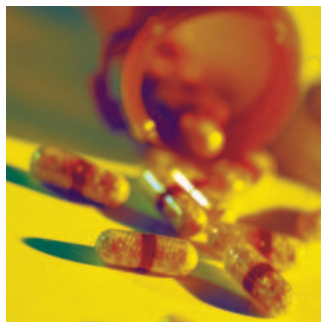


# Developing and Using Analytical Methods to Achieve Quality by Design and Efficiency in Drug Development

Bernard A. Olsen



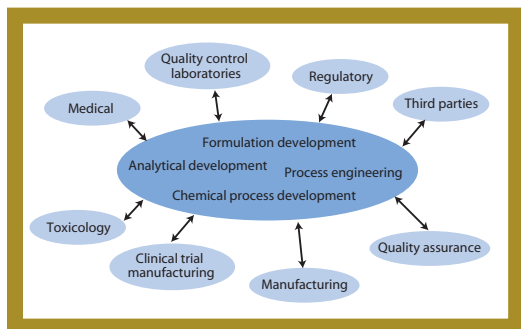
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The author describes strategies for **analytical method development** that are **helpful** in achieving **quality by design** and **efficiency**.

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**A**nalytical method development is a critical part of the drug development process. Analytical methods are used to check the quality of materials that will be used in clinical trials. As drug development progresses toward registration, these and other methods are used to generate information that will enable quality to be designed into the manufacturing processes of drug substances and formulated drug products. This practice can lead to a detailed understanding of production processes and the development of control mechanisms that will ensure product quality.

Effective method development does not occur in a vacuum. Analytical scientists must interact with process chemists, pharmaceutical scientists, and process engineers (see Figure 1). The information needs of these development partners must be well understood to design appropriate methods for the intended use. Other key functions include quality assurance, regulatory, toxicology, medical, quality control, and large- and small-scale manufacturing.



**Figure 1:** Key analytical development partners and functional area interactions.

Method development activities must be appropriate for the stage of the overall drug development process. The development and use of analytical methods evolve from generating information about a manufacturing process and product to using the methods for monitoring and controlling parameters that are critical to a drug's quality. Ever increasing demands for efficiency and productivity require a careful focus on the value of information that is generated at various stages. For example, extensive method validation studies are not needed while the drug substance synthesis or the drug product formulation are still being defined.

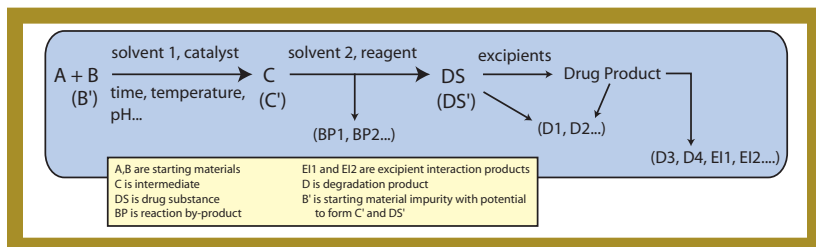
This article describes considerations for analytical method development that may help achieve quality-by-design and efficiency. General strategies are discussed, rather than the details of specific techniques. Areas in which the methods are applied such as impurity investigations, process monitoring, and physical property investigation are addressed. The development of specifications, of

which methods are a key component, also are discussed. Though the discussion focuses on synthetic compound development, many aspects can be applied to biosynthetic products.

### Approaches to method development: impurities

The control of impurities in drug substances and products is a major part of drug development. Analytical methods are needed to determine which of the many possible impurities throughout the manufacturing process are important and to establish appropriate control mechanisms for them. A general example of a process to produce a drug substance and drug product is shown in Figure 2. Starting materials, intermediates, reagents, solvents, and catalysts are obvious potential process-related impurities that could appear in the drug substance. Other impurities can originate from starting materials or be formed as reaction by-products in the synthesis. Once formed, the drug substance may degrade to form degradation-related impurities. The drug product also may degrade to the same, or perhaps different, impurities. Impurities derived from interactions with excipients in the drug product also must be taken into account.

All components other than the drug substance and drug product ingredients are potential impurities that must be investigated. The goal of



**Figure 2:** A hypothetical manufacturing process with potential impurities.

impurity investigations is to determine the origin and fate of impurities so as to have well-understood process controls, storage conditions, and specifications to ensure that impurities do not exceed acceptable levels. The investigations also help rule out hypothetical impurities that are absent or insignificant.

**Screening methods.** A variety of analytical methods are needed to investigate impurities. High-performance liquid chromatography (HPLC) is the workhorse technique for this purpose. Scientists frequently use a broad-scope screening method to detect as many impurities as possible. Gradient HPLC over a wide polarity range is a typical starting point that will provide retention for polar impurities, separation of structurally similar compounds, and elution of nonpolar impurities. For process-related impurities, initial optimization with intermediates and starting materials can provide a basis for a selective method that has a good probability of separating unknown impurities. Access to samples of other predicted impurities such as isomers and by-products also helps in the development of selective methods. As will be described later in this article,

stress testing is needed to develop stability-indicating methods.

Although ultraviolet (UV) detection is used whenever possible, HPLC conditions that are compatible with detection by mass spectroscopy (MS) are very useful in discovering and identifying unknown impurities. Evaporative light-scattering, electrochemical, chemiluminescent nitrogen, and refractive index detection modes are sometimes needed depending on a given compound's properties.

Orthogonal separation techniques such as capillary electrophoresis, gas chromatography, or thin-layer chromatography often are used to supplement the primary screening method or to confirm that the primary method has not missed anything. Alternative HPLC conditions with various stationary and/or mobile phases can be used for this purpose. Peak purity algorithms to evaluate the coelution of impurities with the main component or with each other also can be used to increase confidence in a screening method's selectivity. The effort investment in developing orthogonal methods must be balanced with the information that can be gained. The timing for such effort can

depend on the particular compound and practices of a given firm.

**Targeted methods.** Despite the usefulness of general screening methods, they usually are not capable of detecting all impurities of interest in a drug substance or drug product. In these cases, a method targeted for a specific impurity usually is needed. The determination of the minor enantiomer of a chiral drug with a chiral method is a clear example of this situation. Additional examples in which targeted methods are needed include the determination of metallic catalysts, residual solvents, genotoxic impurities at trace levels, and other known impurities not separated or detected by general screening methods.

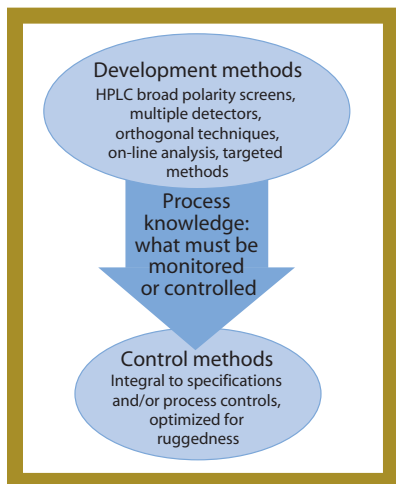
**Stability-indicating methods.** Stress testing is a key part of stability-indicating methods development. In these studies, the drug substance typically is subjected to a range of heat, humidity, acid, base, light, and oxidative conditions to gain information about the molecule's intrinsic stability, to identify degradation products, to elucidate degradation mechanisms, and to establish the analytical methods' ability to detect degradation impurities. Stress studies also are performed on drug products to check for the presence of various degradation products or impurities formed by excipient reactions.

In addition to facilitating method development, information from stress testing studies can guide formulation design and decisions about handling, packaging, and storage conditions. Broad-scope screening

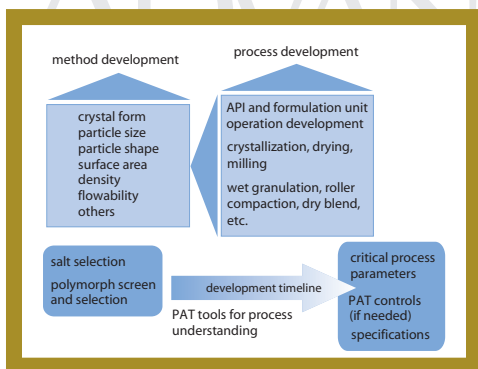
methods similar to those used to investigate process-related impurities are appropriate for initial degradation studies. These methods can be used to identify which degradation products can form under conditions that are usually much more extreme than typical storage conditions.

Stress degradation studies also can be staged according to the development phase. As a new drug candidate progresses, more-detailed information about its stability characteristics is needed. For example, the complete structure elucidation of degradation products may be delayed until a formulation is finalized. The timing and extent of stress studies conducted by various researchers have been summarized by Alsante *et al.* (1).

**Process monitoring.** On-line analytical measurements can provide detailed process information that can lead to the development of more-robust processing conditions. Synthetic reactions can be monitored with on-line Fourier transform infrared (FT-IR) spectroscopy, UV, HPLC, MS, and other techniques to provide information about reaction kinetics, reactive intermediates, and reaction completeness. Blending or drying operations can be monitored by near-infrared (NIR) spectroscopy, FT-IR, and Raman spectroscopy as well as thermal effusivity, acoustic spectroscopy, and other methods. Developing process knowledge using on-line techniques at the laboratory and pilot scales can help evaluate the consistency of scaled-up processes and reveal which operations will require rou-



**Figure 3:** Progression of methods from use in development investigations to use for long-term control.



**Figure 4:** Physical property investigations.

tine monitoring to achieve good process control.

As development progresses, information from screening methods, targeted methods, and on-line analysis is used to determine which of many possible impurities, degradation products, and reaction control points are significant (see Figure 3). Analysis of laboratory, scale-up, and stability samples can be used to

rule out hypothetical impurities by showing that they are not formed or that process impurities are effectively removed at a given step.

Degradation products observed under stress conditions may not be observed under actual storage conditions and can be ruled out as significant. Methods then can be focused on impurities that are likely to be present and optimized for robust and efficient use in a quality control laboratory.

### Physical property investigations

Measurement technology also is needed to conduct physical property investigations. The types of investigations needed during drug development are depicted in Figure 4. A salt screen is performed initially to choose the desired candidate to bring into development. Studies then are performed to identify crystal forms of the drug and, if different polymorphs are found, to choose the desired one (usually the most thermodynamically stable form). X-ray diffraction, Raman, thermal analysis, and solid-state nuclear magnetic resonance are commonly used for these studies (2).

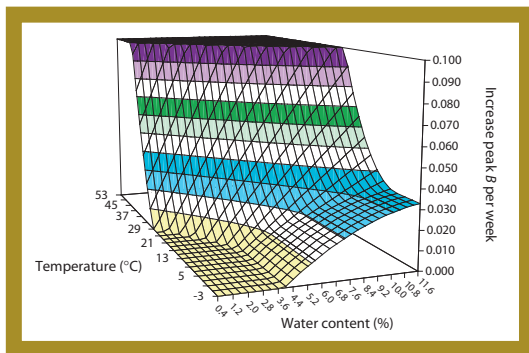
In addition to crystal form, other properties of the drug substance such as particle size, shape, surface area, density, and flowability are often measured. These properties can affect a drug product's bioavailability, dissolution, and stability. A

discriminating dissolution method can indicate process consistency and can sometimes be correlated to bioavailability.

Physical properties also can affect downstream unit operations in a manufacturing process. Drug substance flowability may affect a blending operation in the formulation process, for example. Drug substance particle size generated from crystallization might affect the particle size produced from a subsequent milling operation. Therefore, development methods for physical properties are important for investigating the unit operations that impart a given property as well as operations that are affected by that property. As with synthetic steps, on-line measurements can be useful in studying physical properties. Crystallizations and some milling operations can be monitored using a variety of techniques including FT-IR, Raman, UV, turbidity, reflectance, laser diffraction, and image analysis. NIR spectroscopy has gained popularity for monitoring blending operations in formulation processes.

### Predictive models

Development methods can be used during laboratory studies to generate predictive models of processes that will aid in scale-up efforts. This level of process understanding can help build quality into a product by



**Figure 5:** Example of stability information gained by application of design of experiments.

designing a process that will operate well within the ranges of parameters that will provide predictable quality.

Statistically designed experimentation, sometimes referred to as design of experiments (DOE), is a valuable tool for developing process models. Screening experiments such as Plackett-Burman designs can be efficient means of identifying which experimental parameters have a significant effect on desired responses. These parameters then can be optimized with various factorial design and response surface studies (3, 4). The sensitivity of the response to changes in the operating parameter can be determined to define process robustness. In that way, overly sensitive processes or those beyond the capability of the equipment to control can be avoided.

Statistically designed experiments also can be applied to analytical method optimization and validation. If the method is being designed for long-term use, its robustness with regard to changes in operating variables is an important consideration.

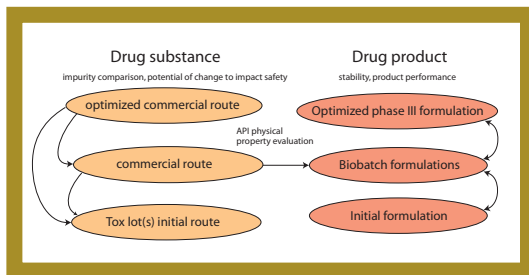
Efficiency in investigating a broad

experimental space can be gained with DOE studies. Figure 5 shows data from a study in which the degradation of a compound over a fairly broad range of water content and temperature were examined. The data, which showed the region of water and temperature that minimize degradation, were used to control the drying and storage of the drug. A nonstatistical approach would require more resources to generate the the stability information.

### Specification development

The development and evolution of specifications have been discussed previously, primarily because tests, analytical procedures, and acceptance criteria comprise specifications (5). During a drug product's early development, specifications focus on the safety of the drug for use in clinical trials. Control limits for impurities based on the quality of materials used in toxicological studies and the known toxicities of impurities such as residual solvents and catalysts can be used for early-phase clinical trial materials.

As development progresses, specifications will become increasingly based on batch histories, process capability, analytical capability, and stability (5). Changes in manufacturing processes must be well documented and connected in a so-called *line of sight* over the course of devel-



**Figure 6:** A line of sight for clinical trial materials used in drug development.

opment (see Figure 6). Impurity profile comparisons for the drug substance are made among batches used in toxicology studies and subsequent batches, especially when a process change has occurred. The potential for changes in the process and/or impurity profiles to affect safety is evaluated. For the drug product, the appropriate bridging of safety and efficacy must be considered. Pivotal studies will form the basis for drug product approval, so the effects of formulation and process changes must be considered to make valid conclusions about whether the registered product reflects the quality of the product used during those studies.

Likewise, analytical methods evolve during development and change as the synthetic process and the formulation change. As previously discussed, the methods also may change as knowledge is gained about what is important to control in terms of impurities, physical properties, and drug product performance characteristics. When setting specifications, it is necessary to understand the effect that method changes may



have on the comparability of results. This process will help determine how batch data collected with various methods should be used in setting specifications.

Specification acceptance criteria also should accommodate a reasonable range of expected analytical and manufacturing variability. In addition to batch history data, results of development studies such as the DOE studies described previously can be used to determine expected variability. Studies that incorporate variability from starting materials, excipients, and equipment capability can provide a very realistic understanding of quality that can be expected over a time frame of several years.

The potential to use interim acceptance criteria, sunset testing, and periodic quality-indicator tests can accelerate development and increase efficiency in future production (5–7). Interim acceptance criteria may be appropriate when limited full-scale manufacturing experience is available at registration and the use of a statistical approach for setting acceptance limits is not justified. Adjustments can be made within safety and efficacy limits when sufficient experience is gained to represent reasonable manufacturing variability. Sunset testing provides the option of discontinuing tests after sufficient data are generated to show the test is no longer needed. Periodic quality-indicator tests performed on batches at designated intervals can be used if it is desirable to show that a given attrib-

ute remains under control but data indicate that testing every batch is unnecessary. Process analytical technology measurements that are predictive of product quality may also offer the opportunity for decreased end-product testing. The options related to specifications are usually applied after approval but can influence the development of specifications during clinical trials.

### Technology development

Several technological advances have affected analytical scientists' ability to be more productive in terms of the quality and quantity of information generated. Despite the relative maturity of the field, new developments in liquid chromatography and other separation techniques continue to be made (8). In many cases, analysis time can be reduced dramatically using fast HPLC techniques that incorporate monolithic and short microparticulate columns (<2  $\mu\text{m}$  particles). Columns and instruments that can accommodate higher flow rates, temperatures, and pressures can offer faster run times often without sacrificing much resolution.

New stationary phases designed for polar-molecule separations or operation at high-pH levels provide increased options for selectivity optimization. Parallel separations by means of narrow small-particle columns or microfluidic devices can provide high-sample throughput for certain applications. Automated routines for screening separation variables such as column, mobile phase pH, and organic solvent can



increase the efficiency of method development.

Advances in MS and nuclear magnetic resonance detection for HPLC have improved capabilities for both quantitative and qualitative analysis. Various spectroscopic techniques applied in off- or on-line modes are improved tools for gaining process knowledge. Raman, NIR, FT-IR, MS, microscopy, image analysis, and other techniques are being adapted to solve pharmaceutical problems such as component distribution within a tablet and blend uniformity as well as correlations with other product characteristics. Multivariate data analysis techniques such as partial least-squares calibration and principal components analysis can provide information not obtainable with a univariate approach.

## Conclusion

The need for increased efficiency and information coupled with situations involving novel dosage forms, high-potency (low-dose) drugs, low-solubility drugs, or complex synthetic molecules and processes provide increasing challenges to analytical chemists and development partners. Continued advances in measurement technology and a regulatory climate that values detailed process knowledge and improvement will help address those challenges.

Performing analytical investigations at the appropriate time in the development process is still an important consideration, given the attrition rate of drug candidates. But a well-designed development pro-

gram can achieve quality by design and overall efficiency for drug candidates that proceed to registration and approval.

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