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Questions and answers on level of detail in the regulatory submissions

What types of risk assessments (RAs) can be included in a regulatory submission?

It is up to the applicant to determine what RAs are included in the submission. This information can be useful to aid the assessor/reviewer for determining how the applicant selected the specific formulation, manufacturing process and controls. For example, the Agencies have seen risk assessments related to selection of formulation variables, delineation of impact of various process parameters and selection of in-process controls.

What level of detail should be considered for an RA related to process design in a regulatory submission?

The level of detail should be commensurate with the significance of the outcome of the RA to the commercial manufacturing process and to the control strategy. For example, a risk assessment pertaining to identification of critical process parameters in a process or to the establishment of a design space for an important unit operation would normally be considered of high significance. The information that should be provided in such cases could include:

- A statement of which RA tool was used; or if a novel RA tool was used, a definition of the RA tool along with sample output from the tool.
- A comprehensive qualitative or quantitative summary of the outcome of the RA (e.g. RPN (Risk Priority Number), threshold value for RPN (and an explanation for why such a threshold was chosen) and final list of all RPNs) supporting and explaining the applicant's rationale for the selection of variables/parameters that warranted further study and those which were not further studied. Information on the way in which risk assessment activities were used to determine which process parameters and quality attributes are to be considered critical or non-critical.

Both agencies acknowledge that regulators should take the following into consideration when requesting additional details regarding an RA in a submission: complexity of the dosage form, the commonality of the risks identified relative to products of the same type (i.e., available prior knowledge), and the amount of commercial scale manufacturing data available at the time of submission (i.e., state of knowledge).

What level of detail should be considered for an RA related to product design in a regulatory submission?

The level of detail should be commensurate with the level of risk presented by the formulation and dosage form, as it is intended to be used by the patient. The information provided can include how the risk assessment approach was used to optimize and select the formulation, and/or to rank or prioritize formulation variables (e.g., raw material attributes) based on their potential effects on finished product Critical Quality Attributes (CQA). The factors considered can also include how the drug product could be unintentionally or intentionally misused. For example, a risk assessment pertaining to a solid modified release oral formulation for an opioid would normally include an analysis of the potential for dose dumping. The factors discussed can also include considerations such as physical and chemical stability over shelf life.

What level of detail should be considered for design of experiments (DOEs) in a regulatory submission?

The level of detail should be commensurate with the significance of the outcome of the DOE to the selection of the product design, commercial manufacturing process and control strategy. For example, a DOE to define operating ranges for an important unit operation would normally be considered of high significance. The information to be provided in such cases could include:

- Type of experimental design and parameter ranges studied. Justification for choice of design could be useful, in particular if the design is not fully balanced.
- Tables summarizing inputs and outputs, including batch size.
- Summary of parameters that were kept constant during the DOE.
- Delineation of factors as scale dependent or independent, with justification (for example experimental results, scientific rationale, prior knowledge).
- Description of main effects and interactions on response variables, including statistical significance of parameters (p-value).
- Discussion of regression model validation parameters (e.g. table of coefficients, output from ANOVA regression analysis, residual plots, goodness of fit (R2), goodness of prediction, table of predicted response values with confidence intervals), if applicable.

What level of detail should be considered for justifying and describing a design space in a regulatory submission?

The level of detail in the information used to support the proposed design space should be commensurate with both the significance of the design space (i.e. role of the design space in the overall control strategy) and its extent. (The extent refers to the degree of additional operational flexibility provided by the design space as compared to fixed set points and normal operating ranges). Other factors can include the ability of the control strategy to detect failures and the degree of commercial scale experience in multiple regions of the design space.

Additionally, both agencies are of the opinion that there are circumstances where a mathematical regression model representing the design space need not be submitted. This is generally the case if the design space is presented as a linear combination of material inputs and process parameters. In situations where a design space presentation includes a surface (e.g. as represented by quadratic terms), the regression model representing the surface should be provided.