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Preliminary QIG Considerations regarding Pharmaceutical Process Models

Background

This Quality Innovation Group (QIG) document follows on from the first QIG Listen & Learn Focus Group (LLFG) on Continuous manufacturing and the second QIG LLFG on Digital novel technologies, held on 13 March 2023 and 12-13 October 2023 respectively. These highlighted the need for more specific regulatory guidance on process models (hereafter called models).

It is recognised that regulatory expectations for process models in pharmaceutical manufacturing are evolving; the intent of this document is to share QIG's current thinking with stakeholders and seek their comments.

Introduction

Pharmaceutical process control consists of a series of measurements and actions within a process (or system), designed to ensure that the desired quality of the output material is maintained over the intended duration of process operation and over the lifecycle of a product. This includes measurements and actions such as end point determinations, feed-forward/feed-back controls, statistical process controls, and process monitoring.

Over the last few years, there has been an acceleration in the advancements for process control and automation including sensor technology, data analytics and system modelling. The combination of these innovative approaches creates a significant opportunity to enhance measurement and control of process variables and output material attributes. This, in turn, supports adoption of advanced process control strategies, continuous process verification, real-time process monitoring and optimisation, and automated or even autonomous operation and management of manufacturing processes. Process models play an increasingly important role in process design and validation, in control strategies and during manufacturing process lifecycle. The expected outcome from the use of process models is enhanced process understanding, (multivariate) monitoring and control, robustness, performance and adaptability.

A model (in the context of pharmaceutical manufacturing) is a mathematical representation of a physical or biological process or system. The model relates one or more input parameters to one or more output parameters or properties relevant to the efficiency of the process and/or quality of the material(s) being transformed by the system.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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There are three main types of models:

1. Mechanistic models (e.g., kinetic models, computational fluid dynamics, fundamental population balances, modelling for chemical reactors),
2. Empirical models (e.g., multivariate models used for Statistical Process Control, regression models derived from data collected from Design of Experiments), and
3. Hybrid or semi-empirical models (e.g., hybrid digital twins).

Models can be utilised for different purposes, for example for process development, process monitoring, or as soft sensors (i.e., software-based models that predict (quality) properties/ attributes based on process data, and thus the properties/attributes in question are not directly measured but are inferred from process data).

Scope

This document addresses preliminary considerations (general principles) for process models, reflecting the use of performance-based approaches in pharmaceutical manufacturing processes.

The scope of this document is limited to process models such as first-principle models, regression models, system models, multivariate statistical process control models, and Machine Learning models (ML).

With the advent of Artificial Intelligence (AI), it is expected that there will be increased use of complex models, such as ML models for manufacturing process monitoring and control. Although the present document does not focus on AI models in particular, the principles which are introduced hereafter may also apply to AI. Applicants developing AI models are strongly encouraged to initiate dialogue with regulatory authorities as early as possible to discuss their developments (e.g., EMA QIG meetings[1], CHMP scientific advice requests[2]).

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?

In line with the ICH Q8/Q9/Q10 Points to consider document[3], the intended use of a model, as well as its function in the control strategy and in any decision-making process(es) should be defined *a priori.*

Models can have different uses, i.e.:

- Model used to support process development,
- Model used in the control strategy in addition to other related measurements,
- Model used in the control strategy without additional related measurements.

For example, a model can be used as a descriptive analytical tool to simulate the process leveraging *in silico* experimentation, as a predictive tool to monitor the process based on actual process data, or as a prescriptive tool to take control actions on the process to adjust it in real-time.

The role of the model in the control strategy together with the frequency of any additional monitoring, the model's performance, and the potential consequence of an incorrect decision, determine the model

[1] https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp/quality-innovation-group
[2] Scientific advice and protocol assistance | European Medicines Agency (europa.eu)
[3] ICH Quality Implementation Working Group: points to consider for ICH Q8/Q9/Q10 guidelines - Scientific guideline | European Medicines Agency (europa.eu)

risk. Additionally, the criticality of the manufacturing operation(s) in which the model is implicated, the manufacturing mode (e.g., continuous versus batch mode), the intrinsic risk of the medicine (e.g., therapeutic index, pharmaceutical form) and the criticality of its attributes for the safe and effective use of the medicine, should be taken into consideration when evaluating model risk.

The risk assessment should consider each model in isolation, and once this has been done, consider its use in conjunction with the other elements of the control strategy (including other process models); this should include assessment of any inter-relationships.

Ultimately it is the model risk together with the applicant's understanding of the model with respect to its intended use, the implementation (including lifecycle management) strategy, and the performance criteria that capture all the critical aspects of the model, which determine the level of data to be included in the dossier and the degree of regulatory oversight.

The evaluation of model risk, 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. This evaluation should consider both the contribution of the model to a decision relative to other available evidence, and the decision consequence (i.e., the model's impact on product quality).

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 dossier (e.g., model description, justification, validation data).

To note, the same process model can be used in the primary control strategy, in a secondary role, or only to facilitate development, and hence, the risk associated with the use of the model can vary accordingly.

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

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 quality. This forms the basis for defining the degree of justification, and the extent of description, in an application. Requirements are defined as a function of the model risk (see Table 1 in question Q3).

Model description

For all model types and in all cases, documentation should describe the model and the intended use of the model within the overall control strategy, as well as justification for the model risk (i.e., risk assessment).

Additional information that should be provided depends on the intended use/risk category:

- For low-risk models, provision of a high-level description and discussion regarding model use is sufficient.
- For medium-risk models, a detailed description and discussion regarding their intended use should be provided. This should include a justification for the choice of model and the type of data used in its development, e.g., data from commercial scale batches of finished product manufactured according to pre-defined process conditions. The focus should be on providing an outline of model development and intended use, rather than model-specific details. For mechanistic models, reference to literature sources may be acceptable - in this case, relevance of the source to the model, its intended use and risk category should be justified. Complex datasets need not be

submitted. A scientifically sound justification of the overall applicant's approach/strategy should also be provided.

- For high-risk models, in addition to the above, a summary of performance metrics and model validity domain, i.e., the range of conditions where the model performance has been demonstrated to meet the criteria for its intended use.

Model scope

The model scope is a set of information described in the dossier, and it is important in the management of future changes to the model. In general, changes within the scope of the model would be subject to GMP only. Changes outside of the approved model scope are subject to variation application.

Depending on its intended use, established risk to product quality and model risk, the scope will include different levels of detail and relevant model description elements:

- For low-risk models, no additional information beyond that defined in the model description and model use described above is required.
- For medium- and high-risk models, the scope should be defined in the regulatory submission. A typical model scope should include, for example:
  - the intended use within the control strategy's context,
  - the type of model,
  - the acceptance criteria for relevant performance metrics (e.g., prediction accuracy, model uncertainty),
  - the model validity domain, and
  - where a reference method is used, this should be described and be appropriately validated.

Details of what to include in the scope should be justified by the evaluation of risk, refer to question Q1.

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

The goal of model validation is to establish the degree to which a model is an accurate representation of a process and can predict the property(ies) or material quality attribute(s) of interest. Model validation includes the process of determining the suitability of a model for the intended use by challenging it with independent test data and comparing the results against pre-determined performance criteria (ICH Q2), for example the model's prediction accuracy. It also implies evaluating the modelling error, or uncertainty.

As stated under question Q1, the demonstration of model performance (i.e., its predictive capability), and the information to be presented in the dossier, should be commensurate with the risk to product quality associated with the role of the model in the overall control strategy. Validation activities are expected to be designed to give confidence in the model for its intended use.

Some illustrative examples are presented in Table 1 below. The exact dossier requirements will vary on a case-by-case basis.

Of note, these are just examples. Based on justifications these types of applications could fall under other categories.

Table 1. Illustrative examples of low, medium and high-risk models, dossier location and requirements.

Risk	Example	Dossier location	Dossier requirements (see also question Q2)
Low	Process development, e.g. used to develop process understanding. Process optimisation (w/o change to registered process details). Mechanistic model used to speed up bioprocess scale-up/down. Digital Twin in shadow mode. Support batch release decisions based on QA predictions.	Dossier sections S.2.6/P.2.3 and S.2/P.3, as appropriate.	High level description of the model intent, type of model and how it is used. Manufacturing process validation data as described in the process validation guidelines.[4,5]
Medium	Process design (change to unit operation principle or setting of in-process control limits). RTD model in combination with in-line NIR process control. Support batch release decisions based on CQA predictions but used in combination with PAT and release testing.	Dossier sections S.2.6/P.2.3 and S.2/P.3, as appropriate.	Detailed description of the model intent, type of model, how model is used and model operation, model assumptions, type of data used and model validation summary. Manufacturing process validation data as described in the process validation guidelines.[4,5]
High	RTD model w/o other related in-process measurement. Real-time release testing (reduced release testing).	Dossier sections S.2.6/P.2.3, S.2/P.3 and S.4/P.5, as appropriate.	As for medium risk above, plus model validation report (training/ validation/ test datasets, prediction metrics acceptance criteria, model validity space, *etc*.).

QA: Quality Attribute; CQA: Critical Quality Attribute; RTD: Residence Time Distribution; NIR: Near infrared

Low-risk: Models that are used for process development and optimisation (process understanding) are considered supportive information and thus low risk. No model validation data are requested for these models in the dossier, and it is assumed that a suitable lifecycle approach (e.g., as per ICH Q14) is adopted by the applicant.

[4] Process validation for finished products – information and data to be provided in regulatory submissions (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1)
[5] Process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission (EMA/CHMP/BWP/187338/2014)

Some models may have a dual purpose e.g., used for process development and used as part of the control strategy e.g., to set control limits. Models which influence the process control design in that manner and are used to support batch release decisions predicting QA(s) (e.g., granulation endpoint) are usually medium risk. They may in certain cases be considered low risk if suitably justified considering the overall control strategy and based on the holistic evaluation of risk as described in question Q1.

Medium-risk: Where a process model predicts a CQA (e.g., blend uniformity) and is used in conjunction with Process Analytical Technology (PAT) and traditional final release testing (e.g., Uniformity of Dosage Units by content uniformity controlled at release), it is considered medium risk. In this case, a summary of model validation activities should be provided in the dossier, confirming that the model has been sufficiently validated for its intended use, thus showing its adequacy.

High-risk: Where a process model is used to support real-time release testing (RTRT) or is the main quality determinant although there is no RTRT, the model is considered high risk. Data required in the dossier includes training, validation (internal) and test (external validation) datasets to support appropriate coverage of the validity domain. The number of independent batches that were used, the number of samples per batch, and evidence that datasets are representative of the expected process variability in routine production, should be presented and discussed. The type, amount and the scale of the data used to develop, optimise and test the model should be justified.

The focus of the model validation should be the model performance e.g., prediction accuracy and model sensitivity. Model uncertainty should be determined and presented, considering the major sources of uncertainty (epistemic/or computational and aleatory/or experimental) e.g*.,* by using tolerance intervals for the prediction. The choice of the performance metrics should be comprehensively justified by the applicant. The rationale for setting the corresponding acceptance criteria should be provided. Comparison of the model predictions with the reference test (or any other justified comparator) should be conducted, and an appropriate level of agreement between properties/attributes of interest and associated errors should be demonstrated. The number of outputs compared, and the tested conditions should be justified and discussed. Where relevant model edge of failure should be addressed as well, considering the ranges the model is applied at, and the robustness of the process. The spectrum of disturbance scenarios implemented to challenge the model (e.g., through *in silico* simulations) should be justified.

Generally, data mathematical treatment and algorithms are not expected to be submitted. The code and calculation verification can be kept on site as these activities are considered manageable under GMP.

The suggested requirements, or lack thereof, should be viewed as general considerations since each model needs to be evaluated case-by-case based on the specifics of its intended use.

Whatever the model category, model adequacy should be supported by manufacturing process validation data at an appropriate (justified) scale, to show that the process is in a state of control. Process validation (as described in the process validation guidelines) has an overarching role to ensure that the process consistently delivers material of the intended quality.

If a model has been developed using laboratory or pilot scale data, the validity of the model at commercial scale becomes a key issue for high-risk models, and on a case-by-case basis for medium risk models (depending on the role in the overall control strategy, the additional controls in place, the criticality of attribute, etc.). Discussion and justification on the proposed approach to demonstrate its validity across different production outputs/scales, based on model risk, are expected in the regulatory submission. This can be addressed by demonstrating scale independence and/or model validation at commercial scale. Depending on the model risk, a model verification protocol may be requested,

including the model performance metrics and the manufacturing process IPC and CQAs that should be followed, the respective acceptance criteria, the number of additional data (independent) that would be used, and the monitoring period (parallel testing).

In line with a risk-based approach, the more a model impacts the design and scope of a process control strategy, the greater the extent of expected validation activities. The granularity and the level of scrutiny in each of the validation activities should be adapted to the intended use. It is acknowledged that all the above-mentioned validation data might not be available at the time of submission, and demonstration of model performance will also occur during the product lifecycle (model maturity). By analogy with continuous process verification (ref. EMA Guideline on process validation for finished products - information and data to be provided in regulatory submissions[4]), continuous model verification should be adopted in this case. This refers to additional validation activities to be conducted post-approval based on an approved continuous model verification protocol. Simulation outcomes obtained during the initial validation activities should be verified with routine use of the model. In any case sufficient evidence should be available at the time of submission to support the model's qualification for its intended use (adequacy assessment). Relevance of the collected validation results in this respect, should be assessed (i.e. applicability of the validation activities to the intended use).

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

The validity of a model should be assured through its lifecycle, from development to external validation, implementation and routine production (lifecycle maintenance). It is important to check that the original assumptions, the conditions for model's applicability, etc., remain valid over the model's lifecycle. To that purpose, models need to be reviewed periodically, and retrospectively, to confirm the consistency and adequacy of manufacturing in view of natural process variation.

For medium and high-risk models, a model maintenance protocol describing the periodic review should be submitted in the regulatory submission as part of the Regional Section 3.2.R of Module 3. For low-risk models, maintenance plans are not required in the dossier. The protocol should describe how the potential changes to the model that may occur during its lifecycle will be handled post-approval. The protocol should include:

- A categorisation of foreseen model updates and the respective criticality analysis, including a discussion on the consequence of a change and how it will be managed (set the conditions for changes that can be managed within the PQS or require submission of a variation).
- The mechanisms by which the performance of the model is monitored and the criteria under which model update occurs should be defined as well (e.g. model type/principle, update model every 10 operating hours, after an alarm or OOS, etc.).
- As for model validation at the time of submission, the focus for model lifecycle should be on model performance. 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. In case an acceptance criterion is not met, the procedure explaining how this is handled should be described.

The extent of model maintenance activities described in the protocol should be commensurate with the type of model and the model risk.

Notification and regulatory action will be required in case of deviation from the approved protocol.