CHAPTER 1

OVERVIEW OF METHODS VALIDATION

1.1 WHAT IS METHODS VALIDATION?

The FDA in its most recent publication, Guidance for Industry on Analytical Procedures and Methods Validation, states:

Methods validation is the process of demonstrating that analytical procedures are suitable for their intended use. The methods validation process for analytical procedures begins with the planned and systematic collection by the applicant of the validation data to support analytical procedures. [1]

What the FDA does not say is that the actual validation component of the methods validation process should be the culmination of a well-organized, well-planned, and systematically executed process that includes method development, prevalidation studies, and finally, methods validation itself. Gone are the days where one did methods development/validation concurrently. Validation is the end game where few surprises and deviations are expected. Validation is executed with a formal, approved and signed methods validation protocol in place which has been reviewed by the quality assurance (QA) unit. Validation is complete when you:

1. Demonstrate that you have met all the acceptance criteria.
2. Clearly document the results in a CGMP compliant fashion.

Validating Chromatographic Methods. By David M. Bliesner
Copyright © 2006 John Wiley & Sons, Inc.
Show how you met the acceptance criteria in a final methods validation report, including references to raw data, all of which have been reviewed and approved by the appropriate personnel including peers, management, and QA.

Some would even argue that the validation process is not complete until the methods are successfully transferred to their end-user laboratories. This sounds like a daunting task. And to be completely honest—it is. There is nothing trivial or easy about methods validation. It takes time, resources, and rarely goes as easy as you think it’s going to go. Methods validation is part science, part art, and a lot of bookkeeping and accounting. To be brutally honest, too few laboratories do a very good job executing all the components.

Due to the magnitude of the task, the time, and the perceived costs, many laboratories try to cut corners. At a minimum, this results in deviations from the protocol which no longer can be “arm waved” away. The FDA expects you to scientifically address failures as you would any other laboratory investigation. This takes more time and effort and often results in delays in the validation timeline. In the worst case, you end up validating a method that is transferred to quality control (QC) labs worldwide, and ends up being the root cause of untold laboratory investigations. It is hypothesized that many of the problems discovered during root-cause analysis of out-of-specification results (OOS) are a direct result of poorly or partially validated methods.

The sections that follow provide a road map and the tools to guide and assist you to properly and efficiently validate your chromatographic methods, ensuring your validated methods do not become the root cause of your future laboratory investigations.

1.2 STEPS IN THE CHROMATOGRAPHIC METHODS VALIDATION PROCESS

The process of validating chromatographic methods can be broken down into four steps. These steps include:

- 1. Method evaluation and further method development,
- 2. Final method development and trial methods validation,
- 3. Formal methods validation, and
- 4. Formal data review and report issuance.

Figure 1.1 graphically represents the process.
The estimates given in Figure 1.1 are only that—estimates. So many variables exist during methods validation that it makes it very difficult, if not impossible, to give an accurate prediction of the length of the validation project. There is an enduring myth in the pharmaceutical industry that it should only take six weeks to validate a method. The formal validation portion itself should only take about six weeks, but the preparation and documentation take significantly more time. Although it can be done, a complete validation, including proper data review and documentation, even for an established product with known properties, has not been satisfactorily completed in such a short time. Industry professionals believe that this is why there are so many bad methods in use today.

Details of the design and implementation for each step are described in the remaining sections of this guide. In addition, many of the tools, templates, and examples needed to complete methods validation are included in the

![FIGURE 1.1 Steps in the chromatographic methods validation process. Total time for method evaluation, validation, data/documentation review, and reporting is approximately 6 to 10 months.](image-url)
appendices. As many examples, based on real-world scenarios, as practical have been provided to give you a framework to validate your own methods. In particular, the following key elements which constitute a methods validation program have been provided:

- A template for a methods validation standard operation procedure (SOP) example
- A template for a standard test method example
- A template for a methods validation protocol example
- A template for a methods validation report example

Each template for these examples represents a significant body of knowledge and experience. It would require a substantial amount of your time to create these templates independently. Modify them and use them to best fit the practices within your organization.

1.3 HOW TO USE THIS GUIDE

Before proceeding, here are some suggestions on how to use this guide. Although this document is a practical guide, it is by no means a technical cookbook on how to validate an analytical method. This would be impossible since every method has its own unique idiosyncrasies. Therefore, it is recommended that you take the following approach to best apply this guide:

- Familiarize yourself with the standard methods validation terms listed in the glossary.
- Read and understand the guide section titled “Components of a methods validation.”
- Review the template for the methods validation SOP example.
- Review the template for the test method example.
- Review the template for the methods validation protocol example.
- Read the template for the methods validation report example.
- Read and understand the flowcharts and checklist related to methods validation in steps 1–4.
- Develop your own systems and templates by adapting the systems and templates presented in this guide to your laboratory as appropriate.
- Train your chemists on the systems.
- Implement your systems.
1.4 ADDITIONAL POINTS TO CONSIDER WHEN VALIDATING CHROMATOGRAPHIC METHODS

In addition to the nuts and bolts of methods validation, many soft skills exist that will improve your chances of success during validation. Therefore, as you apply this guide to methods validation in your own laboratory, please keep the following points in mind.

Do Not Underestimate the Value of Planning and Organization

Much of methods validation is bookkeeping—both figuratively and literally. Therefore, much of the success of methods validation is dependent upon the amount of effort and attention to detail made in steps 1 and 2. The framework of what constitutes a methods validation is predetermined by FDA, ICH, and current industry practice. Think systematically and work with the end in mind. Therefore, by prioritizing and planning your work carefully, allocating your resources efficiently, coupled with good supervision and communications, you will significantly enhance your chances of a positive and timely outcome.

Make It Simple, Keep It Simple and Remember Your End Users

Chromatographic methods are often developed and validated by analytical research-and-development scientists who are not the end users of the method. Because of this, end user requirements are often not taken into consideration, which may lead to an overly complex and scientifically elegant method that will be “thrown over the wall” to the quality control (QC) chemists during technology transfer. Despite the myth, QC chemists and technicians are usually technically sound and well educated. However, they often work in a pressure cooker environment where the complexity and nuances of a method will only make their life more difficult. They need to get product out the door, with minimal complications and effort. Therefore, methods should be made as simple and robust as possible, with the end user’s needs in mind.

QA Is Your Friend

It was once said the best quality assurance (QA) person is the one who eats his or her lunch alone because none of the chemists wants to talk with him or her. Unfortunately there is often an unhealthy tension that develops between QA and the lab. You should make every effort to reduce such tensions during the methods validation process. Remember, in the future your work will be reviewed cold, without coaching from you, by an FDA reviewer. Therefore, you need to develop and present a complete and accurate account of your work
which raises few questions. So look at QA as your first line of defense. If you can’t make them understand your work, how will the FDA understand it?

**Don’t Underestimate the Value of Experience**

As stated, no two methods validations are the same, but each is very similar. This means that someone somewhere has probably encountered the same problems you are encountering. As part of your step 1 planning or troubleshooting, consider who might have experience with your work or work that is similar to what you are doing. Look within your own organization at previous validations. Look to vendors outside your organization such as the API manufacturer, your reagent supplier, and your chromatographic equipment and material supplier. Go to the library, search the literature, and tap into your network within the industry. Chances are someone has an answer or even *the answer* to your question. Avoid the “not invented here syndrome.” Don’t fall in love with your own work and skills to the exclusion of other good ideas. Ph.D. level R&D scientists are particularly bad about this. Remember the goal and resist the temptation of creating another dissertation research project.

**Common Sense Is an Uncommon Virtue**

During the course of the validation process perform what we call periodic sanity checks. Stop and ask yourself: Do these results make sense? Does this solution to the problem make sense for my end users? Am I headed in the right direction? Don’t be shy about talking to your end users as well.

**Mistakes Are Made Under Pressure**

The validation of bad methods invariably comes by having to perform the validation under pressure. Again, this is why it’s so important to expend a significant effort on steps 1 and 2 of the validation process. When you get to month six and still don’t have a functional (let alone validated) method, pressure will make you get the methods out to your end users when they never should have made it out of your lab. People make mistakes, but people make more significant mistakes under pressure.

**Realize the Impact of Your Successes and Your Failures**

The lifetime of a validated chromatographic method can span decades. The method may be used in laboratories all over the world. The financial and resource usage impact of the method can be substantial. Keep this in mind as
you validate your methods. The rule is once the method is validated and
transferred, the chances of changing anything significantly with the method
are very limited. From a regulatory standpoint, this situation raises a signifi-
cant number of questions. From a practical standpoint, it costs too much and
takes away resources from the next project. Be mindful of these points and do
it right the first time. Remember:

Validating an analytical method may be the most important task you
will perform during your tenure with your company.