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KNOW YOUR LIMITS

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About The Author

Roy has over 25 years of experience in technology transfer, process development, scale-up, and validation. His expertise includes factorial experimental design (DOE) and response surface modeling (RSM) used to identify and optimize critical processing parameters. He works with clients to investigate and troubleshoot formulation stability failures, trend analysis, and deviations in manufacturing processes. Roy ensures cGMP compliance for all finished dosage form clinical trial materials and the preparation of CMC documentation and development reports for regulatory submissions.

In order to maintain product consistency, Drug Products are formulated and manufactured within specified acceptable ranges. The establishment of consistent formulation specifications and manufacturing processes is essential to keep the drug development process moving forward smoothly. But frequently these ranges are established early in development, based on small-scale batches that produced
acceptable results. These ranges are then often carried forward without rigorous challenge.

Serious problems can arise if all points within the range are not sufficiently tested. Increased batch sizes and manufacturing scale-up make it unlikely that every batch will be manufactured under exactly the same conditions. Determining fail points allows for the proper setting of critical process variables and formulation specifications. Failure to determine whether the established ranges are correct becomes increasingly problematic as the Drug Product gets closer to process validation and New Drug Application (NDA) filing.

The following scenarios illustrate the critical importance of fully investigating the entire acceptable range of process and formulation variables:

Heating
Example 1. A process has an established temperature range of 15 to 25°C in an unjacketed vessel. All batches were manufactured at 20 to 22°C. During a preapproval inspection, you are asked what happens to the batch when it is manufactured at 15°C? Sponsors need to demonstrate that critical product attributes are not affected by process variability within the specification limits.
Example 2. Temperature control is lost during manufacture and the batch temperature exceeds the specified range by 1°C. Does the batch need to be rejected? Developing data demonstrating that small deviations outside the specification ranges do not adversely impact product quality can reduce the cost and long-term risk of batch failure.

pH
Similarly, what happens to stability when a batch is manufactured at the lower limit of the formulation's specified pH range? Will the drug product remain within pH specification through the shelf life of the batch? Will the drug product have the same stability profile as a batch manufactured at the middle of the pH specification? Rigorous testing of specification ranges should occur before process validation

About DS Inpharmatics

DSI is a full-service CMC Drug Development and Regulatory Affairs consulting firm combining in-depth technical knowledge of product development with regulatory strategy and content authoring for all phases of the review and approval process in the U.S., Canada, and Europe.

Our group practice is composed of pharmaceutical scientists with decades of drug development experience in each subdiscipline of Chemistry, Manufacturing, and Controls. Whether your needs are comprehensive or tightly focused, DSI will help you keep your drug development program on track and under budget.

Not just advice. DSI provides you with flexible scientific resources to fill in-house expertise gaps and expanded operational capability to design and implement compliant drug development programs.

How to Establish Limits

The simplest way to establish formulation specifications such as pH, drug concentration, etc. is to manufacture batches at the extremes of the established or proposed limits and place the batches on stability. However, this is probably no the best way to establish manufacturing process variable limits where there are likely to be multiple critical process variables (e.g. temperature, mixing time) that could interact. To establish these processing ranges it's preferable to use experimental design. Experimental designs can help identify critical process variables and interactions between process variables, as well as eliminating non-critical process variables.

Experimental designs provide the best information if there are significant changes that result from changing the process variables. Performing experimental designs that show no change may establish working ranges (design space) but will not tell you how near or far the process is from a fail point. Keep in mind, it is always better to determine if a processing variable is at or just above a fail point before you begin routine manufacturing.

At some point during batch manufacturing, it is virtually inevitable that a deviation with respect to a process variable will occur. Investigating the deviation and verifying its significance will be easier if there is data to support the belief that processing outside the stated ranges can still result in an acceptable product. Such supporting data may save you from having to reject the batch.

Establish supportable limits for process variables to avoid delays in your development and approval process.

- Test limits at each extreme of the proposed range for each variable
- Use experimental design in the case of multiple critical process variables
- Include a safety buffer between outer limits of the range and fail points
- Investigate any deviations from the stated range to determine whether the resulting product may still be acceptable

Conclusion

Knowing where a process or formulation will fail allows you to set ranges or drug product specifications with a sufficient buffer from the fail point to ensure that all batched will be consistent. If a manufacturing deviation should occur, knowing where the batch or formulation fails will aid in the investigation to determine if the batch will be acceptable for release.

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