Submission of comments on 'Preliminary QIG Considerations regarding Pharmaceutical Process Models'

Fields marked with * are mandatory.

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If you respond on behalf of an organization, please allocate yourself a name abbreviation to be used as "Stakeholder name" in the comment tables below. If you comment as an individual, please ignore this field and use your full name as your "Stakeholder name".

EFPIA

1. General comments on the 'Preliminary QIG Considerations regarding Pharmaceutical Process Models'

Consolidated comments – read this section only

	Stakeholder name	General comment
1	EFPIA	The document gives much clarity on the current expectations of the QIG and seems to represent an expansion of the ICH Q8-10 "Points to Consider" document (section on modeling), with more details added. For clarification on this comparison, is the change of terminology in model classifications from “model impact” to “model risk” intentional or are the three categories meant to of identical categorization? This is particularly relevant as there are a few areas where the QIG preliminary considerations document represents additional or sometimes tighter/more conservative interpretations, for example around “medium risk” models where the document remains very conservative in its approach to medium impact models. Another example is the use of process models only used for product or process design, which in the ICH document generally land in the “low” category but in this document could be “medium”. Medium risk models trigger additional activities (potential maintenance protocols) which seem not applicable for development models. A missing elements seems to be the risk or impact of the model in context with the overall control strategy, where the overall risk could be reduced to the context. Could there for example be a high impact model with medium or low risk to the quality of the product?
2	EFPIA	Beyond the relationship to the ICH Points to Consider document, the categorization of process models (table 1) implies that all process models need to be registered. There could be scenarios especially in the post-approval setting where process models are used for pure process monitoring only, with no connection to control strategy, or resulting actions (digital twin in shadow mode?). The prevalent current practice in the industry would be to not register such applications, but rather completely manage them in the PQS. It would be valuable to also define a “no risk” category or define in the scope of the document that there can be cases where no dossier registration is required, otherwise the

		unintended consequence of the document would be disincentive to use such models because of registration and life cycle burden.
3	EFPIA	From the perspective of harmonization of expectations for process model at least with the FDA, it would be desirable understand the perspective of the QIG to the ASME methodology applied around “context of use” and “risk management”. The current document has a number of places where the terminology or the concepts of the ASME V&V 40 standard are used or applied, without being named as such, however without the greater context on model risk that the ASME standard applies. An incomplete application of the ASME or any other more complete model risk and – robustness methodology would lead to potential misalignment and hurdles to acceptance and application.
4	EFPIA	One item of concern and potential hurdle to adoption is that already for medium-impact models potentially a significant amount of detailed information that is managed by the PQS/GMP framework (Q3 and 4 answers) needs to be submitted in the dossier. This includes, depending on the circumstances, “model maintenance protocol” line 233, “method verification protocol line 208 (analogue to “Design Space verification protocol”), “continuous model verification protocol” line 220. It is generally a hurdle to submit detailed information about PQS procedures in registration dossier, due to the potential chances in PQS procedures which would trigger variation filings. This approach has in the past already slowed down adoption of NIR spectroscopy and Design Spaces due to the link between PQS and registration changes. Suggest to have further reflection on the roles and responsibilities between assessment and inspection for process models.
5	EFPIA	In a number of sections, new or previously unused terminology is chosen, expl. line 177 "validity domain" table 1 QA= Quality Attribute (as opposed to CQA). It is suggested to add a glossary to provide clarity about the definitions or offer cross-references to existing sources for definitions. This includes the use of the terminology of "process model validation" vs. *process model verification" or whether the QIG wants to give details on what types of process models require formal validation (expl. process models used for product development, low impact) Another consideration is to expand on the abbreviated examples in table 1 and give more elaborate examples how models would end up in certain categories, or how models, depending on the use, could transition between different categories (expl. Process models for process development)

2. Specific comments on text

2.1. Background

	Line number(s) of the relevant text ***(e.g. 20-23)***	**Stakeholder name** ***(to be repeated in all rows)***	**Comment and rationale**	**Proposed guidance text**

2.2 Introduction

	Line number(s) of the relevant text ***(e.g. 20-23)***	**Stakeholder name** ***(to be repeated in all rows)***	**Comment and rationale**	**Proposed guidance text**
1	27	EFPIA	Add use of process models for scale-up	Proposed text: The expected outcome from the use of process models is enhanced

				process understanding, (multivariate) monitoring and control, robustness, performance and adaptability including at different scales / configurations.
2	28-30	EFPIA	Models used for predictive approaches are missing	...performance, adaptability, forecasting and predictive control
3	32	EFPIA	Add "chemical", as this is equally relevant	...physical, chemical or biological process or system.
4	35	EFPIA	The 3 different types of models (scientific distinction) are given but there is no further use of the distinction in the rest of the document, for example different expectations for development, validation, extrapolation etc.	Two solutions are proposed: 1) If there is no clear connection to regulatory expectations suggest to remove the classifications. of L36-L40. 2) If the idea is to keep the model types, then we suggest making it clear that: "All three model categories are in scope"
5	40	EFPIA	Definition of "hybrid models" is missing	Define Hybrid models as a combination of mechanistic and data-driven
6	41	EFPIA	The use of process models for process controls is missing.	Expand to with "process control"

2.3 Scope

	Line number of text	**Stakeholder name** ***(to be repeated in all rows)***	**Comment and rationale**	**Proposed guidance text / element of the figure**
1	48-49	EFPIA	Suggest to use consistent language around the types of models, aligned with the definitions in lines 35-40. Semi-empirical models appear to be missing in lines 48-49.	
2	51-56	EFPIA	A further clarification on applicability and terminology around Machine Learning vs artificial intelligence models is desirable in this document. Please clarify what is defined	We recommend updating the scope to include AI models. While we think that the draft guidance would cover AI models as is, including specific guidance on AI models would also be beneficial

			as ML model but not as an AI model. This is with respect to the potentially different risk postures outlined in the EU AI Act definition (AI has an element of autonomy in decision making) vs. machine learning models as empirically developed models.	

Q1. How should the risk to product quality be considered when determining what data is to be included in the dossier in terms of model justification?

	Line number(s) of the relevant text ***(e.g. 20-23)***	**Stakeholder name** ***(to be repeated in all rows)***	**Comment and rationale**	**Proposed guidance text**
1	57-59	EFPIA	The term "risk of product quality" is used in the question while "model risk" is used in the answer. If these terms are considered interchangably, it would be better to make it clear or choose one term for consistency.	
2	60-61	EFPIA	It is assumed that models a.) for fate of impurities for DS processes and b.) process purge models for genotoxic impurities/nitrosamines are not in scope of this document.	Fate of impurities for DS processes and process purge models for genotoxic impurities/nitrosamines are not in scope of this document.
3	69-74	EFPIA	The logic applied here is similar or identical to the ASME V&V 40 standard applied by the FDA for process models, however with less context. it is suggested to formally reference the ASME V&V 40 to provide that context or add significant details to the two dimensions of risk. The term "additional monitoring" also would require further clarification, does this refer scenarios outlined in table 1 (additional tests in parallel) or a more "process monitoring" i.e. for continuous	

			improvement or stage 3 PPQ,	
4	71-74	EFPIA	It is unclear how the manufacturing mode impacts the model risk.	We recommend discussing how these factors impact the risk of the model.
5	75-77	EFPIA	It is unclear the need or the benefit of considering the model in isolation. This is counter to the guidance of ASME VVUQ40 that starts with an assessment of the model's context of use as the primary input to the model's risk assessment.	We recommend deleting this text.
6	79	EFPIA	The term "intended use" is mostly referred as "context of use" in other references (FDA, ASME).	We suggest to use a consistent terminology with existing standards (like ASME V&V40). Change "intended use" to "context of use".
7	78-81	EFPIA	The paragraph is unclear. The model risk assessment should consider the use of the model across the lifecycle of the medicinal product to determine the level of data to be included in the dossier and the degree of regulatory oversight.	We recommend revising this paragraph to consider the use of the model across the lifecycle of the medicinal product to determine the level of data required.
8	82-84	EFPIA	This strongly suggests that all model risk evaluations should be included in the dossier, including models of low-medium risk. It is also not clear if this represents a separate or new type of documentation. Typically a formal risk assessment would be part of the model development and if applicable documentation, so this would be an element of the documentation submitted about the model. Alternatively, like all elements of the control strategy, the model would be risk assessed as part of the overall control strategy and the documentation of the	We recommend the following revision: "The evaluation of model risk <u>and consequence(s) on the overall medicinal product benefit/risk balance</u>~~, including risks of failure of the model or risks arising from its incorrect use, and their consequence(s) on the overall medicinal product benefit/risk balance~~, should be discussed in the dossier <u>only for high-risk models. Documentation of medium or low risk models should be maintained in the PQS.</u>"

			control strategy (for example in the development section of the dossier) would be including the process model aspects. Similarly, risks arising from an incorrect use of a technology are usually not discussed in the dossier. Mistakes in operating a technology (human error) are subject to control via the manufacturer's GMP quality system. This requirement should be deleted from the document.	
9	87-89	EFPIA	Documentation beyond the evaluation of model risk (for high-risk models only) should be maintained in the PQS, and not reported in the dossier.	We recommend the following revision: "The evaluation of the risk associated with implementation of a process model is the basis for any justification for inclusion of model related information in the PQS ~~dossier (e.g., model description, justification, validation data)~~."
10	90	EFPIA	The terms "primary control strategy" and "secondary role" are not clear. Further explanation / definition should be added.	We cannot propose a new guidance text as it is unclear to us what it means.

Q2. What data is expected in the dossier in terms of model description and scope?

	Line number(s) of the relevant text *(e.g. 20-23)*	**Stakeholder name *(to be repeated in all rows)***	**Comment and rationale**	**Proposed guidance text**
1	95-97	EFPIA	Propose to use "product quality" instead of "material quality"	The level of detail regarding the model development and its description in the regulatory submission is dependent on the intended use of the model, its role in the control strategy, and

				the risk to ~~material~~ product quality.
2	95-98	EFPIA	The level of detail regarding the model development and its description should be maintained in the PQS.	We recommend that model risk assessments will be reported in the dossier for high-risk models only.
3	103-117 and 118-134	EFPIA	The differences to the chapter 5.4 of ICHQ8/Q9/Q10 should be clarified (here or in later sections) The concepts of Model Description and Model Scope are unclear/ overlapped. The expectations for medium and high risk differ in the sections model description and model scope. This should be aligned.	Suggest the two sections are combined and the term "scope" is dropped to align with other EMA and ICH guidance where this term isn't needed for other process controls. Focus on what is part of the dossier description of the model, the assumptions and the scope of this document for applicability, and which of these elements are supportive info and which are ECs or "binding information in dossier"
4	111	EFPIA	Why are literature sources only relevant for mechanistic models?	
5	112-113	EFPIA	Please define "complex". Does this conversely mean that non-complex data need to be submitted? Please clarify in the document.	We cannot propose a new guidance text as it is unclear to me what it means. An example would be useful.
6	131-133	EFPIA	In line 106-117, it is described that performance metrics and model validity domain need to be provided only for high-risk models and not for medium-risk models. This is in contrast to the text provided in line 131-133 where this is required also for medium-risk models.	Propose; "the acceptance criteria for relevant performance metrics (e.g., prediction accuracy, model uncertainty), (for high-risk models only) the model validity domain (for high-risk models only), and

Q3. What data is expected to be included in the dossier in terms of model validation?

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	Line 137	EFPIA	Validation is not an appropriate term for what is described for low impact models. The term "verification" is used on other EMA guidance (eg for design space)	Change to model "validation/verification"
2	154 (Table 1)	EFPIA	Examples for low impact models are not clear and dossier requirements are not aligned with descriptions for dossier requirements in Q2, where no validation data are requested;	
3	154 (Table 1)	EFPIA	The risk levels (low, medium, high) are not defined, except for examples in Table 1.	We recommend defining each risk level or including references to prior publications.
4	164-166	EFPIA	It should read CQA instead of QA. (according to Table 1, QA is considered low risk and CQA is considered medium risk)	Models which influence the process control design in that manner and are used to support batch release decisions predicting CQA(s) (e.g., granulation endpoint) are usually medium risk.
5	169	EFPIA	Implies that any model use to determine the control for a CQA is medium impact regardless of the overall control strategy. Such considerations are a significant disincentive to the use of models I the control strategy. Any system where there the control of the CQAs impacted by the model via end product testing makes the model inherently low risk, regardless of the sophistication of the model.	Revise the table
6	189-191	EFPIA	Multiple ideas are being combined in this sentence like edge of failure, applicability range (already in 133), and robustness. This could be made clearer	"Robustness and edge of failure scenarios should be discussed, as applicable"

7	198-201	EFPIA	The connection between model validation and process validation is not clear, or what the expectations are. In any scenario process validation data would be expected for commercial processes, but model adequacy can be shown independent (and prior) to process validation. To an extent this is similar to the concept of analytical method validation (= adequacy) which shows analytical methods and controls are supportive of demonstrating process control including in the process validation exercise.	
8	198-199	EFPIA	This sentence reads a bit in contradiction for low-risk models as described in lines 125-126, 160	Remove lines 198-199
9	208	EFPIA	If needed, a procedure to ensure validity of the model at the full scale should be inherent in the PQS but not part of the dossier. Otherwise this sets a precedent which would require alleviation of life cycle burden through elements of for example ICH Q12 or Q2/Q14 for life cycle management.	
10	202 211	EFPIA	No clear definition of model validation vs verification	Please consider adding a definition of these terms. For example, below are the descriptions in the ASME V&V20 standard: Verification: "In general, code verification assesses code correctness and specifically involves error *evaluation* for a known solution. By contrast, solution verification5 involves error *estimation*, since the

				exact solution to the specific problem is unknown. Code and solution verification are mathematical activities, with no concern whatsoever for the agreement of the simulation model results with physical data from experiments; that is the concern of validation." Validation: "The estimation of a range within which the simulation modeling error lies is a primary objective of the validation process and is accomplished by comparing a simulation result (solution) with an appropriate experimental result (data) for specified validation variables at a specified set of conditions. *There can be no validation without experimental data with which to compare the result of the simulation"*
11	202 211	EFPIA	Clarification of validity of models combining data from different locations and scales should be added. Also data coming from DoE studies should be mentioned here Missing guidance on developing models at laboratory scale on a qualified small scale model, would the perception of risk be different and no model verification protocol at commercial scale be necessary?	
12	202-211	EFPIA	The paragraph does not mention how the transferability between scales differs between	We recommend that the Q&A described this information.

			mechanistic and data driven models.	
13	(lines 208, 220) and Q4 (line 233)	EFPIA	Expectations are unclear concerning: · Model verification protocol · Continuous model verification protocol · Model maintenance protocol.	See also general comment #4: It is suggested to keep these in the PQS not dossier. If anything, established guidances should be used (Questions and answers on post approval change management protocols (europa.eu)) vs creating new expectations.

Q4. What data is expected in the dossier in terms of process model lifecycle?

	Line number(s) of the relevant text ***(e.g. 20-23)***	**Stakeholder name** ***(to be repeated in all rows)***	**Comment and rationale**	**Proposed guidance text**
1	233-237	EFPIA	Model Maintenance Protocol: is this the already known Post Approval Change Management Protocol for submitted models, in which is assessed the different changes that a model can experience during its lifecycle? If yes, then should be considered to include Post Approval Change Management Protocol instead of Model Maintenance Protocol	See also general comment #4: It is suggested to keep these in the PQS not dossier. If anything, established guidances should be used (Questions and answers on post approval change management protocols (europa.eu)) vs creating new expectations.
2	233	EFPIA	In Q-IWG Points to consider for Q8\Q9\Q10 guidelines (europa.eu) section 5.4 Documentation of Model-Related information, medium- impact models do not mention model verification during lifecycle.	Recommendation to align Q-IWG Points to consider for Q8\Q9\Q10 guidelines (europa.eu) concerning medium-impact models.
3	245-247	EFPIA	In line 106-117, it is described that performance metrics need to be provided only for high-risk models and not for medium-risk models. This is in contrast to the text provided in line 245-247 where this is required also for medium-risk models.	Therefore, the list of performance metrics and acceptance criteria to be followed and checked when a model change occurs (e.g., accuracy, control charts on residuals, etc.), should also be included in the protocol (for high-risk models only).

Other comments

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1				

Thank you for your contribution.