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6 Considerations for QbD Use in Stability Studies

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Quality-by-design (QbD) is a systematic approach whereby desired traits and performance are built into a process to ensure expected and intended performance. Making corrections after the project is completed is the very antithesis of QbD. In the pharmaceutical industry, a QbD approach employs scientific techniques to gain knowledge about a product at its inception. Having a better understanding about a drug substance and excipients will help to streamline development and improve processing. Because QbD has existed for several years, it is expected by regulatory bodies to be employed in product development. However, it is not a requirement.

QbD begins by defining traits that are desirable in the finished product. Desirable traits are termed Critical Quality Attributes (CQAs). Once all of the critical attributes are identified, this creates the Quality Target Product Profile (QTTP). The QTTP is used to determine the focus for creating the Design Space. ICH Q8 defines Design Space as “the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.” It is important to establish Design Space because any changes made within the designated Design Space are not considered to be a change. Establishing Design Space provides a level of confidence in the manufacturing process and provides assurance that the finished product will have the expected CQAs. With these concepts in mind, the six considerations for utilizing QbD into stability studies ensue.

1. Product Development

Stability testing places a key role in product development. It provides data to establish shelf-life, information about related compounds, and information about the compatibility and the ability of the container system to protect the product from potential sources of degradation.

Stability testing supports the CQAs that were identified at product conception. Stress testing of the product prior to starting stability testing is used to identify the degradation products so that appropriate testing is done during stability studies.

2. Better Science for Better Quality

You should know the characteristics (e.g., hydroscopic, light sensitive) of the ingredients in your product. Use this knowledge to create experiments that will establish the limits of your design space.

Predicting expiry through sound statistical analysis based on stability data is another way to use better science and incorporate QbD into the product development process. Statistical analysis will produce a more accurate and reliable prediction of performance throughout life cycle of the product.

One common statistical technique is the use of the Arrhenius Equation to predict shelf-life. The Arrhenius Plot will determine the rate a product degrades based on time and temperature. Statistical analysis is useful throughout the product's lifecycle; it can be used in development to determine shelf-life or used with a mature product to determine the effects of ingredient or process changes.

3. R&D Stability Studies

Early stage stability studies can be developed to provide information for clinical studies. Through assay and dissolution profiles, the best prototype can be selected to succeed in clinical trials. Thus, a QbD approach can be beneficial during the R&D stage of a project. You should determine the CQAs—Does heat cause the product to degrade? By pushing the product to the limit, you know what range is safe and then use that knowledge to create your design space. The data obtained from studies that stress the critical to quality traits can provide important storage information to be included on the label or insert.

During R&D stability studies, you must not forget to about products or APIs that may be light sensitive. The following three components comprise photostability testing:

- Forced Degradation Studies: Drug substance alone or solutions/suspensions, in transparent containers; end when degradation occurs.
- Confirmatory studies: Done to verify the degradation point identifies in forced degradation studies.
- Drug Product Testing: Test in intermediate pack and marketing pack; done sequentially until protection from light is demonstrated.

4. Proposed Commercial Stability Studies

First, one must ask the question: Is QbD needed for proposed commercial studies? While QbD is useful in the development stage, specific QbD steps are not necessarily needed for creating the proposed commercial stability protocol. The knowledge gained from creating the design space in development can be used to support the proposed commercial stability protocol. By taking the time to learn the characteristics of the drug substance and how all ingredients work together, a realistic protocol and proposed shelf-life can be used in the submission.

However, any data from accelerated R&D studies needs to be backed up with data from long-term room temperature studies. Statistical calculations and extrapolation may be used for proposed shelf-life, but the room temperature data must support any accelerated study data.

Some companies opt for setting expiration dating at a specified period for all products and adjusting, as necessary, as data is obtained from long-term room temperature studies. If the R&D stability studies were done using QbD, keeping the CQAs in mind, a realistic expiry can be proposed on a product-by-product basis.

5. Lifecycle Approach

Why is it necessary to consider the product's lifecycle when creating stability studies? Reasonably, it is

likely that changes in the process or the ingredients will take place over the lifetime of the product.

The first thing to consider is whether the changes go beyond the established design space. Once again, changes within the design space have already been justified and are not considered to be changes.

It is possible that there may be unanticipated changes in the processing equipment or in the process itself. It is also possible that some materials will no longer be manufactured or some vendors will go out of business. Any of these changes could occur resulting in new validation and stability studies. QbD and potential reestablishment of the design space should be kept in mind.

6. Benefits of Using QbD in Stability Testing

QbD is used in formulation and product development; so what is the benefit to using it specifically in stability studies? Using QbD-based stability studies has the following benefits:

- Valuable knowledge about the product, thereby helping establish reasonable specifications and expiry, is gained.
- Some changes to the product or process may be made based on results of R&D studies, saving time and money once the product goes to market.
- The greater product knowledge helps reduce impact of raw material variability.
- There is faster and more efficient process scale up through knowledge gained from stability testing.
- Creation of a more robust product by highlighting vulnerable areas at a point in the lifecycle where it is possible to optimize relatively easily.
- If the use of QbD in product development is extended to stability studies, better product stability could result.
    - Knowledge gained about the way ingredients perform together can be confirmed with stability studies.

Tags:
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