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IPAC-RS	0	0		This guidelines applies to analytical procedures to analyze drug substance or drug product of only chemical and biological/biotech origin but we believe it's worth to consider or clarify the approach with drug device combination products that contain variability deriving from device, process, product, and procedures.	To expand the guidelines including drug device combination products adding specific examples in the annex (Lana- Do we want to add IPAC-RS are willing to help here?)
IPAC-RS	0	0		General comment on "reference procedure": it seems that a multivariate development is possible only using a pre-existent validated procedure (reference procedure), so that a multivariate approach is possible only where prior knowledge is available (LCM?)	Clarification of the role of reference procedures in multivariate procedure development would be helpful.
IPAC-RS	0	0		Guidelines refers to many statistical concepts that require a certain expertise	Please add references to bibliography that can be used for statistical support
IPAC-RS	0	0		There is a clear analogy with ICH Q8 with minimal approach and enhanced approach, which is helpful. However the analogy is not reflected entirely: the concept of critical method parameters is not mentioned while it's clearly mentioned for process development in ICH Q8 with the Critical Process Parameters. This is a potential gap.	Consider including a discussion of critical method parameters, in particular within the context of Established Conditions for analytical procedures.
IPAC-RS	3	3	1.1.	risk-based: no definition of risk-based approach in the glossary --> what would be feasible as a risk-based approach and what is insufficient?	clarification and further examples of risk-based approaches and outcomes required
IPAC-RS	28	29	2	This guidelines applies to analytical procedures to analyze drug substance or drug product of only chemical and biological/biotech but it is difficult for some products to have a purely chemical/biological procedure: aerodynamic particle size distribution using inertial impactors for inhalers or dissolution tests for solid dosage forms amalgamate both physical and chemical processes.	Consider including sample preparation examples
IPAC-RS	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 pharmacopeial analytical procedures is out of scope.
IPAC-RS	48	50	2	" In general, data gained during the development studies (e.g., robustness data from a design of experiments .....can be used as validation data…and does not necessarily need to be repeated."	Add other examples to illustrate how development data can be utilized . Add justification on the degree of GMP needed for development data .
IPAC-RS	62	62	2.2	The robustness should consider the ability of the **measurement** to meet the predetermined acceptance criteria when method parameters are changed	

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IPAC-RS	68	68	2.2	Should or could?	change 'should' to 'could'
IPAC-RS	70	70	2.2	Don't think this first bullet is just related to the enhanced approach	Aspects of samples properties should also be included in the minimal approach
IPAC-RS	79	79	2.2	Replace 'ensuring' with 'that ensure'	Replace 'ensuring' with 'that ensure'
IPAC-RS	107	107	Figure 1	Validation still seen as a separate one off step rather than the lifecycle concept	Recommend the lifecycle aspect within Figure 1 is further emphasized.
IPAC-RS	118	118	3	missing the word 'quality' between 'single' and 'attribute'	add the word quality' between 'single' and 'attribute'
IPAC-RS	119	126	3	Line 119 and 126 are repetitive	Change line 126 to "The ATP also supports subsequent performance monitoring and continual improvement of the analytical procedure."
IPAC-RS	148	148	4.1	This needs an example to show what is meant by procedure lifecycle management	Further examples of the lifecycle management of analytical procedures would be helpful.
IPAC-RS	151	169	4.2	this part should include a explanation about the establishment of the replicate strategy and corresponding SST (as part of risk management). Reference should also be included in "6. Analytical procedure control strategy (lines 228-230)	The concept of sampling and replication strategy needs to be included in the guideline.
IPAC-RS	151	151	4.2	In the section risk assessment, the objectives are clearly stated. However compared to classical QbD flow, the concept of categorization of method parameters (either in not critical or critical method parameter) is not clearly mentioned. The definition of critical method parameter or "CRITICAL analytical procedure parameter" is not part of the glossary.	Clarify why the categorization of method parameters in critical or not critical is not clearly explained.
IPAC-RS	151	169	4.2	This part should include a explanation about the establishment of the replication strategy and corresponding SST (as part of risk management). Reference should also be included in "6. Analytical procedure control strategy (lines 218-230) See corresponding comment on replication strategy in ICH Q2.	The concept of sampling and replication strategy needs to be included in the guideline.
IPAC-RS	155	155	4.2	"Risk assessment can be formal or informal..." What do we mean by informal ?	Remove this part and replace for instance by "should be formalized"

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IPAC-RS	155	155	4.2	Second 'can' should be 'should'	Change second 'can' to 'should'
IPAC-RS	196	196	5.2	What is meant by attributes in this context?	
IPAC-RS	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 be used 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 identified.	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 be used to identify parameters, attributes and appropriate associated ranges to be investigated experimentally. The aim of this approach is to identify critical attributes which therefore require specific control."
IPAC-RS	231	231	6 and 10	May need a definition of a "skilled analyst"	Better to change to "trained analyst"
IPAC-RS	234	234	6	How can the SST verify selected attributes?	Further clarification and inclusion of examples to demonstrate SST criteria selection and how they are used would be helpful.
IPAC-RS	249	250	6	Software tool definition could be misleading since for some sample suitability assessments a simple statistics can be applied without using any software (e.g. T square and Q statistic)	Substitute “software tool” with “appropriate diagnostic tool”
IPAC-RS	290	290	7	do we mean 'criteria' instead of 'characteristics'	change 'characteristics' to 'criteria'
IPAC-RS	316	325	7	Not clear what this is saying	Change line 291 to "Typically, evolving process knowledge, analytical procedure knowledge and continual improvement are all potential drivers for changes to analytical procedures."
IPAC-RS	354	354	7	What is a bridging strategy?	Further definition of bridging strategy and inclusion of additional examples would be helpful.
IPAC-RS	384	417	8	Not clear the requirements of sample selection (is it mandatory to have appropriate variability up to commercial scale? Or lab/pilot scale approaches could be reasonably sufficient?)	Please provide further clarification on sample selection in multivariate analytical procedure development

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IPAC-RS	385	395	8	Not clear the reason why a separate analytical procedure (reference procedure) is needed to develop a multivariate model. ? For the model building and validation the same procedure is needed. (refer to general comment on reference procedure)	Clarification of the role of reference procedures in multivariate procedure development would be helpful.
IPAC-RS	405	417	8	"Inclusion of commercial scale samples is recommended to capture variability" scientifically sound but impractical and expensive way to validate the model.	More guidance (or examples) on the approaches to be used here would be beneficial (for example: divide variables to study at different levels i.e. lab or pilot scale; start exploring a wide range and then reduce the space; use techniques that ensure pilot batches are representative of commercial)
IPAC-RS	409	416	8	The term "calibration sets" is not defined.	Add explanation or definition of calibration sets.
IPAC-RS	419	422	8	Variable selection should be justified: not clear how ? (methodology, link with molecule structure ?) does need clarification ?	Add clarification or examples on the selection of variables
IPAC-RS	477	479	8	"The last step in model establishment is development of a multivariate model maintenance plan" This indicates that a separate or updated to existing 2nd tier testing, Atypical and OOS procedures. Will other ICH guidelines also be updated to include this proposal?	Alignment with other relevant guidance is recommended
IPAC-RS	482	482	11	Reference procedure definition in the glossary section is not exhaustive (refer to the general comment on reference procedure)	Further clarification of the role and use of a reference procedure during development would be helpful
IPAC-RS	530	531	11	May need a definition of a "skilled analyst"	Better to change to "trained analyst"
IPAC-RS	598	824	11	Glossary should include a definition of replication strategy.	Inclusion of replication strategy in the glossary is recommended
IPAC-RS	939	938	13	Capillary electrochromatography is an alternative chromatographic procedure.	Recommend line changed to "More recently, capillary zone electrophoresis (CZE) and capillary electrochromatography (CEC) have been introduced as alternative chromatographic separation technologies.
IPAC-RS	987	991	13	"...performed and evaluated in an ANOVA experiment" Confusion about a evaluation of results from a precision study	"...intermediate precision between operators, days and instruments were performed and evaluated."

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IPAC-RS	1011	1011	13	"After the performance of the validation study…"	Add a verb in this part of sentence.
IPAC-RS	1034	1045	Table 3	There is an error message in one line, where a link should be included?	Please correct or clarify.
IPAC-RS	1218	1219	13.1.2	Table 4 suggests not feasible criteria for Performance 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	Recommend the target and acceptance criteria in Table 4 are reviewed further.
IPAC-RS	1218	1219	Table 4	Line on TAE: "Different statistical measures…" More details might be very useful.	Further clarification and examples on the total analytical error concept will be helpful.

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