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# Current Practices of Process Validation for Drug Substances and Intermediates

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**Abstract:**

**Process validation includes laboratory optimization, pilot-plant introduction, and process implementation on manufacturing scale, as well as monitoring batches after implementation and continuously improving the manufacturing processes. There are many opportunities to change and optimize operations. The background information in this contribution describes current guidance and terminology for validation, including the integration of validation over the development lifecycle of drug substances. Various examples illustrate challenges and success stories of implementation as part of the overall approach to process validation.**

## Introduction

Creating and implementing processes for the routine manufacture of active pharmaceutical ingredients (APIs) is one of the many roles enjoyed by organic chemists and chemical engineers in drug development. These processes must perform in a manner that is safe, economical, and ideally environmentally benign. For approval to sell medicines for human use, the FDA, EMA, and other global regulatory agencies require that safe, high-quality drug substances and drug products be reliably produced in the equipment to be used for routine manufacturing. The cumulative efforts to demonstrate reliable processing and product quality are termed process validation. Benefits of successful process validation for pharmaceutical companies include not only permission to sell drug products but also improved productivity; examples include fewer rejected batches due to poor output quality, decreased cycle times, and possibly decreased inventories due to more reliable processing and delivery of acceptable batches. In addition to demonstrating the reliability of existing processes, process validation permits change to be introduced in a controlled manner that is compatible with continuous improvement.

Some people have viewed the time and paperwork required for process validation as a burden, but inadequate validation efforts can preclude the ability to sell a drug product. Failing preapproval inspections can delay the launch of a new drug product and greatly diminish revenue over the lifetime of a drug.[2] Not uncommonly a batch of API is valued at millions of dollars, so rejecting a batch due to poor quality or uncontrolled processing can be costly. The FDA's power in overseeing operations has been demonstrated by the suspended sales of a company's drug products due to substandard quality control.[3] Uncontrolled drug quality not only poses a moral issue regarding the welfare of patients, and but also can taint corporate reputations. The reasons to pursue thorough process validation are compelling.

Process implementation and validation are also the fruition of the labor of process chemists and engineers, the ultimate tests of how well one understands a process. Chemists and engineers who have been trained in the basic precepts of thorough scientific investigations, which are the foundations of process validation, often find process validation to be both satisfying and rewarding. Most process scientists eagerly look forward to process implementation and validation as opportunities to advance their knowledge of process operations.

**Brief History of Validation.** Validation was initially applied to assaying drug products, such as ampules of sterile formulations or batches of tablets, to ensure the safety of patients. Key questions included where and how to derive statistically significant samples, and how to assess uniformity within a pill, within a bottle, and within a batch. To ensure reliable results, validating the associated analytical methods for analyses of drug products became necessary. Later, validation was required for processes to prepare APIs and intermediates, by recording compliance of batch operating parameters within specified limits and by subjecting the batch outputs to various pass/fail analyses by Quality Control departments operating independently of their manufacturing counterparts.[4]

Before the 1970s most pharmaceutical companies paid relatively little attention to efficient process development. Scale-ups from the laboratory were often based on lore, with experiences sometimes communicated only verbally. Through reactions on a larger scale, often kilograms, the different mass transfer and heat transfer rates exposed limits underlying seemingly straightforward operations. Subsequent development studies were employed to identify key variables and ranges, and design of experiment studies (DoE) were sometimes carried out to understand the effects of parameters and their possible interactions.

Historically, process control has been achieved by sampling process streams and performing analyses "off-line"; one ex-

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(1) NGA presented excerpts of this material in 2007 at the AMRI Process Chemistry Symposium and the Cambridge HealthTech Institute Symposium, Mastering Process Chemistry. The material has been updated to reflect current regulatory guidance on process validation.

(2) A six-month delay in introducing a drug may reduce profits by 50% over the lifetime of a drug. Ritter, S. K. *Chem. Eng. News* **2002**, *80* (47), 19.

(3) Erickson, B. E. *Chem. Eng. News* **2009**, *87* (9), 30.

(4) Repic, O. *Principles of Process Research and Chemical Development in the Pharmaceutical Industry*; Wiley: New York, 1998; pp 179–94.


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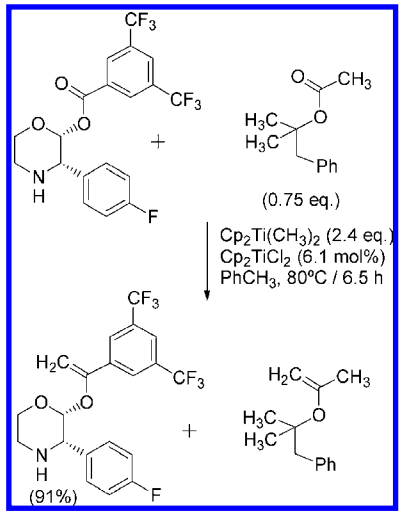
***Scheme 1.*** **Introducing a scavenging substrate to ensure high yields on scale**




ample is monitoring for reaction completion by withdrawing a sample from a process stream, quenching it, and analyzing it by HPLC. Although this approach usually provides consistent analyses during laboratory optimization, the extended times involved in withdrawing a sample from pilot-plant equipment and walking it to the lab for sample preparation can create artifacts in the data. Extended times for off-line assays can also allow significant decomposition of the product within process equipment; to avoid significant degradation of the product enol ether while waiting for in-process analyses, Merck scientists charged a secondary substrate with the starting material to scavenge excess dimethyltitanocene (Scheme 1).[5] The current emphasis on real-time monitoring (see below) affords opportunities for improved control of processing.

To validate manufacturing operations in stationary equipment three sequential, problem-free batches were traditionally considered necessary for validation. Prior to these runs, true "engineering batches" might be carried out, which were essentially one or more large-scale experiments to familiarize personnel with process operations in that equipment and to demonstrate the suitability of the latter for the proposed manufacturing process. Data from subsequent routine manufacturing batches were gathered to monitor and further optimize operations. If the descriptions of the batches filed with regulatory authorities were somewhat general, optimization of routine manufacturing operations was possible within the described conditions. (For example, "Acidify with aq HCl" permits variability in the concentration of HCl charged.)

Until recently the foundation of validation efforts was the FDA's 1987 "Guideline on General Principles of Process Validation."[6] Validation was defined as "establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes", such as potency, residual moisture, and residue on ignition. Recently this approval process has been regarded as testing quality into a product (see below).

The expense of validation and the negative consequences of validation failure can deter innovation in process development and subsequent manufacturing practice. In some cases continuing to use familiar but suboptimal processes was considered safer than introducing an innovative improvement and risking validation failure. Partially due to this reluctance to innovate, the pharmaceutical industry has sometimes lagged behind other industries in adopting new technologies, and such attitudes may contribute to the high cost of many APIs.[7] Current drives to economize have encouraged deeper understanding of processes[8] and promoted process innovations such as continuous processing,[9,10] and by using validation guidelines to optimize operations it may be possible to decrease the cost of APIs.

**Current Focus of Validation Efforts: Process Understanding.** In November 2008 the FDA issued new draft guidelines on process validation, stating that "process validation is the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products." These guidelines emphasize that quality is built into the product through process understanding and cannot be tested into batches.[11−13] Quality by design (QbD) and control of processes is stressed: ".. .a process is generally considered well understood when 1) all sources of variability are identified and explained; 2) variability is managed by the process; and 3) product quality attributes can be accurately and reliably predicted over the design space established for the materials used, process parameters, manufacturing, environmental and other conditions."[11] The latter guidance encourages real-time monitoring and control of processes using online (or inline) analyses, wherein instrument probes are inserted into equipment for direct monitoring of process streams. The benefits of such process analytical technology (PAT) have been discussed.[14,15] The guidelines would allow increased regulatory flexibility for


(5) Payack, J. F.; Huffman, M. A.; Cai, D.; Hughes, D. L.; Collins, P. C.; Johnson, B. K.; Cottrell, I. F.; Tuma, L. D. *Org. Process Res. Dev.* **2004**, *8*, 256.
(6) Guideline on General Principles of Validation ; 1987, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124720.htm (accessed 10/19/10).
(7) Paisano, G. P. *The Development Factory: Unlocking the Potential of Process Innovation*; Harvard Business School Press: Boston; 1997.
(8) Peterson, J. J.; Snee, R. D.; McAllister, P. R.; Schofield, T. L.; Carella, A. http://biometrics.com/wp-content/uploads/2009/06/gsk-bds-tr-2009-2.pdf (accessed 10/19/10).
(9) (a) Roberge, D. M.; Zimmermann, B.; Rainone, F.; Gottsponer, M.; Eyholzer, M.; Kockman, N. *Org. Process Res. Dev.* **2008**, *12*, 905. (b) Mullin, R. *Chem. Eng. News* **2007**, *85* (4), 11.
(10) (a) Thayer, A. *Chem. Eng. News* **2009**, *87* (24), 9. (b) Short, P. L. *Chem. Eng. News* **2008**, *86* (42), 37.
(11) PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, Guidance for Industry; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER): Rockville, MD, 2004; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070305.pdf (accessed 10/19/10).
(12) Process Validation: General Principles and Practices (Draft Guidance); U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER): Rockville, MD, 2008; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf (accessed 10/19/10).
(13) Robinson, D. *Org. Process Res. Dev.* **2009**, *13*, 391.
(14) Hussain, A. S. http://www.pharmamanufacturing.com/articles/2005/278.html (accessed 10/19/10).
(15) Schneider, R.; Huhn, G.; Cini, P. http://www.pharmamanufacturing.com/wp_downloads/tunnell_aligning_PAT_validation_and_post_validation.html (accessed 10/19/10).

continuous improvements within the acceptable design space.[16] In addition the recent guidance emphasizes the importance of understanding and monitoring processes throughout the lifecycle of a drug and encourages the use of statistical tools to manage data generated from operations.[17−20]

The focus on validation has always been on quality, and it is important to note that regulatory authorities require that processes be validated, not optimized.

## Current Process Validation Activities

The term "validation" applies to many areas beyond implementing processes on scale, from initial evaluations in the laboratory to demonstrations of the acceptability of revised (optimized) process conditions after initial implementation of the registered process.[4] To ensure complete validation of a manufacturing process, chemists and engineers may request confirmation that validated analytical assays and equipment are in use, that procedures clean equipment satisfactorily, and that utilities, process equipment, instruments, and computer systems perform adequately.

Historically, three consecutive batches of API have been manufactured at full scale as part of process validation, although the FDA guidance does not specify how many batches are required.[21] The operations used in the production of these batches and the quality attributes of the resulting products must meet predescribed criteria. Such validation is termed *prospective validation* and is generally preferred over alternative types of validation.[4,22,23] If the pre-established validation criteria are satisfied, drug product from the API "validation batches" can be sold for human use.[12] In order for subsequent batches of API to be released, their manufacturing parameters and quality attributes must also fall within the ranges encompassed by the validation protocols.

Other types of validation are concurrent validation and retrospective validation. In certain cases concurrent validation may be an acceptable alternative to prospective validation. For example, it may be uneconomical to prepare more than one batch of drug substance prior to launch of the product. This might apply to drugs for which there is a limited production requirement and for which more than one batch might represent an unreasonably large inventory, especially if batches would expire due to limited shelf life. In this instance it may be possible to gain approval to release drug substance for commercial use before three consecutive validation batches are complete. Under concurrent validation guidelines each successful validation batch can be marketed once production is complete and the batch has passed release testing.[23] Retrospective validation (of as many as 30 batches) has been used to validate manufacturing processes for legacy products, and has fallen out of favor.[24]

**General Guidelines for Validating Processes.** A general sequence for validating processes is shown in Table 1. As with any scale-up operation, safety considerations are foremost. Safety assessments, although not included per se in validation guidance, are shown because safe operations are essential to the development of suitable manufacturing processes. Safety assessments and risk assessments will become increasingly important to demonstrate control of processing and thus to minimize potential impact of adverse processing on API quality and the environment.

In the initial phase safety assessments may be carried out by desktop review, by consulting the primary literature and various resources such as Brethericks[25] or Sax.[26] In general starting materials and reagents with multiple highly reactive functional groups[27] should be avoided if possible. Safety levels for airborne solvents and reagents can be found in literature from the American Council on Governmental Industrial Hygienists.[28] To ease both purification of the API and analyses for residual solvents, solvents for making the API and penultimates should ideally be selected from the list of ICH Class 3 solvents;[29] these solvent classifications are based on demonstrated toxicity. Intermediates and potential API impurities[30] containing groups flagged as promoting genotoxic activity[31] can limit the amounts of such potential genotoxic impurities (PGIs)

(16) *ICH Q8 Pharmaceutical Development*, (R2); U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER): Rockville, MD, Aug 2009; http://www.fda.gov/downloads/Drugs/sGuidanceComplianceRegulatoryInformation/Guidances/ucm073507.pdf (accessed 10/19/10).

(17) *ICH Q9 Quality Risk Management*; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER): Rockville, MD, June 2006; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073511.pdf (accessed 10/19/10).

(18) *ICH Q10 Pharmaceutical Quality System*; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER): Rockville, MD, April 2009; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073517.pdf (accessed 10/19/10).

(19) Torbeck, L. *Validation by Design: The Statistical Handblook for Pharmaceutical Process Validation*; PDA Books: Bethesda, MD; 2010.

(20) Pujols, M. http://pharmoutsourcing.com/ViewArticle.aspx?ContentID=134 (accessed 10/19/10).

(21) Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance Production and Process Controls, 5. Do CGMPs require three successful process validation batches before a new active pharmaceutical ingredient (API) or a finished drug product is released for distribution? http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124782.htm#5 (accessed 10/19/10); http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/ucm137175.htm#_Toc84065761 (accessed 10/19/10).

(22) PMA QC Section, Bulk Pharmaceuticals Committee. *Pharmaceut. Tech. Eur.* **1994**, *37*.

(23) ICH Q7A Good Manufacturing Practices for Active Pharmaceutical Ingredients; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER): Rockville, MD, 2001; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073497.pdf, (accessed 10/19/10). See sections 12.4 and 12.5.

(24) Retrospective validation, mentioned in the ICH Q7A section 12.5, is not mentioned in the November 2008 Guidance.

(25) Urben, P. Ed. *Bretherick's Handbook of Reactive Chemical Hazards*, 7th ed.; Academic Press: New York, 2006.

(26) Lewis, R. J., Sr. *Sax's Dangerous Properties of Industrial Material*, 11th ed.; Wiley: New York, 2004.

(27) Rowe, S. M. *Org. Process Res. Dev.* **2002**, *6*, 877.

(28) http://www.acgih.org/home.htm (accessed 10/19/10).

(29) ICH Q3C Impurities: Residual Solvents; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073394.pdf, (accessed 10/19/10).

(30) ICH Q3A Impurities in New Drug Substances, R2; October 2006 http://www.fda.gov/RegulatoryInformation/Guidances/ucm127942.htm#i, (accessed 10/19/10).

(31) Snodin, D. J. *Org. Process Res. Dev.* **2010**, *14*, 960.

***Table 1.*** **General sequence for validating processes**

| | activity | location | comments |
|---|---|---|---|
| 1 | safety analyses | desktop review | identify and avoid known chemical and toxicological hazards |
| 2 | range-finding experiments | laboratory studies | accurate in-process assays speed process development to find acceptable operating conditions |
| 3 | safety analyses | laboratory testing | quantitate exotherms, identify toxicological hazards of intermediates in proposed process streams |
| 4 | risk assessment (e.g., FMEA) | multidisciplinary review | consider how process variations can impact product quality. Anticipate and avoid scale-up hazards for kilo lab and pilot plant. |
| 5. | scale-up to stationary equipment | pilot plant, glass plant | confirm operating ranges; best if development personnel are present |
| 6 | analyze scaleup data | laboratories | confirm process understanding, or identify areas for further optimization |
| 7 | risk assessment (e.g., FMEA) | multidisciplinary review | consider how process variations can impact product quality. Anticipate and avoid hazards for further scale-up (built upon data since previous assessment). |
| 8 | technology transfer | manufacturing facility | comprehensive, accurate |
| 9 | manufacturing introduction according to validation plan | manufacturing facility | best if scientists that introduced the process to the pilot plant are present |
| 10 | analyze data from initial manufacturing batches | laboratories | confirm that process has been validated; identify areas for further optimization |
| 11 | maintain validated state for registered, commercial process | manufacturing, quality, regulatory, R&D | periodic reviews of production, assessment of changes, e.g. in raw materials |
| 12 | further optimization | laboratory, pilot plant, manufacturing facility | optimization within filed process description does not require further regulatory review or approval. |

in APIs to as little as 1.5 $\mu$g/Da,[32,33] such limits may cause significant challenges for API purification and analyses,[34] and routes generating PGIs are avoided when possible.[35]

Once suitable reagents and route(s) have been identified, laboratory range-finding experiments are often conducted in parallel and on small scale. Parameters to be examined might include the number of equivalents of reagents, choice of solvent, reaction temperature, pressure, duration of addition for a key reagent, and others. Parallel experiments are often employed to select variations of a reagent, e.g., LiHMDS vs NaHMDS or KHMDS.

After a preliminary process has been identified hazard evaluations should be conducted in the hazard evaluation lab to identify any conditions that promote exothermic reactions and gas evolutions. Identifying conditions that lead to runaway reactions is critical. Such evaluations should be carried out prior to scale-up, which might be a reaction run on as little as 100 g. Other circumstances to prompt such investigations would include having a number of highly reactive functional groups present in the reaction mass, having relatively little solvent to act as a heat sink, and maintaining a process just below the boiling point of the mixture. These tests can also quantitatively assess the amount of heat evolved by an exothermic process. The amount of heat that must be removed in processing is valuable information for scale-up operations in fixed equipment, because by correlating with the cooling capacity of the reactor one can estimate the amount of time needed for exothermic additions and thus preclude side reactions occurring at higher temperatures.[36]

Prior to pilot-plant introduction, evaluations of the risk to product quality and safety are often conducted through assessments such as Failure Modes and Effect Analyses (FMEA),[37] which should be used throughout process development. In its application to product quality, during FMEA each operating step is assessed for (1) the likelihood of a deviation outside proven acceptable ranges (PARs, see below), (2) the severity of possible impact on the critical quality attributes (CQAs, as described below) of the product, and (3) the likelihood of the deviation being detected. These assessments are combined to provide a risk value for each control parameter in a process. Such an analysis identifies operations where process knowledge or controls are lacking and where the product quality is most at risk. Depending on the scope of the risk assessment (e.g., quality or safety), members from a group from engineering, operations, chemistry, environmental health and safety, and other disciplines pose "what-if" questions, and contingency plans are developed. For instance, *what if* a key reagent were added too quickly? If the resulting exotherm and off-gassing built up pressure and blew out a rupture disk, the batch could be released from the reactor. As a contingency, a surge tank may be placed inline to contain any material released. To preclude uncontrolled additions, fail-safe operations might be developed such as charging no more than a fraction of the total

(32) Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches. Draft Guidance; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER): Silver Spring, MD, U.S.A., December 2008; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079235.pdf (accessed 11/15/10).

(33) See: Haney, B. P.; Mason, P.; Anderson, N. G. *Org. Process Res. Dev.* **2009**, *13*, 921and references therein.

(34) Thayer, A. M. *Chem. Eng. News* **2010**, *88* (39), 16–27.

(35) Butters, M.; Catterick, D.; Craig, A.; Curzons, A.; Dale, D.; Gillmore, A.; Green, S. P.; Marziano, I.; Sherlock, J.-P.; White, W. *Chem. Rev.* **2006**, *106* (7), 3002.

(36) For an example of over-reduction of a carboxylic acid ester with $BH_3$•THF due to a temperature excursion, see: Lobben, P. C.; Leung, S. S.-W.; Tummala, S. *Org. Process Res. Dev.* **2004**, *8*, 1072.

(37) McDermott, R. E.; Mikulak, R. J.; Beauregard, M. R. *The Basics of FMEA*, 2nd ed.; Taylor & Francis: New York, 2009; http://www.npd-solutions.com/fmea.html (accessed 10/19/10).

reagent to the addition tank.[38] FMEA investigations may prompt the development of continuous operations as safer alternatives.[39]

Scale-up to stationary equipment sets the stage for further process optimization and assessment of the process for introduction to the manufacturing equipment and validation. Although pilot-plant runs often provide material for early demands such as toxicology studies, formulation studies, and clinical trials, such pilot-plant runs can also be viewed as large-scale experiments to confirm desirable operating ranges. By critiquing the operations, in-process data, and product assays one can assess whether the process needs additional development before manufacturing introduction. After another FMEA evaluation, built upon the results of the pilot-plant runs, the process may be ready for technology transfer to the manufacturing facility.

Transferring a process to a manufacturing site, the next step in the validation process, is notoriously difficult.[40] Effective and efficient technology transfer should be comprehensive and accurate. Chemists and engineers involved with the design of the processes and operations in the pilot plant should transfer details to those responsible for manufacturing operations. If the operations and assays of the manufacturing batches proceed as planned, the process may be considered validated, and the process documentation may be filed using data not only from the manufacturing validation batches but also from laboratory investigations and pilot-plant runs. Reassessing the results after the initial campaign may uncover other areas for optimization; if optimal conditions are within the filed PARs (see below), incorporating these changes into manufacturing protocols should be relatively easy as, in principle, no further approval from the regulatory authorities is necessary.

**Identifying Ranges for Robust Processes: CQA, CPP, PAR, and NOR.** The foundation of QbD is thorough process understanding, so that the desired interplay of conditions within the multidimensional "space" of key parameters produces predictable outcomes.[16,41,42] Under QbD and current validation guidelines, demonstrating process understanding is more important than merely successfully executing three consecutive validation batches and relying on those results for assurance of process robustness and reproducibility.[41,43] A number of detailed QbD papers have been published recently.[44−46]

Critical quality attributes (CQAs) are attributes of an API that are essential to ensure the suitability for its intended use, such as purity, content of impurities, product moisture content, residual solvent contents, levels of transition-metal impurities, polymorph composition, particle size distribution, and others.[47] The values of the CQAs must fall within predescribed ranges, limits, or distributions, as defined in the specifications of the API.[48] Any deviation that arises from a process that has operated within its defined acceptable parameters indicates that the process is not completely understood and controlled. In such cases a toxic impurity in the API that is not detected by assays currently in place could be present. Such a batch cannot be released for human use unless further investigation can demonstrate its safety; depending on the outcome of the investigation, the specification may be amended, and improved process controls may be implemented to ensure that a similar failure does not reoccur. Through such investigations, therefore, deviations may lead to a better understanding of quality attributes of the raw materials and/or operations.[49,50]

Critical processing parameters (CPPs) are process inputs that directly influence CQAs. CPPs include operations to monitor and control operations, such as reaction temperature and pH, residual moisture prior to crystallization, and dryer temperature.[48] Table 2 summarizes the types of laboratory experiments typically undertaken to develop optimized and robust processes, with robustness being more important from a quality perspective. Such experiments should be undertaken before implementing a process on scale.

In order to produce API batches with acceptable CQAs, each CPP must operate within a proven acceptable range (PAR), outside of which product failure may result. To optimize operations to increase productivity or to control quality, batch operating instructions may further define operations to a normal operating range (NOR), which lies within a PAR (Figure 1). The PAR describes what is known and does not necessarily include all possible limits of processing that would produce API with acceptable CQAs. An "edge of failure," or the conditions at which process failure will result, lies at the limits of the PAR or beyond them at some undetermined point. After appropriate optimization a robust manufacturing process will "tolerate the expected variability of raw materials, operating conditions, process equipment, environmental conditions, and human factors."[42]

In general, rugged processes operate comfortably far from the edge of failure. Process conditions that respond gradually to changes in parameters are preferred for routine manufactur-

(38) Exothermic nitration performed in batch mode: Dale, D. J.; Dunn, P. J.; Golightly, C.; Hughes, M. L.; Levett, P. C.; Pearce, A. K.; Searle, P. M.; Ward, G.; Wood, A. S. *Org. Process Res. Dev.* **2000**, *4*, 17.

(39) Exothermic nitration performed in continuous mode: De Jong, R. L.; Davidson, J. G.; Dozeman, G. J.; Fiore, P. J.; Kelly, M. E.; Puls, T. P.; Seamans, R. E. *Org. Process Res. Dev.* **2001**, *5*, 216.

(40) Michielsens, P. M. L. J. http://pharmoutsourcing.com/ViewArticle.aspx?ContentID=137 (accessed 10/19/10).

(41) Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach; September, 2004; www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm (accessed 10/19/10).

(42) Process Robustness - A PQRI White Paper. *Pharm. Eng.* **2006**, *26*(6), 1; http://www.pqri.org/pdfs/06ND-online_Glodek-PQRI.pdf (accessed 10/19/10).

(43) *Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance Production and Process Controls*; http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124782.htm#5, (accessed 10/19/10).

(44) Looker, A. R.; Ryan, M. P.; Neubert-Langille, B. J.; Naji, R. *Org. Process Res. Dev.* **2010**, *14*, 1032.

(45) Cimarosti, Z.; Bravo, F.; Stonestreet, P.; Tinazzi, F.; Vecchi, O.; Camurri, G. *Org. Process Res. Dev.* **2010**, *14*, 993.

(46) Cimarosti, Z.; Bravo, F.; Castoldi, D.; Tinazzi, F.; Provera, S.; Perboni, A.; Papini, D.; Westerduin, P. *Org. Process Res. Dev.* **2010**, *14*, 805.

(47) See ref 30. The levels for reporting, identifying, and qualifying impurities fall with increasing daily dosage. This document is not intended to apply to clinical research efforts of new drugs.

(48) Birnbaum, R. http://www.ema.europa.eu/pdfs/conferenceflyers/ICH_regional_meet_brussels/64006008en.pdf (accessed 10/19/10.

(49) Anderson, N. G. *Practical Process Research and Development*; Academic Press: San Diego; 2000; pp 314−319.

(50) Yield is not a CQA, although the yield outcome from a batch may indicate the level of understanding of and control exerted by a process. A low-yielding batch could arise from decomposition or physical losses; if the latter did not cause the lower yield, the product should be scrutinized to detect any previously unidentified degradents that might be toxic. If the yield is above the specified range, output quality may also be compromised due to additional impurities that contribute to the higher yield. Whether a batch yield is less than or greater than the expected range, quality and productivity ramifications exist.

***Table 2.*** **Critical laboratory investigations before implementing a process on scale**

| experiment | type | purpose |
|---|---|---|
| optimization | range-finding | identify NOR[a] |
| stress tests/abuse tests | range-finding | identify PAR[a] |
| extended runs | mimic scale-up runs[b] | identify side reactions and degradents |
| calorimetry | qualitative | safety (avoid runaways) |
| | quantitative | predict processing times for exothermic operations when cooling capability of scale-up equipment is known. |
| tolerance studies | conduct processing with increased inputs of selected impurities under PAR conditions | establish permissible levels of impurities in inputs or process streams to produce APIs and intermediates with acceptable CQAs |
| use-test | subject all inputs to processing conditions | verify success for scale-up operations; identify whether problems of scale-up are related to inputs and/or operations |

[a] NOR is the normal operating range; PAR is the proven acceptable range. [b] For batch processing a 10-fold scale-up can be expected to at least double processing time: Anderson, N. G. *Org. Process Res. Dev.* **2004**, *8*, 260.

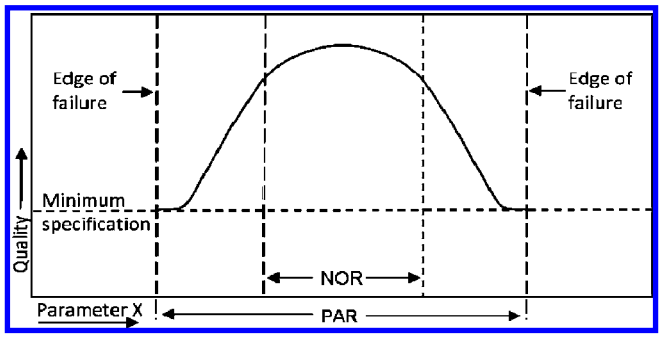
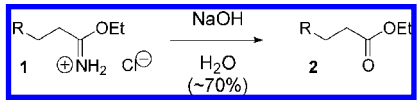



***Figure 1.*** **Relationship of proven acceptable range (PAR) and normal operating range (NOR).**

***Scheme 2.*** **Hydrolysis of imidate salt (Pinner product) analyzed by DoE**




ing. Nonetheless, in some circumstances, such as for maximizing a yield, it may be desirable to operate relatively close to the edge of failure; in such cases it will be necessary to balance the benefit of an improved yield against the difficulty of maintaining adequate process control and an increased risk of batch failure.

In addition to the traditional laboratory experimental approach of changing one variable at a time (OVAT, also known as one factor at a time, or OFAT), applying multivariant DoE can uncover the effects of varying multiple parameters in combination. In the case of the hydrolysis of imidate salt **1** (Scheme 2), analysis of data from five sets of experiments conducted within filed process conditions showed that quench temperature and water volumes were the key variables to optimize yield and minimize impurities, and these variables displayed a second-order interaction.[51] Under optimized, more highly concentrated conditions the yield improved by 5%, and productivity improved without changing product quality. DoE studies prior to process implementation are also part of the quality by design approach currently favored.[12]

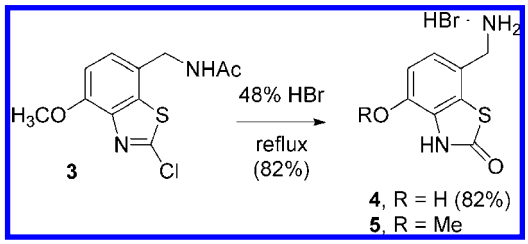
PAT guidelines stress continuous process improvement,[11] and online analyses have proven very useful. The use of in situ analytical techniques provides opportunities to control and optimize operations even when not all the factors in a complex, interacting system are thoroughly understood. For example, monitoring a crystallization process by in situ measurement of particle size and concentration can promote understanding of the interaction of parameters such as agitator type, speed, seeding efficiency, time, and temperature, which may depend on equipment and scale. By controlling the CPPs and confirming the desired particle size distribution through rapid, online measurements the crystals can be harvested by filtration at the optimal time, thus both precluding blinding the filter by excessively small particles and reducing the particle size of dried crystals. Such application of focused beam reflectance measurement (also known by the registered names FBRM and Lasentec) for a crystallization on scale has been described.[52]

PAT can dovetail well with continuous operations. While PAT has the potential to greatly enhance process understanding,[53,54] it has been used more for process investigations, pilot-plant operations, and formulation than for control of API manufacturing.

**Establishing Specifications.** Specifications are used to establish purity guidelines for purchasing starting materials, reagents, and solvents, as goals for materials to be prepared by contract research organizations, or as CQAs for products from pilot-plant operations and routine manufacturing. In particular specifications are established for regulatory starting materials, key intermediates, and APIs.[55] Use-tests are often key to obtain the required data that are necessary to establish specifications. Specifications evolve with the development of a drug candidate, and having more data allows specifications to be set with greater

(51) Gavin, D. J.; Mojica, C. *Org. Process Res. Dev.* **2001**, *5*, 659.
(52) Barrett, P.; Smith, B.; Worlitschek, J.; Bracken, V.; O'Sullivan, V.; O'Grady, D. *Org. Process Res. Dev.* **2005**, *9*, 348.
(53) Rubin, A. E.; Tummala, S.; Both, D. A.; Wang, C.; Delaney, E. J. *Chem. Rev.* **2006**, *106* (7), 2794.
(54) Tummala, S.; Shabaker, J. W.; Leung, S. W. *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 789.
(55) Argentine, M. D.; Owens, P. K.; Olsen, B. A. *Adv. Drug Delivery Rev.* **2007**, *59*, 12.

***Scheme 3.*** **Hydrolysis with demethylation**




confidence;[56] as more manufacturing experience is gained and process control is demonstrated, specifications may be tightened.[57]

Batches whose analyses fail specifications must be investigated,[58] and at any time such investigations can produce useful information. For example, prior to running validation batches a thorough analysis of data from a failed batch of the hydrolysis of **3** showed that high levels of the methoxy impurity **5** were associated with a low concentration of HBr (Scheme 3); this was confirmed by additional kinetic studies. Critical parameters were found to be the HBr concentration (lower PAR limit not less than 46%) and the moisture content of the acetamide input material (which was isolated from an aqueous quench).[59]

**Preparing the Validation Plan.** All operations involved in the production of an API, e.g., reactions, purifications, salt formations, and particle size adjustment, are subject to validation inasmuch as they may impact the CQAs of the product. Various interacting activities must be completed prior to carrying out the formal validation production runs, as outlined below.

For regulatory purposes it is mandatory to define the starting materials[23] and the subsequent steps that will be registered in drug approval documents such as a New Drug Application (NDA). This designation of regulatory starting materials is frequently the cause of much debate, both within companies sponsoring drug manufacture and in their discussions with the FDA.

Validation is performed at stages downstream of the regulatory starting materials, and is necessary only for those processing steps in which API quality could be compromised. In many circumstances this involves validation of all registered processing steps and intermediates. The success of this approach hinges on understanding the CQAs of the regulatory starting materials and the CPPs of the processing.

It is standard practice, although not a regulatory requirement, to map out all validation activities within an overall plan, namely the Validation Master Plan (VMP).[60,61] In addition to making the validation operations easier to manage, it is often used to delineate each portion of an overall synthetic process, so that failure in one part does not necessarily imply overall failure. Should failure of one portion be experienced, then repeated validation need only be applied to that part of the overall manufacturing process. These portions would typically consist of processing between isolated intermediates, with the CQAs of each comprising the success criteria for the validation exercise. The VMP might consist of the following items:

- a summary of the overall synthetic process
- itemization of all the activities that must be completed before the validation runs commence (e.g., completion of equipment qualification, issuing of the Development Report)
- justification for the processing steps that require validation
- definition and justification of the number of production runs
- draft of the protocol(s)
- description of how the outcome of the validation will be reported
- description of how data from routine batches postvalidation will be collected and analyzed
- provision for how failure in any aspect of the validation exercise will be handled
- identification of responsibilities within (and outside) an organization for performing the different tasks

Upon completion of the full-scale validation runs, the results of the measurements specified in the protocol are gathered together for compilation into the Validation Report. The VMP and the validation report are beyond the scope of this discussion.

**Validation Efforts Prior to Process Implementation: DQ, IQ, and OQ.** Before implementing a process on scale to qualify its performance (performance qualification, or PQ, also known as process qualification), the equipment, utilities, and computer systems to be utilized must be subjected to three other aspects of qualification: design qualification (DQ), installation qualification (IQ), and operation qualification (OQ). DQ, IQ, and OQ are carried out to demonstrate that equipment, utilities and computer systems involved in the API manufacturing process will operate in a reliable and robust manner.[60−62]

- Design qualification (DQ). Characteristics of all equipment to be used to process the API and intermediates should be considered to ensure that the equipment is capable of meeting the CPPs. Specifications are set for equipment to be purchased, and specifications are reviewed for equipment in place. For example, a steam-based heating system may be needed with sufficient thermal capacity to boil a high-boiling solvent; a vendor specification may be used as such documentation for

(56) A typical specification for future batches of an API would be calculated from the mean value of all routine batches ± 3× the relative standard deviation: *ICH Topic Q6A. Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*; European Medicines Agency: London, issued May 2000; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002823.pdf (accessed 10/19/10).

(57) *ICH Topic Q6A. Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*; European Medicines Agency: London, issued May 2000; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002823.pdf (accessed 10/19/10).

(58) Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production (October 2006): http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070287.pdf (accessed 10/19/10).

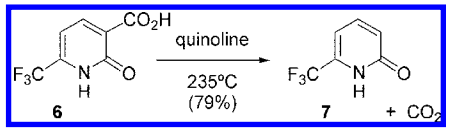
(59) Giles, M. E.; Thomson, C.; Eyley, S. C.; Cole, A. J.; Goodwin, C. J.; Hurved, P. A.; Morlin, A. J. G.; Tornos, J.; Atkinson, S.; Just, C.; Dean, J. C.; Singleton, J. T.; Longton, A. J.; Woodland, I.; Teasdale, A.; Gregertsen, B.; Else, H.; Athwal, M. S.; Tatterton, S.; Knott, J. M.; Thompson, N.; Smith, S. J. Org. Process Res. Dev. **2004**, *8*, 628.

(60) *Validation of Pharmaceutical Processes*; Agalloco, J. P.; Carleton, F. J. Eds.;3d ed.; Informa Healthcare; 2007.

(61) *WHO Expert Committee on Specifications for Pharmaceutical Preparations*, 40th report; World Health Organization: Geneva, 2006; http://whqlibdoc.who.int/trs/who_trs_937_eng.pdf (accessed 10/19/10).

(62) Amer, G. An Overview of Process Validation (PV). *Pharmaceutical Engineering;* **2000**, *62* (Sept.−Oct.).

***Scheme 4.*** **Generating a product prone to subliming under process conditions**




DQ. For existing equipment DQ may include confirming the minimum agitation volume or suitable placement of temperature probes.

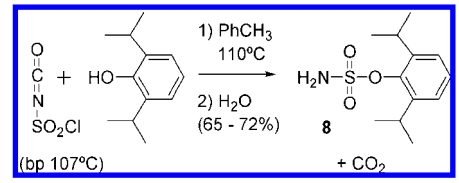
- Installation qualification (IQ). Confirming that equipment has been installed and equipped as required. For example, a reactor system must be set up in accordance with the piping and installation diagram, and documented as such.
- Operational qualification (OQ). Confirming that the equipment installed operates correctly. OQ can include checking that required temperature ranges and stirrer speeds can be achieved, that nitrogen and air are supplied suitably, or that materials can be transferred from one part of a system to another without leaks. Often water or solvent is used as a surrogate for process streams to demonstrate that the equipment can perform as required. To monitor and control operations many measurements must be made, and the accuracy of a number of these, such as weights, temperatures, and times, are routinely ensured by the calibration required for standard GMP operations.

With virgin manufacturing facilities OQ is critical. For example, prior to a manufacturing startup unsuccessful attempts to transfer water from one reactor to another identified a plugged transfer line.[63] The transfer pipe in question had been blanked off for effective welding during construction, and the blank had not been removed. Solvent testing may also clean lines of debris. Special attention should be paid to cleaning all equipment common to more than one operation, e.g., solvent manifolds and vacuum manifolds. At the end of OQ it is important to verify that solvents charged to clean out equipment and transfer lines have been removed.

The physical characteristics of process streams must be considered for safe and effective startups, and the equipment OQ should be reviewed to ensure that this is taken into account. For example, the product **7** from decarboxylation of **6** (Scheme 4) sublimed under reaction conditions and posed a potential danger of plugging and rupturing equipment if **7** sublimed and condensed in the vent lines, thus creating a closed system under heat. To preclude an uncontrolled release, all parts of the vent system were heated to ≥135 °C to prevent condensation of **7**, and any vaporized product was trapped in the scrubbing solution.[64] Similarly, to prevent condensers, including glass lab equipment, from plugging during reflux it is important to select coolant temperatures above the freezing points of solvents such as *t*-BuOH (mp 25 °C) and dioxane (mp 12 °C).[63] The transfer of acetic acid (mp 16 °C) from a tanker into a process facility building was stopped when the ambient temperature became unusually cool; the transfer line was lagged with heat tape to melt the plug of AcOH and complete the transfer.[63] Often physicochemical characteristics have been overlooked.

(63) Unpublished data.
(64) Brown, S. M.; Bowden, M. C.; Parsons, T. J.; McNeilly, P.; de Fraine, P. J. *Org. Process Res. Dev.* **1997**, *1*, 370.

***Scheme 5.*** **Generating a sulfamate using chlorosulfonyl isocyanate**




Material compatibility, including the corrosivity of reaction mixtures, must also be considered for successful OQ. In the pilot plant colored sulfamate **8** was isolated at only about 75% purity[65] (Scheme 5). Subsequent investigations determined that chlorosulfonylisocyanate had degraded the heat exchanger, contaminating the product **8**. Fortunately the heat exchange fluid did not react with chlorosulfonylisocyanate! Checking the compatibility all components, including heat exchangers, reactors, gaskets, and inline filters can avoid such difficulties.

Satisfactory OQ was not performed for an "optimized" variation of another process that had been successfully run in several manufacturing campaigns. To increase productivity, the initial step, involving a very exothermic generation of the key reagent, was run under more concentrated conditions. After successful demonstration in the pilot plant, the process was introduced to the manufacturing facility. Unfortunately, in the dedicated manufacturing equipment at the lower volume, reagents could not be added as rapidly as in the previously validated manufacturing process, negating any productivity gains. The reaction was cooled inefficiently because most of the reaction mass was in the cone of the reactor, below the surface of the reactor contacted by the circulating coolant. The "optimized" process was abandoned.[63]

**Examples of Process Implementation and Process Qualification.** With process introductions unforeseen problems regularly arise, often in the predawn hours, because the process is unfamiliar to the equipment owners and the equipment is unfamiliar to the developers of the process who are helping with the introduction. Such problems identify areas where deeper understanding of operations is necessary.

For successful PQ, confirming all operations whenever possible is key. In a manufacturing batch anhydrous HF (bp 19 °C) was added from custom cylinders to Teflon-lined reactors, and the weight loss of the cylinders was monitored during the charging of HF. Unfortunately the reaction was incomplete, even after adding 10% extra HF (as much additional HF as allowed by the PAR). Routine workup did not produce high-quality product, and no rework procedure had been filed. As a result a batch worth over $10,000,000 failed. Use-tests and other investigations lead to the conclusion that the desired amount of HF had not been delivered to the reactor, and there was no provision to measure the amount of HF actually charged. The probable cause was a leak in the HF charging line, hence an OQ and safety issue. Possible solutions to this problem would include measuring the charge of HF by a load cell on the reactor, or by mass flow meter measuring the amount of HF passing through the charging line just before the reactor.[63] Developing and filing a rework procedure are useful to ensure availability of expensive APIs.

(65) Dozeman, D. G.; Fiore, P. J.; Puls, T. P.; Walker, J. C. *Org. Process Res. Dev.* **1997**, *1*, 137.

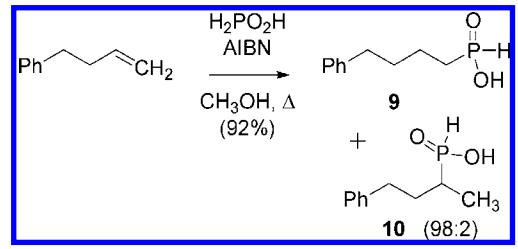
Successful PQ discourages premature changes to operations (as do today's established procedures for change control[23]). Even substituting a reduced-pressure distillation for an atmospheric distillation can lead to unexpected results. In a start-up a reaction product was extracted from the aqueous phase into dichloromethane as the tetrabutylammonium salt, and the extract was concentrated atmospherically. Then methyl isobutyl ketone (MIBK) was added and concentration under reduced pressure led to the volume for crystallization. This process was successfully demonstrated in a pilot plant during five runs. At the request of the equipment owner in the manufacturing plant, the first concentration was conducted under reduced pressure, with the goal of saving time. No other change to the process was made, and the product was isolated at about 60% of the expected yield. Investigations showed that a small amount of water from the initial extract had solubilized a significant amount of the product tetrabutylammonium salt in the mother liquor, decreasing the isolated yield. Reduced-pressure concentration of dichloromethane probably "broke" the azeotrope, leaving water in the mass that was not adequately removed by the concentration with MIBK. By instituting an in-process control to monitor the moisture content of the MIBK concentrate before crystallization, rugged processing resulted.[63]

Suitable in-process assays and in-process controls (IPCs) may be developed during introduction of a new process, as the process is understood further. During the manufacturing startup of an alkylation process the IPC was based on reaching a target ratio of products to starting material (HPLC). On scale it was determined that the products decomposed almost as fast as the starting material was converted to product, greatly extending operations. By setting a time limit for alkylation at this stage (5 h), yields of isolated product stabilized.[63] These validation efforts uncovered opportunities for process understanding and development of suitable IPCs, while allowing manufacturing of API intermediates to continue.

Process validation has failed when processes were not thoroughly described prior to process introduction and changes found to be necessary to the scale-up operations were considered major changes outside the predescribed scope of operations. In one case a polish filtration sometimes had been employed in lab to facilitate a key phase split, but this operation was not described as an option for processing on scale. During the first validation run this phase split was difficult, with product being lost to the high-volume interface. For the second run such a clarifying filtration was proposed, but this operation and the additional equipment required were outside scale-up experience, and adding a polish filtration was deemed a major change[66] that would render that batch inappropriate for human use.[63] Such difficulties would be avoided if more flexibility were built into processing, and if these options were described before a process was implemented.

IPCs are crucial parts of process validation, established to guide operations to meet current CQAs. In one campaign 2−4 h were required from time of sampling to return IPC data to the plant. Hence, processing was substantially delayed if more than one sample was taken. Normally, samples withdrawn after 10 h were close to the limit of ≤0.2% starting material. To minimize resampling in manufacturing the first sample was withdrawn at 11−12 h, routinely giving rise to ≤0.1% starting material. Personnel from the quality department wanted to change the specifications to ≤0.1% starting material, but the operations department felt that the lower limit might be unduly constrictive.[63] IPCs should not be changed unless a change is found necessary to meet the CQAs.

***Scheme 6.*** **Production of a regioisomeric phosphinic acid**




Where necessary to ensure consistent performance of processes, PQ must also include suitable cleaning of equipment, along with successful implementation of the operations. Within a campaign of many batches of the same product or intermediate, minimal cleaning is often carried out, with the reasoning that any impurities remaining from processing are unlikely to impede subsequent processing of the same product. Although this approach might seem reasonable to save time, inadequate cleaning has been shown to allow the buildup of compounds within reactors and impede good crystallization.[63]

**Activities after Process Implementation.** Data are scrutinized after process implementation to confirm that all batches met the predescribed CQAs. Researchers may also submit batches for additional assays to confirm process understanding and identify any additional quality markers. For instance, batches might be characterized by $^{19}$F-NMR, or by an HPLC assay using a different column. While confirming data need not be reported or gathered again if subsequent processing proves to be rugged, such additional data may prove useful in subsequent trouble-shooting.

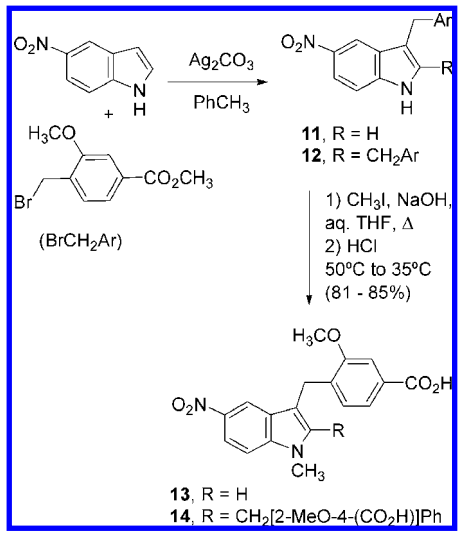
An assay involving a new HPLC column or a new analyst may lead to unexpected observations and process understanding. In the initial manufacturing batch of the phosphinic acid **9**, the use of a new HPLC column produced a new peak with a retention time similar to that of the required product (Scheme 6). Investigations after process implementation identified the regioisomer **10**, and demonstrated that this and derived impurities were removed during subsequent processing.[67] Despite the presence of this hitherto unknown impurity, the processes were under control and consistently provided API meeting CQA requirements.

Changes to manufacturing processes should be readily accepted if those changes are within the PARs. After the successful initial validation runs, researchers at AstraZeneca found that of seven impurities from the alkylation, the 2,3-dialkyl indole impurities were most difficult to purge (Scheme 7). Batches of ester **11** with ≥0.7% diester **12** passed the specification (≤1.0% **12**), but subsequent batches of **13** were

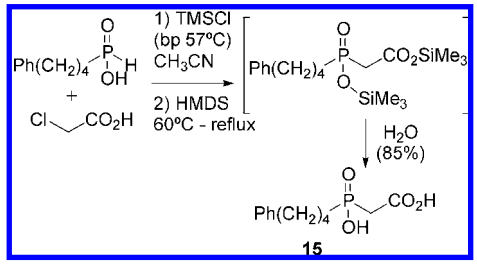
(66) Change control policy is decided by regulatory, quality, and operations departments and can have a large impact on processing and fate of batches.

(67) Anderson, N. G.; Coradetti, M. L.; Cronin, J. A.; Davies, M. L.; Gardineer, M. B.; Kotnis, A. S.; Lust, D. A.; Palaniswamy, V. A. *Org. Process Res. Dev.* **1997**, *1*, 315.

***Scheme 7.*** **Generation of 2-alkyl-indole impurities**




***Scheme 8.*** **Preparation of 15 by modified Arbuzov reaction**




at risk of failing specifications in downstream batches of salt. Investigations showed that the best step to reduce dialkyl impurities was the crystallization of **13** (specification of ≤0.5% **14**). The CPPs found to be critical to removing the diacid **14** from **13** included longer HCl addition times, increased agitation, and a minimized holding period of the acidified slurry before filtration. By acidifying with 2 M HCl instead of conc HCl and changing operations as mentioned above, the quality of the acid **13** was improved by 20−40%. All process changes were within the PARs and scope of the filings.[68]

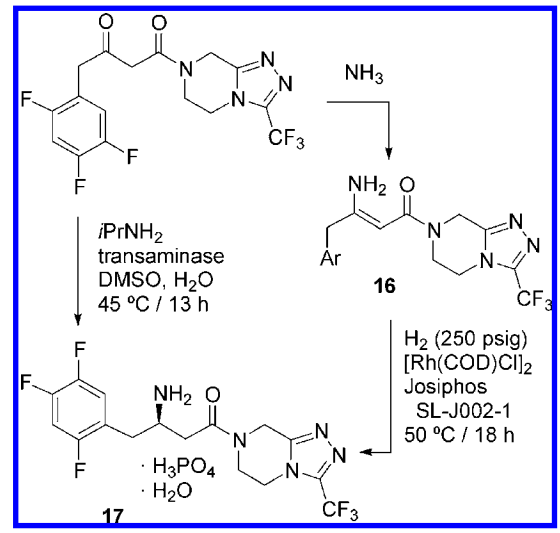
After successful technology transfer, data from routine runs can be examined by statistical process control (SPC) methods to monitor robustness in manufacturing and to point out areas for further optimization.[8,19] A Product Quality Research Institute (PQRI) paper provides an overview of quantitative and graphic tools to aid in analyses.[42]

Despite apparently successful validation, processes sometimes need to be changed outside of the filed descriptions. During routine manufacturing batches from the modified Arbuzov process in Scheme 8 were reworked to raise the quality of this intermediate, despite eight successful pilot-plant runs and five successful runs during the manufacturing startup.[69] Alternative conditions were developed to silylate the intermediates, and an extractive workup was employed to crystallize the product **15** from MIBK, thus raising the purity from 97% to

(68) Ancell, C. L.; Derrick, I.; Moseley, J. D.; Stott, J. A. *Org. Process Res. Dev.* **2004**, *8*, 808.

(69) Anderson, N. G.; Ciaramella, B. M.; Feldman, A. F.; Lust, D. A.; Moniot, J. L.; Moran, L.; Polomski, R. E.; Wang, S. S. Y. *Org. Process Res. Dev.* **1997**, *1*, 211.

***Scheme 9.*** **Manufacture of sitagliptin**




99.9 wt/wt %.[70] After two successful pilot-plant runs the process was successfully introduced to manufacturing. Manufacturing facilities may be the best proving ground for process development.

Other reasons to modify established processes might include the desire to manufacture at different batch sizes, to change operations to increase productivity or safety margins, to use new sources of raw materials with different specifications, to control previously unidentified impurities, or to reduce cost of goods through innovative processes. Merck's manufacturing route to sitagliptin (**17**) initially involved the chiral hydrogenation of an unprotected enamine,[71] for which Merck received a Presidential Green Chemistry Challenge Award in 2006 (Scheme 9).[72] During manufacturing runs a key impurity was identified, and controls were implemented to ensure rugged processing.[73] Recently Codexis and Merck together received a Presidential Green Chemistry Challenge Award for developing a biocatalytic process to manufacture **17**.[72] The benefits of implementing this step include eliminating one intermediate, improved yields and productivity, decreased waste, and more flexibility in selecting process equipment.[74] Implementing the biocatalytic route over the previous manufacturing route indicates clearly that it is possible to improve upon even optimized, creative manufacturing processes that have been validated.

Process validation is a continual effort to ensure the drug substance and drug product are safe for the consumer, and the principles of process validation can be used to increase productivity and lower the cost of manufacturing the API.

(70) For most steps a reasonable purity for an intermediate is ≥94%; see: Belecki, K.; Berliner, M.; Bibart, R. T.; Meltz, C.; Ng, K.; Phillips, J.; Ripin, D. H. B.; Vetelino, M. *Org. Process Res. Dev.* **2007**, *11*, 754. Purity specifications suitable for intermediates depend on the ruggedness of downstream processing.

(71) Hansen, K. B.; Hsiao, Y.; Xu, F.; Rivera, N.; Clausen, A.; Kubryk, M.; Krska, S.; Rosner, T.; Simmons, B.; Balsells, J.; Ikemoto, N.; Sun, Y.; Spindler, F.; Malan, C.; Grabowski, E. J. J.; Armstrong, J. D., III. *J. Am. Chem. Soc.* **2009**, *131*, 8798.

(72) http://www.epa.gov/greenchemistry/pubs/pgcc/past.html (accessed 10/19/10).

(73) Clausen, A. M.; Dziadul, B.; Cappuccio, K. L.; Kaba, M.; Starbuck, C.; Hsiao, Y.; Dowling, T. M. *Org. Process Res. Dev.* **2006**, *10*, 723.

(74) Savile, C. K.; Janey, J. M.; Mundroff, E. C.; Moore, J. C.; Tam, S.; Jarvis, W. R.; Colbeck, J. C.; Krebber, A.; Fleitz, F. J.; Brands, J.; Devine, P. N.; Huisman, G. W.; Hughes, G. J. *Science* **2010**, *329*, 305.

## Conclusions

Besides permitting the sale of drug products, successful process validation is the fruition of the labor of process chemists and engineers, and the ultimate test of how well one understands a process. Various initiatives have been issued to guide process investigations; QbD guidance established the definition of process design spaces, i.e. the envelope that covers the combination of the various control parameters that affect process performance and product quality. A validated process should be permitted to vary within the PAR of the design space, and further regulatory filing may not be required; for manufacturers this approach promises more flexibility in introducing changes after a process is approved. Close attention to details is needed to gather information in the lab and, upon scale-up, to ensure efficient validation. Despite the efforts involved in process validation, the discipline that process validation has brought to the development and operation of processes has undoubtedly increased the safety of APIs, the reliability of API manufacturing, and process optimization, resulting in greater productivity and lower cost of goods. Validation will continue to evolve.

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