The EMA Guideline Draft on the Use of Near Infrared Spectroscopy (NIRS)

Karl Molt

Universität Duisburg-Essen, Fakultät für Chemie

Guideline on the use of NEAR Infrared Spectroscopy (NIRS) by the pharmaceutical industry and the data requirements for new sumbissions and variations

Current status

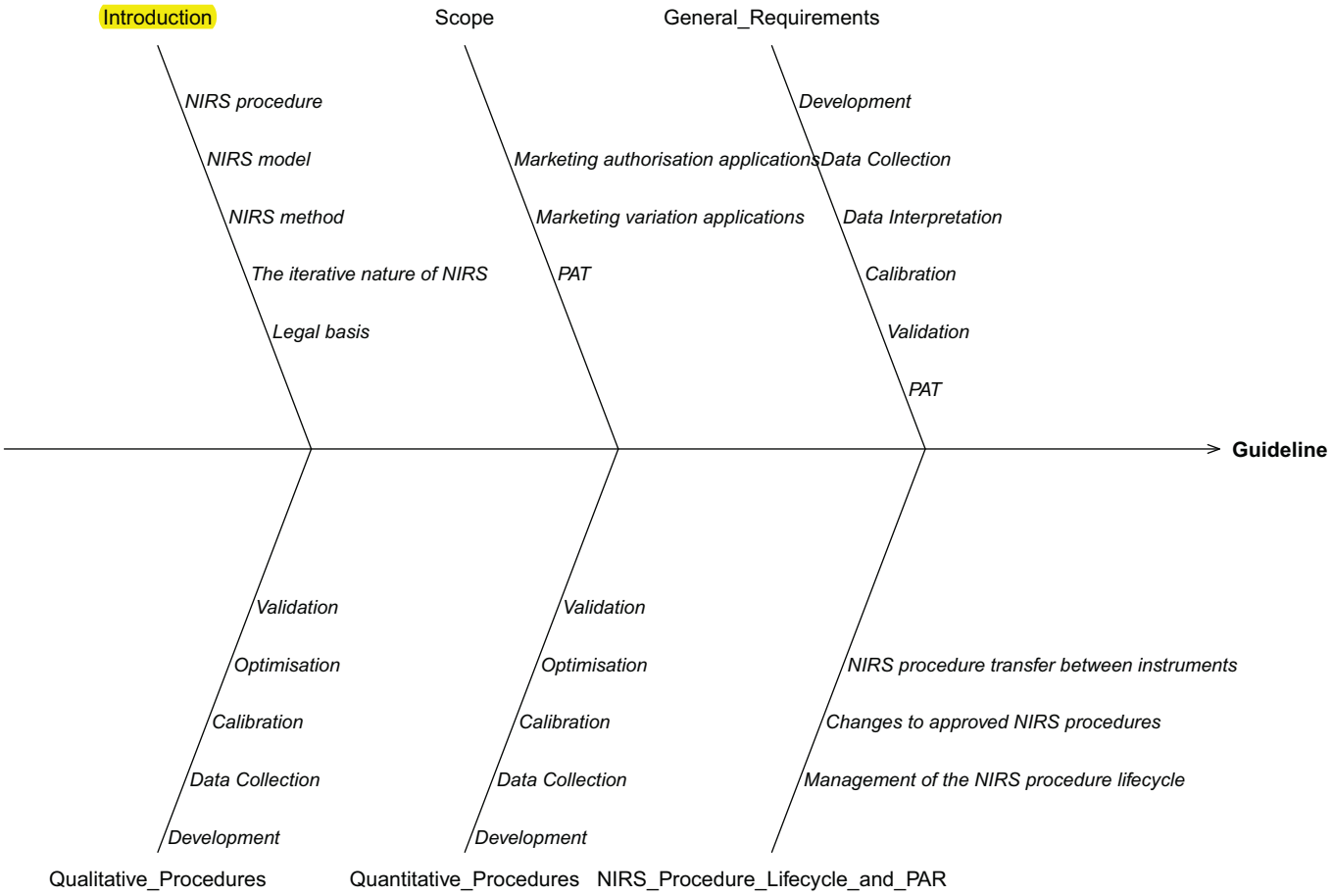
20 January 2012; EMEA/CHMP/CVMP/QWP/17760/2009 Rev2; Committee for Human Medicinal Products (CHMP); Committee for Veterinary Medicinal Products (CVMP)

Draft agreed by QWP	December 2011
Adoption by CHMP for release for consultation	19 January 2012
Adoption by CVMP for release for consultation	12 January 2012
End of consultation (deadline for comments)	31 May 2012

This guideline, once finalised, will replace the Note for Guidance on the Use of Near Infrared Spectroscopy by the Pharmaceutical Industry and the Data Requirements for New Submissions and Variations, CPMP/QWP/3309/01 and EMEA/CVMP/961/01.

Executive Summary

"This document provides guidance on the development, calibration, validation and maintenance of NIRS procedures, when used with chemometric statistics and when used for direct process monitoring."



Terms

- **NIRS method**
  describes the key elements, principally within the NIRS apparatus, which enable NIRS measurement of the analyte of interest.
- **NIRS model**
  describes how the NIRS spectral data measured using the NIRS method are related to the analyte of interest, generally employing chemometric software.
- **NIRS procedure**
  describes how the NIRS method and model are used for the intended purpose, within its defined scope

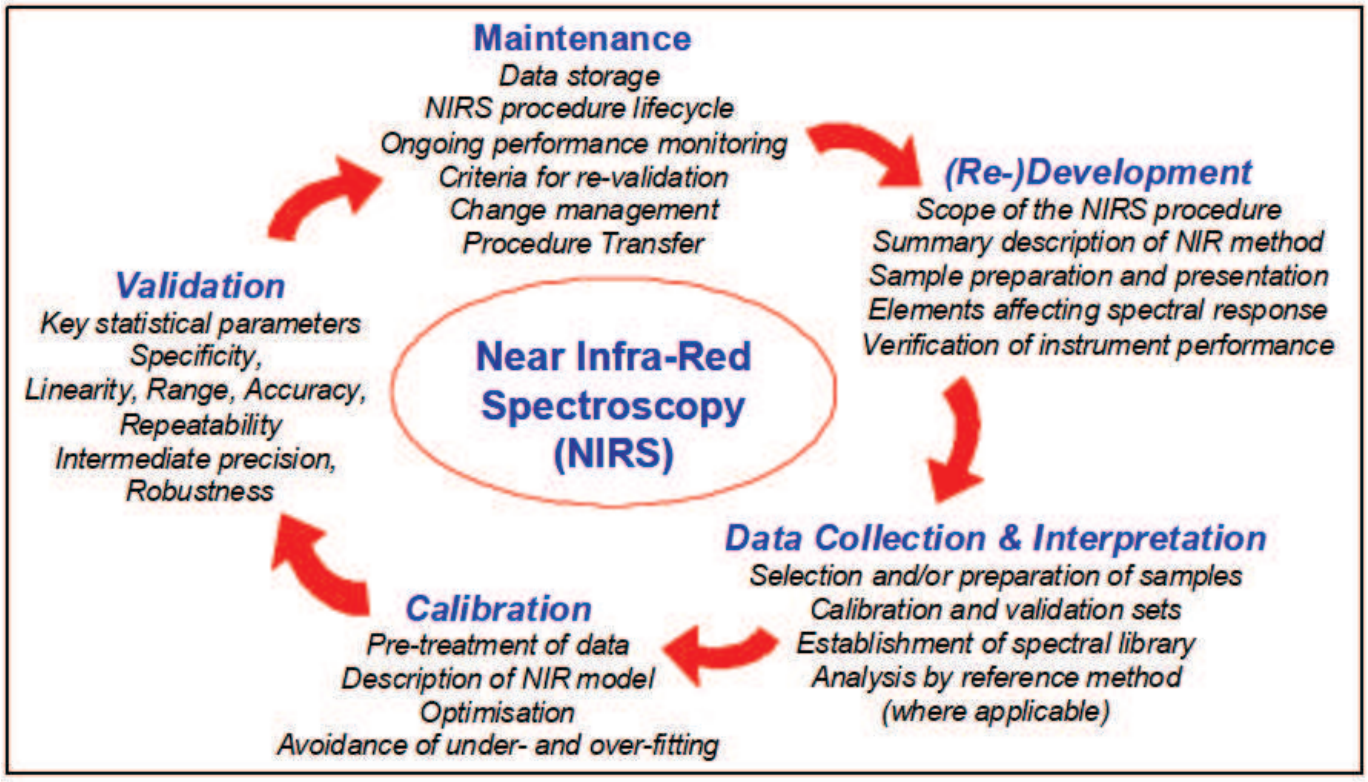
NIRS not a "primary" analytical method

- Chemometric models are developed using carefully selected and representative samples, which have in turn been qualified by a reference analytical method, using analytical reference standards.
- As NIRS procedures cannot be repeated easily by official control laboratories, the reference methods and corresponding specifications should remain in the authorised specifications.
- For PAT NIRS procedures, e.g. dynamic process monitoring of a powder blend, it may not be possible to refer to a conventional reference method.

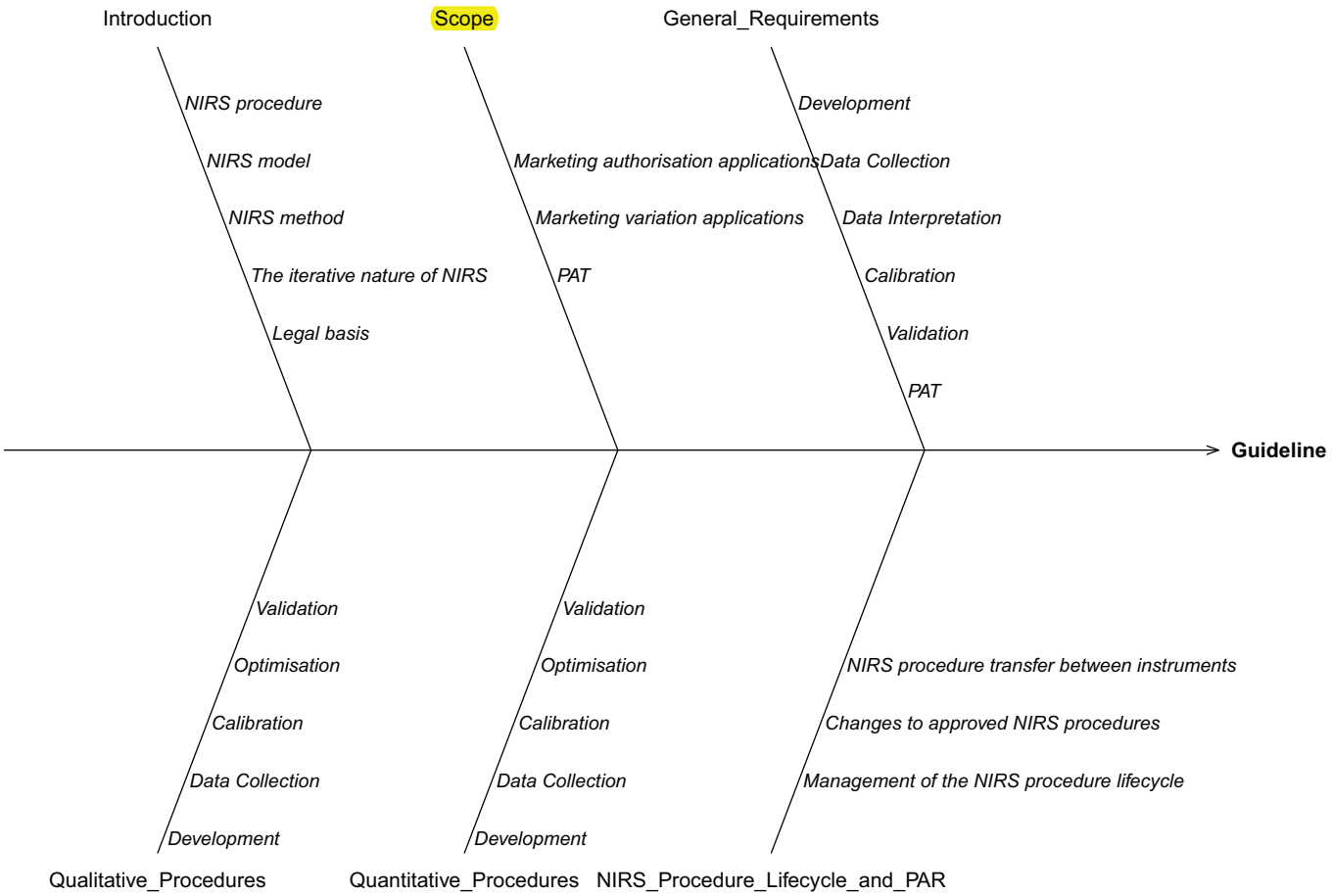
The iterative nature of NIRS

- It is recognized that the development and implementation of an NIRS procedure is iterative and that the stages are interdependent.
- It is possible to update calibration models of NIRS procedures as new data become available following the purchase or production of new analyte batches. This is considered good practice and is recommended.

The iterative nature of NIRS



EMA NIRS Guideline (Jan 2012, draft)



Scope

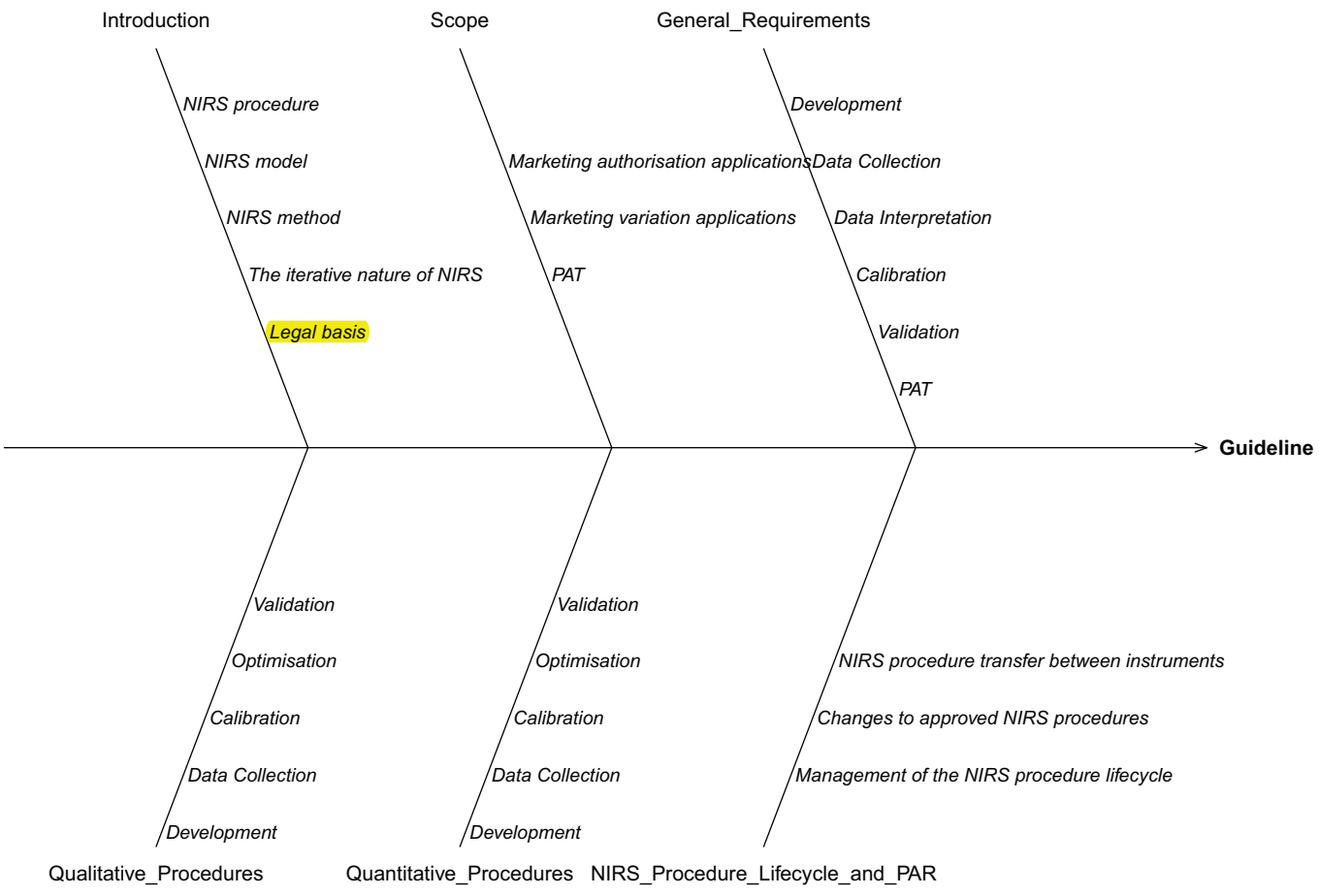
This guideline describes the regulatory requirements for marketing authorisation applications and variation applications submitted for medicinal products for human or veterinary use, which include the use of NIRS.

Scope (cont.)

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

Scope (cont.)

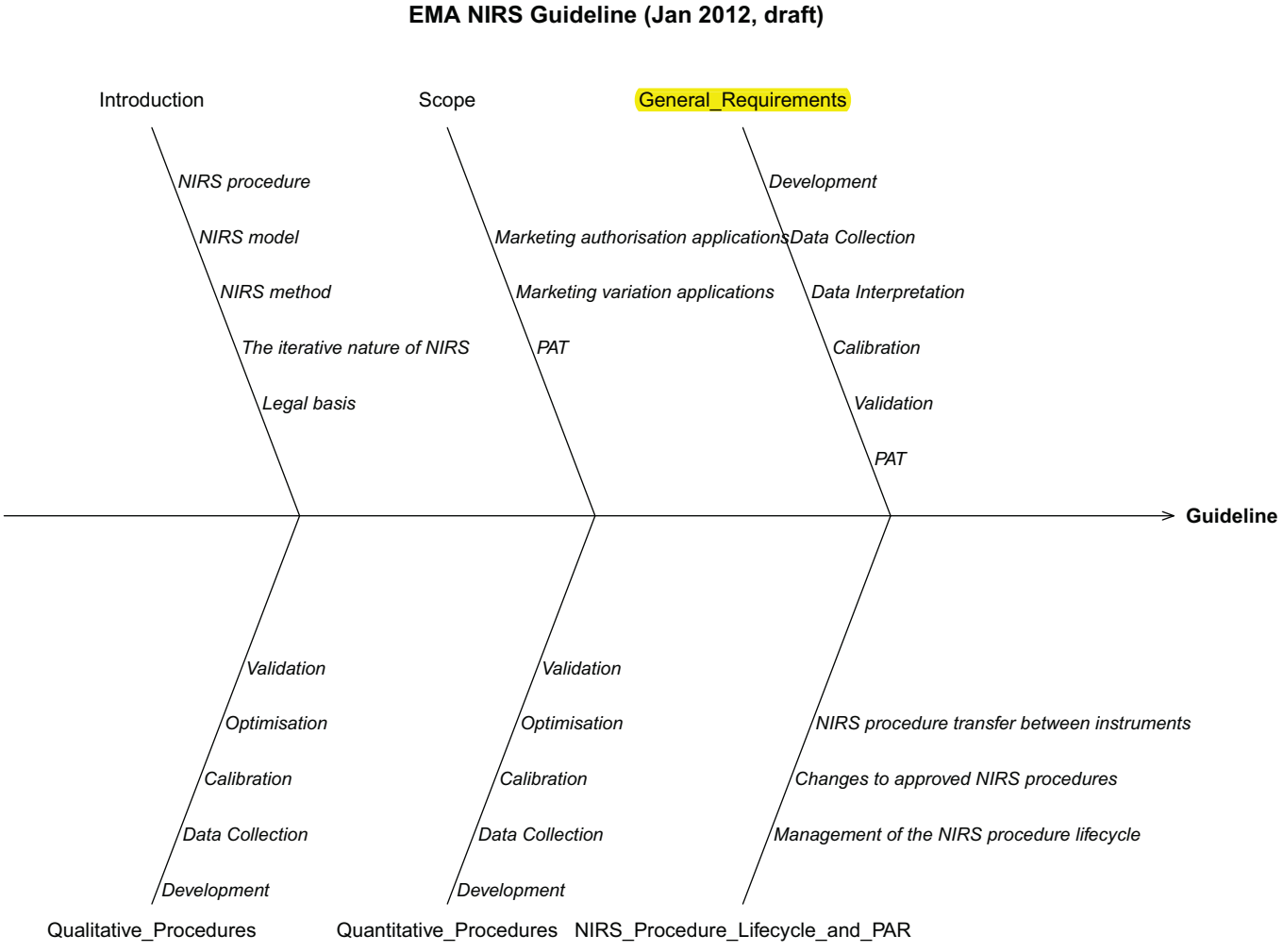
- NIRS is described in the European Pharmacopoeia; however a single reference to the Ph.Eur. general chapter on NIR spectroscopy (Ph.Eur. 2.2.40) as a sole description for the NIRS procedure is insufficient to support the use of such a procedure in marketing authorisation applications or variation submissions.
- This guideline outlines the requirements for applications in which NIRS is used for qualitative and quantitative analysis or where it is used as a process analytical technology (PAT) for monitoring and controlling drug substance synthesis and finished product manufacturing processes.

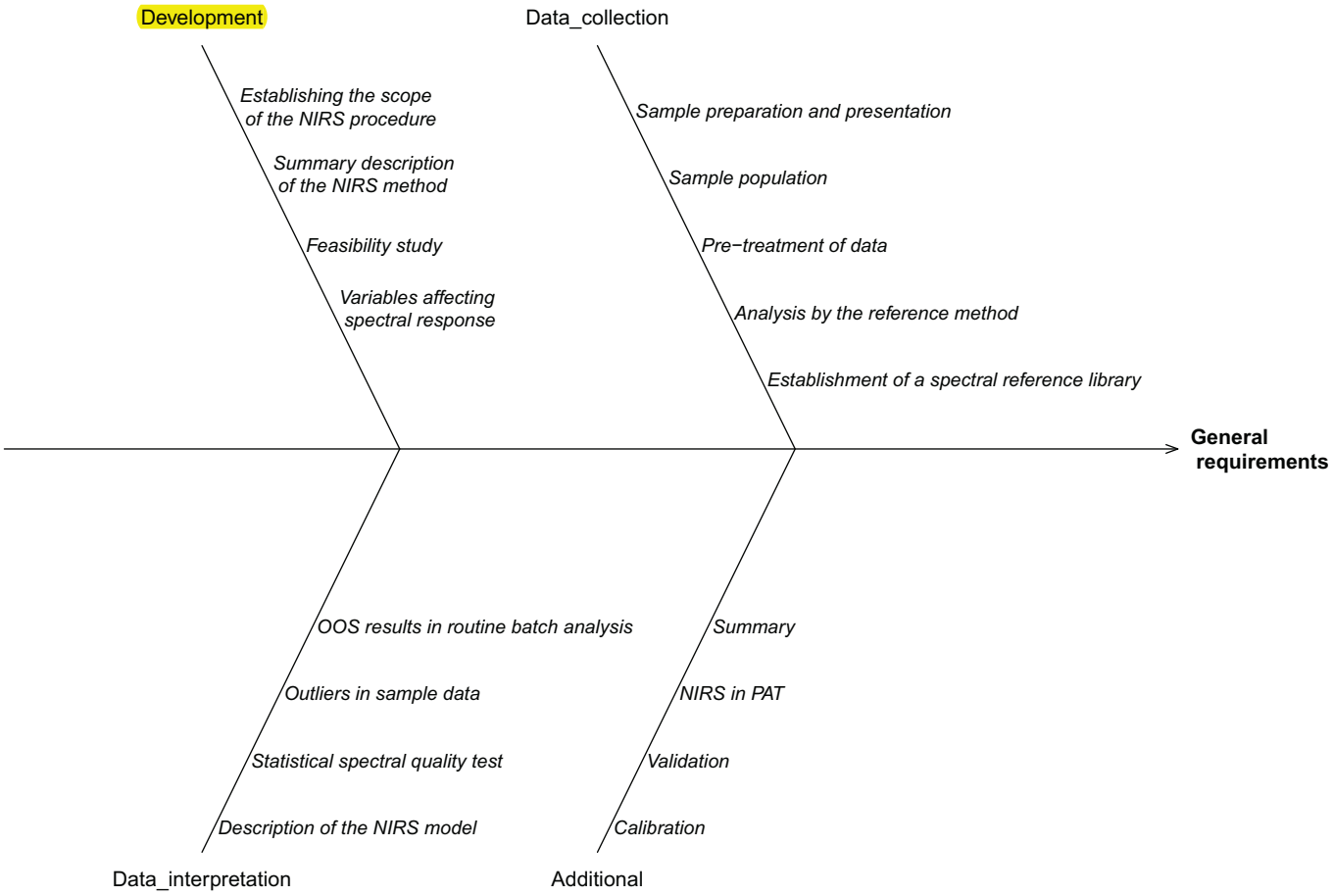


Legal basis

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

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





Establishing the scope of the NIR procedure

How are the NIRS method and model to be used for the intended purpose?
Include details about

- Key elements of the NIR method that enable measurement
- NIRS model
- Limitations of the method
  e.g. operating range of validity with respect to analyte concentration

Establishing the scope of the NIR procedure (cont.)

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

Establishing the scope of the NIR procedure (cont.)

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

Establishing the scope of the NIR procedure (cont.)

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

Establishing the scope of the NIR procedure (cont.)

There is always a risk that the correlations identified by the chemometric software are due to chance only and not to changes in the analyte; therefore chemometric models should always be validated with an independent set of samples.

Feasibility study

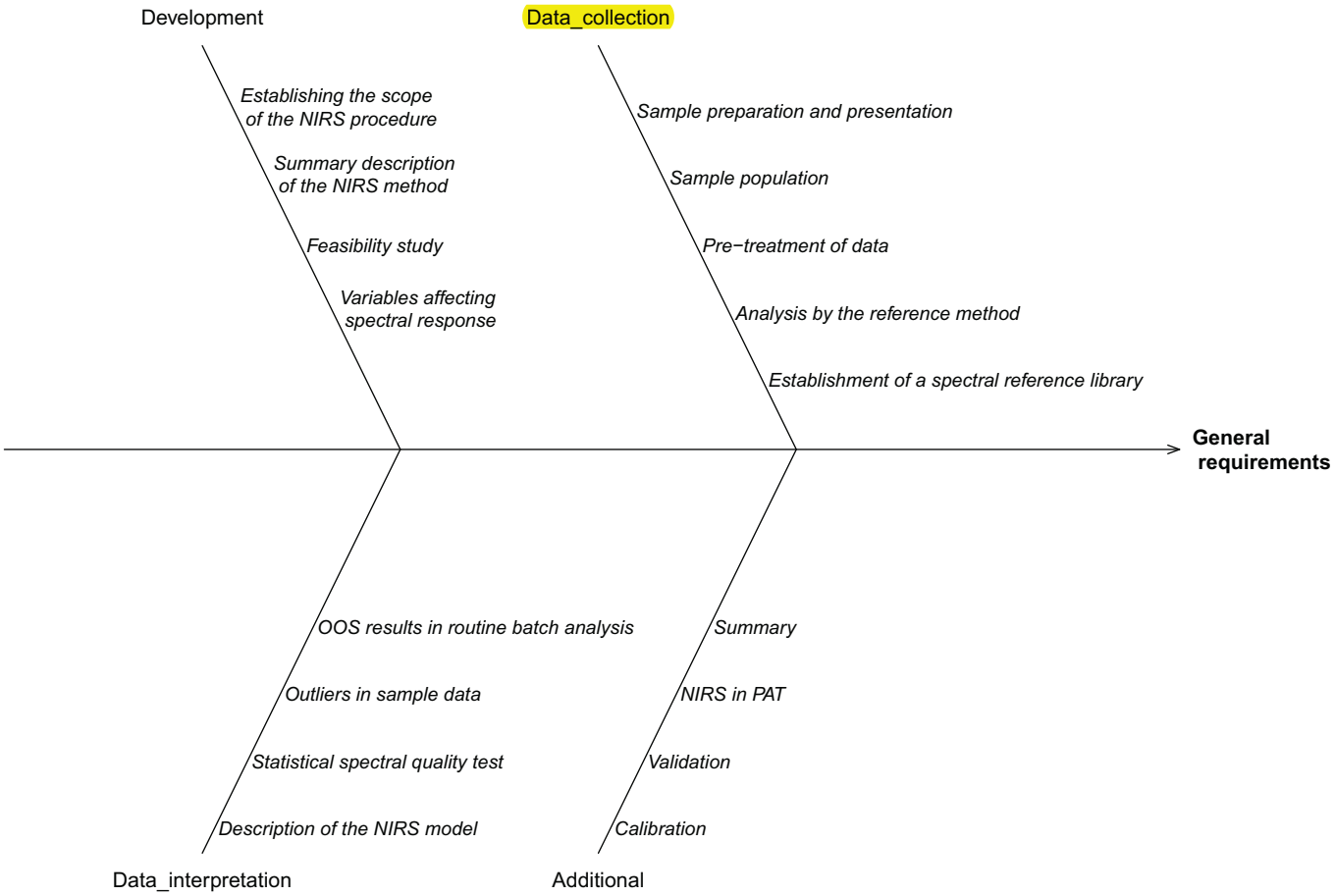
The feasibility of using NIRS should be considered in the development of new procedures to demonstrate that it is suitable for the intended purpose. Such a feasibility study may include (but is not limited to), the determination of a suitable NIR response, investigations into specificity and matrix interference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

Variables affecting spectral response

Background physical and chemical variables, which may affect the spectral response, may be present.

It is not possible to list all possible variables, but these may include the environment in which measurement takes place; sample temperature; residual moisture and solvents; sample thickness; sample optical properties; optical quality of the glassware; polymorphism; particle size; homogeneity and the age of the samples. Time of measurement and instrumental drift should also be considered.

Each known potential variable that may affect the spectral response should be considered and discussed in turn and either shown to be insignificant or controlled satisfactorily (supported by appropriate data).



Sample preparation and presentation

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

Sample population

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

Sample population (cont.)

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

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

Pre-treatment of data

Pre-treatments include (but are not limited to) Normalisation and derivation, which are performed in order to remove unwanted sources of variation from the data prior to treatment and to enhance spectral features.

Any pre-treatment of data should be documented and justified.

Analysis by the reference method

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

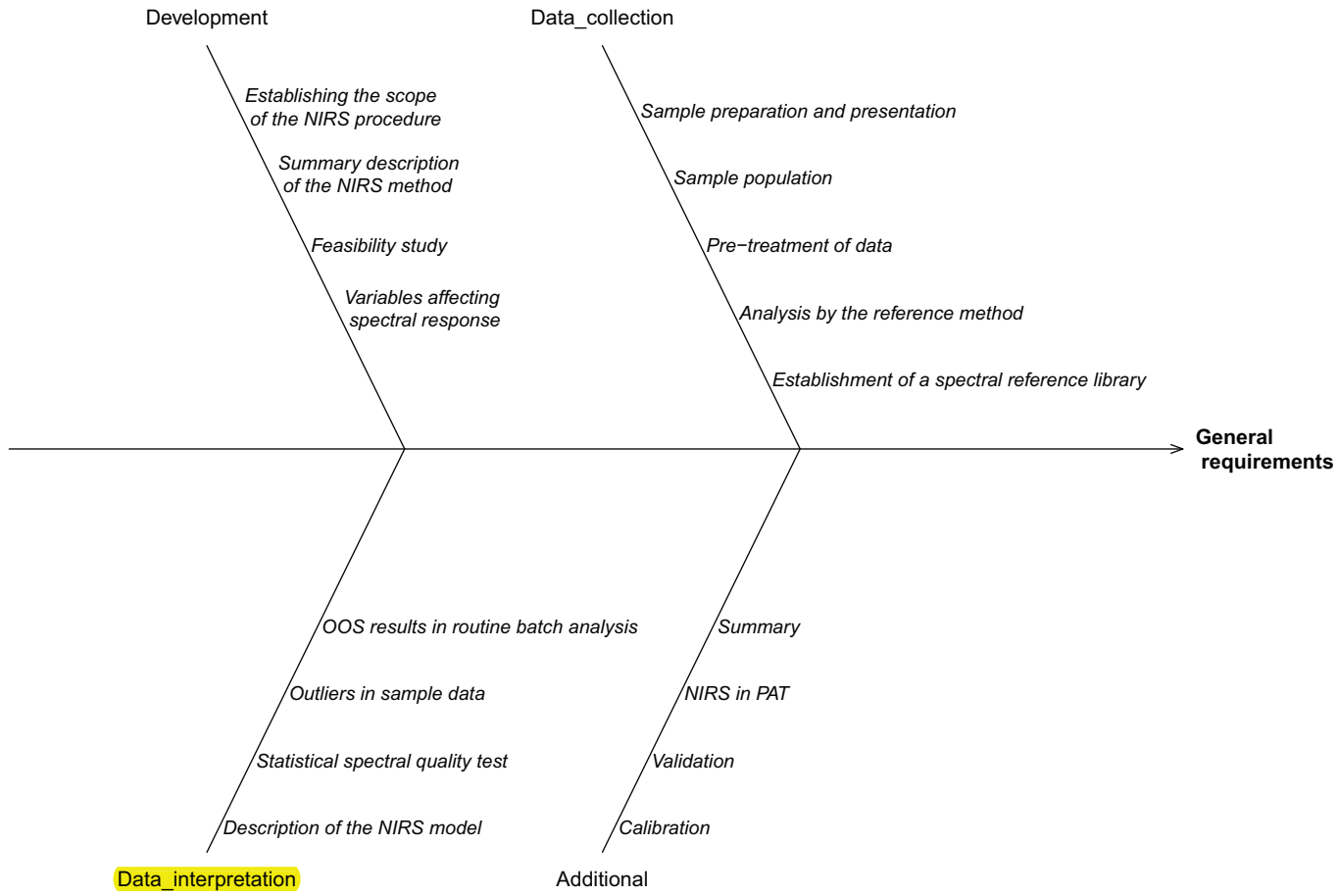
- a description of the analytical procedure according to Module 3.2.P.5.2 data requirements.
- details of the validation of the analytical procedure according to the Module 3.2.P.5.3 data requirements and the ICH Q2(R1) Guideline on Validation of Analytical Procedures (CPMP/ICH/381/95). For Veterinary applications reference is made to the VICH Guidelines GL1 & GL2 Validation of Analytical Procedures (CVMP/VICH/590/98 & CVMP/VICH/591/98).
- details of relevant reference standards and materials according to the Module 3.2.P.6 data requirements.

Establishment of a spectral reference library

- The composition of the spectral reference library should cover the scope of the NIRS procedure and should be subject to a change management system (subject to GMP inspection).
- Batches should be representative of the marketed materials or products and laid down in a list of batch numbers.

Establishment of a spectral reference library (cont.)

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



Statistical spectral quality test

- Before an NIRS model may be applied to a sample, a statistical spectral quality test should be performed, to determine whether the characteristics of the sample fall within the range of variation for which the model was calibrated and validated.
- A clear description of the spectral quality test should be described in any procedure involving the use of NIRS.

Outliers in sample data

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

Outliers in sample data (cont.)

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

Outliers in sample data (cont.)

In practice, there may be several reasons for outliers, e.g. a sample belonging to a different population to the rest of the samples, instrument malfunction, reference method failure or transcription error.

Outliers in sample data (cont.)

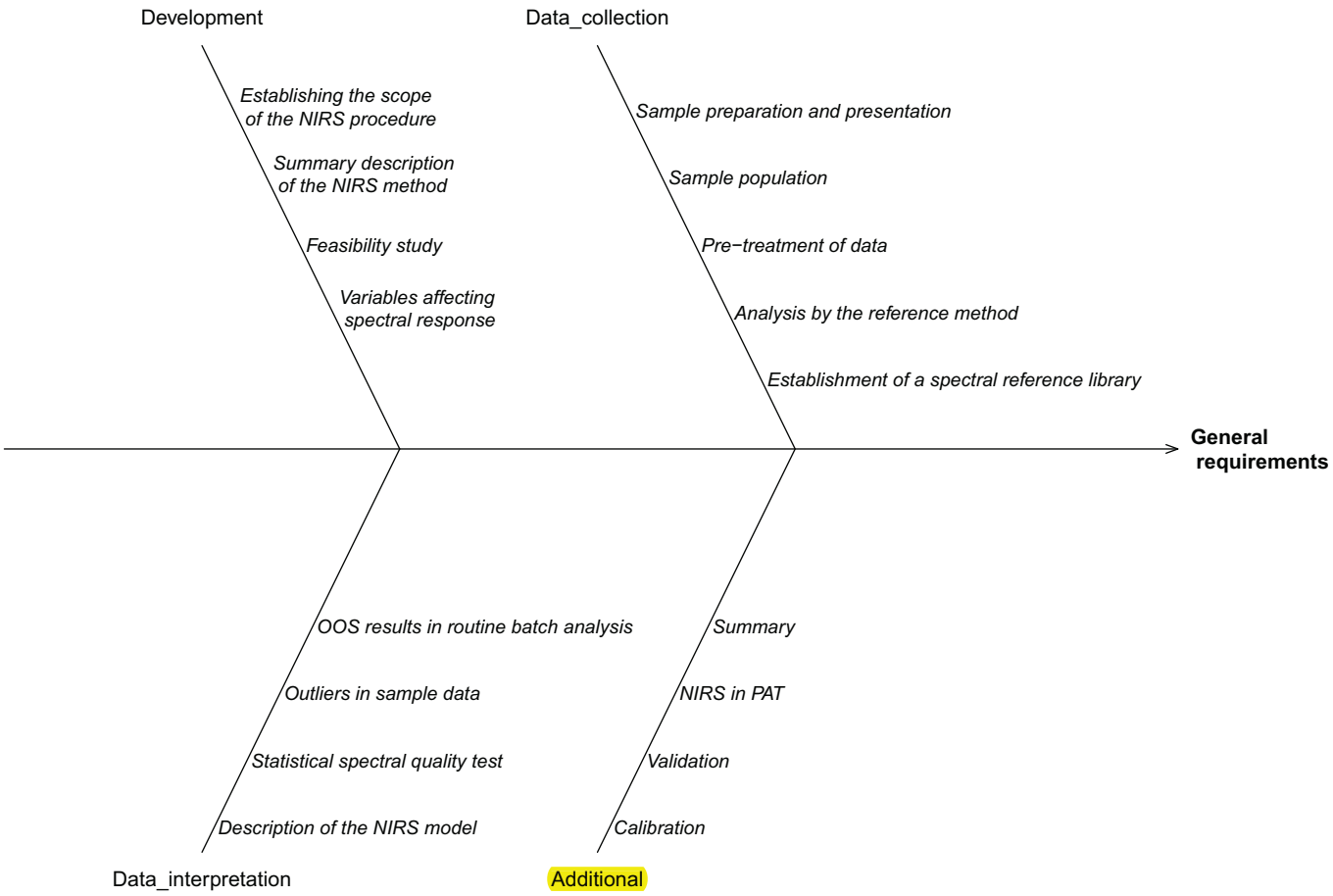
If a sample is shown to be an outlier because of characteristic properties, the sample should be verified using an appropriate alternative analysis. After confirmation of authenticity, the sample may be included in the spectral reference library and the model should be re-validated so as to include this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

Out of Specification (OOS) results in routine batch analysis

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

Out of Specification (OOS) results in routine batch analysis (cont.)

- A batch should not be released based on an OOS NIRS result and a within-specification result when tested using the reference method.
- If, on investigation, the affected batch complies with the specification using the reference analytical method, then this may indicate that the NIRS procedure has not been fully developed. The NIRS procedure may then be updated as necessary (as per the NIRS procedure lifecycle concept) and re-analysis undertaken such that the batch may be released within specification for both the NIRS procedure and the reference method of analysis.



Calibration

Specific requirements for calibrations are described in the sub-chapters for “Qualitative Procedures” and “Quantitative Procedures”.

Validation

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

Validation (cont.)

- The validation set of samples should be completely independent of the calibration set.
- A comparison of results obtained by analysis of the same set of samples by the NIRS procedure and the reference method forms part of the validation of NIRS, along with independently determined parameters, such as intermediate precision.

Validation (cont.)

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

NIRS in PAT applications

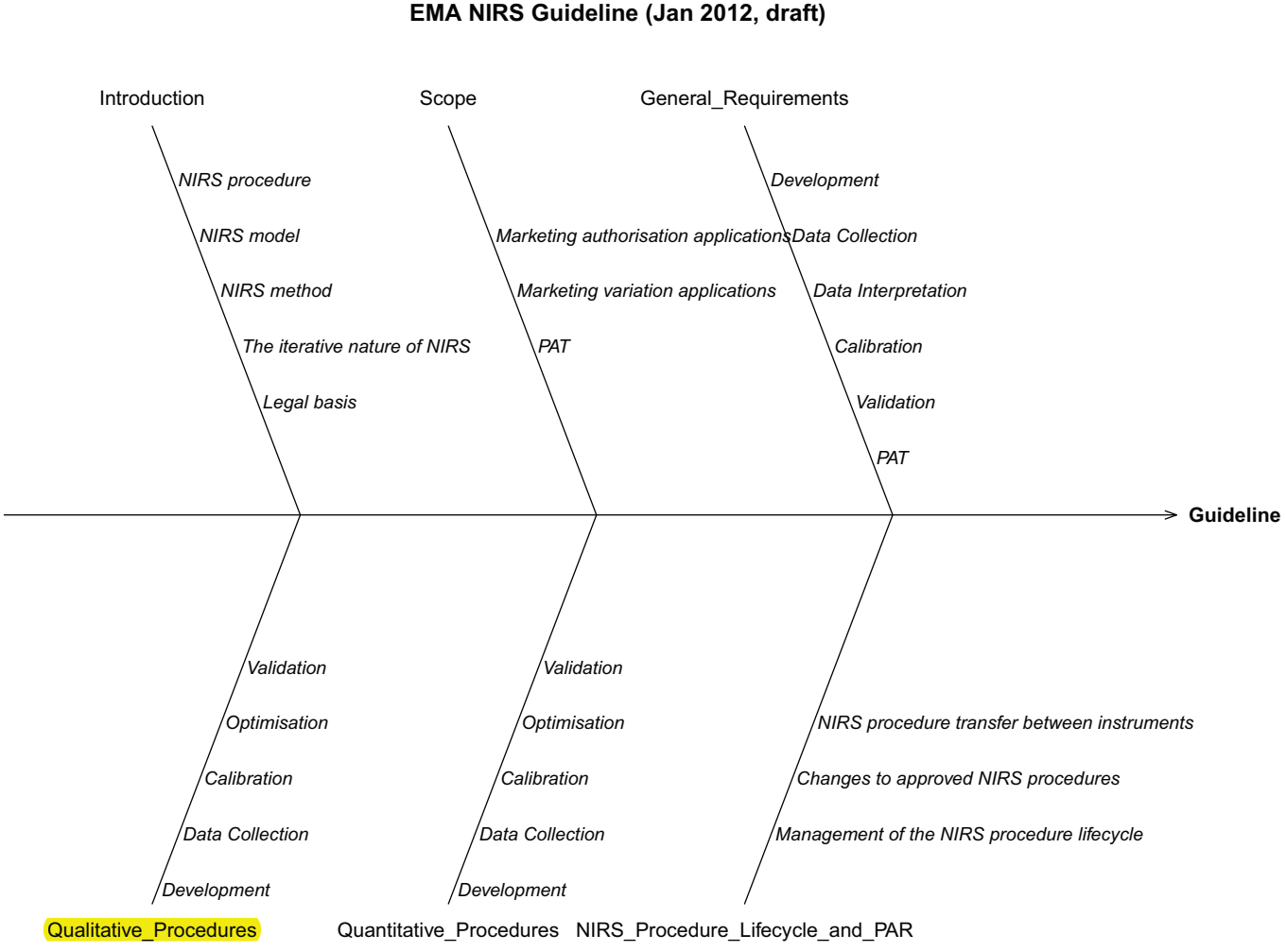
- In the context of PAT applications, almost all NIRS procedures are specific to the nature of the individual manufacturing processes. It is therefore not appropriate to prescribe exact requirements for such procedures in this guideline.
- The general data requirements described in this guideline are also applicable to NIRS PAT procedures and should particularly take into account the intended purpose and scope of the procedure.

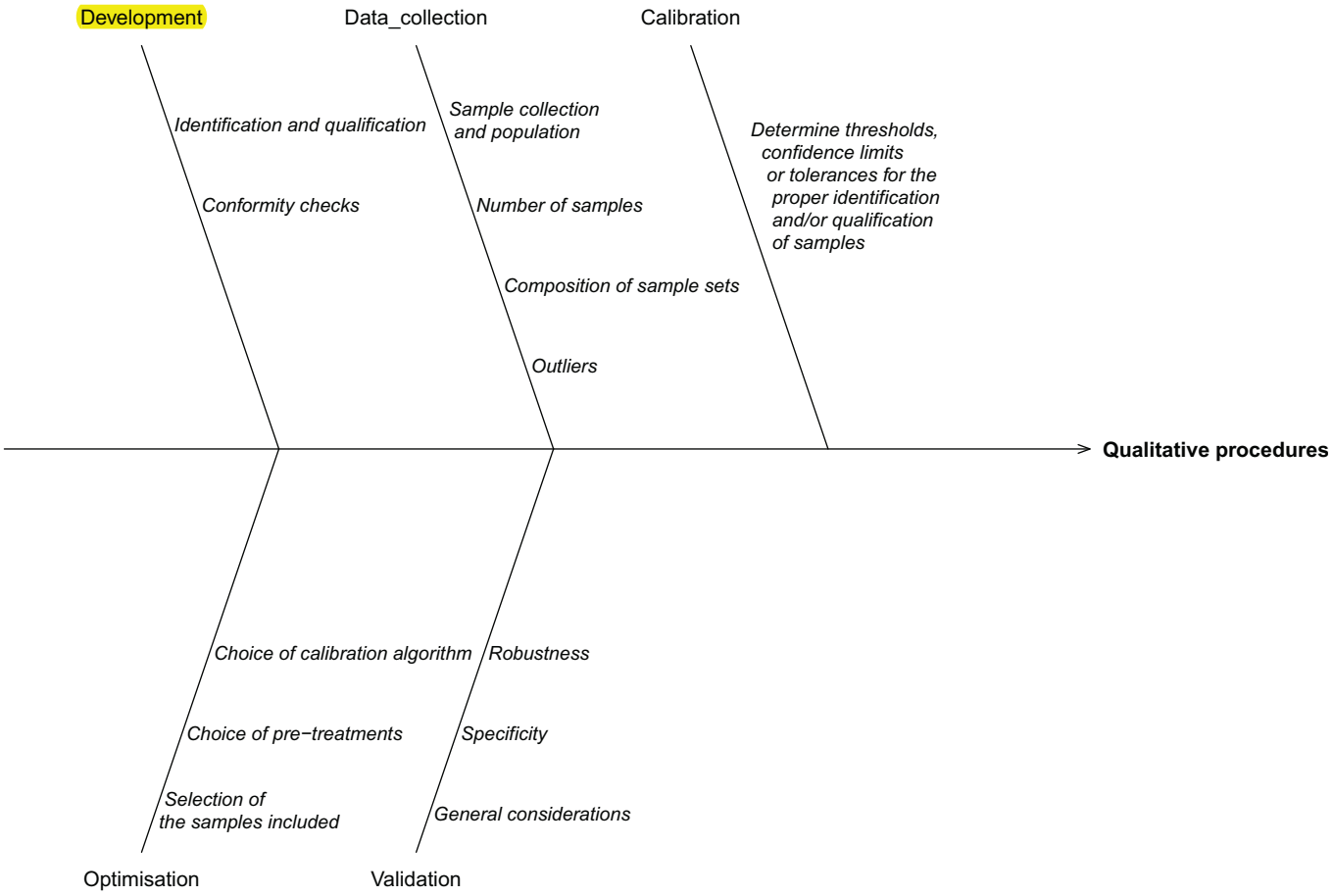
NIRS in PAT applications (cont.)

Examples of NIRS in PAT applications include:

- drug substance manufacturing process steps such as chemical reaction kinetics, crystallisation, drying and milling
- drug product manufacturing process steps such as granulation, blending, tablet hardness and coating

In the case of the monitoring of a powder blend for homogeneity, the blend may be monitored in terms of the measurement of the change of the NIR signal over time, rather than in relation to a reference method such as HPLC.





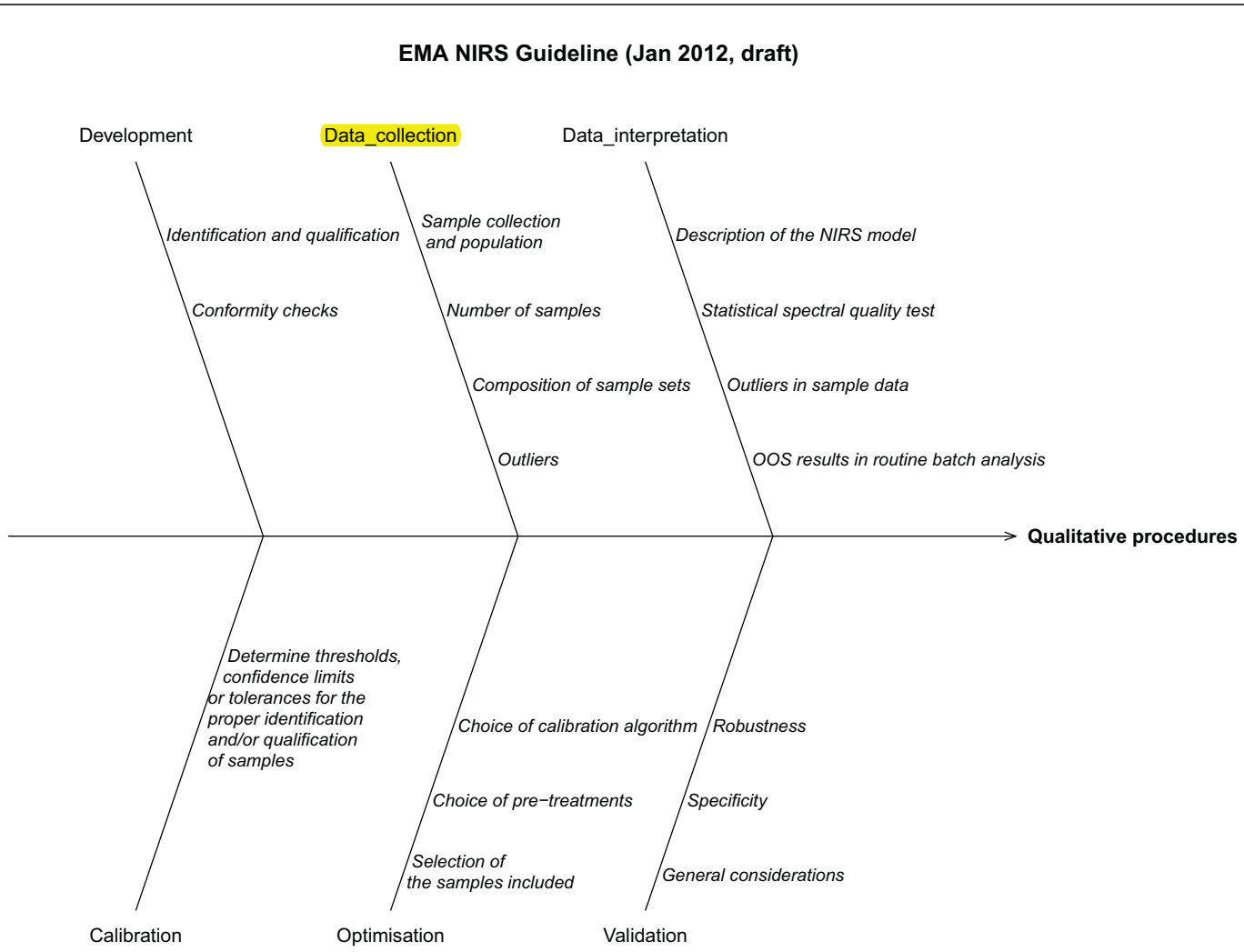
Identification and qualification

- To allow differentiation, this guideline uses the term identification as referring to chemical structure only and qualification as referring to chemical and physical attributes.
- The classification can be performed in several stages.
- Where the NIRS procedure on its own is not sufficient to identify or qualify a substance, it should be supplemented by other different analytical procedure(s) (e.g. chemical reaction or chromatographic methods), so that the tests taken together ensure, as far as possible, specificity.

Conformity checks

(PAT, dynamic process monitoring or trend analysis)

- This guideline uses the term conformity as the conformation of characteristics in accordance with a certain degree of similarity (chemical and/or physical attributes) to a specified standard.
- Such conformity checks refer to process characterisation or trend analysis, for example the determination of the endpoint of a process by monitoring the change in NIRS signal.
- Conformity NIRS procedures will often not involve the use of a reference analytical method because of difficulties in sampling for reference analysis.
- The extent of the calibration and validation work performed will depend on the intended purpose of the procedure.



Sample collection and population

- The validation of the NIRS procedure should demonstrate that spectra of an acceptable minimum number of batches have been included in the spectral library and that these batches are sufficiently representative to cover the normal variation of the substance.
- For procedures used to identify or qualify substances on receipt, samples from all known potential suppliers should be incorporated into the library.

Number of samples

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

Composition of sample sets

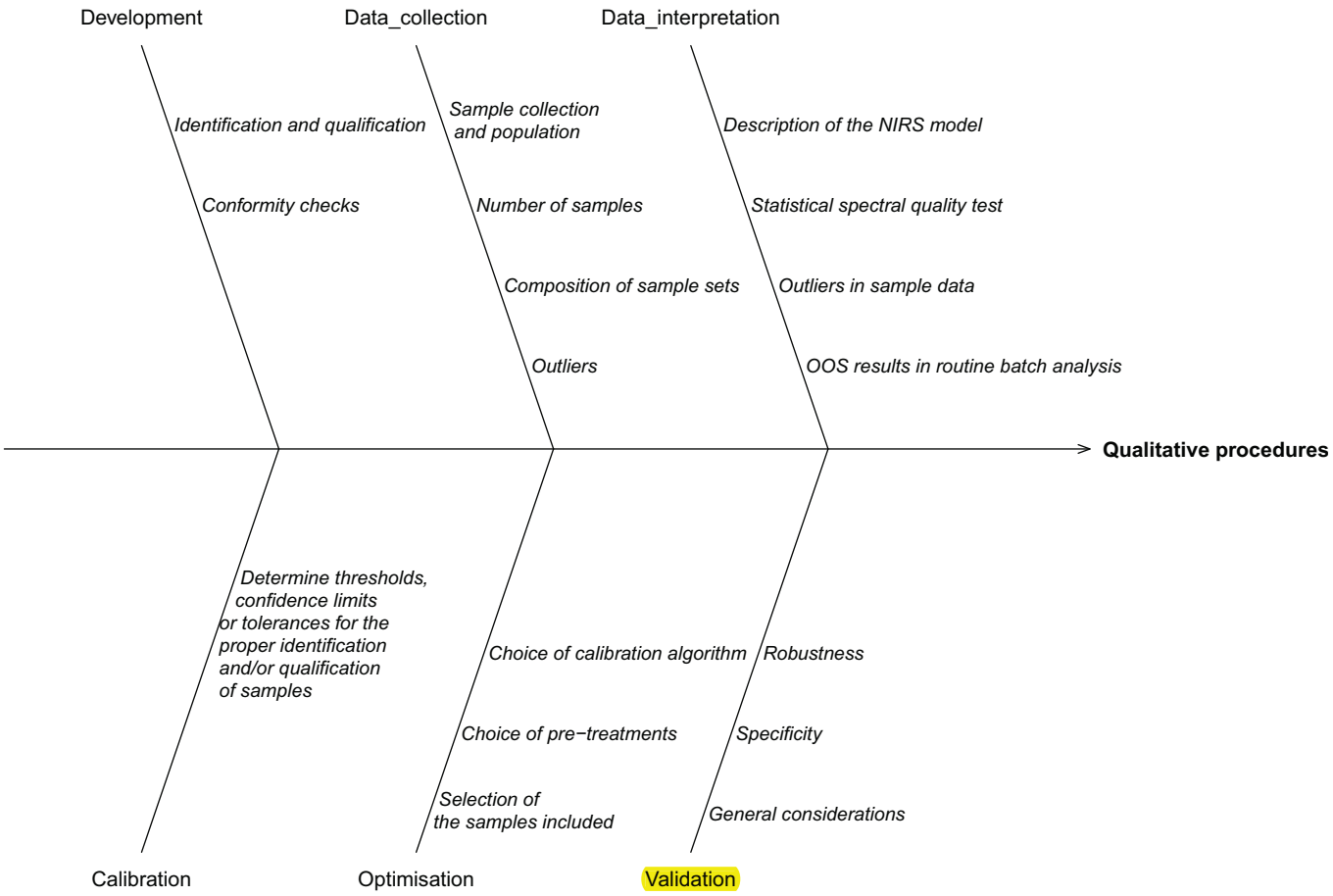
In order to develop, optimise and validate a calibration model for a typical qualitative NIRS procedure used for identification or qualification, two sets of samples are required:

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

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

Outliers

Identified outliers in a spectral reference library should be investigated and should be excluded only based on valid analytical reasons. These should be documented and justified.



General considerations

- Internal validation by cross validation
  This internal validation step should demonstrate that all samples of the spectral reference library are identified or qualified according to the scope of the procedure, within the defined thresholds, confidence limits and/or tolerances.
- External validation
  should demonstrate the performance of the chosen model using an independent validation set consisting of samples that were not used in the creation of the spectral reference library.

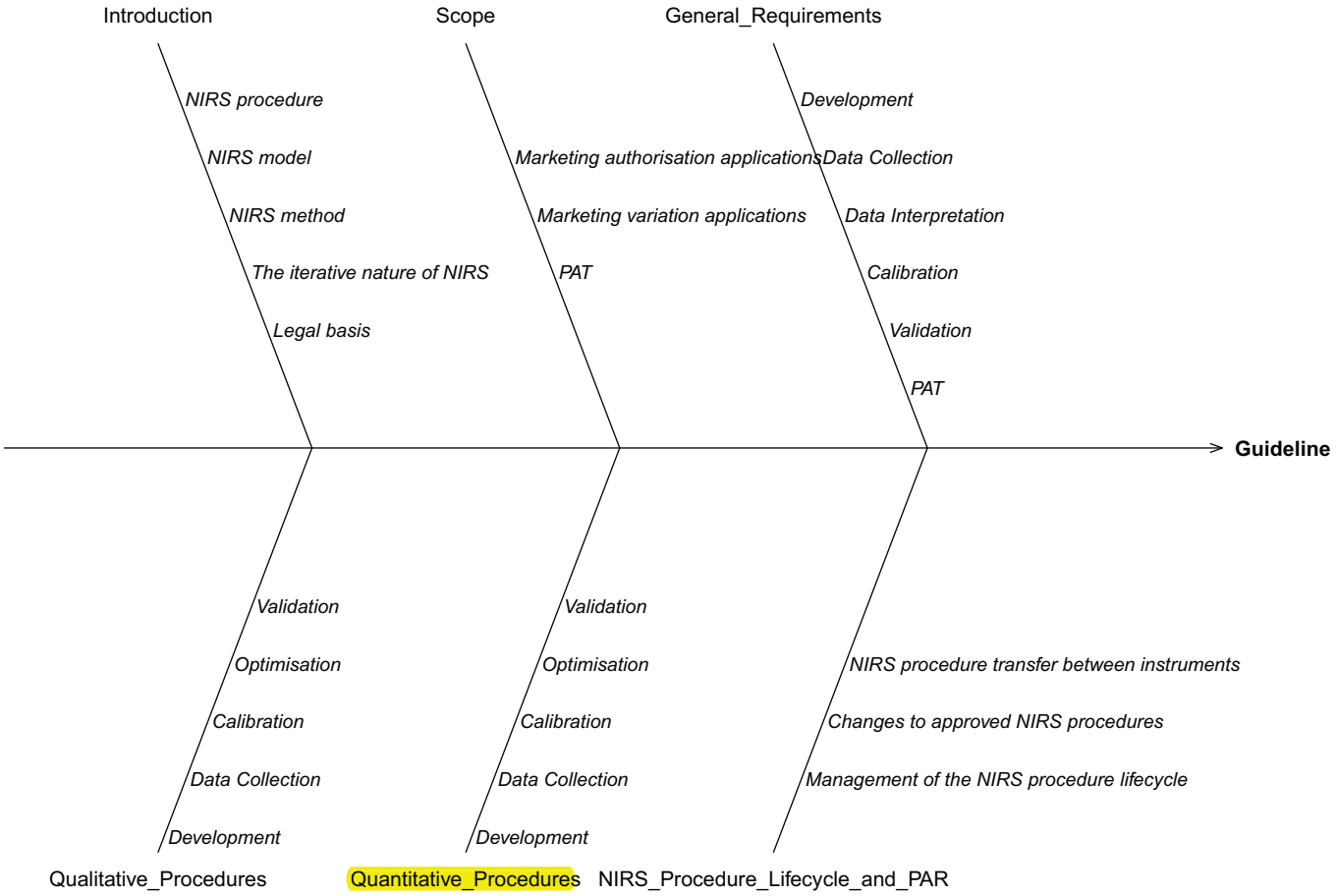
Specificity

- The extent of specificity testing depends on the intended NIRS procedure. A lack of specificity may be compensated for by other supporting analytical procedures.
- Where applicable (e.g. for qualification procedures), validation should include challenge with different grades of the same substance, anhydrous/hydrated material, different polymorphs or material supplied by different vendors.

Robustness

- Effects of relevant variables e.g. temperature (environment and sample), humidity, different position of the sample in the optical window, different sample presentation devices, variation in sample bottles/vials, probe depth or, if applicable, different packaging materials, should be understood, tested and documented. Instrumental variations may also be considered in the validation for robustness, e.g. changing lamps, reflectance standard etc.
- The use of Design of Experiments (DOE) may be considered to maximise the information available.

EMA NIRS Guideline (Jan 2012, draft)



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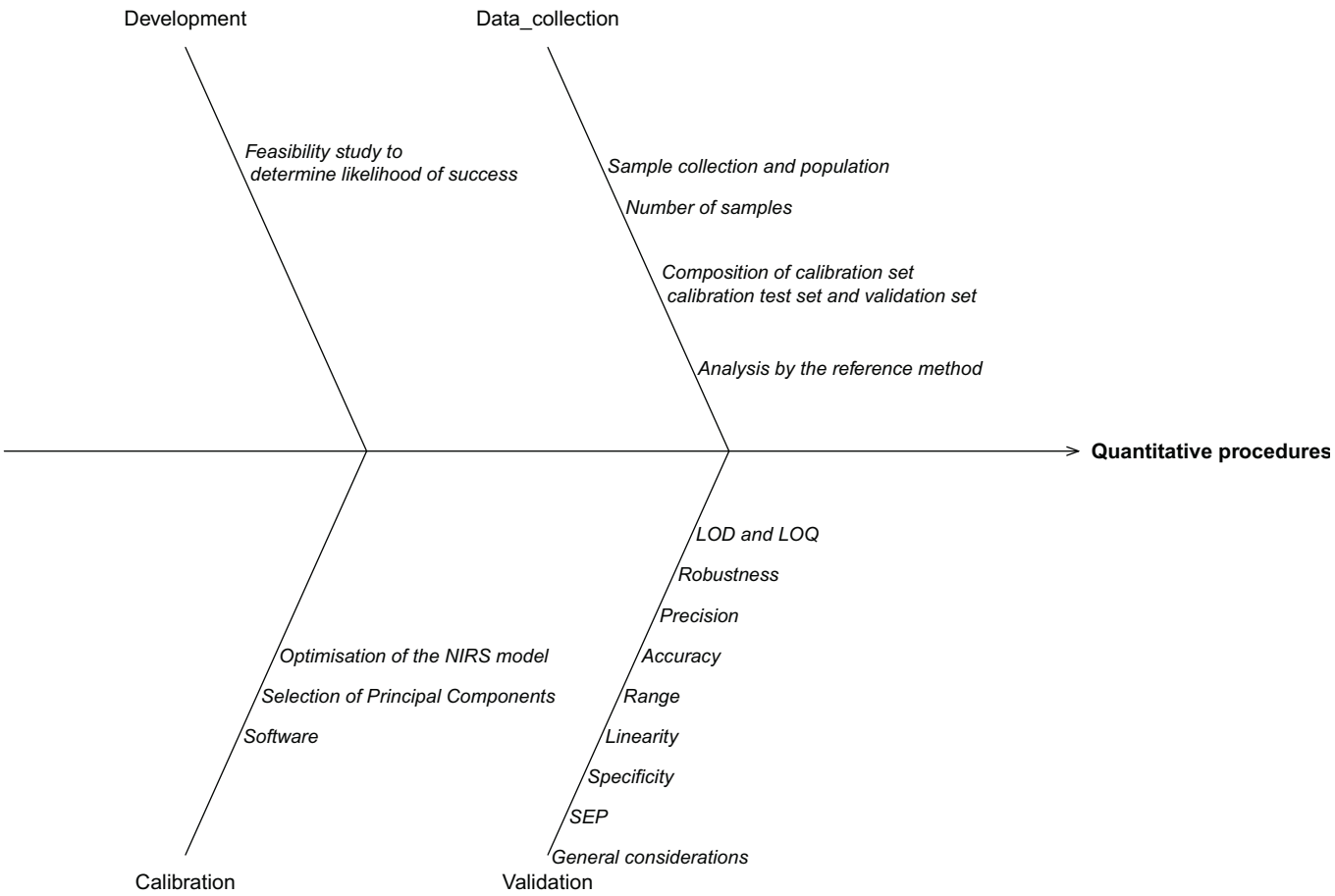

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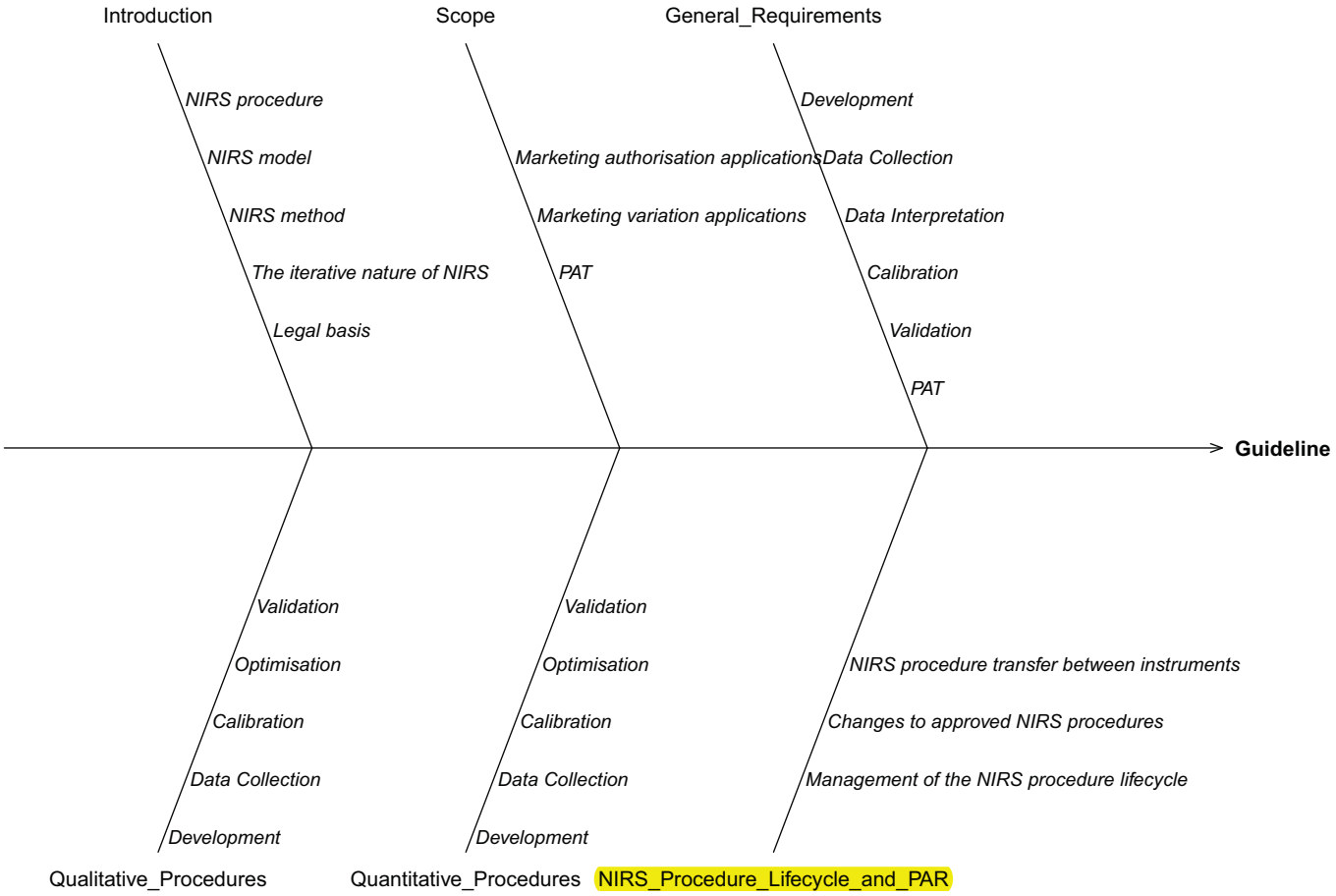

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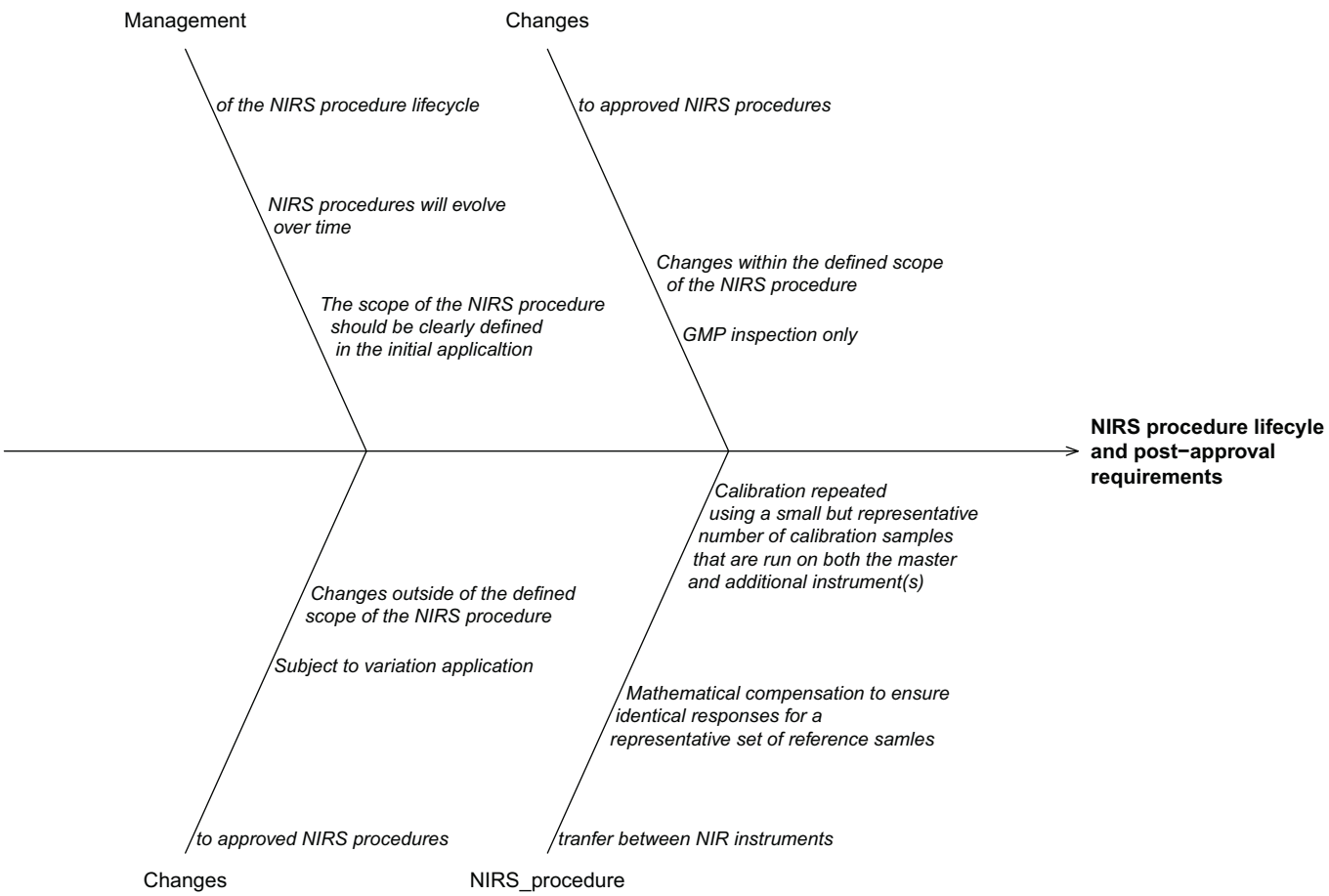

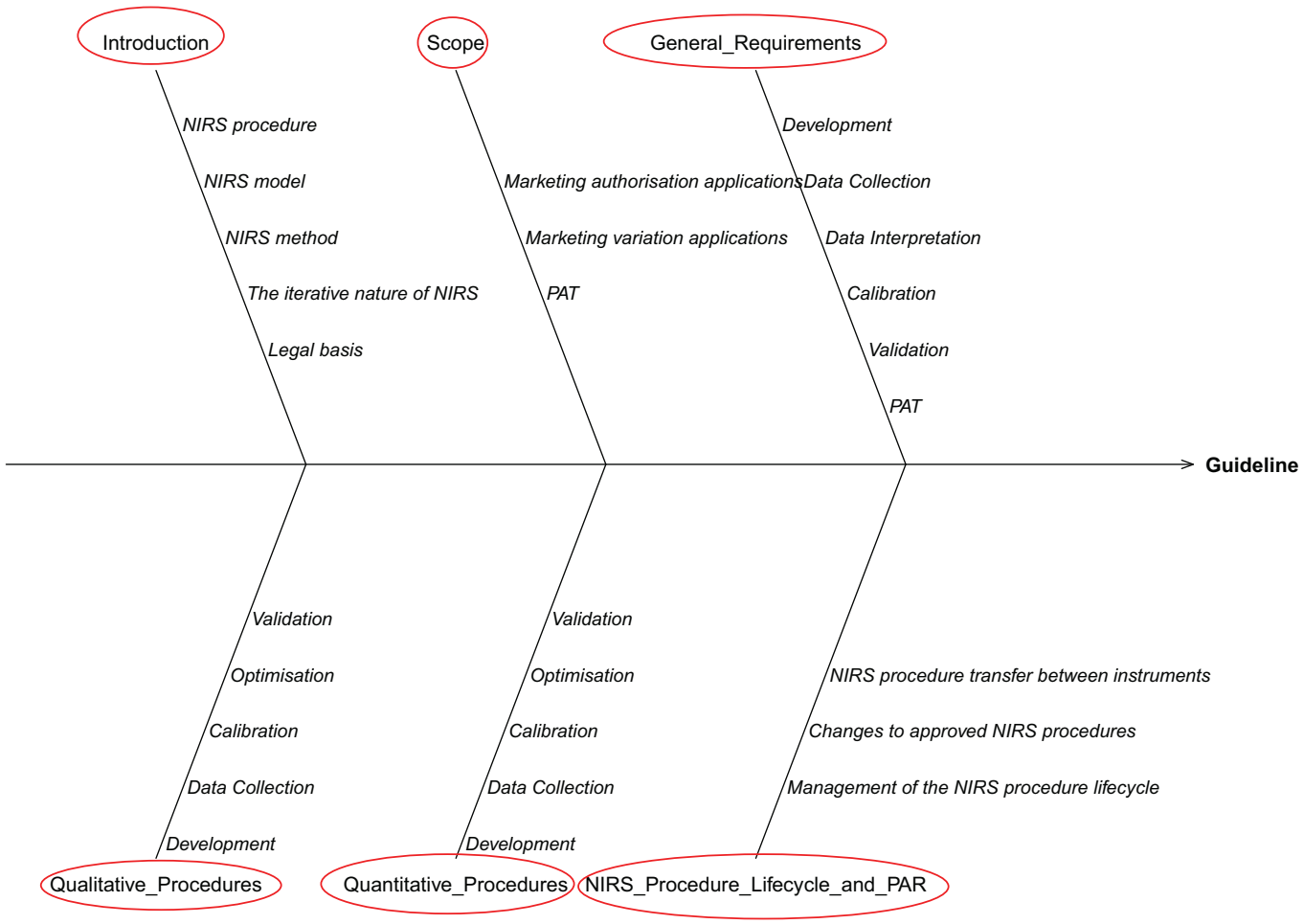

Reminder

Remember: This is a guideline, not an SOP!

"Approaches other than those described in this guidance may be used, if appropriately explained and justified." (section 2)

. . . the end.

Thank you for your attention!

E-mail: karl.molt@uni-due.de

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