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Overview of comments received on ICH guideline Q14 on analytical procedure development (EMA/CHMP/ICH/195040/2022)

Please note that comments will be sent to the ICH Q14 EWG for consideration in the context of Step 3 of the ICH process.

1. General comments – overview

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Vaibhav Anandgaonkar	0	0	General	More detailed and conceptual description on new terms like ATP, EC, PAR, MODR etc is required. Also clarify if this should be defined in the method validation report or not. Elaborate more how these should be documented. Is it expected to get an acknowledgement from regulatory agencies on ATP, EC and reporting categories before commercial batch manufacturing?	Please include Q & A section for this guideline
Vaibhav Anandgaonkar	0	0	General	This guideline is very much an extension of expectation of ICH Q2 guideline and linked with analytical method validation. For better understanding and implementation, content of Q14 draft should instead be added as an annexure to Q2 guideline. This will enhance understanding & effectiveness of implementation by industry.	
GE Healthcare, Oslo	0	0	0	General: Concistenly use "an MODR" (not "a MODR)	Write "an MODR"
PPTA	0	0	General	This guideline is focused on chemical methods. Biological methods are covered only peripherically. Reference is made to PPTA comments on biological methods in Q2(R2) which also apply for this guidance.	
ProPharma Group, Liesbeth van Rooijen	0	0	0	In ICH Q2 (R2) the terminology used related to Reportable/Working Range seems to be inconsistent. Please ensure that the terminology used here is aligned with that used in ICH Q2 (R2)	
APIC	0	0		capability of the method of analysis has to be detailled. It is necessary to evaluate this criteria in order to determine if the measurement system and the analytical operations associated with the analytical procedure are adequate for the intended analysis within the defined specification range (Upper limit - lower limit). this concept is well discussed and used in ISO standards and drives the method development. This would be very useful to introduce this concept in this ICH Q14.	
APIC	0	0		Linked to capabilty, uncertainty should be part of the discussion too	

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European Association of Nuclear Medicine	0	0		The European Association of Nuclear Medicine welcomes the review of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) draft guidelines Q2(R2) on Validation of analytical procedures and Q14 on Analytical procedure development, recently released for public consultation.	
European Association of Nuclear Medicine	0	0		These guidelines represent a general and commonly accepted basis for the development and validation of analytical methods for most of drug substances and products.	
European Association of Nuclear Medicine	0	0		However, in the ICH guideline Q14 it is also stated that "Approaches other than those set forth in this guideline may be applicable and acceptable with appropriate science-based justification. The applicant is responsible for designing the validation studies and protocol most suitable for their product", thus recognizing that the suggested analytical methodology may not be fully applicable in special cases. Although they are not specifically mentioned in ICH texts, radiopharmaceuticals are certainly a special case and should therefore be excluded of the scope of the ICH analytical procedures guidelines.	
European Association of Nuclear Medicine	0	0		Indeed, these guidance documents (ICH Q2 and ICH Q14) do not fully address all the specific tests required for the analysis of radiopharmaceuticals.	
European Association of Nuclear Medicine	0	0		Radiopharmaceutical preparations or radiopharmaceuticals are medicinal products which, when ready for use, contain one or more radionuclides included for a medical purpose. The radioactive compounds in radiopharmaceuticals may contain simple salts, metal complexes, small organic molecules or large molecules as the active pharmaceutical ingredient. As for any other pharmaceutical, their quality (i.e. identity, strength, and purity) needs to be controlled before administration to patients, to ensure that their characteristics are suitable for the intended purpose. However, for quality control of radiopharmaceuticals specific aspects which differ from conventional pharmaceuticals must be taken into account:	
European Association of Nuclear Medicine	0	0		· The strength of a radiopharmaceutical is defined by its radioactivity content, or radioactivity concentration, and it follows the decay law; thus, the strength of a radiopharmaceutical decreases with time.	
European Association of Nuclear Medicine	0	0		· Radioactive standards for the drug substance or radiochemical impurities are not available, the radioactive drug substance itself cannot be isolated.	
European Association of Nuclear Medicine	0	0		· Whilst analytical techniques used to determine the content of non-radioactive components of radiopharmaceutical preparations are generally the same as those used for conventional pharmaceuticals, radioactivity determination requires specific techniques, which make use of dedicated instrumentation capable of specifically detecting, discriminating and quantifying the radioactivity in the sample.	
European Association of Nuclear Medicine	0	0		As a special class of medical products, radiopharmaceuticals require their own guidelines. In this respect, the EANM, in cooperation with EDQM, has recently developed a guideline on the validation of analytical methods for radiopharmaceuticals. This includes recommended approaches to validate analytical methods for radiopharmaceuticals.	

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European Association of Nuclear Medicine	0	0		As such, the Nuclear Medicine community does not see the need for radiopharmaceuticals to be covered by these Q2 and Q14 analytical guidelines, and should be explicitly exempted, but would rather call for a recognition by the ICH of the EANM guidelines on this matter.	
European Association of Nuclear Medicine	0	0		For reference:	
European Association of Nuclear Medicine	0	0		Gillings, N., Todde, S., Behe, M. et al. EANM guideline on the validation of analytical methods for radiopharmaceuticals. EJNMMI radiopharm. chem. 5, 7 (2020). https://doi.org/10.1186/s41181-019-0086-z	
European Association of Nuclear Medicine	0	0		European Directorate for the Quality of Medicines & HealthCare: Revised guidance for elaborating monographs on radiopharmaceutical preparations: new section on validation of methods : https://www.edqm.eu/en/-/revised-guidance-for-elaborating-monographs-on-radiopharmaceutical-preparations-new-section-on-validation-of-methods	
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.
EFPIA	0	0	General Comment	The title "Analytical Procedure Development" is misleading as Q14 does address the overall lifecycle of analytical procedures and is not restricted to the development stage	Change title to "Development and Lifecycle of Analytical Procedures"
EFPIA	0	0	General Comment	The term "minimal" has a negative connotation and should be replaced with an alternate term (e.g., traditional, suitable/historic, classical, fit for purpose). There is also a continuum from information shared in the traditional approach to the enhanced approach. Additional development and robustness information can enhance demonstration of knowledge gained and support risk management to facilitate more streamlined, post-approval method changes if desired.	A few clarifications within the guidance are encouraged to continually acknowledge that the "traditional" approach remains appropriate.
EFPIA	0	0	General Comment	The guidance document provides a reasonable framework for analytical procedure development and method lifecycle management. While the examples in appendices are very helpful, the guidance is short on the expected/anticipated content for communicating enhanced knowledge in a submission. This must be globally accepted for appreciable benefit. Great value will exist in future implementation training case studies to ensure alignment between industry and regulatory agencies on expectations for regulatory change management. Additional examples using multivariate models would also be very informative in additional training.	Great value will exist in future implementation training case studies to ensure alignment between industry and regulatory agencies on expectations for regulatory change management. Additional examples using multivariate models would also be very informative in additional training.

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Jazz Pharmaceuticals	0	0		The guidance provided on analytical development and on use of design space to support method lifecycle is welcomed. The additional time and resource required for applying the enhanced approach is likely to be a greater challenge for smaller biopharma to incorporate, and therefore less likely to be utilised. A risk-benefit assessment of methods will be required to identify where this approach would be most effectively applied and most beneficial to the lifecycle management where resource is limited.	
Jazz Pharmaceuticals	0	0		We particularly support the use of Analytical Target Profile (ATP) which can easily be introduced for method development and help to progress to an enhanced approach over time.	
Parexel General comment	0	0	0	The text is well wirtten and instructive. It is, however, not yet fully clear how this will be implemented in practice. Many analytical procedures are carried out by CROs and in particular smaller biotech companies having limited influence of the approach that is taken for many of the assays.	None
Parexel general comment	0	0	0	It is unclear where and how much of this information should be presented in a regulatory submission and where within the dossier/analytical sections.	Set out where to present the information
Dr. Uwe Lipke as Member of EDQM Group of Experts 7	0	0		Reference solution stability and relative response factors should be addressed in ICH Q14. The stability of the reference solution is crucial for the complete analysis as the concentration of the reference solution is considered as true value and basis for all calculations of results. Any deviation from the true value determined by weighing would impact on the result of the analysis. The reliable determination of relative response factors and the limited use for very small (<0.2) or very high factors (> 5) should be addressed. The latter may be addressed within one of the examples.	
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 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 .	
ECA Foundation / European QP Association	0	0	General	ICH have failed to write a single integrated document to provide an encompassing approach to procedure development, validation and operational use	Integrate ICH Q2 with Q14
ECA Foundation / European QP Association	0	0	General	The operational phase of the life cycle is omitted entirely from both documents. There is zero mention of the most important and longest phase of the life cycle	Rewrite the two documents: USP <1220> is far superior
ECA Foundation / European QP Association	0	0	General	Regulatory issues about validation that should be in ICH Q2 are actually found in ICH Q14 Section 10	Transfer Section 10 from ICH Q14 into Q2

2. Specific comments on text

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ISCT	1	1718	All	General comment: The document is well written. Its scope and purpose are clear. It is relevant to analytical procedure development for cell and gene therapy. It covers current operating environments (e.g. at-line, in-line, off-line) and knowledge management. It distinguishes clearly between minimal and enhanced approaches to analytical procedure development and their use, and discusses possibilities for the evolution of established conditions. It gives good guidance on regulatory requirements and links well to other relevant ICH guidelines. The examples in the Annexes are appropriate. The biological example of anti TNF alpha is complex but there are now more complex products such as cell therapy products. For future proofing, it would be good if the document could address these or (if knowledge about the issues is not yet sufficiently mature/disseminated for incorporation into an ICH guideline) at least acknowledge them as an example of how complex things are and will be.	None
PPTA	1	1718	General	To help readers with different knowledge backgrounds, all acronyms such as DoE, ATP, EC, PAR, MODR, CQA, AP, QTPP, PQS, QRM, CTD, CPPs, PACMP, MAH, PLCM, PA, NM, NL, SST, and R at first use in the text and also in Section 11, Glossary need to be defined. This also includes the terms "reference standard" and "reference material", which are used in the guideline, but which are not present in the glossary.	Please define all acronyms at first use in text and also include in Section 11, Glossary: DoE, ATP, EC, PAR, MODR, CQA, AP, QTPP, PQS, QRM, CTD, CPPs, PACMP, MAH, PLCM, PA, NM, NL, SST, and R. Please add also the terms "reference standard" and "reference material" to the glossary.
Pharmabiotic Research Institute - PRI (www.pharmabiotic.org) - contact person: Magali Cordaillat-Simmons [mcs@pharmabiotic.org] or Céline Druart [celine@pharmabiotic.org]	2	3	0	In the context of microbiome-based medicinal products, complex analytical methods such as OMICS methods (i.e. NGS, transciptomics, metabolomics and proteomics) are currently developed and their validation will be necessary for both quality control of products composed of complex microbial ecosystems, or of substances of Human Origin containing complex microbial ecosystems and used as starting material of complex medicinal products. Also those methods are currently in development in the context of efficacy assessment of these products in clinical trials (through microbiome-based biomarker discovery and qualification). Therefore, while this guideline does not cover validation of methods used for biomarkers measurement and efficacy assessment, the principles described in this document (such as the ATP and risk analysis) could be applicable to both quality and efficacy assessment in the context of complex microbiome-based medicinal products. An extension of the scope and objective of this guideline to cover validation of analytical methods in the context of quality of product assessment as well as efficacy assessment could be very useful.	introduce examples for OMICS methods in the annex at the opportunity of future revisions. (the EU Human Microbiome Action Project [https://cordis.europa.eu/project/id/964590; https://humanmicrobiomeaction.eu/] aims at producing proposals for standardization on NGS for microbiome composition and function and will take these concepts into consideration when making recommendation).

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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."
EFPIA	11	14	1,1	Validation data is the minimum requirement for submission to demonstrate method is appropriate for intended purpose. ICH Q2 refers to ICH Q14 with respect to robustness. This paragraph regarding the relationship between Q2 and Q14 should not discuss what should be submitted to regulatory agencies. The reason to submit additional information/knowledge has to do with the next paragraph in relation to Q12 principles.	Change to "Knowledge and information gained during validation provides evidence to demonstrate that the analytical procedure is appropriate for its intended purpose. Additional development (including robustness) studies can enhance demonstration of knowledge gained in development and support risk management and evidence that a method is fit for purpose."
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"
EFPIA	15	16		Change "Using the tools described in ICH Q12 Technical....." to "Using the tools **and concepts** described in ICH Q12 Technical……"	ICH Q12 introduces concepts such as 'established conditions' and discusses them in the context of procedures.
Medicines for Europe	23	25	1,1	"… submission of analytical procedure development…" this statement contradicts the line 11 "This guideline is intended to complement ICH Q2…". It should be clear that the purpose of this guideline is to provide information for the development of analytical method, by pointing out how risk assessment and analytical knowledge may be helpful on finalizing methods appropriate for specific applications, not to prepare parts for CTD that is out of its scope.	This part could be rephrased to: "The guideline also describes how to document analytical procedure develpoment and related lifecycle information that is not part of CTD format (ICH...) but may be shared to support the appropriateness of the analytical methodology for specific application".
Medicines for Europe	28	29	2	Scope only for release and stability testing. Its good for life cycle management of QC methods	for Biosimilars it is crucial to add here characterizational assays (other than relase /stability). As the Guideline is about Analytical development, we reccomend to keep the focus on general aspects and not to be too descriptive.

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Pharmabiotic Research Institute - PRI (www.pharmabiotic.org) -	28	29	2	The guideline states that it is applied to new analytical procedures, however none of the OMICS methods have been discussed within the annexes and examples provided. however, OMICS methods are now currrently used for biologicals and biotechnological products quality assessment.	Introduce annexes on various OMICS methods which are now useed in quality control of complex biological products such as microbiome-derived medicinal products.
EFPIA	116	116	3	Draft Q2 guideline mentions in the examples section: stability indicating properties and discriminatory properties. Typically studied/established during development. Nevertheless, nothing is said about these topics in Q14.	As a minimum, mention these properties as an example in Section 3. Or provide text to harmonise expectations for these 2 properties. Suggestion for line 116: An ATP consists of a description of the intended purpose (e.g. relevance of the test in the control system, requirements regarding stability indicating properties or discriminatory power) appropriate details on the product attributes
EFPIA	145	147	4	A more explicit reference to re-use of knowledge resulting from enhanced approach provides a basis for operational "return of investment" for dedicating efforts to enhanced approach and is missing in this chapter.	Existing platform analytical procedures (e.g., protein content determination by UV spectroscopy for a protein drug) can be leveraged to evaluate the quality attributes of a specific product without conducting additional procedure development. Knowledge generated from applying the enhanced approach (e.g., ATP elements, analytical procedure range) can also be used to support the selection of analytical technologies and development of
EFPIA	164	166	4	Analytical procedure monitoring should be based on risk and not required for each procedure and/or parameter/procedure output. Current text is mis leading and should be revised.	add: "Risk assessment informs the identification of procedures in scope as well as the appropriate analytical procedure performance data to be evaluated as part of ongoing monitoring to provide useful insight into procedure performance."
EFPIA	175	176	5	Sample and /or solution(s) stability over the time of analysis is an important aspect and should be addressed during robustness evaluation.	Change to: Robustness is tested by deliberate variations of analytical procedure parameters and also considering the duration of the analysis.
EFPIA	202	204	5	PAR and MODR adds unnecessary complexity to the guidance and should be replaced by the term "acceptable ranges".	Recommend to use the term "acceptable ranges" instead of PAR and MODR. If used, include a definition of PAR in the glossary and include a discussion on the use and difference between PAR and MODR.
EFPIA	222	222	6	A key step in defining the Analytical Control Strategy is determination of the number of replicates for certain analytical procedure steps within the analytical procedure that contribute to a large part of the overall variation. Text should be added to this section to cover choice of the number of replicates for these analytical procedure steps	Insert following text after "Prior knowledge could also be used to develop the analytical procedure control strategy." "Replicating analytical procedure steps (e.g. sample preparation, sample injection, standard preparation etc.) that contribute to a large part of the overall variation followed by an appropriate analysis to generate the reportable value will lead to improved precision
EFPIA	228	330	6	The establishment of a suitable calibration model is not discussed in ICH Q14 and this is an important item in the context of method development. This topic should be addressed in conjunction with the linearity/response paragraph from Q2.	Change following text on line 229 from "...use of the apparatus, generation of the calibration curve, use of the…" to "use of the apparatus, generation of the calibration curve across the working range for the type of response (linear, non-linear or multivariate), use of the..."

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EFPIA	258	258	6	Established conditions represents a regulatory tool to provide clarity on binding elements of a regulatory submission. EC's are not part of the analytical procedure control strategy and their primary scope is not to ensure that the analytical procedure performs as expected during routine use throughout its lifecycle.	Chapter "6.1 Established Conditions for Analytical Procedures" should be a chapter on its own an not a subchapter to chapter 6 "ANALYTICAL PROCEDURE CONTROL STRATEGY"
EFPIA	266	269	6	Understanding the relationship between analytical procedure parameters and performance is only one benefit from applying the enhanced approach. Understanding the measurement requirements and the suitability of available technologies are at least as important and lacking here. The current text is misleading and gives the impression that ECs consit only of analytical procedure parameters only. The knowledge gained through the enhanced approach enables not only the	Change To: With an enhanced approach to development, there should be an increased understanding of the measurement requirements, the suitability of available technologies and/or the relationship between analytical procedure parameters and performance. This knowledge facilitates identification of which factors require control and thus enable a more an appropriate set of ECs and
EFPIA	271	273	6	The fact that ECs cold consist of different elements (as exemplified in Annex A) should be introduced earlier in that chapter and spelled out clearer.	Change to: ECs could consist of one or more of the following elements: • Performance criteria (e.g., ATP, technology specific validation criteria, SST) • Analytical procedure principle (i.e., the physicochemical basis or specific technology), • Other elements of the analytical procedure control strategy (e.g.
EFPIA	310	312	7	The current sentences are misleading as methods developed in the minimal approach can also profit from tools described in ICHQ12 (e.g. Structured Approach). In addition the regulatory pathway is not only dependent on the development approach rather than on the submitted data. Often analytical devlopment is performed using elements of the enhanced approach but the data submitted could reflect a minimum approach	If a minimal approach no EC's are proposed in the dossier 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 as compared to the minimal approach.
EFPIA	310	315	7	In essence, this implies that the minimal approach will result in set points as ECs, enhanced approach will result ranges. So there is little 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 - there is no clear description that a performance based approach (utilising the ATP and quality risk management) is acceptable - other than in annex A	The concepts exemplified in Annex A should be clearer stated in the main text.
EFPIA	336	342	7	The concepts applied in Annex A should be better introduced in the main body of the guideline. ECs could consist of different elements (see commment to line 271-273) which differ in the associated risk if changed. Adherence to the ATP and the analytical procedure control strategy ensures that the analytical procedure remains fit for purpose subsequent to changes and thus forms the basis of a bridging strategy.	Change text in line 336 - 342 to: Fixing performance criteria for performance characteristics identified as ECs with supporting rationales, for example, in an ATP, can help mitigate risk associated with changes. This could include changes in analytical procedure parameters, which are considered low risk, SST or a change in technology which is considered a higher risk. Widening of ATP acceptance criteria represents the highest risk and
EFPIA	352	354	7	Table 2 is disconnected from the main text and should be better introduced	Table 1 provides examples of data recommended to support a change dependent on the extent of the change and the identified risk category . For example, the implementation of an already validated analytical procedure at a different location, including the concepts of the analytical procedure transfer, should could follow the same verification and bridging strategies described in Table 2 (Tables 1 and 2)
EFPIA	356	358	7	It remains unclear what Table 1 is trying to communicate. It seems in order to achieve the same goal, in the case of high knowledge and low risk a confirmatory study according to previously defined protocol is required whereas in the case of low knowledge and low risk only a confrmatory study and a study design is enough. This seems to be strange.	Remove table 1 from the guideline as it is misleading and does not provide tangeable guidance

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EFPIA	368	368	7	In certain cases a transfer waiver can be used if justified. This option is missing in table 2.	add a footnote to table 2 to allow for transfer waiver if justified
EFPIA	371	373	7	As written the text suggests that analytical performance monitoring is mandatory for all methods during the commercial lifecycle. This is in contradiction to line 165 of chapter 4 were ongoing monitoring is recommended. Language needs to be softened to align with chapter 4	During the lifecycle it is recommeded to the MAH should evaluate performance, perform appropriate trend analysis, assess knowledge gained and re-evaluate if the analytical procedure remains fit for purpose
EFPIA	375	375	8	Chapters 8 seems to stand for its own and disconnected from the concepts described in other chapters. E.g. No proposal how to define ATP, and EC for a multivariate model are procided	The multvariate procedure chapter need to be better connected with the concepts described in the guideline i.e. ATP, EC
EFPIA	386	389	8	Although qualitative methods are mentioned in Section 8, the general guidance is mostly applicable to quantitative methods in creation of a single model and its maintenance via changing the model calibration dataset over time. Qualitative methods generally require hierarchical models—2 or more models where a final identity determination is based on the output of all models—in order to maintain specificity during analytical procedure lifecycle management. For unsupervised algorithms (e.g., PCA), maintenance may require updating the model calibration	Recommend providing guidance that reflects the unique considerations of qualitative vs quantitative methods. It may be appropriate to separate them out into different sections, given that qualitative methods need to be updated to ensure specificity as new materials are received and processed. An example included in the document Annexes would be welcome, as all of the existing examples are for quantitative methods
EFPIA	444	494	8	The header of this chapter is limited to re-calibration and model maintenance and guidance for routine use for release testing is lacking or not well described. e.g. There is the only sentence describing the use of outlier diagnostic for release procedure, which is very critical point applying mutlivariate models. More guidance would be very helpful for this point.	Change the header to include routing use and start the chapter with adding guidance on routine use for release testing (high impact models)
EFPIA	515	517	9	RTRT is not included in current ICH Q6A and ICH Q6B.	The RTRT approach should be included in the product specification along with a reference to the RTRT analytical procedure(s) and the related acceptance criteria, which are discussed in ICH Q6A and Q6B.
EFPIA	518	521	9	Inclusion of both off-line testing and RTRT, would make RTRT redundant and is not fully aligned with the subsequent sentence.	Quantitative RTRT results should be expressed in the same units as those for traditional testing. The product specification will typically also include the analytical procedures to be used for off-line testing. If the dossier includes a registered alternate control strategy to RTRT (e.g., traditional end-product testing for when process analytics are unavailable), the related analytical procedures and when they would be applied should also be included in the submitted
EFPIA	645	645	Glossary	Crossvalidation has a different meaning for multivariate analytical procedures. Describing the current definition only may lead to confusion.	Include definition of crossvalidation for multivariate analytical procedure in the glossary

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EFPIA	1685	1686	Annex B	Validation Strategy: Option 2 has mostly scientific value and is concisered impractical to be used by industry. The statement in line 1685 "typical approaches" is misleading and should be changed to manage expectation.	Change "typical approaches" to "possible approaches"
EFPIA	1717	1717	Annex C	The title is more general but the table provides information for synthetic molecules only. There no example covering biotech products or RAMAN .	Provide examples covering biotech products or RAMAN
EFPIA	1029 /1489	1031 / 1492	Annex A	"depending on region": It is not clear for a company how to deal with that, how can a company find out wich region, why is the concept not applicable to all ICH regions? This could turn out as a road-block for companies to apply the enhanced development concept	If adherence to ATP is commited and ensured by the PQS, the concept should be applicabe to all ICH regions and the diclaimer that there maybe be differences in requirements by different regions be removed
ProPharma Group, John den Dunnen	28	29	2	The guidance stated "This guideline applies to new or revised analytical procedures". A clarification would be helpful when an analytical procedure is considered as revised.	
ProPharma Group, Bertine Vorstenbosch - de Wijs	31	32	2	"The scientific principles described in this guideline can be applied in a phase-appropriate manner during clinical development."	Please indicate whether this ICH Q14 approach will impact the Guidelines on the requirements for the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials EMA/CHMP/QWP/545525/2017 and Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials EMA/CHMP/BWP/534898/2008 requirements listed for phase I, phase II and III clinical trials. Please provide some examples on how ICH Q14 can be applied in a phase-appropriate manner.
EFPIA	34	34	2	Doesn't make sense to exclude Pharmacopeial analytical procedures as most of them start off being developed by industry	Remove: Development of pharmacopoeial analytical procedures is out of scope.
ProPharma Group, Anna Klein	37	39	2.1	The goal of development is to obtain an analytical procedure fit for its intended purpose: to measure an attribute or attributes of the analysed material with the needed specificity/selectivity, accuracy and/or precision over the reportable range.	The range of the method is always reportable since it is confirmed by the accuracy and precision, so maybe 'within the range' instead of 'the reportable range'.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	38	38	2,1	replace attribute by quality attribute to clearly distinguish between analytical procedure attributes and quality attributes related to the material to be tested	to measure a quality attribute or quality attributes of the analysed material with the required ....
EFPIA	39	39	2,1	The method should provide adequate accuracy and precision, we would propose to use 'and' instead of 'and/or', furthermore, this requirement is only applicable to quantitative procedures, but not to qualitative procedures, any need to be more specific?	with the needed specificity / selectivity, accuracy and precision over the reportable range
EFPIA	41	43	Q14 2.1	Q14 - standard vs enhanced approach. **We like the direct statement that the minimal approach remains acceptable**;	add an example of when an enhanced approach is better over a minimal approach, an example in training material
Parexel	45	46		"certain validation tests can be omitted based on a science-and risk-based justification". This needs elaboration- for example which tests and how to justify it. The default will be very few tests and a justification that exceeds the amount of work that to perform the specific test	Include more specifics concerning this point- this will be one of the few economic incentives to perform the enhanced appraoch
APIC	48	50	2,1	The guideline should be more specific regarding the development data that can be and that cannot be used as validation data.	The guideline mentions robustness as example. However, besides robustness it would be important to clarify if there are any other parameters for which the development work does not need to be repeated or if this is something usually limited to robustness. Forced degradation studies could also be considered?
EFPIA	48	50	2,1	It is not clear how robustness data based on DoE development data can be used for validation. Another example could instead be LC-MS identification of peaks under development, which can be used for the specificity study in the validation.	Consider replacing the robustness example with another more obvious validation example
EFPIA	48	50	2,1	"In general" is a weak statement and would allow for any kind of data. Validation data ar data generated following a validation protocoll. As such development data can not be used as validation data but can be leveraged for valdation.	Approriate data gained during the development studies (e.g., robustness data from a design of experiments (DoE study)) can be leveraged for validation for the related analytical procedure performance characteristics and does not necessarily need to be repeated.
Vaibhav Anandgaonkar	48	50	2,1	The statement says "data gained during the development studies (e.g., robustness data from a design of experiments (DoE study)) can be used as **validation data** for the related analytical procedure performance characteristics and does not necessarily need to be repeated". Use of word **validation data** here is suggesting that this exercise is linked with method validation data.	Can you please clarify what is meant by validation data?
ISCT	49	49	2,1	Typo	Suggest '…experiments (DoE) study can…' OR ' '…experiments (DoE study) can…' INSTEAD OF '…experiments (DoE study)) can…'
EFPIA	52	100		Add additional emphasis that the minimal vs enhanced is a continuum, and not either / or.	Consider modification to lines 68-69 to add "to represent a continuum of enhancements over the "traditional" approach."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	56	57		Reference pCQAs/CQAs (Q8)	The minimal approach starts by stating that the attributes should be identified but doesn't link this to Q8. The beginning of Q14 states that the intent is to use this guideline with Q8 and Q9 but it should be clear that a CQA assessment should ultimately determine the analytical testing panel.
EFPIA	56	56	2,2	definition which attributes, quality attributes or AP attributes	Identifying which quality attributes of the ...
EFPIA	58	58	2,2	"analytical procedure technology" is confusing	replace with "analytical technology" or define
Dr. Uwe Lipke as Member of EDQM Group of Experts 7	60	62	2.2	Any existing experience and knowledge of analytical procedure parameters and sample properties that can impact performance of the procedure should not be neglected or ignored for the minimal approach. The minimal approach will not lead to sufficient results if experience and common knowledge are not taken into account.	Add after the last word (robustness) the following sentence: "*Available experience and common knowledge of analytical procedure parameters and sample properties that can impact the performance of the procedure should be taken into account during these development studies.*"
EFPIA	60	61		Analytical procedure performance characteristics at this point should include the alignment of suitable accuracy and precision to support the specification. All too often this link is overlooked and attention is focused on the raw performance of a method.	For example with suitable accuracy and precision to support the specification need to connect the link here between accuracy and precision with the specification too because the accuracy and precision in particular need to be supportive of the specification. If no consideration is given at this point of method development we end up with a method that is great in terms of performance but high risk in terms of causing OOS The ATP plus combined accuracy/precision (TAE) is a potential solution to this.
International Society for Pharmaceutical Engineering (ISPE) Trar	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."
EFPIA	61	63		Change (including the calibration model, limits at lower and/or higher range ends) to (including the calibration model with upper and lower limits)	Clarification

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	66	99	2.2	Misconception with the term "Enhanced approach" (Chapter 2.2) A new Chapter should be included: "Performance based approach" (see slide 9)" to be in line with the logic, hierarchy, and terminology of ICHQ12 (please compare with ICHQ12, Chapter 3.2.3.1, Page 12 below, and page 13 above, and chapter 3.2.3.2) to ensure more clarity e.g., using the following structure for the chapter: - Parameter based approaches ☐ Subpoint: "Minimal approach" (Setpoints) ☐ Subpoint: "Enhanced approach" (PAR, MODR) - Performance based approach (Performance based ACS) In a performance-based approach, ECs could be primarily focused on the control of performance outputs laid down in the ATP and enabled by a performance based Analytical Control Strategy (ACS) rather than parameter inputs. Without this explicit additional point/option, only regulatory burden would be introduced to overemphasizing of parameter aspects, and less further regulatory flexibility is gained as before. The parameter-based approach (both basic and enhanced) have no significant positive potential for NCE. ICHQ12 does not mention "QbD" as a regulatory enabler. MODR is not mandatory for a performance-based approach and should not be part of the regulatory filings if a performance-based approach is intended. the examples in the appendix of the ICHQ14 guideline are the best proof of this: None of them use the MODR (!). The regulatory flexibility of the "performance-based approach" is the most extensive, works with or without MODR, and ensures sustainably safety and efficacy if supported by an adequate ACS.	
Vaibhav Anandgaonkar	66	100	2,2	1. Is it intended that companies define analytical target profile (ATP), proven acceptable ranges (PARs), Method operational design regions (MODRs) for already existing methods and communicate this to regulators? 2. Is it required to revise existing method validation reports to include this information? Please clarify this part.	
EFPIA	70	71	2,2	Please clarify the meaning of "expected variability of the sample". Is it the process and/or analytical variability?	Please clarify
EFPIA	70	82	2.2	should be clarified where/when in the process the analytical technology is defined. One could understand that to define the ATP, one need to have the technology defined, while ATP is technology-independent	add a sentence after "defining the Analytical Target Profile (ATP)" : "select the technology driven by the ATP"
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.
EFPIA	77	79		Long sentence, could be restructured	Change to "Defining an analytical procedure control strategy based on enhanced procedure understanding. This would include appropriate set-points and/or ranges for relevant analytical procedure parameters to ensure adherence to performance criteria."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	79	79	2,2	supporting comprehensibility	ensuring adherence to predefined performance criteria, e.g. based on an ATP.
EFPIA	81	82	2,2	alignment with glossary	"Method Operable Design Regions (MODRs)" instead of "Method Operational Design Regions (MODRs)"
EFPIA	84	99	2,2	Information in lines 84-87 can also be found in the bullet list in lines 89-99	Consider to combine line 84-87 with line 89-99
EFPIA	85	85	2,2	To achieve further clarification especially to those readers which are not yet fully familiar with these concepts	better understanding of the impact of analytical procedure parameters on the analytical procedure performance and …
International Society for Pharmaceutical Engineering (ISPE) Trar	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"
PPTA	90	90	2,2	To improve readability, please remove unnecessary text.	Please remove "of" after "Understanding"
EFPIA	91	92	2,2	It would be good to highlight that the greater knowledge acquired in enhanced approach would be help to define those attributes which need ongoing monitoring	Suggest additional bullet point: 'Understanding of which analytical procedure attributes/outputs be seected for ongoing monitoring'

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	92	95	2.2	Make the sentence more general as the analytical procedure does not always measure a CQA, and also to align with the other parts of the text (e.g. Fig.1, or line 863)	Employing predefined performance characteristics (e.g., in the ATP) linked to **the measured** critical quality attributes (CQAs) and their acceptance criteria (...)
EFPIA	99			"Reducing the amount of effort across the analytical procedure lifecycle" can be mis understood as the wrong intend. - consider rewording 'Allowing more efficient use of resources across the analytical procedure lifecycle.' or something similar.	Consider rewording 'Allowing more efficient use of resources across the analytical procedure lifecycle.'
EFPIA	101	110	2.3	The paragraph and the figure do not depict the reduced development approach (sometimes just based on Risk assessment) for platform analytical procedures	Proposal: in the figure addition of dashed arrow from Risk assessment to Validation in case of platform analytical procedure
EFPIA	107	107	2.3	Figure 1: The blue box (analytical procedure development) should be depicted as a circle in itself, including another arrow from control strategy back to risk assessment. This is desribed in lines 153 to 155, but not reflected in the figure. Furthermore, robustness studies should be explicitly mentioned within the blue box. Having the analytical procedure control strategy within the blue box without a link back to the product control strategy is considered as not ideal.	Update Figure 1: Add arrow from procedure control strategy to risk assessment (circle). Inlcude robustness studies in workflow (with preceeding risk assessments)
Vaibhav Anandgaonkar	107	107	Figure 1	Mention where EC, PAR, MODR stand in the analytical procedure lifecycle	Revise figure 1 to include EX, PAR, MODR and reporting categories to make it more meaningful
APIC	108	108		The figure 1 for analytical procedure lifecycle is complex. The USP-NF published with the general chapter <1220> a more comfortable and comprehensible overview to the analytical procedure lifecycle.	
EFPIA	108	109		Figure 1 - Prior knowledge could also apply to identification of parameter set-points / ranges.	Prior knowledge bar should be extended across the top of the box (see draft suggested figure
EFPIA	108	108	2.3.	Retro-arrow should exist between validation and control strategy definition	add an arrow between validation and control strategy definition
EFPIA	108	109	2,3	Figure shows a risk assessment within the development box. Recommend adding a separate RA prior to or after control strategy to highligh that other RA's occur. The RA in the box is simply for the selected technology which seems limiting.	Put an asterisk next to "risk assessment" box to capture comments "risk assessment is repeated throughout analytical procedure lifecycle when more information becomes available"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Evolve-France	108	109	2	Figure 1: "The Analytical Procedure Lifecycle" do not indicate relevant guidelines.	We propose to indicate in Figure 1:"The Analytical Procedure Lifecycle" appropriate guidelines directly in the boxes featuring in the figure. For instance, it may be useful to indicateICH Q2 in the box "validation"; indicate ICH Q9 for the box "risk assessment"; indicate ICH Q12 for "change management" as well as ICH Q8 and ICH Q11 for "Product and process understanding".
International Society for Pharmaceutical Engineering (ISPE) Trar	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"
PPTA	111	130	Analytical Target Profile (ATP), Appendix A	Clearer example regarding ATP expectation needs to be provided.	Please provide a clearer example regarding ATP expectation in Annex A.
EFPIA	116	116	3	Draft Q2 guideline mentions in the examples section: stability indicating properties and discriminatory properties. Typically studied/established during development. Nevertheless, nothing is said about these topics in Q14.	As a minimum, mention these properties as an example in Section 3. Or provide text to harmonise expectations for these 2 properties. Suggestion for line 116: An ATP consists of a description of the intended purpose (e.g. relevance of the test in the control system, requirements regarding stability indicating properties or discriminatory power) appropriate details on the product attributes to be measured and relevant performance characteristics with associated performance criteria.
EFPIA	116	125	3	In general, the distinction between performance characteristics and analytical procedure attribute is not introduced in the text (only in the glossary). As a consequence, there is no clear explanation in the guideline about what is the purpose and use of the analytical procedure attributes. We recommend to highlight the fact that AP attributes are technology dependent, in contrast with ATP performance characteristics. This will help to understand the whole text and ensure appropriate use of this overall complex terminology. It should be embedded in chapter 6 if necessary.	Line 116: An ATP consists of a description of the intended purpose, appropriate details on the product attributes to be measured and relevant **technology-independent** performance characteristics with associated performance criteria. Line 121: Once a technology has been selected, the ATP serves as a foundation to derive the appropriate **technology-dependent** analytical procedure attributes and acceptance 122 criteria for analytical procedure validation (ICH Q2).
EFPIA	116	116	3	clarification	An ATP consists of a description of the intended purpose of the analytical procedure, appropriate …
EFPIA	118	118	3	missing the word quality between single and quality	change to: The ATP includes the performance requirements for a single quality attribute or a set of quality attributes.
EFPIA	119	126	3	Line 119 and 126 are repetitive	combine line 119 and 126

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	121	123	3	"Once a technology has been selected, the ATP serves as a foundation to derive the appropriate analytical procedure attributes and acceptance criteria for analytical procedure validation (ICH Q2)." ICH Q2 does not mention once the notion of analytical procedure attribute. Alignment is needed between the two guidelines.	
EFPIA	123	125	3	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 to take advantage of lower reporting categories the performance characteristics and criteria should be included as ECs in 32S42/32P52.
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.
EFPIA	138	138		replace 'for informing' to 'to inform'	
EFPIA	144	144	4,1	The text indicates that one specific technology must be chosen. If another technology fulfills the ATP it could be changed at a later stage.	The sentence could be extended: " ….. technology for the given purpose at the given time".
EFPIA	145	147	4	A more explicit reference to re-use of knowledge resulting from enhanced approach provides a basis for operational “return of investment” for dedicating efforts to enhanced approach and is missing in this chapter.	Existing platform analytical procedures (e.g., protein content determination by UV spectroscopy for a protein drug) can be leveraged to evaluate the quality attributes of a specific product without conducting additional procedure development. Knowledge generated from applying the enhanced approach (e.g., ATP elements, analytical procedure range) can also be used to support the selection of analytical technologies and development of analytical procedures for similar quality attributes.
EFPIA	148	149		More emphasis on knowledge management in relation to analytical TT would be helpful.	Knowledge management plays a very important role in the technology transfer of analytical procedures and should therefore be comprehensive and well documented to ensure laboratories are fully equipped to understand the performance and failure attributes of the method.
PPTA	152	152	4,2	To help readers with different knowledge back grounds, add acronym of QRM for quality risk management here and in Section 11 Glossary because is used elsewhere in document.	Please add the acronym for "QRM" for quality risk management here and in Section 11, Glossary.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	164	166	4	Analytical procedure monitoring should be based on risk and not required for each procedure and/or parameter/procedure output. Current text is mis leading and should be revised.	add: "Risk assessment informs the identification of procedures in scope as well as the appropriate analytical procedure performance data to be evaluated as part of ongoing monitoring to provide useful insight into procedure performance."
EFPIA	164	166		Clarification is required when ongoing monitoring is expected. To maintain a state of control for analytical procedure performance during routine operation, ongoing monitoring is recommended as part of risk review.	Change to: To maintain a state of control for analytical procedure performance during routine operation, ongoing monitoring is recommended as part of risk review.
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."
EFPIA	165	166	4,2	It is indicated in the text that ongoing monitoring should be part of the risk control, but presumably the ongoing monitoring is part of the analytical control strategy established on the basis of a risk review.	Suggests to change the wording to: "To maintain a state of control for analytical procedure performance, ongoing monitoring is reccomend as part of the control strategy".
EFPIA	171	188		Why has ICH Q14 shied away from explaining 'Ruggedness' which is equally important given 90% of our methodologies are not routinely applied at the development site but in external QCs and CMOs in the commercial space.	Ruggedness is designed to test the externals factors that could affect the performance of the method. eg Analyst, Lab, Day, instruments. In a commercial setting the Analyst, lab and instruments types will be the single largest unknown variable that is not typically assessed as part of robustness
Dr. Uwe Lipke as Member of EDQM Group of Experts 7	173	187	5.1	Reference solution stability should be explicitly mentioned here in an own paragraph as reference solution stability is very crucial for reliable results. Degradation of a reference solution would lead inevitable to a higher result for any sample as the actual concentration of the reference solution would be lower than the concentration determined by weighing.	Add the following: "*The solution stability of any reference solution should be carefully evaluated as any degradation of the reference solution will lead to falsely higher results for the sample.*"
EFPIA	173	189		Should clarify the relationship between robustness and parameter ranges.	It seems like sec 5.1 and 5.2 are discussing the same thing -
EFPIA	175	176	5	Sample and /or solution(s) stability over the time of analysis is an important aspect and should be addressed during robustness evaluation.	Change to: Robustness is tested by deliberate variations of analytical procedure parameters and also considering the duration of the analysis.
EFPIA	180	180	5,1	Add that robustness can also be collected through prior knowledge	Robustness can also be established through prior knowledge, notably for platform analytical methods.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	180	182	5,1	This is true as long as development was done appropriately for this purpose (e.g., data collected and stored appropriately).	Propose to rewrite the text to indicate that the studies used need to be performed and data collected and stored (etc.), appropriately
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".
Medicines for Europe	180	182	5,1	The calculation of correction factors is usually carried out during development phase. It should be clear if it can be included in validation set.	Apart from robustness testing, the calculation of correction factors may be carried out during development phase. If so, there is no need for re-calculation during validation phase.
ProPharma Group, Bertine Vorstenbosch - de Wijs	180	182	5.1	If robustness was already conducted during development, it does not need to be repeated during validation as discussed in ICH Q2.	Please clarify and confirm whether the additional development data (e.g. robustness) provided in S.4.3/P.5.3 should be considered as non-binding information.
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."
EFPIA	191	192	5.2.	can you please clarify : "The respective analytical procedure attributes and criteria could be derived from the ATP"	
EFPIA	194	197		The text says "In an enhanced approach, the ranges for the relevant parameters and their interactions can be investigated in multi-variate experiments (DoE). Risk assessment and prior knowledge should beused to identify parameters, attributes and appropriate associated ranges to be investigated experimentally." It does not explain that at the end of this process the critical attributes of the procedure must be identifieds.	Proposed rewording: "In an enhanced approach, the ranges for the relevant parameters and their interactions can be investigated in multi-variate experiments (DoE). Risk assessment and prior knowledge should beused to identify parameters, attributes and appropriate associated ranges to be investigated experimentally. The aim of this approach is to identify attributes which require specific control."
EFPIA	196	196	5,2	What is menat by attributes in this context?	
EFPIA	202	204	5	PAR and MODR adds unnecessary complexity to the guidance and should be replaced by the term "acceptable ranges".	Recommend to use the term "acceptable ranges" instead of PAR and MODR. If used, include a definition of PAR in the glossary and include a discussion on the use and difference between PAR and MODR.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	205	207		"moving within an established parameter range does not require a regulatory notification".	In essence, it has been made clear that minimal approach gets set points as ECs, enhanced approach gets ranges. So there is little 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 As written, there is no room for a performance based approach to analytical procedure management
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.
EFPIA	209	210	5	Since the MODR information is obtained from development, the statement "The part of a PAR or a MODR intended for routine use in the analytical procedure must be covered by validation data." appears to conflict with the instruction later in the same paragraph "Analytical procedure validation is required only for those performance characteristics not covered by data from analytical procedure development." To avoid confusion regarding the requirements for including performance characteristics in the validation exercise versus the ability to leverage development data it would be helpful to clarify this paragraph.	change Line 209-210 "The part of a PAR or a MODR intended for routine use in the analytical procedure must be supported by data." (i.e., remove "validation")
EFPIA	209	209	5,2	spelling	an MODR (twice in this line)
EFPIA	209	210	5,2	The meaning of "The part of a PAR or a MODR intended for routine use" is unclear. Does this mean the parameter(s) that might be changed/adjusted during routine analysis within PAR or MODR?	rewrite for better understanding
EFPIA	213	214	5.2	In the case that the analytical procedure validation is omitted for the performance characteristics covered by the analytical procedure development data, will it be required to submit the development data on the omitted parameter to the agency?	we need to be clear that in this case development data has to be submitted
EFPIA	213	214	5,2	This would need to be appropriate development data for only certain validation aspects. This should be explained.	Propose to rewrite the text to indicate that the studies used need to be performed and data collected and stored (etc.) appropriatly
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.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
PPTA	218	285	6	The section contains the term "sample suitability" but not "assay control" nor "control chart", terms wich are commonly used in biological methods.	Please add "assay control" and "control chart" and distinguish in glossary from "sample suitability"
EFPIA	219	222		Suggest splitting into 2 sentences '….throughout its lifecycle. It consists…'	To improve the readability of this paragraph.
EFPIA	222	222	6	A key step in defining the Analytical Control Strategy is determination of the number of replicates for certain analytical procedure steps within the analytical procedure that contribute to a large part of the overall variation. Text should be added to this section to cover choice of the number of replicates for these analytical procedure steps	Insert following text after "Prior knowledge could also be used to develop the analytical procedure control strategy." "Replicating analytical procedure steps (e.g. sample preparation, sample injection, standard preparation etc.) that contribute to a large part of the overall variation followed by an appropriate analysis to generate the reportable value will lead to improved precision. Consideration should be given to including the acceptable variability among the individual results for the analytical procedurs steps being replicated in the system suitability test criteria."
EFPIA	223	224		The analytical procedure control strategy should be defined before validation - there are situations where numeric criteria for SST are defined during the validation or as a result of experiences during validation.	Should this sentence therefore be adjusted to 'before or during' validation.
EFPIA	225	226		"The analytical procedure control strategy includes analytical procedure parameters needing control and the system suitability test (SST) which is part of the analytical procedure description." is missleading as the parameters requiring control should also be part of the analytical procedure description.	Change to: "The analytical procedure control strategy includes analytical procedure parameters needing control and the system suitability test (SST) which are part of the analytical procedure description."
EFPIA	228	330	6	The establishment of a suitable calibration model is not discussed in ICH Q14 and this is an important item in the context of method development. This topic should be addressed in conjunction with the linearity/response paragraph from Q2.	Change following text on line 229 from "...use of the apparatus, generation of the calibration curve, use of the…" to "use of the apparatus, generation of the calibration curve across the working range for the type of response (linear, non-linear or multivariate), use of the..."
EFPIA	231	232		such as the level of detail in a regional pharmacopoeia for a similar method for a similar substance)	Presumably it's the level of detail wrt analytical methodology that we are interested in - not for example the quality standards for a substance.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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).
EFPIA	233	243	6	Since SSTs and their suggested acceptance criteria (for several analytical techniques) are also part of Pharmacopoeia SST, should their consideration be mentioned here? Or at least clarify the approach, e.g. in chapter 6 is to overcome "generic" values set by global pharmacopoeias.	
EFPIA	233	233	6	clarification	The design of the SST depends ...
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.
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

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	237	237	6	The test is used to verify... Should the term SST be used here instead of test to add clarity.	replace test with SST
EFPIA	237	240	6	The test is used to verify that the measurement system and the analytical operations associated with the analytical procedure are adequate during the intended time period of analysis and enable the detection of potential failures. Validity of the results of the analytical procedure depends on the outcome of the SST. These sentences go beyond the current state of the art for SST used for multivariate procedures where SST is focusing on the measurement sutem applied with certified standards.	Add a aclarification that for multivariate procedures the SST is focusing on the measurement system applied with certified standards
EFPIA	240	243	6	As written, a good SST sample is not specific to the enhanced approach and might suggest a good SST can only be defined in an enhanced approach.	suggest removing "in an enhanced approach"
EFPIA	241	241	6	"method" should generally replaced by "procedure"	to ensure analytical procedure performance could represent ...
EFPIA	242	243	6	What is meant by using 'appropriate software tools' for data quality verification as part of an SST for analytical control strategy for procedures based on multivariate models?	With increasing adoption of continuous manufacturing and a consequent use of multivariate models to assure product and process quality, adding more details around using appropriate software tools for data quality verification for SSTs of such analytical procedures is highly recommended. An added example in the annex may also help. The reader can then be aligned to better understand the intended scope of lines 249-251, in conjunction with rest of the guidance.
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.
EFPIA	244	249	6	Unclear when a sample suitability assessment is needed and when it is not needed.	Provide more guidance

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	249	251	6	After "... using...", please add "standard instrument tests (e.g. those suggested by USP or EMA) and..."	The combination of instrument tests and multivariate outlier detection would distinguish instrument issues from changes in the product/process that may affect the performance of the analytical procedure.
EFPIA	253	254	6	Ongoing monitoring of selected analytical procedure outputs is recommended to look for any trends, in line with PQS expectations.' Could we please clarify what the PQS expectations in relation to ongoing monitoring are?	Risk that there are different interpretations of the PQS expectations of routine monitoring. Suggest change to remove reference to PQS
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"
EFPIA	254	254	6	editorial: Add an "A" before the start of sentance that starts with with "Review of analytical procedures..."	add an "A:
EFPIA	258	258	6	Established conditions represents a regulatory tool to provide clarity on binding elements of a regulatory submission. EC's are not part of the analytical procedure control strategy and their primary scope is not to ensure that the analytical procedure performs as expected during routine use throughout its lifecycle.	Chapter "6.1 Established Conditions for Analytical Procedures" should be a chapter on its own an not a subchapter to chapter 6 "ANALYTICAL PROCEDURE CONTROL STRATEGY"
EFPIA	261	263	6,1	Prior knowledge is also an element to leverage for the identification of ECs?	Reference that PK can also be evaluated to determine ECs
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."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	266	269	6	Understanding the relationship between analytical procedure parameters and performance is only one benefit from applying the enhanced approach. Understanding the measurement requirements and the suitability of available technologies are at least as important and lacking here. The current text is misleading and gives the impression that ECs consit only of analytical procedure parameters only. The knowledge gained through the enhanced approach enables not only the identification of an appropriate set of ECs but also appropriate reporting categories.	Change To: With an enhanced approach to development, there should be an increased understanding of the measurement requirements, the suitability of available technologies and/or the relationship between analytical procedure parameters and performance. This knowledge facilitates identification of which factors require control and thus enable a more an appropriate set of ECs and related reporting categories (see chapter 7). These EC's can focus on performance characteristics (e.g., specificity, accuracy, precision) when supported by knowledge and risk management.
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"
EFPIA	271	273	6	The fact that ECs cold consist of different elements (as exemplified in Annex A) should be introduced earlier in that chapter and spelled out clearer.	Change to: ECs could consist of one or more of the following elements: • Performance criteria (e.g., ATP, technology specific validation criteria, SST) • Analytical procedure principle (i.e., the physicochemical basis or specific technology), • Other elements of the analytical procedure control strategy (e.g. set points and/or ranges for one or more parameters)
ProPharma Group, Liesbeth van Rooijen	278	279	6.1	In section 10.2 (line 552-553) it is stated that "parameters that are not ECs are typically not included in a minimal procedure description". It is not clear how that relates to the text in 6.1: "Use of the enhanced approach should not lead to providing a less detailed description of analytical procedures in a regulatory submission".	Please clarify and confirm whether the non-binding part of the method description can be very limited/reduced.
EFPIA	290	290	7	do we mean criteria instead of characteristics	change characetristics to criteria

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	290	290	7	Product attributes or method attributes? This is definitely true for product attributes.	Change to "Major changes in the performance characteristics or additional information on **product quality attributes** could, in certain instances, lead to reevaluation of the ATP itself and/or a new procedure.
ProPharma Group, Bertine Vorstenbosch - de Wijs	294	308	7	Note on EU implementation of ICH Q12 EMA/CHMP/ICH/78332/2020: However, additional scientific risk-based approaches to defining Established Conditions and associated reporting categories, and the Product Lifecycle Management (PLCM) Document are not considered compatible with the existing EU legal framework on variations. Legal framework: The definition of Established Conditions (mirror information and quality characteristics that are subject to a variation) and their reporting categories must follow the requirements laid down in the current EU Variations Regulation and associated EU Variations Guidelines.	Please indicate the regulatory strategy to be applied for PLCMs submission to EMA and the national competent authorities. Please confirm the regulatory strategy to be applied for PACMPs. Can they be submitted as a Type II submission of B.I.e.2 Introduction of a post approval change management protocol related to the active substance or B.II.g.2 Introduction of a post approval change management protocol related to the finished product, whichever is applicable, or by applying a different variation classification category.
EFPIA	300	301	7	This does not provide certainty - knowledge is gained and things change.	change to: Post-Approval Change Management Protocols (PACMPs) which provide a detailed explanation of how future changes will be managed and provide the marketing authorization holder (MAH) with increased assurance about the acceptability of future changes and an associated reduced reporting category.
EFPIA	310	312	7	The current sentences are misleading as methods developed in the minimal approach can also profit from tools described in ICHQ12 (e.g. Structured Approach). In addition the regulatory pathway is not only dependent on the development approach rather than on the submitted data. Often analytical devlopment is performed using elements of the enhanced approach but the data submitted could reflect a minimum approach.	If a minimal approach no EC's are proposed in the dossier 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 as compared to the minimal approach.
EFPIA	310	315	7	In essence, this implies that the minimal approach will result in set points as ECs, enhanced approach will result ranges. So there is little 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 - there is no clear description that a performance based approach (utilising the ATP and quality risk management) is acceptable - other than in annex A	The concepts exemplified in Annex A should be clearer stated in the main text.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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."
EFPIA	313	313	7	Wasn't clear if this paragragh is an extension of what applies for the traditional approach or if this is starting a discusion of the enhanced approach, or both?	Add clarification
EFPIA	316	325	7	Not clear what this is saying	add clarification
EFPIA	316	317		ECs should be assessed upfront…	Should ECs be defined in S and P modules or PLCM? Proposal - table to show where ECs go and supporting information (cf. ICH Q12)
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.
EFPIA	317	317	7	The phrase, "the importance of a quality attribute" seems really vague, arbitrary and subjective. Is there some language to replace this with that is in Q8, Q9, or Q10 that is more appropriate (eg. attribute criticality, etc...)	clarify wording

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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,.."
EFPIA	326	327	7	Revised text clarifies that this description is for the enhanced approach.	Figure 2 summarizes how risk assessment and risk reduction measures can help identify appropriate reporting categories for ECs **using the enhanced approach**.
EFPIA	327	328	7	confusing language: "Fixing performance criteria for performance characteristics identified as ECs,…"	Change 'fixing' which sounds like 'correcting' to "Specifying performance criteria…" This is an important concept - that if the changed method meets the same validation characteristics, then it should be considered 'equivalent'.
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."
EFPIA	336	342	7	The concepts applied in Annex A should be better introduced in the main body of the guideline. ECs could consist of different elements (see commment to line 271-273) which differ in the associated risk if changed. Adherence to the ATP and the analytical procedure control strategy ensures that the analytical procedure remains fit for purpose subsequent to changes and thus forms the basis of a bridging strategy.	Change text in line 336 - 342 to: Fixing performance criteria for performance characteristics identified as ECs with supporting rationales, for example, in an ATP, can help mitigate risk associated with changes. This could include changes in analytical procedure parameters, which are considered low risk, SST or a change in technology which is considered a higher risk. Widening of ATP acceptance criteria represents the highest risk and thus an associated higher reporting category assignment. Adherence to the ATP and the analytical procedure control strategy This ensures that the analytical procedure remains fit for purpose subsequent to changes and thus forms the basis of a bridging strategy
PPTA	336	337	8	For readers not familiar with multivariate analytical procedures, please provide examples at the end of the first sentence.	Please consider adding "(e.g., a spectrum with many wavelengths variables)" at the end of the first sentence.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Dr. Uwe Lipke as Member of EDQM Group of Experts 7	339	339	7, figure 2	The decision tree excludes many evaluations and decisions about changes to analytical procedures from the assessment by competent authorities. Misinterpretation of so-called "Established Conditions" will not be assessed at all by competent authorities. Moreover, the registered dossier will not describe the actual performed analytical procedure after such a change. This will impact on the work of inspectors. Underestimation of a potential impact of a change (decision regarding risk: low instead of medium or high) lead to the classification "notification low". Notification low will be a type IA variation in Europe. Solely fulfilment of conditions can be evaluated when type IA variation are processed but not evaluation of risks. As the answer of the question on risk characterisation (low, high, or medium) is given by the MAH only, the authorities getting the notification low have to assess whether the judgement of the MAH is acceptable. Such an assessment is currently not foreseen.	Question *"Is the factor proposed as an EC?"* – Answer: *No -> reporting category as notification low* (annual reporting will suffice). Question: *"Considering product and procedure knowledge and understanding *, what is the risk associated with the prospective change(s) to the analytical procedure?"* Answer: *Low or medium: reporting category as notification moderate – in Europe type IB variation* Answer: *High: reporting category as prior approval, in Europe type II variation*
EFPIA	342	343	7	Why does it say "future" bridging studies?	delete "future"
EFPIA	342	343	7	It's not clear what this means.	leave as is without sufficient knowlegde an appropriate bridging strategy cannot be defined
APIC	348	348	7	The abbreviation QRM is not defined anywhere in the document.	
EFPIA	348	349	7	Add the full text for the acronym "QRM" as it is not included prior to this point in the guideline.	When implementing changes to analytical procedures, **Quality Risk Management** (QRM) can be used to evaluate the impact of the changes and re-confirm that the originally agreed reporting category is still appropriate.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	352	354	7	Table 2 is disconnected from the main text and should be better introduced	Table 1 provides examples of data recommended to support a change dependent on the extent of the change and the identified risk category . For example, the implementation of an already validated analytical procedure at a different location, including the concepts of the analytical procedure transfer, should could follow the same verification and bridging strategies described in Table 2.(Tables 1 and 2).
EFPIA	353	354		Refers to analytical procedure transfer. Is it in scope or out of scope of this guideline	Should be in scope.
EFPIA	354	354	7	What is a bridging startegy - it isnt defined	add definition to the glossary
EFPIA	356	358	7	It remains unclear what Table 1 is trying to communicate. It seems in order to achieve the same goal, in the case of high knowledge and low risk a confirmatory study according to previously defined protocol is required whereas in the case of low knowledge and low risk only a confrmatory study and a study design is enough. This seems to be strange.	Remove table 1 from the guideline as it is misleading and does not provide tangeable guidance
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.
EFPIA	361	364	7	this paragraph suggests that the applicant proposes a new analytical method developed according to enhanced approach. However the applicant may choose to use the traditional approach for the introduction of the new method, in which case the risk assessment is optional. Suggestion to make this paragraph less prescriptive.	"If an applicant proposes a new analytical procedure and if this new analytical procedure follows the enhanced approach, a thorough..."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	363	363	7	If ECs are used.	Change to: "If used, ECs associated with the new procedure should be justified when reporting the change."
EFPIA	368	368	7	In certain cases a transfer waiver can be used if justified. This option is missing in table 2.	add a footnote to table 2 to allow for transfer waiver if justified
EFPIA	368	368	7	Currently, analytical transfers from the site of vaildation to an additional testing site is handled under GMP and not described in the regulatory submission documents. Unclear if this approach is still acceptable.	
EFPIA	368	368	7	Should provide explanation for 'and/or' , regarding when both are required or just one.	
EFPIA	368	369	7	suggest to clarify that the content of this table refer to post approval changes. Indeed evaluation of changes of analytical procedure before MAA/BLA filing can be addressed in a lighter way especially regarding comparative analysis of representative samples and standards.	modify Table 2 title to "Examples of Analytical Procedure Post Approval Change Evaluation"
ISCT	368	369	Table 2	A change of analytical procedure principle may not just be a change in physicochemical/biochemical basis, but could be a change in biological basis such as changing from an ELISA binding assay to a cell based assay (such as illustrated for determining potency of anti-TNF alpha in Annex A on p 56).	Suggest '(e.g., physicochemical/biochemical/biological basis)' instead of '(physicochemical/biochemical basis)'
Medicines for Europe	368	368	table 2	It should be clarified how it is demonstrated that the analytical procedure's ability to discriminate between acceptable and non acceptable results remains comparable	Examples would be helpful
EFPIA	370	371	7	Change "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 should be **utilised** effective and in line with recommendations described in ICH Q12."	Effectiveness' of license holders PQS is the subject of GMP inspection etc and is covered in other guidance/legislation.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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."
EFPIA	371	373	7	As written the text suggests that analytical performance monitoring is mandatory for all methods during the commercial lifecycle. This is in contradiction to line 165 of chapter 4 were ongoing monitoring is recommended. Language needs to be softened to align with chapter 4	During the lifecycle it is recommeded to the MAH should evaluate performance, perform appropriate 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	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."
EFPIA	375	375	8	Chapters 8 seems to stand for its own and disconnected from the concepts described in other chapters. E.g. No proposal how to define ATP, and EC for a multivariate model are procided	The multvariate procedure chapter need to be better connected with the concepts described in the guideline i.e. ATP, EC
Jazz Pharmaceuticals	375	494	8	Section 8 provides a useful overview of development of multivariate analytical procedures.	
Parexel	375	494	section 8	The MVDA discussion seems more like a white paper than guidance. It does elaborate principles, but the details of implementation are a challenge. Does ICH publish white papers? The discussion illustrates that this area is complex and case-dependent- but that is not the role of guidance	Move section 8 to a white paper or appendix.
EFPIA	376	383		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	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	376	380	8	It is missing the selection of the appropriate chemometric algorithm to be used for building the multivariate calibration model (PCA, PCR, PLS, ANN, etc.)	To add appropriate chemometric algorithm as PCA, PLS, PCR, ANN, etc.
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."
EFPIA	378	380		This text is too vague to add value, especially due to the lack of discussion/guidance regarding neural networks and other related machine learning methods.	The principles underlying neural networks and other related "black-box" machine learning techniques are not necessarily related to models based on factor analysis. Most of the physically meaningful information that can be gathered through latent variable models are lost with "black-box" modeling. Therefore, it is a misstatement to suggest that similar principles apply. I suggest that if these methods are not going to be discussed in detail, then there is really no reason to mention them as the text stated clearly in the previous sentence that all discussion will be centered around latent variable models.
EFPIA	386	389	8	Although qualitative methods are mentioned in Section 8, the general guidance is mostly applicable to quantitative methods in creation of a single model and its maintenance via changing the model calibration dataset over time. Qualitative methods generally require hierarchical models—2 or more models where a final identity determination is based on the output of all models—in order to maintain specificity during analytical procedure lifecycle management. For unsupervised algorithms (e.g., PCA), maintenance may require updating the model calibration dataset. However, with common linear and nonlinear classification techniques (e.g., PLS-DA), expanding the calibration set may result in a model with no suitable discriminant (reference: Brereton, R.; Lloyd, G. Journal of Chemometrics 2014, 213–225.).	Recommend providing guidance that reflects the unique considerations of qualitative vs quantitative methods. It may be appropriate to separate them out into different sections, given that qualitative methods need to be updated to ensure specificity as new materials are received and processed. An example included in the document Annexes would be welcome, as all of the existing examples are for quantitative methods.
GE Healthcare, Oslo	388	388	8	change text.	Change "and" to "or".
EFPIA	394	394		"homogeneous". What does that mean? How do you assess suitability of homogeneity for model development. Not value added in this introductory context.	replace homogeneous with "suitable for their intended use"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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."
GE Healthcare, Oslo	395	396	8	Difference in spacing between paragraphs compared to others.	Add space following paragraph (line 395) and remove line 396.
GE Healthcare, Oslo	397	397	8	Difficult to understand.	Consider rewrite text for better comprehension.
EFPIA	407	408		"inclusion of commercial samples is recommended". Not really. It is essential that the calibration model performs as intended and is proven to meet the ATP for the application on real commercial samples	The multivariate model must be assessed to meet the ATP requirements on actual commercial scale equipment as there is a potential that the commercial scale contains different variability that the calibration set.
EFPIA	409	410		Sample selection for calibration and validation can be performed in various ways. The sample distribution will certainly affect model quality and require careful consideration. Chemometric algorithms exist to aid with this task.	Consider referencing well-established chemometric methods that allow automatic selection of calibration and validation samples from a larger set of experimental samples. A widely used algorithm is the Kennard-Stone (already implemented in chemometric packages). The algorithm selects samples to provide uniform coverage over the data set and keeps boundary samples in the calibration set.
EFPIA	409	416	6	The term "calibration sets" is not defined.	Add explanation on this topic.
EFPIA	409	410	8	how does the composition of the validation set influence the models predictive capability?	Careful consideration should also be given to sample distribution in the calibration set as this will influence the model predictive capability. An independent external test set, or validation set, should be applied to independantly assess the model performance.
EFPIA	411	413	8	What is meant by "complexity of the sample matrix" in addition to what is explained in lines 397-410. The statement that the claibraton design will always be dependent on the complexity of the sample matrix is to strong:	Propose to change to: The number of samples used to create a calibration model for quantitative analysis **may** depend on the complexity of the sample matrix

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	416	416	8	Align "Internal testing sets" with terminology from EMEA/CHMP/CVMP/QWP/17760/2009 Rev2 uses "Calibration test set"or FDA Development and Submission of Near Infrared Analytical Procedures considers "internal validation set". Consider avoiding creating new terms for supporting harmonization.	Reword using "internal validation set" or "Calibration test set"
EFPIA	419	422	8	Variable selection should be justified: not clear how ? (methodology, link with molecule structure ?) does need clarification ?	Add clarification or examples
EFPIA	423	427	8	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.	To include terms of Data pre-processing and Spectral pre-treatments in the text.
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.
GE Healthcare, Oslo	426	426	8	Insert.	Insert "can be" before essential information.
GE Healthcare, Oslo	432	432	8	Edit text.	Change "or other factors" to "etc".
GE Healthcare, Oslo	433	433	8	Delete and.	Delete and.
EFPIA	444	494	8	The header of this chapter is limited to re-calibration and model maintenance and guidance for routine use for release testing is lacking or not well described. e.g. There is the only sentence describing the use of outlier diagnostic for release procedure, which is very critical point applying mutlivariate models. More guidance would be very helpful for this point.	Change the header to include routing use and start the chapter with adding guidance on routine use for release testing (high impact models)
EFPIA	444	451	8	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.	To include Bias, RMSEP and Test of Equivalency as tools for diagnostic tools.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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
EFPIA	448	450		The suggested diagnostic tools are important to assess model performance and are usually based on statistical bounds.	Add "95% Confidence limits are generally used to establish bounds for spectral residuals and sample leverage (or Hotelling's T2). These are valid bounds but not necessarily applicable to all cases." (It would be helpful to provide a comment about establishing appropriate statistical limits without necessarily using a 95% bound by default.)
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.
EFPIA	460	461	8	A process shift might not be an appropriate reason to be changing a model/removing older data; the data should often remain relevant, and therefore, this is not a good example of a justification for removal of data.	Recommend to add another reason for removal of data
EFPIA	466	466	8	"analytical method selection"is maybe missing in the "multivariate model selection" rectangle?	Pleaseconsider to add a box similar to "Analytical method selection"
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.
EFPIA	468	468	8	There is no reference made to Figure 3 in Chapter 8. Need to integrate this figure with the discussion of the multivariate model lifecycle as a complement to the text.	The multivariate model **lifecycle (see Figure 3 above)** is iterative and can be broken down into 3 major components:
EFPIA	473	475	8	Repetition of what was already said before	Can we remove?
EFPIA	477	479	8	why is establishing a maintenance plan using language that is not ligned with prior sections and why is it the last step? In the regular enhanced method it is called an analytical method control strategy and is performed early in the process. Consider harmonzing with earlier sections. Why are we not using common terms across univariate methods and multivariate sections of this guidance? For example, validation is used with a specific purpose in early sectinos but is used inconsistently in the MVA section. What constitutes method development history vs method validation in an MVA application? It is not clear from this guidance.	Consider harmonzing with earlier sections. Why are we not using common terms across univariate methods and multivariate sections of this guidance?
EFPIA	480	481		After "... includes...", please add "regular standard instrument tests and..."	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	488	489	8	Additional sentence was included to make this explicit that in addition to model assessment, model development and revalidation would also be performed in the PQS.	If an issue is identified, model development and revalidation may be needed, for example, to add samples into the calibration set and remove those that are no longer relevant. **This model development and revalidation is performed within the PQS.**
EFPIA	493	493	8	Addition to clarify the reference to the figure.	The dashed arrows in the figure **Figure 3** illustrates reintroduction into the lifecycle flow…
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.
EFPIA	503	508	9	Parametric release could be based on continuous reaction CPP ranges that are known to ensure control of an IPC quality attribute. If a regulator interpreted this as RTRT instead of an IPC, potentially a sponsor could be asked to "validate" the measurement procedure for the CPP ranges (e.g., reaction temperature, residence time, etc.), and could be asked to demonstrate "specificity" for control of the CQA using method validation concepts.	Suggest adding language to clarify the requirements for RTRT vs IPCs.
EFPIA	506	506	9	Please clarify what is meant by "RTRT procedure". If useful include/ammend the definition in the glossary.	
EFPIA	506	508	9	Chapter 9 refers only to the minimal approach (ICH Q2) to validation with no reference to the elements of Q14 to reap the benefits afforded by the enhanced approach across the RTRT procedure lifecycle.	As appropriate, an RTRT procedure should be validated as recommended in ICH Q2 and **may include one or more elements of the enhanced approach described in this document.** It should be demonstrated that the process measurements have appropriate specificity for the targeted product quality attribute.
EFPIA	510	511	9	Clarify "measurement points" in the context of frequency or location of the probe.	The location of the probe and sampling frequency should be chosen to be representative....
EFPIA	515	517	9	RTRT is not included in current ICH Q6A and ICH Q6B.	The RTRT approach should be included in the product specification along with a reference to the RTRT analytical procedure(s) and the related acceptance criteria, which are discussed in ICH Q6A and Q6B.
EFPIA	517	518	9	"Quantitative RTRT results should be expressed in the same units as those for traditional testing" Considering that RTRT can use some process measurements, it does not seem that the same units as traditional testing can be used. Please clarify the expectations.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	518	521	9	Inclusion of both off-line testing and RTRT, would make RTRT redundant and is not fully aligned with the subsequent sentence.	Quantitative RTRT results should be expressed in the same units as those for traditional testing. The product specification will typically also include the analytical procedures to be used for off-line testing. If the dossier includes a registered alternate control strategy to RTRT (e.g., traditional end-product testing for when process analytics are unavailable), the related analytical procedures and when they would be applied should also be included in the submitted product specifications.
EFPIA	524	596	10	It's suggested that Established Conditions be located in a regional section (3.2.R); if different countries agree to different change notification categories, or different EC we may end up with multiple versions which will be more easily managed outside of S.4.2/P.5.2. Also some EC may not fit as easily in S.4.2/P.5.2 (e.g. column flow as an EC fits easily in S.4.2/P.5.2) but if a performance characteristic serves as EC, it doesn't.	development/supportive information best belongs in a development section like S.2.6 or P.2 as is suggested for multivariate model development, OR in the same document with the EC in 3.2.R
EFPIA	525	540	10,1	For clarity, write a paragraph for 3.2.S.4.2/3.2.P.5.2 expectations, then a paragraph on 3.2.S.4.3/3.2.P.5.3 expectations rather than intertwined. Within each section then define 'minimal' vs. 'enhanced'.	3.2.S.4.2/3.2.P.5.2: lines 525, 530, 535, 528; 542-549 3.2.S.4.3/3.2.P.5.3: lines 526, 531, 532, 533, 536; 554-556 Separate paragraph: line 538 32R: PLCM for 550-551?
Medicines for Europe	526	534	10,1	It should be clarified in which part of the dossier the analytical development report/summary should be included	It should be clarified in which part of the dossier the analytical development report/summary should be included
EFPIA	528	529	10,1	The scope of the guidance (line 28) is release and stability methods, with other methods on risk-based approach. Having this sentence (line 528) intertwined with what needs to be submitted in 3.2.S.4.2/3.2.P.5.2 and 3.2.S.4.3/3.2.P.5.3 is confusing.	This sentence should be moved to a paragraph by itself. "Other analytical procedures used as part of the control strategy can be included in relevant CTD sections (e.g., 3.2.S.2, 3.2.P.3, and 3.2.P.4) if necessary."
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."
EFPIA	533	534		Where it mentions submitting development data for justification (e.g. dissolution) it would be useful if they state where in the CTD they these data should reside. (e.g. as attachement to P2)	Harmonize expectations for which section that dissolution method development story is submitted in CTD.
EFPIA	533	534	10,1	It would be extremely helpful to have some examples of "selected technique" because this statement is extremely vague. If in general, development data will be used to support validation, what is the expectation of the level of this testing since it will be included in the filing? For example, training program for analysts performing the testing (e.g., robustness), qualification status of instruments used, etc.	Provide some clarification on general requirements for development data used to support method robustness inCTD sections S 4.3 and P 5.3

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	535	539		Clarity on the location of ECs	It is not clear whether the intention is to have the ECs summarised as part of the PLCM or not. Provide consistent guidance on the reporting loocation for EC supportive and justification information.
EFPIA	547	549	10,2	This sentence is redundant. The same sentence appears in lines 278-279 first.	include additional information of pp.549 in pp.278 where ECs are explained, skip lengthy text about ECs in pp.549 / submission chapter
Jazz Pharmaceuticals	557	596	10,3	Section 10.3 provides detail on regulatory documentation expectations for multivariate models, as described in Section 8. However, not enough guidance is provided on lifecycle management in relation to model maintenance. In particular, additional guidance is required on expectations for updates based on model monitoring and maintenance strategy.	
Parexel	557	597		Multivariate Analytical Procedures- this type of information will require specialized review staff. traditional CMC reviewers are chemists or biologists, not trained in complex analytical math. Also- small agencies may not be able to handle this type of information.	Make multivariate approaches clearly optional and require high level summaries or abstracts in language understandable to non-experts
EFPIA	560	564	10,3	Remove the sentence "The process development section of the dosier (e.g., 3.2.S.2.6 or 3.2.P.2) should include the model development infomration 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 commesurate with the level of impact of the model (Guide for ICH QA8/Q9/Q10). Supportive development information for RTRT multivariate models can be included in either the appropriate analytical procedure validation or process development section.
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.
EFPIA	598	825	11	Glossary: - line 622: add the term "technology independent" to the Definition of the ATP. Use in the examples (tables) a consistent wording: also: instead "acceptance critera" use "performance critera". Unfortunately, "Performance criteria" is not an established term in other guidelines. - ANALYTICAL PROCEDURE ATTRIBUTE (line 606 and 435 (ICHQ2)). "A technology specific property that should be within an appropriate limit, range or distribution to ensure the desired quality of the measured result. For example, attributes for chromatography measurements may include peak symmetry factor and resolution". -> The purpose and context of this element should be clarified. If needed, it should be part of Chapter 6 (Control strategy)	
EFPIA	598			Any changes to the glossary (see comments on Q2) should also be reflected in the glossary for Q14.	Current presentation, with 2 glossaries, one for 'normal' and one for 'multivariate' methods is confusing.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	603	697	11	Ensure appropriate accronym is defined (AP, DL, QL, TAE) and add CPP, MAH, NL, PA, PQS	
EFPIA	610	612	11	definition can be improved for clarity	Add "for example procedure parameters and system suitability" for clarity as stated in line 64.
EFPIA	616	616	11	"Analytical procedure principle" is not defined.	Add definition for "Analytical procdure principle"
EFPIA	616	621	11	The current definition of "Analytical Procedure Validation Strategy" is to much focused on MODR and PAR amd should be better aligned ho the concept is used in ICHQ2 e.g in figure 1	Adapt the definition for "Analytical Procedure Validation Strategy" to allow for a broader use of the term and to better align with ICHQ2. Reconsider the ownership of the term if it should be owned by ICHQ2.
EFPIA	622	624	11	Considering the central role of ATP the definition is not very operational. If you are not already familiar with ATP the wordings "prospective summary" and "anticipated performance" do not provide much guidance.	The definition should preferably also state that ATP is a key element in life cycle management especially for the enhanced approach.
EFPIA	638	641	11	should this be validation (not revalidation)? Revalidation would be a tech transfer.	change "full revalidation" to "full validation" or "full lists of validation tests"; change "partial revalidation" to "partial validation" or "partial lists of validation tests"
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. "
Medicines for Europe	638	641	N/A	Is the meaning of "Co-validation" also include "Co-development"? For example, duirng method development, analyst from recieving laboratory participate the testing to get understanding the analytical method. Through this, development can include variability from different analyst, and tech. transfer may obmit the analyst training for validation at the receiving laboratory.	Please make clear the meaning of "co-validation" whether it includes "co-development" or not. If not, how about add "co-development"?
EFPIA	642	644	11	Since "Cross-vaslidation" has a different meaning for multivariate methods (bootstrapping), it can cause confusion.	Either add the term also in the multivariate glossary or add a note that the term is often used in a different meaning for multivariate methods.
EFPIA	645	645	Glossary	Crossvalidation has a different meaning for multivariate analytical procedures. Describing the current definition only may lead to confusion.	Include definition of crossvalidation for multivariate analytical procedure in the glossary

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	645	647	11 (Glossary)	The concept of cross-validation is defined in Q14 (and Q2), but no real discussion of how cross validation may be employed within the method development lifecycle is provided. It should be made clear that demonstration of cross validation can allow application of either method if filed as equivalent methods.	Add discussion of cross-validation applications. Including cross validation in the example provided in the annex describing a change between Chiral CZE and Chiral HPLC may be an appropriate means of introducing this concept.
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."
EFPIA	648	648	11	Add DL in the glossary	Add DL in brackets for Detection Limit
EFPIA	652	653	11	propose text change to "per the validation or method protocol"	propose text change to "per the validation or analytical procedure description"
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 "
PPTA	693	693	Quality Risk Management	The section is unclear and open to interpretation.	Please provide additional clarification for this section.
EFPIA	697	697	11	Add QL in the glossary	Add QL in brackets for Quantitation Limit
EFPIA	711	715	11	The working range could also be lowest /higest column load for HPLC methods - not noly concentration	Please add examples other than concentration (loads, volumes, masses ..)
APIC	751				SELECTIVTY to be replaced by SELECTIVITY
GE Healthcare, Oslo	762	762	11	Missing a period at the end of the sentence.	Add a period at the end of the sentence.
EFPIA	766	769	11	TAE was not mentioned anywhere else in Q14	Provide a more clear definition of TAE

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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)"
EFPIA	836	1718	Annexes	The annexes are difficult to read because sections and sub-sections are not visually distinct.	Reformat or restructure the annexes for ease of navigation by a naive reader.
EFPIA	838	840	13,1	A caveat should be added to make it clear that other approaches may be used if properly justified.	Add sentence: "Other approaches are acceptable if properly justified"
Medicines for Europe	844	848	13	performance characteristics described in the ATP could be applied to select a suitable analytical technology as well could aid the design of the validation study for the analytical procedure	Qualification of analytical method might give performance of ATP(specificty ,precisio, LOQ)..etc .most of industries follow qualifying the methods . would it be better to add about qualification of method in the scope of guideline as we mentioned about Analytical method life cycle.
EFPIA	860	866	Annex A	Selected risk (risk factors). The relevance of the test to mitigate risk to patients is an important concept and links the analytical procedure development into the control strategy and should be further explained.	Please provide additional clarification on the context of the relevance of test also in the main body of the document. Please consider e.g. to include a small paragraph below fig 1 to provide the information on the two main different purposes of an analytical procedure for generating knowledge (product and process understanding) and risk to patient mitigation by batch testing
ISCT	867	867	13,1	Suggest to give examples of simple versus complex technology in parentheses	Suggest 'Simple versus complex technology (e.g., defined chemical drug versus cell or gene therapy)'
EFPIA	889	890	13. Annex A	Clarify the abbreviation "AP", since the abbreviation "AP" is not utilized in previous or subsequent text.	Well justified ***analytical procedure*** *AP performance criteria cover/link to CQAs and their acceptable*

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	920	1676	Annex A	The 2 examples are very useful and should be kept in the guideline, however they are rather long. Moreover, it would be helpful to provide an additional example for a multi-variate method covering several CQAs	The 2 examples are very useful and should be kept in the guideline, however they are rather long. Moreover, it would be helpful to provide an additional example for a multi-variate method covering several CQAs
APIC	933	933	1.3.1.1	Based on the example provided for the definition of the ATP, does the ICH implies that the rationale for the accuracy and repeatability limits must always be justified in a procedure-by-procedure basis or can this justification be referenced to another quality documentation in force?	
EFPIA	933	933	13.1.1	Table 1: impurity J is also a degradation product: should it be included in the ATP	
EFPIA	933	934	13.1.1	"CQA chiral purity >99.0%": I do not think that a CQA has a value, a specification limit does.	"to verify the CQA chiral purity with a specification of ≥99.0%"
EFPIA	933	933		Bias of NMT 0.01%	presume this is a typo based on the allowable precision
EFPIA	933	1014	13.1.1	Table 1 (line 933) and the method validation part (line 978-1009) seem to suggest that the ATP equals to the method validation acceptance criteria. While the ATP and validation criteria are very closely related, and the validation criteria are often derived from ATP. We need to clearly distinguish them. As I understand, ATP described the required performance characteristics for reportable results (more like required population distribution of the reportable results, from the statistics point of view), while the method validation criteria are what the validation data (sample from the population) are supposed to meet to provide good confidence that the entire population will meet the ATP. They are related but different. One from the population perspective that describes the acceptable distribution. The other from the sample perspective that takes into consderation the validation study design, sample sizes and confidence level/power. It is critical to clearly explain the two different concepts.	Revise the ATP verbiage and example in Table 1 (line 933) to clearly distinguish ATP and method validation criteria (and other acceptance criteria for various studies that are derived from ATP, such as method transfer, robustness assessment, method performance monitoring, etc.)

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	933	933	13	Analytical target profile	Mentioned example in annex is late stage ATP. But would it be better to have Draft ATP (Generic ATP) during method design and evaluation, which is locked before validation (after qualification) and gets finalized (becomes effective) after validation (Commercial ATP). The evolution of an ATP also depends on the tested attribute/purpose of the measurement
Medicines for Europe	934	978	13	Initial technology selection, Analytical procedure developemnt, analytical procedure description and Method validation	Qualification should be included in order to evaluate performance of ATP and set criteria for validation. Therefore we reccomend to add examples or suggestions about qualification of methods.
EFPIA	952			No consideration given in either ICH Q2 or Q14 to the ruggedness of a analytical procedure.	After procedure development and validation what use is the procedure if it cannot work as intended on only one manufacturer or type of instrument. This is a particularly acute problem for UHPLC, CZE, PSD, where instrument design can at times have a significant impact on the successful operation of a analytical procedure as intended.
EFPIA	960	960		Word is missing: reasonable excluded	change to: ....reasonably be excluded.....
PPTA	960	961	13.1.1	To improve readability, add text and missing punctutation and incorporate last sentence with this sentence.	Please add "be" before "reasonably" and adding a comma after "excluded". Please consider rephrasing text as "…were identified in the Ishikawa diagram below:"
PPTA	961	969	13.1.1	For consistency, "Corrected peak areas" should be changed to "migration time corrected peak areas".	Please replace "Corrected peak areas" with "migration time corrected peak areas"
EFPIA	972	972	13	Replace LOQ by QL to harmonize definition	Replace LOQ by QL
EFPIA	972	972	13	missing comma in text list ...established on relative migration times resolution,…	...established on relative migration times, resolution,…

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Vaibhav Anandgaonkar	972	972	13.1.1	Comma required after "relative migration times" and before "resolution"	
EFPIA	976			CE conditions specify 100 mM beta cyclodextrin in Table 2. Beta cyclodextrin is only soluble to ca. 16 mM under purely aqueous conditions. Suggest modifying this to HP-B-CD which has much higher solubility as an example. Will require an update in Table 3 also.	Experimentally impossible
PPTA	976	977	13.1.1	There is no column used in CE. Therefore,"Column temperature" should be changed to "Capillary temperature" .	Please change "Column temperature" to "Capillary temperature" .
PPTA	986	986	13.1.1	A period (.) is missing at the end of the sentence.	Please add a period at the end of the sentence (.).
EFPIA	987	991	13	"...performed and evaluated in an ANOVA experiement" Confusion about a evaluation of results from a precision study	"...intermediate precision between operators, days and instruments were performaned and evaluated."
Dr. Uwe Lipke as Member of EDQM Group of Experts 7	1002	1006	13.1.1	The judgement "linear" is based on the correlation coefficient only. This is contradictory to ICH Q2 (R2). The correlation coefficient alone is not sufficient to establish linearity. Residual plot and y-intercept should be taken into consideration. The wording should be amended to be in line with ICH Q2 (R2).	Line 1004: Add the following sentence after the words "… the drug substance": "*The residual plot showed random pattern. The y-intercept was found not significantly different from the origin.*"
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
EFPIA	1033	1038	Table 3	Established Condition: Technology Specific Analytical Procedure Attributes The criteria for the AP attributes should be listed in "Established condition" column and not in "Justification" Rationale: table structure consistency	
EFPIA	1033	1038	Table 3	ICH Q12 reporting category for non-EC: Consider writing NR instead of - to be aligned with examples from ICH Q12.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	1033	1035		PA and NL are not defined (prior approval and notification low?)	Add a footenote to the table
Dr. Uwe Lipke as Member of EDQM Group of Experts 7	1034	1034	13.1.1, Table 3	Row "Technology Specific Analytical Procedure Attributes": The judgement "linear" is based on the correlation coefficient only. This is contradictory to ICH Q2 (R2). The correlation coefficient does not predict linearity or non-linearity alone. Residual plot and y-intercept should be taken into consideration. The wording should be amended to be in line with ICH Q2 (R2).	*"Linearity: R NLT 0.990 with at least 5 points in the range between 0.05 % - 2.0 % for impurities A-F. The residual plot showed random pattern. The y-intercept was found not significantly different from the origin"*
EFPIA	1034	1034	Table 3 - Page 33	Remove "bookmark not set error (English translation of the French comment)"	Table 3: Proposed established conditions and reporting categories applying principles of ICH Q12 in the enhanced approach Section, "The following conditions are not ECs in this example" Justification/Rationale for Established Condition, "Capillary rinsing conditions Clear scientific relationships between pressure, capillary length and rinsing volume exist, allowing adjustments between various equipment1**Erreur ! Signet non défini.**
EFPIA	1034	1034	Table 3 - Page 33	Spelling error.	Table 3: Proposed established conditions and reporting categories applying principles of ICH Q12 in the enhanced approach Section, "The following conditions are not ECs in this example"; Justification/Rationale for Established Condition "API Reference Standard" The performance over the reportable working range has been demonstrated though **through** the linearity experiments at validation.
EFPIA	1034	1034		separation principle should be non EC	The technology is already an EC, as is the SST. The rationale is a change in this will result in change in SST, so therefore controlled through performance (As per line 275 and 276)
EFPIA	1034	1034	13.1.1	Table 3: ATP: What does "widening" mean in this context? What if it changes in a way that is not clearly widening or tightening? What if it is tightening due to an issue?	Clarify what widening of ATP means. Widing of acceptance critria, Addition or deletion of new performance characteristics?

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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.
PPTA	1034	1035	13.1.1	To improve readability and consistency of acronyms, please add a space between "SST" and any number for each of its occurences; please remove document error message, and remove lettering.	Please add a space between SST and its number for each occurrence. Remove document error message from page 33, row 5, column 4. Remove "(a)" from page 33 row 6, first column.
PPTA	1059	1059	13.1.1	To improve readability, please remove document formating markings/ highlights from the final document.	Please remove grey box after "#2".
PPTA	1069	1101	13.1.1	To be consistent with how an acronym presented, please put space between "SST" and its number for each occurrence.	For each occurrence, please add a space between SST and its number.
EFPIA	1091	1097	13	The question "are criteria of relevant performance characteristics defined as ECs which ensure the Post-change quality of the measured results after the change?" seems to be inconsitent between the decision tree for Low risk (Decision tree in line 339).	Rework the example to put the appropriate questions to the example description in alignment with the decision tree (line 339, figure 2).
EFPIA	1114	1114	13.1.1.	Terminology: chiral describes a molecular property, but cannot describe an analytical technology	Replace "chiral" by "enantioselective"
EFPIA	1144	1144	Change #2: from chiral CZE to chiral HPLC	The specification will need to be updated to change the listed test from CZE to HPLC and/or delineate when the alternative technique is applied. However, the acceptance criteria will remain unchanged.	…the specifications **acceptance limits** for the chiral impurities remain unchanged.
EFPIA	1155	1157	13.1.1	As the risk is medium for the change on the reportable values, should there be a bridging study implemented or described? If the risk evaluation includes the briding study, could we elaborate it in the description?	Add a bridging study will be performed for this change in the text.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
PPTA	1196	1197	13.1.2	"in addition" suggests that potency is not a CQA. Contradictory to that, the biological activityin table 4 is a CQA.	Please change wording.
EFPIA	1218	1219	13.1.2	Table 4 suggests not feasible criteria for Performace characteristics. For the purpose of this example, it is assumed that the specification limits for the relative potency are 80% to 125% . With a Relative bias criteria of 20% and a Precision Criteria of 20% , the probability of failure or the residual risk can be not acceptable	
EFPIA	1218	1218	13.1.2	Table 4: TAE: Acceptance Criteria: HAs are likely to expect an actual value. In addition it is questionnable if TAE approach for a biological assay is suitable to support the specification limits provided	Propose to remove the optional TEA aproach from this example or add data to show that secification limits can be supported.
EFPIA	1218	1219	13.1.2	Forced degradation may identify modifications that do not impact potency - statement may be a misleading example and be interpreted that all changes would be detected by potency methods. It is not possible for all degradation products to be detected by potency - clarification on the rationale as to why this method is implicated is required. Pertains to link to CQA.	Recommend including additional information as to why the particular degradation product influences potency (was detected in the CDR region, perhaps, or the product is clipped such that the CDR region is no longer part of the molecule). Pertains to link to CQA
EFPIA	1218	1474	13.1.2	Table 4 (line 1218) and the method validation part (line 1400-1474) seem to suggest that the ATP equals to the method validation acceptance criteria. While the ATP and validation criteria are very closely related, and the validation criteria are often derived from ATP. We need to clearly distinguish them. As I understand, ATP described the required performance characteristics for reportable results (more like required population distribution of the reportable results, from the statistics point of view), while the method validation criteria are what the validation data (sample from the population) are supposed to meet to provide good confidence that the entire population will meet the ATP. They are related but different. One from the population perspective that describes the acceptable distribution. The other from the sample perspective that takes into consderation the validation study design, sample sizes and confidence level/power. It is critical to clearly explain the two different concepts.	Revise the ATP verbiage and example in Table 1 (line 933) to clearly distinguish ATP and method validation criteria (and other acceptance criteria for various studies that are derived from ATP, such as method transfer, robustness assessment, method performance monitoring, etc.)
Parexel	1218	1218		Not clear why total analytical error as well as accuaracy & precision are needed.	Use one or the other- regulators in some regions may view TAE as a new mandate- in addition to precision and accuracy

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	1219	129		might the inclusion of USP references as justificaiton in the example lead to false assumption that EU/Japan will accept USP rationale? Options: include simliar EP/JP reference	include similar EP/JP refrence in footnote
PPTA	1227	1227	Technology selection	The risk assessment link to technology selection is unclear in term of expectations.	Please clarify the expectation of the technology section.
EFPIA	1249	1249	13.1.2	It's not clear what a "like for like" reference standard is. Is it just the "applicable" RS?	Change "like for like reference standad" to "applicable reference standard"
EFPIA	1306	1306	13.1.2	Spelling error.	"**wavelength**"
Parexel	1306	1306		Wave length is misspelled in the Isiakawa diagram	correct typo
PPTA	1306	1307	13.1.2	Please correct spelling error, and improve consistency of font formatting.	Please correct spelling of "wavelenght"; please make bold "n" at end of "construction" in bottom right box.
EFPIA	1311	1311	13.1.2	Table 5: Rationale: What does rationale mean in this context? Rationale for why this parameter was investigated?	propose to add the meaning of "rationale"
Parexel	1311	1311		Cell passage number for the bioassay cells is probably most important development aspect.	Include passage number as criteria
EFPIA	1313	1313	13.1.2.	below table 5 - Typo, one bracket is missing	add bracket
EFPIA	1351	1351	13.1.2	mis-alignment with table 5 (L1310) pre-incubation temperature?	change the table to 36-38°C
ProPharma Group, Bertine Vorstenbosch - de Wijs	1356	1356	13.1.2	On page 44, it is stated that analytical procedure descriptions contain binding information (ECs) and non-binding information.	It is foreseen that CTD sections S.4.2/P.5.2 will need to be corrected in case of changes to registered non-binding information (under the enhanced approach). Please clarify the regulatory strategy to be applied for changes to registered non-binding information (incl. changes to/deletion of non-binding parameters (non-ECs)) in analytical method descriptions.
PPTA	1382	1382	System Suitability Test (SST)	Please clarify in more detail is acceptable/required/expected for a standard curve (e.g. parallelism of standard curve for ELISA method, origin, stability)?	Please provide additional clarification for a standard curve.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
PPTA	1449	1450	13.1.2	"known" should be replaced by "assumed" or "calculated"	Please change wording for "known", either to "assumed" or "calculated".
PPTA	1461	1468	13.1.2	Please note that as per EP and USP also, a confidence interval for the combined potency result should be calculated - i.e. combined potency results are not created out of individual potency results (by averaging) but of all data of the indiviual potency test. The confidence interval should be within predefined limits. Also calculating a CV for the single potency results is not sufficient	Please add the confidence interval of the combined potency result.
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
EFPIA	1497	1502	13.1.2	Remove line "Analytical procedure parameters": the elements listed below are mixed, combining parameters, analytical procedure attributes, and SSTs	
EFPIA	1497	1502	13.1.2	It is not clear why in this examples, most of the paramers tested are still reportable, while in the first examples they were not Ecs anymore. The explanation of this difference needs to be reinforced.	
PPTA	1497	1497	Table6	The coefficient of determination or coefficient of variation is a widely used acceptance criterion for linearity, however it does not distinguish between systematic curvature and random error. In addition "nlt 0.97" is extremely tolerant	Please add criteria that measure the systematic curvature such as mean squares of quadratic term or mean squares of nonlinear term in relation to mean squares of linear term (used e.g. in collaborative studies for assignment of WHO standards).
Parexel	1498	1498		Even if this is a case study- giving specific targets for R2 values, minimum ratios, etc. may prompt regulators in some regions to view these are regulatory standards. This is what happened with the RVLP safety factor case study in ICH Q5A.	Need to reiterate that these are illustartive and the cited R2 values are not regulatory requirements.
EFPIA	1500	1500	13.1.2	Is there doubt that this would require details that are basically the same as a PACMP? Why indicate that the example would be NM without providing the reality of what would be needed to support this?	More guidance on the type of information is required which would support the propose reporting catgory
Parexel	1503	1505		Only two parameters are listed as "not-ECs". this implies that everything in the table is an EC. This is very restrictive if assay changes are needed later. Also contrdicts language in line 266-69 which says that the number of ECs are more limited after an enhanced approach.	Provide justification why so many parameters must be ECs.
EFPIA	1588	1588	13.1.2	Spelling error.	Appropriate**d** development data demonstrating suitable absence of impact on cell performance…

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
PPTA	1588	1588	13.1.2	To improve readability, please correst misspellt word.	Please remove "d" from the end of **"Appropriated".**
PPTA	1635	1635	13.1.2	To improve readability, please add missing punctuation.	Please add a comma (,) after "extent of change" and after "new procedure".
PPTA	1636	1636	13.1.2	To improve readability, please add missing punctutation.	Please add a comma (,) after "ATP".
EFPIA	1659	1669	v)	Impact on specification is expected, but no further information is provided on how to deal with this impact.	add an introductory sentence to the example to mention that this is a fictive example and the conclusion is based on the assumptions that the relative potency specification acceptance criteria remain unchanged.
ISCT	1676	1676	Annex A	Suggest to add a short section (as 1.3.1.3) about special considerations (or issues) in Advanced Therapy Medicinal Products (ATMPs) (such as gene modified anti-tumour cell therapies) where the mode of action is less clear than with biologicals such as monoclonal antibodies (as in the anti-TNF alpha example in 1.3.1.2).	
EFPIA	1677	1677		13.2 Annex B: **Example** Validation Strategies for MODRs	Strengthen the point that these are 'examples' and 'typical approaches' and other approaches may be used where justified?
EFPIA	1677	1689	13,2	How is MODR validation different from robustness. The approach described in this section is not very clear.	provide a more clear example on MODR validation
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	1677	1716	13,2	The discussion of MODR expectations may reflect a significant decrease in operational freedom. Annex B implies that full validation is required at the extremes of method variables to allow parameter adjustments within an MODR. This is not consistent with our historical application of robustness data. Chromatographic robustness data (wherein system suitability criteria are demonstrated within a given parameter's PAR) have been judged sufficient evidence of freedom to operate within that PAR. Instructions here imply that additional validation would be expected to move from the center target condition. Some of the examples given (e.g. repeatability/intermediate precision validation across the MODR) seem unwarranted given the other controls in place (Precision SSR during method execution). Establishing this high bar within the ICH example seems unwarranted.	Propose Section 13.2 Annex B is retitled to Example Validation Strategies for MODRs and "This annex describes validation strategies for MODRs and includes an example table to present the performance characteristics combined with the attribute acceptance criteria, parameter ranges, control strategy and validation strategy." is changed to "This annex describes example validation strategies for MODRs including a table to present the performance characteristics combined with the attribute acceptance criteria, parameter ranges, control strategy and validation strategy. Other MODR validation strategies may be justified and used. "

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	1677	1716	13,2	Clarification of how data sets used in proposing MODRs established during development can be incorporated into the validation dataset intended for registration, supported by further training material examples illustrating this concept, will be very helpful.	Further examples clarifying how data sets used in proposing MODRs (and PARs) established during development can be incorporated into the validation dataset intended for registration, and comparing/contrasting these approaches with the establishment of proven acceptable ranges will help to demonstrate the advantages of investigating design regions. This should be supported by additional training material examples illustrating these concepts.
EFPIA	1682	1684	13,2	Revise wording – current text is awkward and unclear.	The extent of validation activities and the respective operational flexibility associated **needed should** requires to be assessed and justified on a case-by-case basis.
EFPIA	1685	1686	Annex B	Validation Strategy: Option 2 has mostly scientific value and is concisered impractical to be used by industry. The statement in line 1685 "typical approaches" is misleading and should be changed to manage expectation.	Change "typical approaches" to "possible approaches"
EFPIA	1694	1699	13,2	Does Option 2 refer to robustness evaluated within MODR? Or does it mean evaluating accuracy, precision, etc. at the extremes in addition to the centerpoint?	Provide more clarity about what would be done for Option 2.
EFPIA	1697	1697		Figure 1 is difficult to read.	Change from white to black letters.
EFPIA	1714	1714		Table 1 very small letters, too difficult to read.	Cange to landscape
EFPIA	1714	1715	13,2	In the the last row and last column of Table 1 it is stated that "Intermediate precision: Delta versus repeatability ≤ NNN%". It is not clear what the purpose of this proposed validation criteria is and this can lead to confusion. The individual criteria for repeatability and intermediate precision already provide a lower limit to the delta and the actual difference is expected to be greater than this delta (not smaller). It is therefore not clear what the additional criterion is intended to accomplish. If this language is maintained, a brief explanation may be helpful.	
PPTA	1714	1715	13,2	To improve readability of text in Table 1, please enlarge the font size.	Please enlarge the font size of Table 1.
EFPIA	1717	1717	Annex C	The title is more general but the table provides information for synthetic molecules only. There no example covering biotech products or RAMAN .	Provide examples covering biotech products or RAMAN
EFPIA	1717	1717	13,3	last line of table: Additional text added to make more explicit regarding what is meant by change management. This maximizes the flexibility for the analyst.	Change Management (model assessment/monitoring, maintenance, redevelopment, and revalidation) per PQS

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	1717	1718	13,3	In the example (Glucose Raman model for qualitative ID testing) it is proposed to maintain the model based on a Model Monitoring and Maintenance Strategy. It is not clear how this is done in practice as it is a qualitative method where the result is either Yes or No to whether the ID is correct.	Suggests changing to "updates should be triggered on an event-driven basis."
EFPIA	1717	1717	Annex C	Table should have header row for the examples given	Consider: Column 1 header as "Example 1", column 2 header as "Example 2", and column 3 header as "Example 3".
EFPIA	1717	1717	Annex C	Cells in the table containing same directive can be merged for brevity	
EFPIA	1717	1718	13,3	Please confirm if "performance monitoring" is equivalent to "ongoing monitoring" as introduced by ICH Q14	Please confirm if "performance monitoring" is equivalent to "ongoing monitoring" as introduced by ICH Q14 and use aligned terminology
EFPIA	1717	1718	13,3	For the blending example, this might not reflect real cases during development, where unsupervised models are also used and might not undergo a full validation or models might only be developed for information purposes.	Please consider adaption of the text
EFPIA	1717	1717	Annex C	The tile is more general but the table provides information for synthetic molecules only. There no example covering biotech products or RAMAN . No proposal how to define ATP, and EC (PACMP) for a multivariate model	Provide examples covering biotech products or RAMAN. The multvariate method chapter need to be better connected with the concepts described in the guideline i.e. ATP, EC, (PACMP)
EFPIA	1029 /1489	1031 / 1492	Annex A	"depending on region": It is not clear for a company how to deal with that, how can a company find out wich region, why is the concept not applicable to all ICH regions? This could turn out as a road-block for companies to apply the enhanced development concept	If adherence to ATP is commited and ensured by the PQS, the concept should be applicabe to all ICH regions and the diclaimer that there maybe be differences in requirements by different regions be removed
EFPIA	1044, 1051			Change MAH to 'sponsor'?	More widely applicable - could then cover both CTs and MAs. Not sure how much flexibility wrt language would be helpful wrt enabling principles to be applied in a clinical setting - or if this is a step too far…
EFPIA	1389 / 1498	1390/ 1498	13.1.2	The coefficient of determination (r^2) should not be used for a nonlinear model such as the 4PL.	Recommend an appropriate goodness-of-fit measure for this example. One option is to calculate the coefficient of determation on the linear fit between the observed and predicted responses.
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".

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
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.
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."