given in the sub-chapters for 'Qualitative Procedures' and 'Quantitative Procedures' (Sections
290 5.3 and 6.3).

291 **4.3.2. Statistical spectral quality test**

292 Before an NIRS model may be applied to a sample, a statistical spectral quality test (e.g. a model
293 suitability diagnostic) should be performed, to determine whether the characteristics of the sample fall
294 within the range of variation for which the model was calibrated and validated. In practice, such tests
295 (e.g. Hotellings T₂ or Distance to Model (DModX) plots) show whether the spectra for the sample fall
296 within a pre-defined range of variation or if the sample is an outlier. The steps taken to address
297 spectral outliers should be described (see Section 4.3.3).

¹ Or equivalent in the Notice To Applicants format for Veterinary dossiers.

298 If a sample fails this initial spectral quality test, it is poor scientific practice to test the sample using
299 the developed calibration model regardless, since a 'false' positive or otherwise invalid result would be
300 obtained.

301 A clear description of the spectral quality test should be described in any procedure involving the use
302 of NIRS. Such a test will often be performed automatically by the computer software but should
303 nevertheless be described and shown to be understood by the applicant.

304 **4.3.3. Outliers in sample data**

305 Any suspected outliers in the sample data (NIRS or reference data, where applicable), which are to be
306 included in the calibration, calibration test or validation data sets should be investigated and any
307 exclusions justified.

308 The term 'outlier' within this guideline refers to unexpected results or results outside of the specified
309 range. An outlier may be a 'spectral outlier' (spectral data outside but prediction result within the
310 range), a 'reference outlier' (spectral data within the range but reference value outside) or both
311 spectral and reference data beyond the proposed scope of the NIRS procedure.

312 In practice, there may be several reasons for outliers, e.g. a sample belonging to a different population
313 to the rest of the samples, instrument malfunction, reference method failure or transcription error. In
314 this sense, such a result may not necessarily be a false observation but merely an observation that is
315 different from the rest and that could have an undefined influence on the results of the analysis.

316 If a sample is shown to be an outlier because of characteristic properties, the sample should be
317 verified using an appropriate alternative analysis. After confirmation of authenticity, the sample may
318 be included in the spectral reference library and the model should be re-validated so as to include this
319 source of variation. This is an important part of the NIRS procedure lifecycle (see Figure 1, Section 1
320 and Section 7) and it is important to ensure that the procedure is updated and optimised.

321 At any stage of NIRS procedure (re-)development, calibration or validation, systems and procedures
322 should be in place to ensure that the handling of outliers in the data is performed properly. Such
323 procedures should be described.

324 **4.3.4. Out of Specification (OOS) results in routine batch analysis**

325 An OOS result for routine batch analysis by NIRS analysis should result in the investigation of the
326 affected batch under the company's pharmaceutical quality system. A rejection should be performed if
327 the OOS result is confirmed by a failure investigation.

328 A batch should not be released based on an OOS NIRS result and a within-specification result when
329 tested using the reference method (if available).

330 If, on investigation, the affected batch complies with the specification using the reference analytical
331 method, then this may indicate that the NIRS procedure has not been fully developed. The NIRS
332 procedure may then be updated as necessary (as per the NIRS procedure lifecycle concept, see Figure
333 1) and re-analysis undertaken such that the batch may be released within specification for both the
334 NIRS procedure and the reference method of analysis.

335 **4.4. Calibration**

336 Specific requirements for calibration are described in the sub-chapters for 'Qualitative Procedures' and
337 'Quantitative Procedures'.

338 **4.5. Validation**

339 Validation of NIRS procedures should comply with the data requirements for Module 3.2.P.5.32 and
340 the guidance given in ICH Q2(R1) Guideline on Validation of Analytical Procedures (CPMP/ICH/381/95).
341 For veterinary applications reference is made to the VICH Guidelines GL1 & GL2 Validation of Analytical
342 Procedures (CVMP/VICH/590/98 & CVMP/VICH/591/98).

343 The validation set of samples (for external validation) should be completely independent of the
344 calibration set (see 5.5 and 6.4).

345 A comparison of results obtained by analysis of the same set of samples by the NIRS procedure and
346 the reference method (if applicable) forms part of the validation of NIRS, along with independently
347 determined parameters, such as intermediate precision. In all cases, whether a reference method is
348 used or not, the acceptance criteria for validation should be specified and justified with reference to
349 the intended purpose of the NIRS procedure.

350 If the NIRS procedure is being presented in the initial registration dossier, validation data should also
351 be presented for the reference analytical method, if used (see section 4.2.4 Analysis by the reference
352 method).

353 If the NIRS procedure is being registered as a variation to a marketing authorisation for which a
354 reference method is already approved, then a summary of the validation data for the reference
355 method, in compliance with the current (V)ICH guidance on validation of analytical procedures, should
356 be provided.

357 Specific requirements for validation are described in the sub-chapters for 'Qualitative Procedures' and
358 'Quantitative Procedures'.

359 **4.6. NIRS in Process Analytical Technology (PAT) applications**

360 In the context of PAT applications, almost all NIRS procedures are specific to the nature of the
361 individual manufacturing processes. It is therefore not appropriate to prescribe exact requirements for
362 such procedures in this guideline.

363 The general data requirements described in this guideline are also applicable to NIRS PAT procedures
364 and should particularly take into account the intended purpose and scope of the procedure.

365 It is important that the NIRS methods are described in detail, with specific information in relation to
366 the applied PAT application (e.g. spatial placement of the devices, structural peculiarities of the
367 manufacturing facility and the nature and extent of sampling).

368 The amount of information required for an NIRS PAT procedure will depend on its intended purpose.
369 Any reduction in the extent of the description or control of the procedure (e.g. sampling, data pre-
370 treatment, NIRS model, calibration, validation, etc) should be fully described and justified scientifically.

² Or equivalent in the Notice To Applicants format for Veterinary dossiers.

371 Examples of NIRS in PAT applications include:
372 • drug substance manufacturing process steps such as chemical reaction kinetics, crystallisation,
373 drying and milling

374 • drug product manufacturing process steps such as granulation, blending, tablet hardness and
375 coating

376 In the case of the monitoring of a powder blend for homogeneity, the blend may be monitored in
377 terms of the measurement of the change of the NIR signal (e.g. its standard deviation) over time,
378 rather than in relation to a reference method such as HPLC.

379 **4.7. Summary of general data requirements**

380 The following data requirements apply to both qualitative and quantitative NIRS procedures.

381 Additional specific requirements for these are outlined in Sections 5 and 6 respectively.

- 382 • the scope of the NIRS procedure (see definition and explanation in Section 4.1.1)
- 383 • details of the composition of the calibration set, calibration test set and validation set of samples,
384 with justification
- 385 • description of the reference analytical method (where applicable)
- 386 • report(s) of the calibration and validation of the NIRS procedure and reference method (as
387 applicable, with summary details if already approved)
- 388 • details of how the NIRS procedure lifecycle will be managed (e.g. in accordance with this guideline)

389 If an applicant wishes to use terminology other than that described in this guideline, the terminology
390 should be fully and clearly explained (e.g. using a glossary).

391 **5. Qualitative procedures**

392 **5.1. Development**

393 NIRS has a wide range of qualitative applications, almost all of which could be divided into the three
394 areas of identification, qualification and conformity checks.

395 Identification and qualification

396 In pharmacopoeial monographs, identification is defined as the confirmation of a certain chemical
397 entity; however, the pharmaceutical industry uses a wider concept, implying that identification may
398 also include differentiation between different quality attributes of one chemical entity (e.g. particle
399 size, polymorphs).

400 To allow differentiation, this guideline uses the term identification as referring to chemical structure
401 only and qualification as referring to chemical and physical attributes.

402 If identification and/or qualification are based on more than one analytical method, then it should be
403 clear, if applicable, which reference method(s) will be replaced by the proposed NIRS procedure.

404 The identification or qualification of a substance (e.g. drug substance, excipient, blend, drug product,
405 intermediate) using NIRS is based on the comparison of the spectral data of the substance with the

406 spectral data of several samples of several batches of different substances present in a spectral
407 reference library. It may be necessary to apply chemometrics in order to compare the data and to
408 draw conclusions (pass, no match or ambiguous). The appropriate confidence level of the conclusion
409 should be justified.

410 If an ambiguous conclusion is obtained, the NIRS procedure should be adjusted such that the
411 substance will be correctly approved or rejected, or those substances that interfere should be excluded
412 from the scope of the procedure. Interfering substances or grades of substances may be identified as
413 one single entity if desired (e.g. different grades of lactose).

414 The classification of a substance can be performed in several stages. For example, the identification of
415 a chemical identity or a group of related substances may be performed, followed by the use of more
416 selective libraries for each individual grade or substance. This approach can be used to decrease the
417 likelihood of false positives/negatives. Qualification is often performed after the identification of the
418 sample has been ascertained. In this case, the library for qualification measures how well a sample
419 fits in with a library derived from samples chosen to represent the defined variability of a chemically
420 identical substance.

421 Where the NIRS procedure on its own is not sufficient to identify or qualify a substance, it should be
422 supplemented by other different analytical procedure(s) (e.g. chemical reaction or chromatographic
423 methods), so that the tests taken together ensure, as far as possible, specificity.

424 Conformity checks (PAT, dynamic process monitoring or trend analysis)

425 This guideline uses the term conformity as the conformation of characteristics in accordance with a
426 certain degree of similarity (chemical and/or physical attributes) to a specified standard. Such
427 conformity checks refer to process characterisation or trend analysis, for example the determination of
428 the endpoint of a process by monitoring the change in NIRS signal. These NIRS procedures are based
429 on processes that yield continuous values.

430 Conformity NIRS procedures may also be known as 'dynamic process monitoring', trend analysis or
431 Process Analytical Technology procedures (PAT, see Section 4.6) and will often not involve the use of a
432 reference analytical method because of difficulties in sampling for reference analysis.

433 Conformity checks should generally be treated in a similar way to qualitative procedures with respect
434 to calibration and validation, however the extent of the calibration and validation work performed will
435 depend on the intended purpose of the procedure. For example, validation of a 'moving block
436 standard deviation' procedure will focus mainly on a specific end-point, supported by sound rationale
437 and analytical evidence of the procedure's predictive ability (see Section 4.1).

438 **5.2. Data collection (qualitative procedures)**

439 **5.2.1. Sample collection and population**

440 The selection of samples, and where necessary the subsequent extent of spectral library development,
441 will depend on the complexity of the procedure. All samples should be verified with the approved
442 reference methods where applicable, or authenticated by appropriate means (certificate of analysis or
443 relevant testing). The validation of the NIRS procedure should demonstrate that spectra of an
444 acceptable minimum number of batches have been included in the spectral library and that these
445 batches are sufficiently representative to cover the normal variation of the substance.

446 Where laboratory or pilot scale samples are required to present wider variability than that shown for
447 production samples, such samples should be prepared using the same manufacturing procedure as
448 used for routine batches, unless otherwise justified. The balance of production to development
449 batches in all sample sets should be justified with respect to the variation expected in routine
450 production. The choice of samples should be sufficient to ensure the robustness of the NIRS procedure
451 for routine use.

452 For procedures used to identify or qualify substances on receipt, samples from all known potential
453 suppliers should be incorporated into the library.

454 For conformity checks (in-process controls and monitoring purposes), the sample population should be
455 justified with respect to the intended purpose of the procedure.

456 **5.2.2. Number of samples**

457 The number of samples to be included in the spectral library in order to create a valid calibration model
458 for qualitative analysis will depend on the complexity of the sample matrix and/or interference by the
459 matrix of the analyte signal of interest. In general, the more complex the sample matrix, the more
460 samples will be required to cover the statistical population.

461 The number of samples per batch and the number of batches used for calibration and validation should
462 be sufficient to cover normal production variation and should be fully justified.

463 **5.2.3. Composition of sample sets**

464 In order to develop, optimise and validate a calibration model for a typical qualitative NIRS procedure
465 used for identification or qualification, two sets of samples are required:

- 466 • a calibration set for creating the calibration model
- 467 • an independent validation set for (external) validation of the proposed chosen model

468 The calibration set of samples contains all those samples proposed for inclusion into the spectral
469 library. In the simplest form of spectral library, samples of all material groups (i.e. all materials used
470 at a particular site) are included in one library and chemometric analysis is applied to this library.
471 Since this may not always provide adequate specificity, sub-libraries are often used, containing all
472 samples of a particular class, to ensure the required specificity. Identification and qualification may
473 therefore be an iterative process, with identification of a substance in the first instance using the main
474 spectral library followed by qualification of, for example, the polymorphic form of that substance using
475 a sub-library.

476 Each set of samples should be representative of the intended scope of the NIRS procedure and include
477 samples covering the full range of potential variation in the sample population.

478 The independent validation set of samples should be entirely independent of those samples used to
479 build the spectral library and should include qualitatively positive and negative samples.

480 The selection of an appropriate calibration model may be aided by so-called 'internal validation'
481 methods. 'Internal validation' is the application of resampling statistics to cross-validate and provide
482 an 'internal check' of the performance of the model for the purposes of optimisation. A subset or
483 subsets of the spectral reference library data are subjected to a variety of statistical processes to
484 identify which calibration model (generated by the software) may best fit the available data.

485 For conformity procedures, the principles given above apply; however, samples would be expected to
486 cover the range of variability shown within the process being monitored and to give correct
487 determination of an end point. Positive and negative results would be expected to be included in the
488 independent validation set of samples, to ensure that the NIRS procedure is fit for purpose (e.g.
489 homogeneity and in-homogeneity in a blending process, with the inclusion of samples that have been
490 under-blended or over-blended to the point of de-mixing).

491 **5.2.4. Outliers**

492 Identified outliers in a spectral reference library should be investigated and should be excluded only
493 based on valid analytical reasons. These should be documented and justified. See also Section 4.3.3.

494 **5.3. Calibration**

495 Examples of calibration algorithms are Principal Component Analysis (PCA), Discriminant Analysis
496 (linear or quadratic), Soft Independent Modelling of Class Analogues (SIMCA), Cluster Analysis
497 (dendograms), k-Nearest-Neighbourhood-Analysis (kNN-Analysis), Supported Vector Machines (SVM)
498 and correlation algorithms such as distance-match.

499 The selection of the most appropriate algorithm for calibration depends on the scope of the spectral
500 library. In general, the simplest available algorithm that gives successful results should be used.

501 It is almost always necessary to determine thresholds, confidence limits or tolerances for the proper
502 identification and/or qualification of samples. The relevant values for the chosen calibration model
503 should be stated, explained and justified in the validation report.

504 **5.4. Optimisation**

505 In general, the optimisation of a qualitative procedure is confined to the selection of the samples
506 included in the model and the choice of pre-treatments and the calibration algorithm.

507 **5.5. Validation (internal and external)**

508 **5.5.1. General considerations**

509 The objective of internal validation is to ensure the performance of the spectral reference library.
510 Generally, this is evaluated by testing the samples of the spectral reference library using cross-
511 validation techniques or where necessary, a discrete set of samples. This internal validation step
512 should demonstrate that all samples of the spectral reference library are identified or qualified
513 according to the scope of the procedure, within the defined thresholds, confidence limits and/or
514 tolerances.

515 External validation of the procedure should demonstrate the performance of the chosen model using
516 an independent validation set consisting of samples that were not used in the creation of the spectral
517 reference library.

518 The applicant should demonstrate that the NIRS model is suitable for the intended purpose by the
519 means of appropriately defined and justified confidence limits. Alternative thresholds and/or statistical

520 parameters may be used to evaluate the performance of the model, which should be stated, fully
521 explained and their suitability for the intended purpose should be justified.

522 Qualitative procedures should be validated for a minimum of specificity and robustness.

523 **5.5.2. Specificity**

524 The extent of specificity testing depends on the intended NIRS procedure. A lack of specificity may be
525 compensated for by other supporting analytical procedures.

526 Independent samples of substances represented in the spectral reference library, but not used to
527 create it (e.g. different batches, blends), must be tested and all should be approved correctly (pass).

528 Potential challenges should be presented to the spectral reference library. These challenges should be
529 rejected (no match). For the identification or qualification of pharmaceutical substances, relevant
530 existing name and structure analogues (if available) should be included in the validation set, unless
531 their absence is justified. A risk assessment of the goods-in and manufacturing operations should be
532 used to justify the analogues and challenges presented to the model.

533 Where applicable (e.g. for qualification procedures), validation should include challenge with different
534 grades of the same substance, anhydrous/hydrated material, different polymorphs or material supplied
535 by different vendors.

536 The results of the validation of the NIRS procedure should demonstrate that for each tested
537 parameter, the procedure is sufficiently selective to discriminate between batches that comply with the
538 tested parameter and batches that do not, as effectively as the reference method.

539 The composition of the independent (external) validation set of samples should be described
540 unambiguously and should be justified.

541 **5.5.3. Robustness**

542 Effects of relevant variables e.g. temperature (environment and sample), humidity, different position
543 of the sample in the optical window, different sample presentation devices, variation in sample
544 bottles/vials, probe depth or, if applicable, different packaging materials, should be understood, tested
545 and documented. Instrumental variations may also be considered in the validation for robustness, e.g.
546 changing lamps, reflectance standard etc.

547 The use of Design of Experiments (DOE) may be considered to maximise the information available.

548 **6. Quantitative procedures**

549 **6.1. Development**

550 It is in the interests of the developer to perform a feasibility study to determine the likelihood of
551 success of any quantitative NIRS procedure and to outline the minimum requirements that should be
552 built into the development and validation protocols (e.g. the consideration of tablet weight as a
553 variable in the determination of uniformity of dosage units to ensure the measurement is total content
554 rather than concentration).

555 **6.2. Data Collection (quantitative procedures)**

556 **6.2.1. Sample collection and population**

557 Where feasible, samples of production batches should be augmented with those from development
558 batches, manufactured specifically to simulate the limits of potential variation in the sample. Where
559 laboratory samples are required to expand the narrow range of production samples to properly assess
560 linearity in line with specification limits, such samples should be prepared using the same
561 manufacturing procedure.

562 The balance of production to development batches in the sample set should be justified with respect to
563 the variation expected in routine production.

564 In keeping with the fundamental assumptions made in the application of regression correlation
565 statistics and to prevent bias, a uniform distribution of samples throughout the range of potential
566 variation should be ensured (when feasible). At the same time, the possibility of the introduction of
567 undesirable correlations and systematic errors should be considered, taking account of the known NIRS
568 signal of the analyte of interest.

569 The distribution of samples should be evaluated with respect to the intended purpose of the procedure.
570 For cases in which the NIRS procedure is used to test whether a sample meets a specified limit, it may
571 be acceptable to include more samples around the proposed specification limit. This should be
572 explained and justified.

573 The choice and number of samples should be justified and if possible, supplemented using DOE
574 correlated with the intended purpose of the procedure.

575 **6.2.2. Number of samples**

576 Calibration algorithms are generally based on the correlation of variance in the NIRS signal to a
577 number of principal components, constrained by a set of calibration reference data. To avoid bias, the
578 number of samples used to develop the calibration model should be very much greater than the
579 number of principal components used (or equivalent, where applicable). In all cases, the number of
580 samples used to develop the calibration model should be justified.

581 The number of samples to be included in order to create a valid calibration model for quantitative
582 analysis will depend on the complexity of the sample matrix and/or interference by the matrix of the
583 analyte signal of interest. In general, the more complex the sample matrix, the more samples will be
584 required to cover the statistical population. For example, if the sample matrix consists of two simple
585 ingredients only, the number of samples required will be lower than if a multi-ingredient, complex
586 system is to be analysed. For the latter, a complex chemometric model, with more principal
587 components, may be required, for which a greater number of samples will be necessary to ensure its
588 validity.

589 The number of samples per batch and the number of batches included in the calibration and validation
590 sample sets should be fully justified.

591 **6.2.3. Composition of calibration set, calibration test set and validation set**
592 **of samples**

593 To develop, optimise and validate the calibration model for quantitative analysis, three sets of samples
594 are required (similar to those described for qualitative procedures, however nomenclature may be
595 different):

596 • the calibration set for creating the calibration model
597 • the calibration test set for optimisation and choice of calibration model (if used)
598 • the independent validation set for external validation of the proposed chosen model

599 The calibration set of samples is used to generate potential calibration models and as such, should
600 include samples covering the full range of potential variation, within the defined scope of the NIRS
601 procedure.

602 The optimisation/choice of the calibration model is normally undertaken by so-called 'internal
603 validation' methods. These methods involve the application of re-sampling statistics to cross-validate
604 and provide an 'internal validation' of the performance of the model for the purposes of optimisation.
605 A subset or subsets of the spectral data are subjected to a variety of statistical processes to identify
606 which calibration model (generated by the software) may best fit the available data.

607 The calibration test set is used to provide the first 'test' or check of the validity of the model. The
608 calibration test set does not represent independent validation of the NIRS procedure (which must be
609 carried out using an entirely independent set of samples), since the samples are taken from different
610 batches within the same (historical) population of batches. In practice, the calibration set often
611 consists of two thirds of the available sample population and the calibration test set is the remaining
612 third, however this is not always the case and the calibration set should always contain a sufficient
613 number of samples to ensure that the generated calibration model is robust. The applicant should give
614 the rationale for the composition and number of samples in the calibration and calibration test sample
615 sets and justify their suitability.

616 The validation set (for external validation) is an entirely independent third set of samples, which is not
617 taken from the same (historical) population as those batches used to generate the calibration model.
618 In principle, this external validation set should cover the full range of variation in the sample
619 population and should include production-scale batches, where possible. The number, scale and
620 composition of batches included in the validation sample set should be discussed and justified.

621 The validation set of samples is used to validate the calibration model and is used to generate the
622 statistical parameter, the Standard Error of Prediction (SEP), which is an indicator of the validity and
623 predictive ability of the calibration model. An SEP will also have been generated for the calibration test
624 set, however this is used as an initial indicator of the predictive validity of the model only. The SEP for
625 the external validation set of samples is the pivotal statistical parameter for the model.

626 An analyst may choose not to apply 'internal validation' methods during development and optimisation
627 of a calibration model. In such cases, a calibration set and an independent validation set of samples
628 would be the minimum requirement.

629 **6.2.4. Analysis by the reference method**

630 The performance of a quantitative NIRS procedure is dependent on the performance of the reference
631 method (if used). Poor precision and accuracy of the reference method will limit the performance of

632 the NIRS procedure. It is important that care is taken to ensure that uncertainty in the reference
633 method is low in relation to the intended performance of the procedure.

634 Repeated sample analysis by the reference method should be discussed and reference data should be
635 tabulated and presented graphically. The number of replicates to be averaged to provide reference
636 data for the calibration model should be stated and justified with reference to the performance
637 (precision and accuracy) of the reference method and the NIRS procedure.

638 ***6.3. Calibration***

639 ***6.3.1. Software***

640 Following acquisition of spectral and reference analytical data for the calibration set of samples, it is
641 necessary to carefully pair and match these data prior to any chemometric modelling.

642 Using paired data, the chemometric calibration model should be developed using the specified software
643 package. Such software empirically characterises and correlates the variation within the data. The
644 result of this correlation may be presented in different ways depending on the algorithm used (e.g.
645 latent variables for PLSR or principal components for PCA).

646 ***6.3.2. Selection of Principal Components***

647 The number of principal components (or similar, which describe the variability in the data) to be used
648 in the calibration model is of critical importance to avoid under or over fitting of the data.

649 The scope of the proposed NIRS procedure and the suitability of the calibration samples to adequately
650 represent the product to be marketed should be taken into account when selecting the number of
651 principal components for inclusion into the calibration model.

652 The following should be considered when choosing the number of components to use:

- 653 • co-linearity
- 654 • minimal contribution to the data variance arising from spectral variations of the analyte of interest
- 655 • contribution to the data variance arising not from the spectral variations of the analyte of interest,
656 but from other components of the sample matrix, e.g. excipients or other characteristics.

657 The above list is not exhaustive. The analyst should take into account all relevant issues revealed by
658 the feasibility study and the known nature of the analyte. Loadings plots (describing the variation
659 explained by each component) may be useful when choosing the number of components to use. For
660 procedures in which principal components are not used (e.g. neural networks), the chosen key
661 parameters should be stated, explained and justified.

662 Once selected, the proposed calibration model should be characterised, by graphical and statistical
663 means, the characteristic statistic being the Standard Error of Calibration (SEC) or equivalent.
664 Parameters such as bias and intercept may also be reported.

665 ***6.3.3. Optimisation of the NIRS model***

666 From the chemometric data generated by the software, the selection of the optimum calibration model
667 is a pivotal step in the development of the NIRS procedure. Optimisation of calibration models may be

668 performed by 'internal validation' methods as described in Section 6.2.3. These methods are used to
669 aid assessment of the suitability of the calibration model in its ability to predict the correct quantitative
670 result.

671 It is accepted that the use of resampling statistics for optimisation is a rapidly developing field and that
672 more appropriate statistical processes may be available, particularly relating to the assessment of
673 under- and over-fitting. Any process used should be explained and justified.

674 For internal (cross) validation methods of optimisation, the characteristic statistic is usually the
675 Standard Error of Cross Validation (SECV). Other statistical parameters such as bias or the coefficient
676 of variation may also be used. Any statistical parameter(s) used during optimisation of the model
677 should be stated, explained and justified.

678 **6.4. Validation**

679 **6.4.1. General considerations**

680 The independent (external) validation set of samples may be supplemented by specially prepared
681 samples to demonstrate linearity, range and specificity.

682 Since quantitative NIRS analysis relies upon reference data obtained from a reference method or very
683 rarely, samples of known composition in order to impart meaning to the sample spectroscopic data
684 collected, a statistical acceptance criterion is used as a measure of the model's ability to predict the
685 correct quantitative result. This is the SEP, for the independent validation set of samples (external
686 validation).

687 Quantitative NIRS procedures should be validated with respect to the following parameters:

688 **6.4.2. Standard Error of Prediction (SEP)**

689 The SEP and the SEP/range ratio should be determined for the external validation set. The value of
690 these parameters should be explained, discussed and justified with respect to the intended purpose of
691 the NIRS procedure. These are considered pivotal statistical parameters. Other equivalent terms
692 should be explained and justified.

693 It may be helpful or appropriate to report and justify the SEP/Standard Error of Laboratory (SEL).

694 **6.4.3. Specificity**

695 The specificity of an NIRS procedure is dependent upon its intended purpose, scientific basis and
696 scope.

697 For specificity, the procedure should be able to reject samples that are outside of its defined scope,
698 such as out of specification product, placebo, samples containing different quantitative composition of
699 proposed excipients, and samples containing different active substance and excipients (see also
700 section 4.3.2 Statistical spectral quality test).

701 The following may be used as supportive evidence of specificity:

702 • reference to the feasibility study data demonstrating a suitable NIR response based on the known
703 NIR characteristics of the analyte

704 • comparison of the loadings plots for the components used to develop the chemometric model,
705 against the known NIR characteristics of the analyte (where applicable)
706 • validation data to demonstrate accuracy and robustness

707 **6.4.4. Linearity**

708 To demonstrate linearity, it is required that samples in the validation set are distributed across the
709 specified range of interest. Otherwise, linearity cannot be adequately confirmed and validated.
710 The NIRS results should be compared with those of the reference method (if applicable). The
711 correlation coefficient and analysis of residuals (indicators of linearity), should be explained, justified
712 and supported by graphical representation.
713 The applicant should justify the choice of statistics applied to determine linearity if these differ from
714 those described in this guideline.

715 **6.4.5. Range**

716 The range should be confirmed by use of a suitable validation set which matches in extent the
717 proposed range for the intended use of the procedure. Validation samples having analyte content
718 outside of the calibration range should appear as outliers when tested by the NIRS procedure.

719 **6.4.6. Accuracy**

720 Accuracy should be established across the specified range of the NIRS procedure and should be
721 appropriate for its intended use. In some case, the NIRS procedure may have a higher error than the
722 reference method. In such cases, limits may be set that are tighter than those set for the reference
723 method.

724 **6.4.7. Precision**

725 Precision and the SEP should be appropriate for the intended use of the NIRS procedure. Bias should
726 be as close to zero as possible.

727 The suitability of the determined precision of the NIRS procedure should be fully discussed and
728 justified, in the context of the analyte of interest.

729 Dependent upon the nature by which samples are presented to the NIRS instrument, repeatability
730 should be demonstrated through the analysis of replicate measurements. Repeatability should be
731 demonstrated across the range of sample variation.

732 Intermediate precision should be demonstrated by the statistical evaluation of repeatability determined
733 by different analysts over different days.

734 **6.4.8. Robustness**

735 Generally, the reference methods used to generate the reference data for quantitative NIRS
736 procedures measure chemical or physical properties of samples whereas the vibrational characteristics
737 measured by NIR spectral analysis take into account both physical and chemical properties.

738 Evidence to demonstrate the robustness of an NIRS procedure should cover chemical and physical
739 variables, dependent upon the purpose of the procedure and the conditions employed for sampling.
740 These variables may include temperature and humidity, sample handling and instrument changes as
741 discussed in Section 4.1.4 (Variables affecting the Spectral Response). The use of DOE may be
742 considered to maximise the information available.

743 Robustness should be addressed within the scope of the NIRS procedure. If this has been considered,
744 reference to data generated from the development and optimisation of the calibration model and the
745 validation data described above would be considered sufficient to demonstrate robustness. Otherwise,
746 validation data for the determination and assurance of robustness should be provided.

747 **6.4.9. Limits of detection and quantification**

748 Limits of detection and quantification for the proposed NIRS procedure need only to be demonstrated
749 when relevant and where the analyte is considered to be an impurity (e.g. water content).

750 **7. NIRS procedure lifecycle and post-approval requirements**

751 **7.1. Management of the NIRS procedure lifecycle**

752 It is recognised that NIRS procedures (qualitative or quantitative) will evolve over time (see Figure 1,
753 Section 1). The applicant should indicate how they will manage the NIRS procedure lifecycle in the
754 initial application.

755 The scope of the NIRS procedure should be clearly defined in the initial application (see definition in
756 Section 4.1.1). This is critical with respect to how post-approval changes to the NIRS procedure
757 should be implemented.

758 Any extension of the scope of the NIRS procedure should be implemented by variation application only.

759 **7.2. Changes to approved NIRS procedures**

760 Changes (both planned and unplanned), which might affect the performance of an NIRS procedure,
761 may necessitate re-calibration and/or re-validation of the NIRS model to demonstrate continued model
762 suitability. All changes should be validated accordingly, appropriately documented and recorded
763 according to valid change management protocols.

764 **7.2.1. Changes within the defined scope of the NIRS procedure**

765 In general, changes within the scope of the NIRS procedure would be subject to GMP inspection only.
766 Relevant examples include the maintenance of the spectral library and replacement of equipment
767 consumables with similar, including lamps, sampling devices, location and software upgrades.

768 Changes should be fully documented, and include appropriate re-validation and comparability reports
769 to show that the revised NIRS procedure is consistent with the approved procedure. A risk assessment
770 should be conducted to determine the risk associated with the change being made.

771 For qualitative NIRS procedures, suitable change management tests should be in place for each NIRS
772 procedure and spectral reference library (where applicable). A change management test should be

773 composed of a minimum of two standard sets of samples (i.e. two classes or substances) for which
774 separation is most critical. If the NIRS procedure does not comply with the change management test
775 (meaning that the procedure is unable to distinguish between the two sets of samples), the model
776 should be fully re-validated. The suitability of the change management test should be subject to
777 periodic re-evaluation.

778 Quantitative NIRS procedures should only be used within the calibrated concentration range and using
779 conditions defined in calibration. It may be appropriate to add sample observations into the calibration
780 model (within the calibrated range detailed in the defined scope of the NIRS procedure) via model
781 updates. Such changes require re-validation and documentation should be available for GMP
782 inspection.

783 **7.2.2. Changes outside of the defined scope of the NIRS procedure**

784 To enable the dossier to be updated, extensions outside of the approved scope of the NIRS procedure
785 are subject to variation application, including an appropriate comparison of the updated NIRS
786 procedure with the current procedure and/or reference analytical method, if applicable.

787 For extensions of the scope of a qualitative NIRS procedure e.g. to include a new substance
788 (previously not included) into a spectral library, a statement of compliance with this guideline and a
789 comparison of the updated NIRS procedure with the current procedure would be considered sufficient.

790 For quantitative analysis, extensions of the scope of NIRS procedures include for example, changes of
791 ranges and/or specification limits. Variation applications for such changes require evidence of re-
792 calibration and validation of the NIRS model.

793 **7.3. NIRS procedure transfer between NIRS instruments**

794 The aim of NIRS procedure transfer is to ensure that the calibration model generated on one NIRS
795 instrument will work on another instrument, based on the validation parameters detailed in Sections
796 5.5 and 6.4 of this guideline. Samples analysed on the original 'master' instrument should give
797 equivalent results on all additional instruments to which the calibration model is transferred. The
798 following parameters are essential to judge the similarity of instruments:

- 799 • hardware (e.g. identical spectrometer type and measuring set-up)
- 800 • software (including mathematical algorithm and how the spectra are treated in the calibration
801 model)
- 802 • interfaces (e.g. probes and waveguides)

803 Depending on the scope of the NIRS procedure (e.g. qualitative, trend analysis or quantitative) and the
804 degree of similarity of the instruments involved, it may be necessary to apply one of the following
805 options:

806 1. Where there are NIRS method changes only:

807 It may be possible and sufficient to include a mathematical compensation in the applied software of
808 the NIR instrument to ensure that identical spectral responses are achieved for a representative set
809 of reference samples when tested by all instruments. In general, a bias and or slope or vector
810 correction is undertaken.

811 2. For all other cases, for which mathematical compensation is insufficient:

812 Calibration and validation should be repeated and confirmed on the additional instrument(s).

813 Calibration transfer models may be developed using a small but representative number of
814 calibration samples that are run on both instruments (the master and the additional instrument). A
815 convenient method for choosing samples is one that is based upon their good multivariate
816 leverage. In this method, samples are selected that have a large influence on the calibration
817 model. Depending on the complexity of the multivariate model, a smaller representative number of
818 samples (in comparison with the number used to calibrate and validate the model originally) should
819 be sufficient to support model transfer between instruments.

820 In the event that the master instrument is no longer available, an appropriate number of samples
821 should be justified and used to build the calibration model on the additional instrument(s).

822 In both cases (1) and (2), the transfer of an NIRS procedure to another instrument should be the
823 subject of an appropriate comparability protocol.

824 The comparability protocol for NIRS procedure transfer(s) may be submitted with the initial application
825 as a 'post approval change management protocol' if changes are foreseen in the applicant's strategy.
826 Alternatively, the comparability protocol may be submitted at the time of the variation application to
827 register the transfer itself. The protocol should include criteria that have been justified to be
828 acceptable to demonstrate a satisfactory transfer.

8. Glossary

Ambiguous conclusion The sample is considered identical to more than one entity present in the reference library

Bias (mean of the errors) A statistic measuring the mean of the errors between the NIRS and reference quantitative analyte values

$$\text{Bias} = \frac{\sum_{i=1}^n (y - Y_i)}{n}$$

y = NIRS predicted value
 Y = reference method value
 n = number of samples

Calibration The process of creating a model relating two types of measured data. For NIRS, a model that relates concentrations or properties to absorbance spectra for a set of reference samples (the reference library or the calibration set)

Calibration set The set of samples used for creating the calibration model

Calibration test set The set of samples, which are drawn from the same population as the calibration set, but were not used to generate the calibration model. In practice, the calibration set often consists of two thirds of the available sample population. The calibration test set is the remaining third

Calibration test set validation The application of possible chemometric calibration models to the calibration test set. The derived characteristic statistical parameter is the Standard Error of Prediction (SEP)

Change management protocol A protocol listing potential future changes in the NIRS procedure and the actions considered necessary to prove the maintained reliability of the procedure

Change management test Test used to demonstrate unchanged NIRS procedure reliability following a change

Chemometrics Mathematical multivariate methods to analyse or compare data

Cross-Validation See Internal validation

Conformity Characteristics in accordance with a certain degree of similarity (chemical and/or physical entities) to some specified standard

Design of Experiments (DOE) (factorial experimental design) Two or more treatments are evaluated simultaneously in the same set of subjects through the use of varying combinations of the treatments. The simplest example is the 2x2 factorial design in which the parameters are randomly allocated to one of the four possible combinations of two treatments. Such an experiment allows studying the effect of each factor on the response variable, as well as the effects of interactions between factors on the response variable

Identification Determination of the chemical identity

Internal validation	The application of resampling statistics such as cross-validation. Subsets of the calibration data set are subjected to a variety of statistical processes to identify which calibration model may best fit the available data. Each model is characterised by a statistical parameter. For cross-validation, the entire data set of samples is split into individual samples or groups of samples, which are removed individually from the rest of the samples and tested as unknowns against a calibration model constructed using the rest of the samples. The characteristic statistic is the Standard Error of Cross Validation (SECV)
Latent variable	See Principal component
Leverage	In chemometrics the leverage is a concept related to the Mahalanobis distance and is used to measure the influence of a sample in a model based on its similarity to the rest of the population. The Mahalanobis distance takes into account the correlations of the data set and is scale-invariant, i.e. not dependent on the scale of measurements. The leverage of a sample is the distance to the centre of all samples relative to the variability in its particular direction
Loading plot	The loading plot for each principal component indicates the magnitude (small or large correlation) and the manner (positive or negative correlation) of how each original measured variable (e.g. wavelength of the NIR spectra) contributes to the variance seen for the analyte signal
NIRS Procedure	Describes how the NIRS method and model are being used for the intended purpose.
NIRS Method	Describes the key elements that enable the NIRS measurement of the analyte of interest. This includes for example, the equipment and spectrophotometer type (e.g. FT, grating etc), the sample measurement interface (e.g. probe, sample stage etc), the number of scans or measurements and the spectral range of the instrument.
NIRS Model	Describes how the NIR spectral data are related to the analyte property of interest or the intended use of the procedure.
No match conclusion	The sample is not considered identical to any entity in the reference library
Pass conclusion	The sample is considered identical to an entity in the reference library
PCA	Principal Component Analysis
PCR	Principal Component Regression
Performance verifications	Tests to control the instrument performance
PLS (PLSR)	Partial Least Squares (Regression)
Pre-treatment	Processing of the spectral data, with mathematical or other techniques, prior to chemometric analysis
Principal component or latent variable	Principal components are calculated by means of chemometric software from a set of original variables (e.g. NIR spectra) by linear transformation of the original variables into a lower dimensional space. The principal components have the characteristic that a maximal amount of information about the original variables is retained

Process Analytical Technology (PAT) A system for analysing and controlling manufacture through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality. PAT is the sum of tools that allows enhanced control of manufacturing process, can improve process understanding and so facilitates building quality into products

Qualification

1. Characterisation based upon chemical- and physical attributes.
2. Determination of the chemical identity and the variability of the sample within the defined variability of the material

Qualitative procedure Procedure with a yes or no result, e.g. identity

Quantitative procedure Procedure with a numerical result, e.g. assay

Ratio of deviation (RPD) A statistic measuring the ratio of the standard deviation of the reference values of the calibration set (SD_{ref}) and the Standard Error of Prediction (SEP)

$$RPD = \frac{SD_{ref}}{SEP}$$

Reference library (spectral reference library) Database containing spectra of several batches of several substances to be tested. Spectra of unknown samples are compared with this database

Reference method The conventional analytical method that is used to determine the concentration or property value of the samples

Re-sampling Statistics Statistical methods to aid the optimisation of the calibration model by using subsets of the calibration set, e.g. cross-validation

SEC See Standard Error of Calibration

SECV See Standard Error of Cross-Validation

SEL See Standard Error of Laboratory

SEP See Standard Error of Prediction

Standard Deviation (SD_{ref})

$$SD_{ref} = \sqrt{\frac{\sum_{i=1}^n (y_{mean} - Y_i)^2}{n-1}}$$

y = reference method value

y_{mean} = arithmetic mean of the reference method values

Standard Error of Calibration (SEC) A statistic measuring the difference between the NIRS procedure and reference method quantitative analyte values of the calibration set

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

y_C = NIRS predicted value of calibration set

$y_{C,i}$ = reference method value of calibration set

n = number of samples

p = number of coefficients, e.g. wavelength (MLR), principal components (PCR), factors (PLS)

Standard Error of Cross-Validation (SECV) A statistic measuring the difference between the NIRS procedure and reference method quantitative analyte values of the calibration set using a cross-validation method.

$$SECV = \sqrt{\frac{\sum_{i=1}^n (y_{CV,i} - \bar{Y}_{CV})^2}{n}}$$

Y_{CV} = NIRS predicted value
 y_{CV} = reference method value
 n = number of samples

Standard Error of Laboratory The SEL concerns to the intermediate precision (intra-lab) or (SEL) reproducibility (inter-lab), whichever is applicable

$$SEL = \sqrt{\frac{\sum_{i=1}^n (y_{1,i} - y_{2,i})^2}{n}}$$

$y_{1/2}$ = reference method value measured at different laboratory conditions
 n = number of samples

Standard Error of Prediction (SEP) A statistic measuring the difference between the NIRS procedure and reference method quantitative analyte values of the calibration test set and the independent validation set. The SEP derived from the independent validation set is considered a pivotal statistical parameter.

$$SEP = \sqrt{\frac{\sum_{i=1}^n (y_{V,i} - \bar{Y}_V)^2}{n}}$$

Y_V = NIRS predicted value
 y_V = reference method value
 n = number of samples

Threshold Limiting value, for qualitative procedures, decisive for a 'pass' or a 'no match' conclusion

Validation set Independent set of samples used in validating the model

Wavelength Correlation The correlation between spectra, i.e. the sum of the individual correlation of absorbances of each included wavelength