

ANALYTICAL TRAINING SOLUTIONS  
Premier Training for Analytical Chemists



## Principles of HPLC Validation

A short course in the systematic validation of HPLC methods



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## WHAT DOES IT COVER?

This class focuses on validating high-performance liquid chromatographic (HPLC) methods developed for the analysis of pharmaceutical drug substance (pure drugs), drug product (formulated drugs), impurities, and degradation products. It does not focus on bioanalytical methods (drugs in plasma or tissue) – for these, see additional material in Section 11 of LC-MS/MS for Chromatographers [[CLICK HERE>>](#)]. Although the focus is on pharmaceuticals, the principles apply for most quantitative HPLC methods, such as environmental or general chemical analyses.

## WHO SHOULD TAKE THIS COURSE?

This course is designed for laboratory personnel responsible for validating HPLC methods. It will also be useful for managers and quality assurance staff involved in the method validation process. For workers who develop, but do not validate methods, this class will give insight into how to develop methods that will be easier to validate. No prior experience is needed, although those with some laboratory experience will certainly benefit more than those with no experience at all.

## WHAT DO YOU GET?

You get full access to the 21 video modules and approximately 5.5 hours of instruction. You also get handouts containing copies of all of the approximately 250 PowerPoint slides used in the class. These are arranged for easy note-taking while you view each module and give you a valuable resource for future reference. Also included in the class is a brief review and references to documentation, both regulatory and general, that will help you through the validation process.

## PHILOSOPHY

Our philosophy is that the best approach to successful validation of chromatographic methods is to establish a system in advance of the project and follow it. There are many regulations written by the International Committee on Harmonization (ICH), the United States Food and Drug Administration (US-FDA), and the various national pharmacopoeial organizations (*USP, EP, BP, JP*). Although there are some specific requirements for validation included in these documents, there is much room for good scientific judgment, as well. For this reason, rather than just reading the regulations to you (which would be boring, and you need to do this yourself, anyway), we focus on the validation process – what should be included and why. We believe that a reliable HPLC method must be designed that way, paying attention to the results from the first injection during method development. This is the basis of Quality by Design (QbD), which is a central element of this class. We feel that we can best serve you by giving you a set of tools and an understanding on how to use them for validation, so that you can design your own unique validation process that fits the needs of your organization. Because each organization, and sometimes each method is different, we feel that it is unwise to try to give you a “one size fits all” formula for validating all methods. Rather we think of this more like giving you a toolbox full of tools so that you can pick out the right tools for each job.

## HOW IS IT ORGANIZED?

This is a unique web-based class. For convenient access and viewing, the course is split into 5 major sections and each of these sections is broken down into 3-5 modules, ranging from 7 to 25 min, with an average running time of 16 min. The 21 modules contain approximately 5.5 hours of comprehensive method validation information. We have divided the course into 5 sections that cover the main topics involved in the validation of pharmaceutical HPLC methods, specifically drug substance (the pure active ingredient) and drug product (the

formulated product sold to the consumer). We first introduce what validation is and some of the basic concepts (Section 1). Next, we consider the things that take place before validation, with a brief touch on method development, system suitability, and a discussion of why pre-validation is important and what should be included (Section 2). Section 3 covers the validation process itself, some of the regulations, and the all-important documentation process. Section 4 focuses on Quality by Design and robustness testing – two aspects of validation that pervade the process from method development through method application. This discussion includes examples of how QbD is implemented for real samples. We finish the class with a discussion about various aspects of data handling, integration, calibration, and method control (Section 5).

## ACCESS

We recommend that you watch the entire course, from beginning to end, at a pace that meets your schedule. This may mean a module a day or a marathon of all the modules in a single day. Because of the dense nature of the content, however, we suggest that you'll get the most out of the class if you spread the viewing over several days, rather than get through it in one sitting. Once you have taken the class, you'll find that the topical organization of the sections and sub-sections will allow you to go back and watch an individual module again as a review or to more fully understand a particular topic.

Here's what the course covers:

- What the steps are that need to be undertaken during validation
- Why quality is so important
- What basic chromatographic measurements will be used
- Why to approach validation as part of a larger process
- Which regulatory documents are important
- What parameters of the method need to be tested
- What are the different standardization techniques, and when are they used
- What is Quality by Design, and why is it important
- What software tools are available to simplify the process
- What pitfalls should be avoided in validation
- What is pre-validation, and why is it worth my time
- How do I choose a system suitability sample
- How can I tell if the method is out of control
- How much can I adjust a method before I have to re-validate

## WHAT WILL I GET FROM THIS COURSE?

You will understand how to organize a validation project. By planning ahead, you will see how to develop better methods that will validate more easily and will function more reliably in routine use. You will realize how by using Quality by Design principles during development, the methods will be easier to validate and be more robust in routine use. You will learn how to decide which variables are important and which ones are not. You will see how software tools can help you to get much more mileage out of your experimental runs. You will gain a better understanding of the calibration process and how to examine data for problems. Learn when method adjustments are allowed without re-validating the method. Find out why uncertainty plays such a big role in validation.

## INSTRUCTORS

The course was designed by John Dolan, Tom Jupille, and Lloyd Snyder. This class is taught by John Dolan, considered to be one of the world's experts in HPLC. He has written more than 350 user-oriented articles on HPLC troubleshooting over the last 30 years in addition to more than 100 peer-reviewed technical articles on HPLC and related techniques. His three books (co-authored with Lloyd Snyder), *Troubleshooting HPLC Systems*, *Introduction to Modern Liquid Chromatography* (3rd edn), and *High-Performance Gradient Elution*, are standard references on thousands of desks around the world. He also was intimately involved in the preparation of Snyder, Glajch, and Kirkland's *Practical HPLC Method Development* (2nd edn) book. John is the author of Separation Science's popular "HPLC Solutions" articles. From a validation standpoint, he directed LC Resources' Northwest Laboratory, a contract laboratory for the pharmaceutical industry, specializing in method development, validation, and application of HPLC methods for drug substance, drug product, and bioanalytical samples. He has taught HPLC training classes around the world to more than 10,000 students and has received the Palmer Award (Minnesota Chromatography Forum) and the Dal Nogare Award (Chromatography Forum of Delaware Valley). His casual style and ability to get information across in a practical and understandable manner make him in high demand as a training instructor and conference speaker.

## COURSE DETAIL

Below are listed each section and sub-section of the class. A brief summary of each section is given first. After the subsection in parentheses is the approximate running time of that module.

### Section 1. Introduction

We start by taking an overview of the validation process and review some of the key references that will be useful in setting up a validation process. We also discuss the terminology and some important measurements that will be encountered during validation.

- *Introduction & Resources (20 min)*
- *Steps in Validation (17 min)*
- *Quality (7 min)*
- *Chromatography Basics (17 min)*
- *Terminology (11 min)*

### Section 2. Method Development and Pre-Validation

The validation process is best started with the first injection during method development. We discuss the importance of having an overall plan for the method development / validation / method application life cycle. A brief overview of method development is given (see Advanced HPLC Method Development [[CLICK HERE>>](#)] for details on method development). The importance of pre-validation is emphasized along with key tests that should be undertaken. No method is complete without a well designed system suitability test, so we discuss what is appropriate for this.

- *The Plan (17 min)*
- *Pre-Validation (22 min)*
- *System Suitability (15 min)*

### Section 3. Validation and Documentation

In this section, we go through the various validation steps in detail. We review the key regulatory requirements from the International Committee on Harmonization (ICH), which also apply to the national pharmacopoeial organizations (*USP, EP, BP, JP*). To illustrate the outcome of validation, we review the results of a drug potency method validation and one for related substances.

- *The Validation Process (9 min)*
- *Regulatory Requirements – Part 1 (22 min)*
- *Regulatory Requirements – Part 2 (19 min)*
- *An Example (13 min)*

### Section 4. Quality by Design and Robustness

We introduce Quality by Design (QbD) as a laboratory lifestyle described in ICH Q8. QbD translates into more efficient method development, easier validation, more manageable methods in real applications, and higher quality data in the laboratory. We demonstrate QbD with two examples, one in the screening phase of method development, and one in the validation stage for a pharmaceutical product.

- *What is Quality by Design? (17 min)*
- *Example 1: QbD Screening Experiments (17 min)*
- *Example 2: QbD Robustness Testing (14 min)*
- *Example 3: Design of Experiments QbD Assessment (18 min)*

## Section 5. Data Analysis

This section covers various aspects of data analysis including how and when external standardization, internal standardization, and the method of standard additions should be used for calibration. We consider how to properly measure peaks and how to evaluate the quality of the data gathered. Control charts are not often used in the analytical laboratory, but we consider how they may provide an additional degree of method control – from data you are gathering anyway. Finally we consider how much a method can be adjusted before it must be re-validated.

- *Quantitative Analysis – External Standardization (12 min)*
- *Other Standardization Techniques (15 min)*
- *Evaluating Data Quality (16 min)*
- *Integration & Peak Measurement (17 min)*
- *Control Charts & Method Adjustment (25 min)*