EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

6 June 2017
EMA/CHMP/CVMP/QWP/354895/2017

Questions and answers: Improving the understanding of NORs, PARs, DSp and normal variability of process parameters

1. What is a Normal Operating Range (NOR) and how should NORs be presented in the marketing authorisation dossier?

Answer:

NOR is not an established ICH term.

The NOR describes a region around the target operating conditions that contain common operational variability (variability that can't always be controlled).

A NOR can be established for several process parameters of the same process step, with the understanding that the NOR does not represent deliberate adaptation of the process, and that the NOR does not cover a parameter range that affects the quality of the process output. Otherwise, a PAR or a multivariate Design space should be established.

The use of NORs alone is not intended to introduce flexibility in the conditions for manufacturing but to better quantify the actual uncontrollable operational variability of process parameters. NORs should therefore be presented in marketing authorisations as what is practically achievable.

2. What is a Proven Acceptable Range (PAR) and how should PARs be justified and presented in the marketing authorisation dossier?

Answer:

The PAR is defined as 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 Q8 R2).

A PAR allows deliberate change in one parameter without changing the others outside their NOR/ target. PARs could be presented in the description of the manufacturing process of the drug substance and/or the drug product (in S.2.2 or P.3.3 of the Module 3, respectively) as ranges.

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PARs for single parameters are proposed by the applicant and are subject to regulatory assessment and approval.

The PAR should be adequately justified regardless of whether the process parameter is considered a critical process parameter (ICH Q8 R2) or not.

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.

PARs can initially be established at a smaller scale than the commercial scale. If so, the applicant should ensure that the PAR is scale independent and applicable across alternative manufacturing sites, if relevant. Verification of PAR at commercial scale could be included in a post-approval verification protocol if appropriate.

Working within the approved PAR is not considered as a change to the marketing authorisation dossier. Changes to the target value within the registered PAR can be managed under the company's Pharmaceutical Quality System without regulatory action. Consequently, there is no specific need to include a target set point within the registered PAR, but if included no variation will be required when changed. Any unexpected result should be reported forthwith to the competent authorities. Movement out of the PAR is considered to be a change and will initiate a regulatory post approval change process.

Considerations for development (S.2.6 / P.2.3 of Module 3): Several PARs can be presented and investigated as part of the process understanding and development.

3. What is a Design Space (DSp) and how should design spaces be justified and presented in the marketing authorisation dossier?

Answer:

The design space is defined by the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the approved design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval (ICH Q8 R2).

A design space (DSp) can pertain to an isolated process step, or it can cover parameters of several process steps.

A DSp can be supported by suitable in-process controls, or output material quality can be assured by working within the DSp ranges alone.

A DSp can be restricted by ranges of process parameters only, input material attributes only, or a combination of process parameters and input material attributes.

Material attributes and process parameters that can affect quality, but are not described by ranges in the DSp would need to be controlled by their specification or target/NOR, respectively. Critical processes should always be included as part of the formal DSp, even if they are controlled. Process

parameters (non-critical process parameters) that have been demonstrated to not be critical within their studied range can be defined by target or range outside the formal DSp.

The justification of a DSp should be presented in the development of the manufacturing process of the drug substance and/or drug product (S.2.6 or P.2.3 of Module 3, respectively). The necessary level of details will depend on the significance, or the impact, of the DSp. The following should be considered:

- Does the DSp represent parameter ranges that are much wider than what would normally be accepted as NORs?
- Does any area of the DSp represent greater risk to quality than the rest of the DSp?
- To what extent do other elements of the control strategy contribute to ensuring output material quality? Examples include in-process controls, PAT analytics and downstream processes and controls.

Any multivariate interactions between the DSp parameters need to be studied. In particular, when the acceptable range of one parameter within a DSp is dependent on any other parameter, this should be thoroughly investigated, including consideration of scale. If it is claimed that no interaction exists between parameters, this should be adequately justified.

Depending on the significance of the DSp, its development should be guided by risk management as appropriate (ref. ICH Q8 and Q9).

4. How to manage post-approval changes to approved design spaces?

Answer:

Extension of a design space (DSp) should be submitted as a Type II variation (B.I.e.1 or B.II.g.1). By 'extension', the following is understood: 1) introduction of new material attributes or process parameters, 2) extension of the range of existing material attributes or critical process parameters.

If the change has been foreseen as described in an approved post-approval change management protocol (PACMP), depending upon what was agreed, the change can either be submitted as a Type IA_{in} or IB notification (B.I.e.5 or B.II.g.5). In accordance with the variation classification guideline, changes foreseen in PACMP for a biological/immunological medicinal product are Type IB.

Restrictions to an approved design space would typically only be necessary if part of the DSp was discovered to not produce satisfactory quality material. Such changes to the manufacturing process should be submitted as a Type II variation (B.I.a.2.b or B.II.b.3.b): substantial changes to a process that may have a significant impact on the quality, safety or efficacy of the product.

Some changes to input material attributes (specifications) or process parameter settings/ranges can be relevant to the DSp, even if the DSp does not specifically cover these parameters. For example, the DSp can be established on the condition that other non-critical process parameters, which are required in the manufacturing process description, but have been demonstrated not to be critical within the range studied, are kept constant or within their range. Changes to any of these elements should be sought in accordance with the variations classification guideline, where, depending upon the nature of the changes and type of product some will be possible as Type IA, provided the relevant conditions and documentation requirements are fully met, whereas others will be possible as Type IB notifications. In all cases the new process must lead to an equivalent product regarding all aspects of quality, safety

and efficacy and the change should not adversely affect the reproducibility of the process and it should be shown that the criticality of the parameter in question is unchanged.

The variation categories related to changes to manufacturing sites apply regardless of DSp or not. However, the continued relevance of any registered DSp should be considered whenever there is a manufacturing site change.

It should be noted that this Q&A has been developed considering the current variation classification; *Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures* (2013/C 223/01).

5. What type of process flexibility can be acceptable in the marketing authorisation dossier, regardless of any mentioning of NOR, PAR or DSp?

Answer:

The degree of process flexibility is dependent upon how the manufacturing process and its development is presented in the marketing authorisation dossier.

Irrespective of the development approach, the same requirements apply to the level of details in the manufacturing process description.

Steps in the process should have the necessary details in terms of appropriate process parameters, along with their target values or ranges.

The establishment of a DSp is optional. 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. Reference is made to Q/A # 3, where it is indicated that the justification for the DSp should be commensurate with the actual degree of flexibility represented by that DSp, the impact of the DSp and the risk to quality.

The process description is considered to be one element of the overall control strategy that is presented in an application. Accordingly, the necessary level of details will be considered during assessment on a case-by-case basis for example based on the suitability of any supporting in-process controls, PAT analytics or downstream processes and controls. Typically, a one-sided parameter range (for example an upper range only) represents great flexibility and will have to be justified by scientific rationale.