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CONSEIL DE L'EUROPE

**European Pharmacopoeia Commission Secretariat**

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DG Health and Food Safety
Unit D6 "Medicinal products – Quality, Safety and Efficacy"
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**Comments by the PAT working party on draft of revised EU GMP Guidelines, Annex 17 on Real Time Release Testing**

To whom it may concern,

The PAT (process analytical technology) working party of the European Pharmacopoeia Commission, which is composed of experts in the field nominated by the contracting parties of the Convention on the elaboration of a European Pharmacopoeia, has the following comments on the draft of the revised Annex 17 of the EU GMP Guideline published for consultation.

The working party wants to highlight some general remarks on the draft and to add as examples some comments on specific items. The absence of comments on other parts does not imply full agreement with these parts of the text.

**General remarks:**

The new Annex 17 gives the general impression of building up new requirements. This is emphasised by the introduction of new wording like "RTRT master plan" or "RTRT strategy" that has not previously been used by experts in the field. The document lacks clear explanations of these expressions which leaves them open to assumptions as to their meanings. It is presumed that the intention might be to give clear guidance on what information is required by inspectors to be in place during inspections.

If this is the case, it should not introduce expressions never used before. If such new expressions cannot be avoided, very precise definitions should be included in the text or glossary.

It should be the intention to encourage manufacturers to increase process and method understanding by using quality-by-design approaches which may include RTRT, and not to discourage them by unclear and additional expectations.

The text should strictly focus on Real-Time Release Testing and should not quote what is already written elsewhere within the EU GMP-Guideline and its annexes. As an example the two last sentences of point 3.8 focus on qualification and validation. It is unclear why this part of Annex 15 is repeated here and why a cross-reference is made.

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**Examples of specific remarks:**

Point 3.1

Line 24: Interaction with regulatory authorities can be appropriate before filing a market authorisation application. Manufacturers are encouraged to participate in a dialogue as early as possible.

It is recommended that this should read: "Interaction with the relevant authority prior to regulatory approval should be considered."

Point 3.3

It is not seen as helpful to introduce new wording and requirements which are already covered by several existing guidelines. The intention and meaning of a "RTRT master plan" is unclear and is not explained in the document.

Other existing documents already include the outlined information. It is captured for example in modules of the dossier submitted for marketing authorisation (control strategy, quality risk assessment) or in the quality system of the manufacturer including internal standard operating procedures of the manufacturer already required by other parts of the GMP regulation (e.g. personnel training programme, deviation/CAPA system, equipment and facility design and qualification programme).

If the intention is to name a collection of documents that should be available for inspections, this could be explained directly while avoiding new wording. The expression "RTRT master plan" would preferably be deleted, or alternatively be properly defined, e.g. in the glossary. Otherwise it gives the impression of raising additional requirements without improving quality and safety of the medicinal product.

A proposal could be to change the first sentence to: "A collection of essential documents related to RTRT should be prepared."

Point 3.4

The item links Critical Process Parameters and Critical Quality Attributes. It is not clear which of the two is referred to and what is controlled. Is it the process or the product? In addition the risk assessment mentioned has already been assessed during licensing and it should be part of the filed dossier. It is not clear why the risk assessment is requested again at this stage. The point seems not to fit into the document.

Point 3.5

"A proactive approach should be facilitated." It is unclear towards what the "proactive" is directed.

Point 3.6

The control strategy is part of the regulatory dossier. It is not clear why in this context especially AQL and UQL are highlighted. Alternatives might be acceptable and it is recommended to describe the item in a more general way. It is suggested to remove the second part of the sentence from lines 76-78 "The control strategy should also describe the sampling plan and acceptance/rejection criteria."

Point 3.7

It is not clear why expertise seems to be specifically limited to statistical expertise in a multi-disciplinary team. It is mentioned twice without referring to other experience. Relevant expertise from engineers, analytical and process experts as well as specialists in chemometric modelling is important.

It is suggested that this should read "Successful implementation of RTR testing should involve input from a cross-functional/multi-disciplinary team with relevant experience on specific topics such as engineering, analytics, chemometric modelling or statistics."

Point 3.8

The general intention seems unclear and it gives the impression of a collage of different other documents. Process validation is e.g. topic of annex 15 of the EU GMP-Guideline.

There seems to be a mix up regarding chemometric methods and use of reference spectral libraries. Comparison to a reference spectral library is not linked to the use of chemometric methods. It is proposed to introduce "or" instead of "and". It is further recommended to replace "chemometrics" by "chemometric methods", a wording that is used in the newly elaborated chapter 5.24 *Chemometric methods applied to analytical data* of the European Pharmacopoeia 8.7.

It is therefore proposed to change the wording to "... and spectroscopy techniques**,** where the sample is evaluated by chemometric methods or by comparison with a reference spectral library."

The point considers "in-line and "on-line" analytical methods as synonyms meaning a method, "where the sampling probe is placed within the reactor". This is not in accordance with current understanding of the terms of the experts of the working party. Both terms are often mixed up, but usually mean different items. It is the common understanding of the working party that the definition provided is valid for "in-line" measurements. "On-line" measurements require an (automated) sampling to extract and condition the sample and present it to an analytical instrument. The sample for on-line measurements might not be reintroduced into the reactor.

Point 3.11

The purpose of the first sentence might be expressed more clearly and more directly. It is proposed to replace it by "End product testing (of active substances or finished products) should not overturn a failure in meeting the specifications of the RTRT."

Point 4.3

The different ways of sterilisation are alternatives.

Sterilisation procedures are described within the European Pharmacopoeia which is the legally binding Pharmacopoeia in all member states of the European Union and the European Economic Area. It is suggested that it be made clear that it is *these* requirements that are to be met and not those of e. g. the Korean Pharmacopoeia, the Indian Pharmacopoeia or the USP.

Therefore it is suggested that it should read: "Parametric release can only be applied to products sterilised in their final container using steam, dry heat or ionising radiation, according to requirements of the European Pharmacopoeia."

Glossary

The selection of items explained in the glossary seems not to be complete. It is unclear on what basis the selection was made and it is proposed that it should be extended.

We remain at your disposal for any further information you may need

Yours faithfully

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Dr Susanne KEITEL
Director