DSI INPHARMATICS

TIMING ANALYTICAL METHOD VALIDATION

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About The Author

With over 30 years of industry experience, Mr. Byrne is our most senior Analytical Services expert at DSI. Colman is technically proficient in all aspects of analytical services having spent years managing both contract laboratories and AR&D groups at pharma and biopharma companies. This includes both biologic large and synthetic small molecules, raw material release testing, HPLC, GC, and TOC testing, protein/peptide sequencing, API manufacturing processes, lipid-based product testing, and various forms of drug product testing, and support of combination products.

While there's no fixed timetable for performing method validations within the overall context of drug product development, circumstances dictate that certain points in the process may be better than others. So, what is the optimal time to perform method validation? No absolute answer is applicable in all cases, but there are a few logical parameters that can guide the timing of method validations.

Method validation could theoretically be done as early as the pre-Investigational New Drug (IND) or Phase I stage of development. Realistically, however, it's highly unlikely that sufficient data about the drug substance and drug product, their related substances and degradation pathways will be available at this early stage to make a final validation practical. The likelihood that a new degradant will be discovered during a stability study, that a process improvement will change the impurity profile or that the clinical data will cause the entire program to be abandoned or delayed is too high to justify the expense of performing full scale final method validations early in the development process.

Delaying validation towards the end of Phase III clinical trials may have the advantage of delaying significant financial expenditure until absolutely necessary or until methods are known to be in their absolute final format. However delayed validation runs the risk of inadequacies being discovered that require a new method to be developed and validated on a very short timeline. Similarly, poorly performed validations can mean the difference between success and failure. Delays in the filing and approval of a New Drug Application (NDA) mean revenues from a commercialized product are also delayed-a cost that can drastically outweigh that of performing the validation in the first place.

Method validation is best performed at the late Phase II/ early Phase III stage of product development. A useful rule of thumb is to complete critical method validations by the time of the manufacture and testing of the Active Pharmaceutical Ingredient (API) and drug product registration batches used to provide stability data for the final regulatory filing. By this stage, the manufacturing processes will be fairly well established, and changes rarely amount to more than minor tweaks to account for scale-up or post "design of experiment" study or process changes. Additionally, by this stage, some early product lots will likely be approaching multiple years of long term stability storage, minimizing the likelihood that any novel related substances will crop up in later batches. In the event that something does change, a brief supplemental validation is likely to be all that's necessary to complete the validation package for the method.

The precise determination of when validations should be performed depends on a multitude of factors the stability of the product; the complexity of the API molecule and the excipient matrix; and the potential for interactions between them.

About DS Inpharmatics

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The more stable and simple the molecule, the earlier that the necessary validations can be done without fear of new information arising that will change the requirements for the method. The choice of when to perform validations depends on the individual circumstances of the method. Start the validations too early and you may be forced into a longer and wider validation process as new information becomes available later. But wait too long and the scramble to catch up may tempt you to cut corners and cause even greater delays.

Citius, Altima, Fortius

The development of a validation study shouldn't be merely a "check the boxes" exercise that has to be completed. The true purpose of a validation study is to establish the acceptable operating range of a method as part of an ongoing monitoring process in order to ensure the highest possible product quality. The method development process should address all of the parameters required for validation. In addition, it must provide background information as to the range of conditions under which the method gives sufficiently accurate and precise data, along with the factors which affect those conditions. A validation study should be just the formal current Good Manufacturing Process (cGMP) means for proving what you already know.

The robustness parameter, while one of the least defined in the ICH guideline is one of the more critical sections of the validation.

It needs to be based on experimentally determined criteria, tested under normal conditions and with controlled modifications. The focus shouldn't simply be on meeting standard and arbitrarily selected criteria. Acceptance criteria must be appropriate for your assay as they will directly affect the quality of the data that it will routinely generate. Don't always assume a one size fits all approach works best.

Planning a series of analytical method validations for a regulatory filing requires careful forethought. A well designed method validation study should provide data:

- To assist in investigations of whether inadvertently modify conditions during routine testing still can provide valid data
- To establish the level of control required during task performance
- To determine the sensitivity of test data to message changes within a specific range

Validation is a living process. Suitability parameters in the precision of replicate preparations of sample should be routinely tracked in the validation study and the data augmented and updated using data from routine release and stability studies. The accumulated data can then be used in a predictive and preventative fashion to prevent problems such as impending column failure or injector malfunction before they occur; as well as investigating anomalous incidents that occur during routine testing.

The method development process requires widespread cooperation between many different groups. Product knowledge must be transferred to cleanly from manufacturing to analytical development to quality to regulatory affairs, throughout the product development process. This data may be about the API or drug product; the potential analytes or related substances; the desired analytical parameters and specifications; and how all of these factors may change and become more stringently controlled as the product gets closer to the final NDA or Common Technical Document (CTD) filing. It is essential for method development reports to thoroughly document the reasons why specific test parameters are required for the API or drug product, why specifications are set where they are in the rationale for selecting specific method conditions. It allows for the smooth transfer of the validated method between testing between testing laboratories.