

<p>Subject</p>	<p>Questions and Answers on: "Improving the understanding of NORs, PARs, DS and normal variability of process parameters". EMA/CHMP/CVMP/QWP/354895/2017</p> <p>Summary of collated comments from EFPIA and EBE Nov 2017.</p>
<p>Introduction</p>	<p>The draft EMA question and answer paper (Q&A) was shared by EMA with EFPIA and other industry associations as an agenda item at the May 2015 QWP interested parties meeting.</p> <p>At that meeting EFPIA& EBE welcomed the opportunity to review the draft Q&As, and presented a summary of the main industry concerns. EFPIA/EBE subsequently provided detailed written feedback on the Q&As. Central to the EFPIA/EBE feedback was a request to hold a face to face discussion between industry and regulatory experts prior to publication of the final Q&As.</p> <p>The final Q&As were published in June 2017 and this written response includes a further clarification of industry's concerns. Given the complexity and importance of the issues raised, EFPIA/EBE strongly recommend that a further face to face discussion between industry and regulatory experts should occur.</p>

**EFPIA
comments**

Q&A 1: What is a Normal Operating Range (NOR) and how should NORs be justified and presented in the dossier?

EFPIA/EBE recognise and appreciate the simplification and improvements made to this Q&A, and have no further comments at this time.

Q&A 2: What is a Proven Acceptable Range (PAR) and how should PARs be justified and presented in the dossier?

EFPIA/EBE continue to have major concerns that this is a regionally-specific view of the ICH concept of PARs. Furthermore, EFPIA/EBE believe that the Q&A, as currently worded, will have a detrimental effect on the implementation of enhanced development and ICHQ8-11.

Specifically, EFPIA and EBE have major concerns with the critical paragraph:

"Where interaction effects between different parameters exist and the acceptable range for one process parameter depends on the setting of another parameter, the parameters should be included in a Design space. Alternatively, a PAR can be defined for only one of the parameters in the process description, and other process parameters will be limited to target operating condition or NOR".

The following explains the basis of EFPIA/EBE's major concerns.

1. Optionality of Claiming Design Space

EFPIA and EBE support clarifications that facilitate the use of Design Spaces, since some EFPIA companies have become discouraged from attempting to secure a Design Space by the attendant regulatory and statistical expectations that had become associated with the term.

However, EFPIA/EBE are concerned that a potential interpretation of this Q&A on PARs is that where interactions are identified, applicants must register a Design Space, or be restricted to target values/NORs. This contradicts the ICH principle that a Design Space is not mandatory (reaffirmed in Q&A 5) and the *ICH Quality Implementation Working Group on Q8, Q9 and Q10 Questions & Answers (R4) Q&A 8 (Does a set of proven acceptable ranges alone constitute a design space?) June 2009*, which states:

"...proven acceptable ranges continue to be acceptable from the regulatory perspective but are not considered a design space..."

2. Understanding and Impact of Interactions

The ICH definition of a PAR is

"a characterized range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria".

ICH does not explicitly discuss situations where interactions have been established through first principles or a multivariate development approach, but where a design space is NOT claimed by the applicant.

Where a process is defined by PARs, interactions may or may not have been identified, dependent on the scientific knowledge and the development approach taken. However, by definition, and in accordance with ICH, where a process is defined by PARs, the applicant is not claiming that all combinations of the parameter ranges will work together. In order to make such a claim, an applicant would define a design space (or some equivalent such as multivariate ranges as per Q&A 5).

As written, EFPIA and EBE believe the statement in the EMA Q&A

"Where interaction effects between different parameters exist and the acceptable range for one process parameter depends on the setting of another parameter, the parameters should be included in a Design space"

contradicts ICH and specifically *ICH Quality Implementation Working Group on Q8, Q9 and Q10 Questions & Answers (R4) Q&A 8*

Most significantly, it will lead to restrictions for an applicant who has applied multivariate development to identify interactions and define PARs, over one who has taken a purely univariate approach to defining PARs. **EFPIA and EBE believe it is detrimental to the implementation of ICHQ8-11 to introduce regional**

specific restrictions triggered by increased process knowledge.

3. Restrictions on registration of PARs

The subsequent sentence states "...Alternatively, a PAR can be defined for only one of the parameters in the process description, and other process parameters will be limited to target operating condition or NOR".

EFPIA again refers to the ICH Quality Implementation Working Group on Q8, Q9 and Q10 Questions & Answers (R4) Q&A 8 assertion that PARs continue to be acceptable, and notes that restricting an applicant to defining only one PAR in the process description therefore contravenes ICH (as well as further restricting applicants who have identified interactions via a multivariate development approach).

Summary and Recommendations on Q&A 2

In order to address the major concerns identified in Q&A 2 and to address these points, EFPIA/EBE propose that Q&A 2 be revised (following dialogue between industry and EMA experts) and the following points clarified:

- As per ICH, an applicant should be able to continue to define the manufacturing process by multiple PARs.
- All PARs should be adequately justified during development. This may involve both univariate or multivariate experimentation, or a combination of the two.
- The acceptability of PARs and the ability to make univariate changes to parameter target values should not be restricted by knowledge of interactions.
- EMA expectations for successive univariate changes within multiple PARs remain unclear, and should be clarified.

EFPIA and EBE believes that the flexibility to change parameter targets should be related to process knowledge and an applicant's control strategy and change management processes (as per ICHQ10). Scientific knowledge of risk and interactions will evolve over the Product lifecycle (whatever the development approach) and hence the risks of making changes to the manufacturing process conditions cannot be mitigated without consideration of all such elements together.

In addition, since ICH does not explicitly address the situation where PARs are claimed based on a multivariate approach this commonplace scenario should be discussed.

EFPIA/EBE note that other ICH regions have also recently published interpretations of PAR and change management which are not aligned with EMA – for example Health Canada ADDENDUM - Quality (Chemistry and Manufacturing) Guidance: Questions and Answers (adopted 2017/10/30).

Overall, EFPIA/EBE maintain that further detailed reflection on change management restrictions to setpoints within PARs is required, ideally within the framework of ICH guidelines.

Q&A 3: What is a Design Space (DSp) and how should design spaces be justified and presented in the dossier?

EFPIA/EBE have no further comments on this Q&A at this time.

Q&A 4: How to manage post-approval changes to approved design spaces?

EFPIA/EBE have no further comments on this Q&A at this time.

Q&A 5: What type of process flexibility in the dossier can be acceptable regardless of any mentioning of NOR, PAR or DSp?

EFPIA and EBE welcome the clarification that a design space is optional (as per ICH), although note the points made regarding Q&A 2 that a design space should also remain optional where interactions have been identified.

Regarding the statements:

"A flexible manufacturing process (ranges) can be registered when justified, or alternatively fixed process parameters. However, when a flexible manufacturing process is requested (i.e. ranges of process parameters that are wider than what would be accepted as a NOR; ranges of input material attributes that can affect the quality of the process output), then the process should be established within the framework of a DSp"

As written, this could be taken to imply that the only options available are flexible

	<p>parameter ranges (established as per a design space) or fixed process parameters. As previously noted, this would be in contradiction with the ICH position in <i>ICH Quality Implementation Working Group on Q8, Q9 and Q10 Questions & Answers (R4) Q&A 8</i> that</p> <p><i>"...proven acceptable ranges continue to be acceptable from the regulatory perspective but are not considered a design space..."</i></p> <p>The wording for this section should be clarified and fully aligned with ICH guidance.</p>
<p>Summary</p>	<p>EFPIA and EBE recognise the EMA intent to link change management of manufacturing process parameters to differentiated levels of knowledge, and recognise that the cases considered in the Q&A highlight the practical issues encountered by companies and regulators.</p> <p>However, key points in the Q&A suggest there remain different interpretations between companies and regulators, and there are major concerns that the EMA position is not aligned with ICH guidelines.</p> <p>EFPIA/EBE maintain that, given the major concerns and lack of clarity highlighted, and the impact of the Q&As on implementation of ICHQ8-11, a face to face discussion should occur between EMA (for example the EMA PAT team) and industry experts. At that meeting, EMA can help clarify the meaning of several key points in the Q&A and work with industry experts to develop improved guidance based on a shared understanding of the underlying principles.</p> <p>Ultimately EFPIA believes that the concepts described in this Q&A should be agreed globally, within the framework of ICH.</p>