Method Development and Validation Sessions – Abstracts

HPLC and UHPLC Method Development 1: Overview, Traditional Approaches, and Tools
Michael Dong, MWD Consulting

This presentation is the first segment of a two-series seminars on HPLC method development in pharmaceutical analysis focusing on stability-indicating assays of small molecule drugs. The presentation starts with an overview of the fundamentals, regulatory requirements, and modern trends in this method development process including the rationales for using gradient reversed-phase chromatography (RPC) with UV detection and the role of UHPLC in expediting this arduous process.

The presentation describes a 5-step traditional method development strategy proposed by Snyder et al. based on a process of selectivity tuning in the separation of critical pairs of close-eluting solutes of the sample. Other common techniques and automation tools discussed include the use of forced degradation studies to confirm method specificity, automation column/mobile phase screening systems and software tools such as DryLab and S-Matrix's Fusion QbD. Case studies of method development of new chemical entities (NCEs) are used to illustrate the benefits and utility of these tools.

HPLC and UHPLC Method Development 2: Easier Approaches for Early-Phase Methods
Michael Dong, MWD Consulting

This presentation is the second part of the series, which describes two easier approaches for the rapid development of early-phase analytical procedures for NCEs (drug substances and products) using HPLC with UV detection.

The first is a three-pronged template approach for rapid method development. The method templates are:

1. Fast LC isocratic methods for potency or performance assessment (< 2min/sample).
2. A generic broad-gradient method(s) for purity assessments of raw materials, starting materials, critical reagents, and simpler NCEs.
3. Multi-segment gradient methods for ICH-compliant stability-indicating assays of complex molecules.

Case studies include complex drug molecules with multiple chiral centers and drug products with several active ingredients.

The second approach is the introduction of a modernized universal generic gradient RPC method(s), capable of peak capacities of 100-300 in 2 to 6 minutes. Rationales on the selection

of optimum column and operating conditions are discussed together with adjustment procedure to customize the standard generic method for stability-indicating applications by the alternation of the gradient profiles. Case studies include methods for cleaning verification of multiple NCEs and stability-indicating assays of complex drug candidates.

Analytical Quality by Design; aQbD for Analytical Methods
Jane Weitzel, Independent Consultant

The analytical Quality by Design (aQbD) focuses on the lifecycle approach to analytical procedures. With this approach the use of the reportable value is first defined. Then an analytical procedure can be designed for that use. With aQbD the focus is on the suitability of the reportable value for its use, for the decisions that will be made using it. This ensures adequate quality is built into the analytical procedure.

The design begins with an understanding of the use of the reportable value. This can be done by creating a decision rule. Next what is being measured, the measurand, is clearly defined. This information allows the Analytical Target Profile (ATP) to be defined. The method can be selected and the analytical procedure designed, developed, and validated based on the ATP. A brief example will be presented to illustrate the process.

Forced Degradation Studies
Geoff Carr, Patheon by Thermo Fisher Scientific (Ontario)

Forced degradation studies are very important in order to demonstrate that the analytical test methods that are being applied to stability samples are really capable of detecting any chemical degradations in the products being studied ie to answer the question of whether test methods are stability indicating. There are regulatory requirements for conducting these studies that will be reviewed but the importance of understanding and applying principles of chemistry are particularly important here. The presentation will then discuss practical approaches for stressing and testing pharmaceutical materials in these studies and how to process the data generated.

HPLC Method Validation: Overview, Methodologies, and Case Studies
Michael Dong, MWD Consulting

This seminar provides an overview of the regulatory requirements, performance parameters, and methodologies used in HPLC method validation studies. Case studies include several validation studies for early- and late-phase stability-indicating HPLC methods of NCEs.

The phase-appropriate method development and validation is the term of a strategy proposed by Rasmussen et al. that is intended to accommodate the rapidly-evolving process changes by the development of a primary and a secondary method. A method robustness case study using a Design of Experiment (DoE) approach is also described.

Uncertainty and Statistics for Method Validation
Jane Weitzel, Independent Consultant

The Lifecycle approach to analytical procedures and analytical Quality by Design provide the information on how "good" a reportable value needs to be. The target measurement uncertainty is known. The acceptable probability of being wrong is decided. These provide the acceptance criteria for the experiments performed during method validation.

This talk will present various experimental designs that are commonly used in method validations. The statistical tools, such as tolerance intervals and ANOVA, will be presented. A brief example will demonstrate these experiments and the statistical tools. The emphasis will be on the statistical tools presented in the new USP General Chapter <1210> *Statistical Tools for Procedure Validation*.