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An agency of the European Union

27 July 2022

Submission of comments on ICH Guideline Q14 Analytical Procedure Development Step2B

EMA/CHMP/ICH/195040/2022

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.
When completed, this form should be sent to the European Medicines Agency electronically, in Excel format (not PDF), to the following address:
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All the cells with an asterisk (*) should be filled in prior to completing the columns "Comment and rationale" and/or "Proposed changes / recommendation".
For more details on how to use this template please refer to the tab "Manual for commenter".

Name of organisation or individual*	Line from* (line Nr or 0 for general comment)	Line to* (line Nr or 0 for general comment)	Section number	Comment and rationale (to go to next line within the same cell use Alt + Enter)	Proposed changes / recommendation (if applicable - to be used if you want to propose specific text changes)
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	0	0	Q14 General	Additional examples covering analytical procedure development and nomenclature specifically associated with large molecules are requested to demonstrate the practical application of the guidance concepts for this molecular modality.	Expansion of the current Annexes and development of additional large molecule examples so that the language and concepts in Q14 are demonstrated over all modalities, in particular to demonstrate enhanced approaches and outcomes, for large molecules, further examples of how to establish ECs and their change categories across all modalities, and inclusion of stability indicating properties for analytical procedures is encouraged.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	0	0	Q14 General	ISPE recommends that the title is expanded to more fully reflect the content and intent of the guideline, as discussed in the concept paper.	Suggest changing guideline title from "Analytical Procedure Development" to "Analytical Procedure Development and Lifecycle Management"
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	0	0	Q14 General	The concept of analytical procedure reproducibility assesses external factors that could affect the performance of the method. As commercial analytical procedures are often operated in multiple laboratories it is important these aspects are not overlooked.	Recommend that 'Reproducibility" which is equally important as 'Robustness' be included in ICH Q14. Analytical procedures are not routinely applied at the development site, but in external (often multiple), commercial analytical laboratory settings.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	0	0	Q14 General	MVA applications should be managed in an identical manner to other analytical procedures but with additional requirements for the multivariate elements.	Recommend structuring the Multivariate Analysis Chapter content with the same basic content as the preceding sections for univariate procedures. Inherently MVA procedures will follow the the same overall process and registration principles but with additional points to consider for this type of procedure.
International Society for Pharmaceutical	0	0	Q14 Annexes	Examples and text should be developed please which do not contain the phrase "depending on region" since this phrase should be obviated by the harmonisation .	

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International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	3	4	1.1 Objective of the guideline	Clearer statement of the intention an use of the guidance.	Consider changing "This guideline describes science- and risk-based approaches for developing and maintaining analytical procedures suitable for the assessment of the quality of drug substances and drug products." to "This guideline describes the requirements of science and risk based approaches to the development and maintenance of analytical procedures for the assessment of the quality of drug substance and drug products throughout the analytical procedure lifecycle."
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	11	22	1.1 Objective of the guideline	The intent of the guideline to link with Q12 and not introduce new requirements is considered important. The link could be emphasized further by running para's 11-14 and 15-22 together. All submitted, fit for purpose, analytical procedures will, in general, contain sufficient controls to assure their suitability for the intended analysis. Submission of additional development information, as described in ICHQ12, can provide additional assurance, facilitate efficient regulatory processes, and provide a basis for lifecycle management.	Suggest changing "This guideline is intended to complement ICH Q2 Validation of Analytical Procedures. Submitting knowledge and information related to development of analytical procedures to regulatory agencies may provide additional evidence to demonstrate that the analytical procedure is appropriate for its intended purpose." to "This guideline is intended to complement ICH Q2 Validation of Analytical Procedures, link with ICH Q12 to cover the analytical procedure lifecycle, and is not intended to introduce any new regulatory requirements." Suggest changing "Knowledge gained from application of an enhanced approach to analytical procedure development can provide better assurance..." to "Knowledge gained from application of an enhanced approach to analytical procedure development can provide additional information which could support lifecycle management of an analytical procedure"
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	27	34	2 SCOPE	The inclusion of 'other' analytical procedures and the phase appropriate application of the scientific principles during the clinical development phase may be difficult to interpret consistently in practice across the ICH regions.	Recommend removal of the references to "other analytical procedures" and "clinical development" from the Scope section to focus the guideline on marketing applications.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	40	42	2.1 General Considerations for Analytical Procedure Development & LCM	Additional examples/training materials to illustrate an acceptable minimal/traditional approach which is then developed further towards the enhanced approach described to illustrate the concepts further would be very helpful.	Recommend additional examples/training materials be developed to demonstrate how a procedure originally developed using a minimal approach could be supplemented to have features of the “enhanced approach”.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	43	47	2.1 General Considerations for Analytical Procedure Development & LCM	Additional clarity, or additional examples/training materials to illustrate the risk based deployment of platform procedures cross multiple products and applications would be very helpful.	Recommend additional examples/training materials be developed to exemplify how platform procedures can be deployed.

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International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	60	62	2.2 Minimal vs Enhanced Approaches	Need to connect the link here between accuracy and precision with the specification because the accuracy and precision in particular need to support the specification limits. The ATP plus combined accuracy/precision (Total Analytical Error) supports this link.	Recommend changing "Conducting appropriate development studies to evaluate analytical procedure performance characteristics such as specificity, accuracy and precision over the reportable range (including the calibration model, limits at lower and/or higher range ends) and robustness." to "Conducting appropriate development studies to evaluate analytical procedure performance characteristics such as specificity, accuracy and precision to support the required specification (including the calibration model, limits at lower and/or higher range ends) and robustness."
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	75	76	2.2 Minimal vs Enhanced Approaches	Utilization of prior knowledge and relevant experience is an element of quality by design and associated control strategy is an important part of analytical procedure development and ISPE recommends an additional bullet is added	Propose the addition of an additional bullet for enhanced approach: - evaluate and consider prior knowledge of analytical technology platforms, leveraging data/experience from similar or related procedures or relevant analytes.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	86	87	2.2 Minimal vs Enhanced Approaches	"Appropriateness" is a subjective word. A better phrase would be science- and risk-based ECs, or performance based ECs dependent on a company's approach to development and change management. Support for a more focused and efficient post-approval change management process serves is an incentive for companies to pursue the enhanced approach option.	Recommend changing "Applying elements of the enhanced approach to development can lead to more robust analytical procedures, better understanding of the impact of analytical procedure parameters and more flexibility for lifecycle management such as wider operating ranges, a more appropriate set of ECs and associated reporting categories for changes." to "Applying elements of the enhanced approach to development can lead to more robust and reproducible analytical procedures, better understanding of the impact of analytical procedure parameters leading to a more flexible and efficient post lifecycle management process, incorporating wider operating ranges, and the science and risk based justification of ECs and their associated reporting categories for changes. "
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	89	99	2.2 Minimal vs Enhanced Approaches	A description of the efficient management post-approval changes using the enhanced approach could be added. The incentive for executing and filing the enhanced approach for analytical procedure development is efficient post approval change management.	Propose addition of an additional bullet point to "The enhanced approach potentially offers several advantages, including:" list as follows, "•Enabling the reduction of post-approval change notification category, according to the principles outlined in ICH Q12" and changing "•Reducing the amount of effort across the analytical procedure lifecycle." to "•Supporting more efficient management of post approval changes for analytical procedures"

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International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	108	109	2.3 Procedure Lifecycle	ISPE suggests some changes of Figure 1 to assist with completeness and can provide a proposed updated Figure 1 if that would be helpful.	Several editorial updates to Figure 1 are proposed including; Put an asterisk next to "Routine Use" box to capture comments "results from routine use gain Product and Process Understanding" Add an arrow line from Change box to validation box in Figure 1 Put an asterisk next to "risk assessment" box to capture comments "risk assessment is repeated throughout analytical procedure lifecycle when more information becomes available"
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	123	125	3 Analytical Target Profile	Line states that formal documentation and submission of an ATP is optional. However, Figure 2 (line 339) states "are criteria of relevant performance characteristics defined as ECs which ensure the post-change quality of the measured result after the change?" therefore, lower reporting is only possible if the performance characteristics (i.e., ATP) are included as ECs in 32S42/32P52.	It should be made clear in describing what should be submitted (Section 10) that, for the potential of lower reporting categories, the performance characteristics and criteria should be included as Established Conditions in 3.2S4.2/3.2P5.2. Further clarification and exemplification of what is included in a submission and how this translates to lower reporting categories using the enhanced approach, would be very helpful.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	164	166	4.2 Risk Management	Current wording could be misinterpreted that analytical procedure performance monitoring is recommended for all analytical procedures in order to maintain a state of control, whereas procedure performance monitoring would normally be deployed on the basis of risk assessment and the criticality of the attribute being measured.	Recommend changing "To maintain a state of control for analytical procedure performance, ongoing monitoring is recommended as part of risk review." to "To maintain a state of control for analytical procedure performance during routine operation, ongoing monitoring can provide useful insight into method performance as part of an enhanced approach to risk review and lifecycle management."
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	180	180	5.1 Robustness	Robustness can also be established through prior knowledge, notably for platform analytical methods.	Recommend changing "For most procedures, robustness evaluation is conducted during development" to "For most procedures, robustness evaluation is conducted during development and builds on prior knowledge or analytical technologies used".
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	182	183	5.1 Robustness	Intermediate precision does not provide information on the robustness (i.e. deliberate perturbations of parameters) of a procedure.	Suggest "Data from validation studies (e.g., intermediate precision) can be used to complement robustness evaluation." is changed to "Data from validation studies (e.g., intermediate precision) can be used to support the design of subsequent robustness studies."

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International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	205	207	5.2 Parameter Ranges	ICHQ14 Section 5.2 clarifies that the enhanced approach allows for changes within established parameter ranges only, and does not include the concept of performance based approaches. This is of limited value when considering the product lifecycle as most "real" changes will still require a regulatory notification (change in column/ mobile phase), change from HPLC to UPLC.	Lines 205-207 restricts flexibility to movement within established parameter ranges, which is already available to applicants. Recommend the inclusion of some additional text or examples that include performance based approaches to analytical procedure development and lifecycle management where these can be justified. For example where further understanding of the measurement requirement, the suitability of of available analytical technologies, and/or the relationship between analytical procedures parameters is demonstrated, how this knowledge can support the science and risk based justification of ECs related to procedure performance and their related change categories.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	213	214	5.2 Parameter Ranges	Additional examples will aid understanding on the inclusion of development data in submissions.	Additional examples demonstrating the use of development data in a submission would be helpful.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	231	232	6 Control Strategy	Clarification.	Change "The level of detail should enable a skilled analyst to perform the analysis and interpret the results (such as the level of detail in a regional pharmacopoeia for a similar substance)." to "……(such as the level of detail in a regional pharmacopoeia for a similar analyte).
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	233	243	6 Control Strategy	A company may have method performance criteria that are trended to determine method performance over a long period of time, but they are not strictly SST requirements (as these tend to be set based on the minimum requirements from the relevant pharmacopeia)	SST section needs to set expectations of what should be described in the dossier with examples of the expected efficiencies that can be supported using the enhanced approach. For example, where supporting data and knowledge is provided to justify registration of the SST as an Established Condition, other procedure details such as stationary phase, mobile phase composition can be justified as non-ECs.

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International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	233	243	6 Control Strategy	Clarification ISPE recommends that there is a stronger linkage of well designed enhanced studies and risk management, which leads to reduced risk and consequently a reduced number of ECs.	Propose changing "In the enhanced approach, a well-designed set of SST parameters and other criteria to ensure method performance, supported by development data, could represent an important aspect of risk mitigation" to "In the enhanced approach, a well-designed set of SST parameters and other criteria to ensure method performance, supported by development data, could represent an important aspect of risk mitigation and thereby support a reduction on the number of ECs or their reporting category" ISPE recommends that an example is developed which shows how well designed, enhanced studies lead to reduced risk and lower number and/or lower categorization of ECs
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	242	243	6 Control Strategy	With increasing adoption of continuous manufacturing and a consequent use of multivariate models to assure product quality, adding more details around using appropriate software tools for data quality verification for SSTs of such analytical procedures is highly recommended such as an added example in the annex. The reader can then be aligned to better understand the intended scope of lines 249-251, in conjunction with rest of the guidance	Additional examples/training materials demonstrating the use of appropriate software tools for data quality verification as part of the SST for analytical control strategy for procedures based on multivariate models, would be helpful.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	253	254	6 Control Strategy	As PQS expectations for analytical procedure monitoring are not explicitly defined the statement risks different regional interpretation.	Recommend changing "Ongoing monitoring of selected analytical procedure outputs is recommended to look for any trends, in line with PQS expectations." to "Ongoing monitoring of selected analytical procedure outputs is recommended to look for any trends"
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	261	263	6.1 Established Conditions	Prior knowledge is also an element to leverage for the range extent of EC.	Consider revising to: "The nature and extent of ECs will depend on the development approach, the complexity of the analytical procedure, the amount of prior knowledge available, and a demonstrated understanding of how parameters and other factors impact its performance."
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	266	269	6.1 Established Conditions	Clarification - to indicate that a more focused set of ECs will result from the enhanced approach compared with the minimal approach in order to demonstrate the potential benefits of the enhanced approach.	Recommend changing "With an enhanced approach to development, there should be an increased understanding of the relationship between analytical procedure parameters and performance to facilitate identification of which factors require control and thus enable a more appropriate set of ECs." to "With an enhanced approach to development, there should be an increased understanding of the relationship between analytical procedure parameters and performance to facilitate identification of which factors require control and thus enable a more focused set of ECs to be justified"

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International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	310	312	7 LCM & post-approval changes	per line 295, either approach can use ECs, or structured approach (Q12), etc. Line 310 should not exclude ability for regulatory reporting relief for minimal approach.	Recommend changing "If a minimal approach to development is taken, then any changes should be reported according to existing regional reporting requirements. The use of different elements of the enhanced approach can facilitate management and regulatory communication of post-approval changes." to "Communication to the regulatory agency through ECs, PACMP, PLCM, or enhanced approach using risk managment allows the potential for reduced reporting requirements. The use of different elements of the enhanced approach can facilitate more flexibility by establishing more extensive MODR or PARs, or fewer ECs."
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	316	317	7 LCM & post-approval changes	Should ECs be defined in S and P modules or PLCM/PACMPs? Proposal - table to show where ECs go and supporting information (cf ICH Q12).	Recommend changing "In cases where ECs are proposed, the risk associated with prospective changes should be assessed up front to define the appropriate reporting category." to "ECs should be proposed up front along with assessment of risk associated with prospective changes to define the appropriate reporting category." Further clarification on Lines 316-317, to cross reference or expand on where ECs should be proposed to facilitate 'up front' assessment would be helpful. For example via the relevant CTD modules or via PLCM/PACMPs.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	317	317	7 LCM & post-approval changes	The phrase, "the importance of a quality attribute" seems vague, arbitrary and subjective. Is there some language to replace this from Q8, Q9, or Q10 that is more appropriate (e.g. criticality, highest risk etc...)	Propose changing "Factors to consider include the importance of the quality attribute being measured,.." to "Factors to consider include the criticality of the quality attribute being measured,.."
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	327	328	7 LCM & post-approval changes	The language: "Fixing performance criteria for performance characteristics identified as ECs,..." should be clarified please. This is an important concept - that if the changed method meets the same validation characteristics, then it should be considered 'equivalent'."	Recommend changing "Fixing performance criteria for performance characteristics identified as ECs, for example, in an ATP, can help mitigate risk associated with changes." to "Defining performance criteria for performance characteristics identified as ECs, for example in an ATP, can help mitigate risk associated with changes."
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	356	358	7 LCM & post-approval changes	The concept Table 1 is trying to convey from low to high knowledge and low to high risk is clear. However the words within Table 1 are not necessarily consistent with Table 2. Table 2 says what you need to do – which could allow for comparable approaches. As example, using the same validation protocol/criteria as initial may be still appropriate whether you have low or high knowledge (Table 1 implies only acceptable for high knowledge "according to previously defined protocol".)	The text in Table 2 should be consistent with Table 1, should contain risk language and information.

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International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	370	371	7 LCM & post-approval changes	Effectiveness' of license holders' PQS is the subject of GMP inspection etc. and is covered in other guidance/legislation.	Recommend changing "To support the use of the tools described in this guideline, the company´s PQS change management process should be effective and in line with recommendations described in ICH Q12" to "To support the use of the tools described in this guideline, the company´s PQS change management process (as described in ICH Q10) should be used in line with recommendations described in ICH Q12."
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	371	373	7 LCM & post-approval changes	As written it could be misinterpreted that analytical procedure performance monitoring is recommended for all methods in order to maintain a state of control. Risk based deployment of analytical procedure monitoring is considered more appropriate. Periodic risk review is aligned with the wording on Line 164	Recommend changing "During the lifecycle the MAH should evaluate performance, perform trend analysis, assess knowledge gained and re-evaluate if the analytical procedure remains fit for purpose." to ""During the lifecycle the MAH should periodically based on risk evaluate performance, perform trend analysis, assess knowledge gained and re-evaluate if the analytical procedure remains fit for purpose."
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	376	383	8	An assessment of model fit should also be included depending on the model type e.g. R^2 and Q^2 for regressions to ensure that the model is fit for purpose and correlates strongly to the offline analysis. Selection of the appropriate chemometric algorithm to be used for building the multivariate calibration model (PCA, PCR, PLS, ANN, etc.) should be added.	Recommend changing to: "Development of a robust multivariate analytical procedure includes selection of the appropriate algorithm to build the calibration model, scientifically justified sample selection and distribution over the range, sample size, model variable selection and data pre-processing and assessment of model fit."
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	394	394	8 Sample & Population	"Suitable for intended purpose" terminology is preferred over "homogeneous"	Recommend changing "Care should be taken to ensure that uncertainty in the reference analytical procedure is sufficiently low in relation to the intended performance of the multivariate analytical procedure and that prepared reference samples are homogeneous." to "Care should be taken to ensure that uncertainty in the reference analytical procedure is sufficiently low in relation to the intended performance of the multivariate analytical procedure and that prepared reference samples are suitable for the intended purpose."
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	423	427	8 Data transformation	Data transformation / Data pre-processing. In spectroscopic techniques is usual to introduce spectral pre-processing (spectral pre-treatments) with the aim to maximize the differences of the selected chemical or physical property to be modelled.	Consider inclusion of data pre-processing and spectral pre-treatment terms and concepts in the text.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	444	451	8 Recalibration & Model maintenance	Bias, RMSEP (Root Mean Square Error of Prediction), Test of Equivalency between chemometric model and reference method should also used to ensure that model is working well during the ongoing monitoring of the chemometric model.	Recommend including Bias, RMSEP and Test of Equivalency as diagnostic tools in the text

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International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	450	451	8	The suggested diagnostic tools are important to assess model performance and are usually based on statistical bounds.	Propose "the choice of statistical confidence interval for the two diagnostics should be justifiable by the development data package and historical commercial lot data" is added as further clarification.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	466	466		A box titled "analytical method selection" before the "multivariate model selection" in the "Model Establishment" rectangle will aid understanding. The two different colors of "Model maintenance" and "Routine production" may be confusing as "Model Maintence" is part of "Routine production".	Proposed updates to Figure 3; Please add a box titled similar to "Analytical method selection". Maybe add "within PQS" to the "Routine production" rectangle.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	495	496	9 RTR testing	Analytical tools mainly used to understand the manufacturing process, achieve quality control and ultimately to attain real time release testing (ICH Q8). Advanced Process Control (APC) provide the ability to monitor and control the quality of in-process and thus the final product based on process data. It will be good to include this concept in the Real Time Release Testing section.	Suggest changing "DEVELOPMENT OF ANALYTICAL PROCEDURES FOR REAL TIME RELEASE TESTING: SPECIAL CONSIDERATONS." to "DEVELOPMENT OF ANALYTICAL PROCEDURES & ADVANCED PROCESS CONTROL STRATEGIES FOR REAL TIME RELEASE TESTING: SPECIAL CONSIDERATONS. Consider adding the definition of Advanced Process Control (APC) to the Glossary.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	532	533	10.1 General Considerations	Clarification	Change "The criteria used in the validation study should be included in the submission." to "The criteria used in the validation study can be included in the submission."
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	560	564	10.3 Documentation for RTRT & MVA	Remove the sentence "The process development section of the dossier (e.g., 3.2.S.2.6 or 3.2.P.2) should include the model development information for multivariate models used as part of manufacturing development studies or for in-process controls or tests". Rationale: depending on the dossier structure, the story flow could be kept together in 3.2.S.5 or 3.2.P.5.	Development information related to multivariate analytical procedures should be provided commensurate with the level of impact of the model (Guide for ICH QA8/Q9/Q10). Recommend that the supportive development information for RTRT multivariate models is included in 3.2.S.5 or 3.2.P.5.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	638	639	CO-VALIDATION	In the definition of co-validation, please replace "revalidation" with validation.	Recommend changing "Demonstration that the analytical procedure meets its predefined performance criteria when used at different laboratories for the same intended purpose. Co-validation can involve all (full revalidation) or a subset (partial revalidation) of performance characteristics potentially impacted by the change in laboratories. " to "Demonstration that the analytical procedure meets its predefined performance criteria when used at different laboratories for the same intended purpose. Co-validation can involve all (full validation) or a subset (partial validation) of performance characteristics potentially impacted by the change in laboratories. "

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International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	645	647	CROSS VALIDATION	It will be highly confusing for machine learning experts, chemometricians and other multivariate modelling practitioners to not even mention the most common meaning of this term in the glossary. The current definition in lines 645-647 could be kept in the glossary but with a different title, e.g. Comparability Validation.	Suggest replacing "Demonstration that two or more analytical procedures meet the same predefined performance criteria and can therefore be used for the same intended purpose." with "Cross-validation is a method for internal testing where segments of the calibration data set are set aside in successive steps to provide internal test sets, commonly done until all parts of the calibration data have been used as internal test set."
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	652	653	DETERMINATION	propose text change to "per the validation or method protocol"	Recommend changing "The reported value(s) from single or replicate measurements of a single sample preparation as per the validation protocol." to " The reported value(s) from single or replicate measurements of a single sample preparation as per the validation protocol or analytical procedure "
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	766	769	TOTAL ANALYTICAL ERROR	The proposed update conbines the current GLOSSARY definition with the useful claryfying text in Table 4 Section 13.1.2	Propose that the definition of TAE is updated to "Total analytical error (TAE) is a statistical measurement that can be used to evaluaate the overall capability of an an analytical procedure, by combining accuracy and precision (i.e. the combination of both systematic error of the procedure and random measurement error). TAE represents the overall error in a test result that is attributed to imprecision and inaccuracy. (ICH Q14)"
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	838	840	13.1 Procedure Lifecycle	A caveat should be added to make it clear that other approaches may be used if properly justified.	Recommend changing "The examples provided in this Annex are mock examples for illustrative purposes." to "The examples provided in this Annex are mock examples for illustrative purposes, other approaches are acceptable when justified."
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	1029	1031	Annex A	"depending on region": It is not clear for a company how to deal with this posiition for a global appliaction. This could turn out as a road-block for companies to apply the enhanced development concept	If adherence to ATP is committed and assured within the PQS, the concept should be applicable to all ICH regions and the disclaimer that there maybe be differences in requirements by different regions should be removed
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	1034	1035	13.1.1	Table 3 - add definitions for ICH Q12 reporting categories (PA, NL) - prior approval and notification	Table 3 - add definitions for ICH Q12 reporting categories (PA, NL) - prior approval and notification. Consider adding a justification why a bridging study is not required for the change to the example.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	1489	1492	13.1.2 Mab Potency	It is not clear for a company how to deal with the phrase ""depending on region": Ideally the concepts in ICHQ14 would be applicable to all ICH regions. This could turn out as a road-block for companies attempting to apply the enhanced development concept	The phrase "Other parameters and conditions that are not identified as ECs in the table below may be required as ECs for some cases depending on the region.", should be deleted