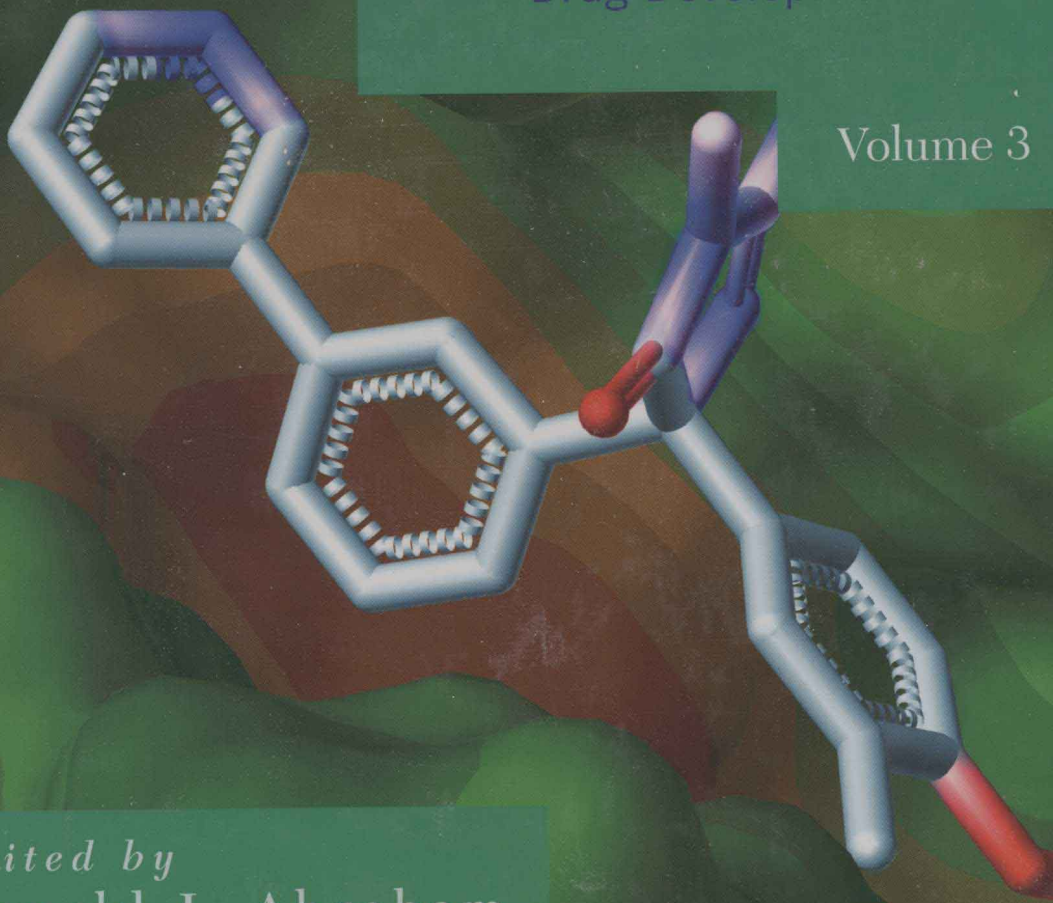
SEVENTH EDITION

BURGER'S MEDICINAL CHEMISTRY, DRUG DISCOVERY, AND DEVELOPMENT

Drug Development

Volume 3



Edited by
Donald J. Abraham
David P. Rotella

WILEY

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Seventh Edition

Volume 3: Drug Development

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PREFACE

The seventh edition of Burger's Medicinal Chemistry resulted from a collaboration established between John Wiley & Sons, the editorial board, authors, and coeditors over the last 3 years. The editorial board for the seventh edition provided important advice to the editors on topics and contributors. Wiley staff effectively handled the complex tasks of manuscript production and editing and effectively tracked the process from beginning to end. Authors provided well-written, comprehensive summaries of their topics and responded to editorial requests in a timely manner. This edition, with 8 volumes and 116 chapters, like the previous editions, is a reflection of the expanding complexity of medicinal chemistry and associated disciplines. Separate volumes have been added on anti-infectives, cancer, and the process of drug development. In addition, the coeditors elected to expand coverage of cardiovascular and metabolic disorders, aspects of CNS-related medicinal chemistry, and computational drug discovery. This provided the opportunity to delve into many subjects in greater detail and resulted in specific chapters on important subjects such as biologics and protein drug discovery, HIV, new diabetes drug targets, amyloid-based targets for treatment of Alzheimer's disease, high-throughput and other screening methods, and the key role played by metabolism and other pharmacokinetic properties in drug development.

The following individuals merit special thanks for their contributions to this complex endeavor: Surlan Alexander of John Wiley & Sons for her organizational skills and attention to detail, Sanchari Sil of Thomson Digital for processing the galley proofs, Jonathan Mason of Lundbeck, Andrea Mozzarelli of the University of Parma, Alex Tropsha of the University of North Carolina, John Block of Oregon State University, Paul Reider of Princeton University, William (Rick) Ewing of Bristol-Myers Squibb, William Hagmann of Merck, John Primeau and Rob Bradbury of AstraZeneca, Bryan Norman of Eli Lilly, Al Robichaud of Wyeth, and John Lowe for their input on topics and potential authors. The many reviewers for these chapters deserve special thanks for the constructive comments they provided to authors. Finally, we must express gratitude to our lovely, devoted wives, Nancy and Mary Beth, for their tolerance as we spent time with this task, rather than with them.

As coeditors, we sincerely hope that this edition meets the high expectations of the scientific community. We assembled this edition with the guiding vision of its namesake in mind and would like to dedicate it to Professor H.C. Brown and Professor Donald T. Witiak. Don collaborated with Dr. Witiak in the early days of his research in sickle cell drug discovery. Professor Witiak was Dave's doctoral advisor at Ohio State University and provided essential guidance to a young

scientist. Professor Brown, whose love for chemistry infected all organic graduate students at Purdue University, arranged for Don to become a medicinal chemist by securing a postdoctoral position for him with Professor Alfred Burger.

It has been a real pleasure to work with all concerned to assemble an outstanding and up-to-date edition in this series.

DONALD J. ABRAHAM
DAVID P. ROTELLA

March 2010

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BURGER'S MEDICINAL CHEMISTRY, DRUG DISCOVERY AND DEVELOPMENT

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LARGE-SCALE SYNTHESIS

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1. INTRODUCTION

The ability to produce active pharmaceutical ingredients (APIs) to support the various disciplines of the drug development process is an enabling element of pharmaceutical product development. In the initial stages of drug development, bulk active materials are typically supplied from bench-scale laboratory synthesis. However, API requirements can quickly exceed the capacity of normal laboratory operations, thus making it necessary to carry out the synthesis of the drug candidate on a larger scale. Section 32.2 is devoted to providing a general overview of the issues and requirements associated with the scale-up of chemical processes from the laboratory to pilot and commercial-scale operations.

Section 3 describes the process development of nevirapine, a novel nonnucleoside reverse transcriptase (NNRT) inhibitor used in the treatment of AIDS. This case study details the evolution of the nevirapine process from conception in medicinal chemistry through process development, pilot plant scale-up, and commercial launch of the bulk active drug substance. Restricting the case study to nevirapine allows the process and rationale to be described in more detail. The author is aware of the vast amount of excellent process development that has been performed in the commercialization of other drug products. The processes described herein are not necessarily unique solutions to this particular synthesis. To some extent, they reflect the culture, philosophy, raw materials, equipment, and synthetic tools available during the period 1990–1996, as well as the ingenuity of the process chemists.

2. SCALE-UP

2.1. General

The process development and scale-up of APIs require a multidisciplinary cooperation between organic chemists, analytical chemists, and engineers, quality control, quality assurance, and plant operations. Furthermore, the development of a drug candidate requires collaboration with pharmaceutics for formulation studies, drug metabolism and pharmacokinetics, toxicology, clinical studies, purchasing, and marketing. Outsourcing specialists, working in concert with purchasing, also play a key role in identification, coordination, and procurement of key raw materials in support of the scale-up effort. This particular function has gained greater importance in recent years as a result of the increasing emphasis in the pharmaceutical industry to improve the overall efficiency of the drug development process.

In the early stages of process development, the chemist must often balance the need to optimize each synthetic step with the API delivery requirements for toxicology, formulation, and clinical trials. To fulfill these requirements, the process chemist may often scale-up a process in the pilot plant with less than optimal process conditions. As a result, the first quantities of API produced in the pilot plant can be the most challenging to prepare. However, as the drug candidate passes through the various stages of drug development, the probability of commercialization increases and the need to address the commercial viability of the process becomes more important. This section presents an overview of the issues associated with the preparation of multi-kilogram quantities of APIs throughout the drug development process.

2.2. Synthetic Strategy

The types of development activities that are associated with the large-scale synthesis of a drug candidate can be divided into a series of discrete functions. Although the terminology used to describe these activities may vary, for the purpose of these discussions the specific functions of the drug development process

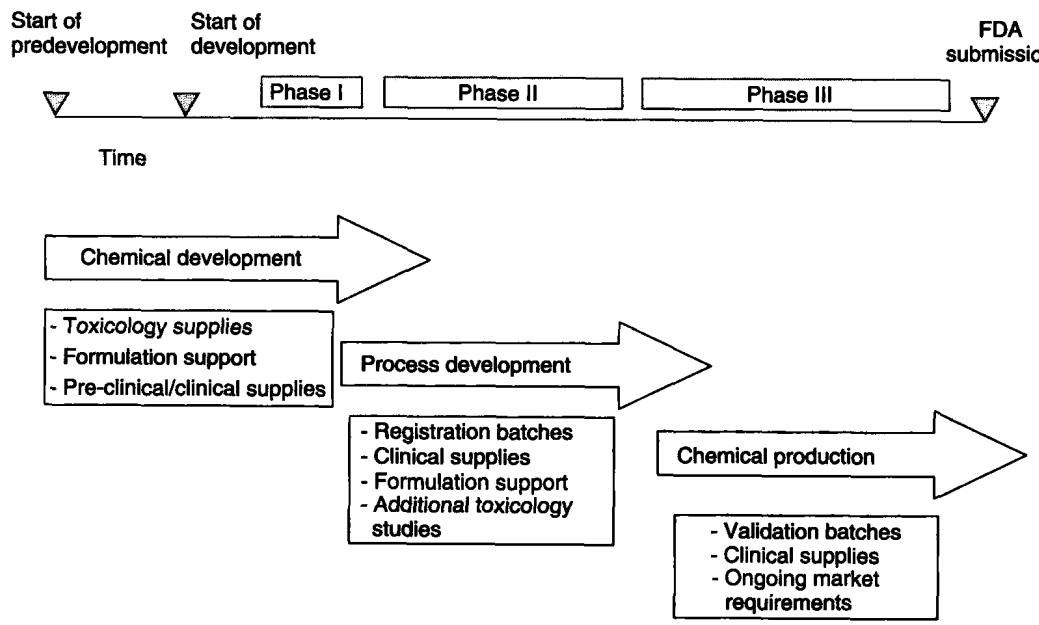


Figure 1. Large-scale synthesis requirements for drug.

related to chemical synthesis will be divided into the following three categories: (1) chemical development, (2) process development, and (3) commercial production.

Figure 1 indicates the specific areas of the drug development process where each of these activities occurs. Although each function has specific requirements and outputs from its respective activities, the overlap that is indicated between these activities is critical to the successful implementation of the project.

In the initial stages of *chemical development*, the focus of the effort is to supply materials to assess the viability of the drug candidate. The emphasis of this effort is on the expeditious supply of these materials rather than the commercial viability of the process used to produce the compound. Unique raw materials, reagents, solvents, reaction conditions, and purification techniques can and will be employed in this phase of the process to produce the desired compound in a timely fashion. The initial transition from laboratory to pilot-scale operations typically takes place during this portion of the drug development process to supply larger quantities of the bulk active material for toxicology, formulation, and preclinical evaluations. As the project proceeds through drug development, chemical development personnel continue to evaluate potential improvements to the synthesis. The insights obtained from these efforts provide the platform for future process development investigation.

The role of *process development* is to balance the timeline and material requirements of the project with the need to develop a commercially viable method for the preparation of the drug candidate. This stage of the drug development process will concentrate on such issues as (1) synthetic strategy, (2) improvement of individual reaction yields, (3) identification and use of commercially available raw materials and reagents, (4) evaluation of alternative solvent systems, (5) compatibility of process conditions with existing manufacturing assets, (6) identification and quantification of potential process safety hazards, (7) simplification of purification methods, (8) evaluation of process waste streams, and (9) the improvement of the overall process economics.

Both chemical and process development activities typically require that the drug candidate be prepared on a pilot plant scale. Although the batch size may vary depending

on the drug substance requirements, these operations are usually conducted in 100–2000-L reactors. The scale-up factor from the laboratory to the pilot plant is quite large (1–200 or more), and particular emphasis is placed on detailed safety analysis of this scale-up. The outcome of these efforts is a documented process that is included in the drug submission package to the U.S. Food and Drug Administration.

The overall objective of *chemical production* activities is to reproduce the process that has been transferred from process development to meet the current and future market requirements for the drug product. Particular emphasis is placed on issues related to process safety, environmental issues, equipment requirements, and production economics. The scale-up factor from the pilot plant to commercial production is usually rather small (approximately 1–20). As a result, the information obtained from the process development efforts can be quite valuable in the successful implementation of the commercial process. The reproducibility of the process is confirmed and documented as part of the process validation package, which in turn is part of the transfer process.

2.2.1. Route Selection When considering the merits of alternative synthetic pathways to produce a specific molecule, the route that incorporates the most convergent subroutes is generally the most advantageous option, provided yields for the individual steps are essentially equivalent [1]. For example, an eight-step linear synthesis (Fig. 2), in which each step has an 85% yield, results in a 27% overall yield (Case I). However, if the eight steps can be divided into two three-step converging pathways leading to two final steps, as in Case II, the overall process yield is increased to 44%, which is a 63% improvement over the Case I scenario. Furthermore, if the process is broken down to even shorter converging pathways, as in Case III, the overall yield improves by 25%, from Case I, to 61%.

In addition to the obvious yield advantages, an important benefit of a convergent approach is the proximity of the starting materials to

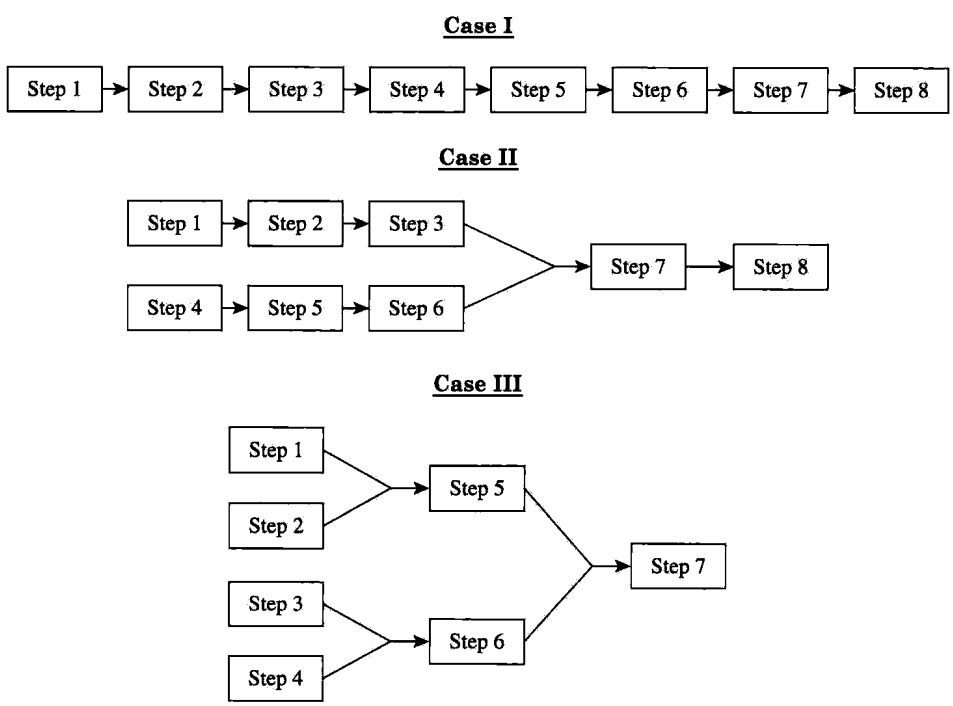


Figure 2. Convergent synthesis.

the product. In Case II, the raw materials are only five steps away from the product and only three steps away in Case III. This can significantly reduce the time required to respond to an unexpected need for additional product. Also, the value of each intermediate in a linear synthesis becomes greater with each additional step as a result of the resources required to produce material from that step. In a convergent synthesis, the cost is spread over two or more intermediates, thus reducing the overall risk in the event of material losses. Convergence may also provide an advantage in developing the regulatory filing strategy. In this manner, greater chemical complexity can be built into the registered starting materials that can greatly simplify the ability to implement process improvements following the product launch.

2.2.2. Chiral Requirements Over the last several decades, drug development efforts have placed increasing emphasis on the development of the biologically active stereoisomers of drug products. Chiral APIs offer the opportunity to provide higher drug potency while reducing the metabolic burden and risk of undesirable side effects to the patient [2]. It has been estimated that over half the best-selling drugs worldwide are single enantiomers [3]. As a result, the process chemist is presented with the challenge of developing commercially viable processes for the production and isolation of these chiral compounds. Several approaches can be used to produce enantiomerically enriched bulk active pharmaceutical products. The resolution of racemic mixtures with chiral adjuvants has been a common approach in the past to isolate the desired optical isomer of drug products. Chiral amines and acids are typically used to isolate an enantiomer by crystallization of the diastereomeric salt. The major drawback with this approach is the significant loss of material as the undesired enantiomer. This can be mitigated by racemization of the off isomer followed by recycling of the racemate back into the resolution. However, the equipment requirements to execute this procedure can be significant and must be economically justified.

An alternative approach for the preparation of chiral APIs is the use of chiral raw materials. The increased availability of functionalized chiral raw materials from both synthetic and natural sources has made this a more viable option in recent years. When desired chiral precursors are not commercially available, asymmetric synthetic techniques may be employed to introduce one or more stereogenic centers into the molecule. Many elegant techniques have been developed using chiral induction [4], chiral templates [5], and chiral catalysts [6] to produce enantiomerically enriched drug substances, and this area of research continues to be at the forefront of organic chemistry.

Regardless of the approach used to introduce the stereogenic center(s) into the molecule, a significant cost is incurred in achieving this objective. For this reason, it is important to introduce the chiral component later in the synthesis and employ the principles of convergent synthesis (Section 2.2.1) to effectively minimize the impact of this cost to the overall process economics.

2.3. Bench-Scale Experimentation

A significant laboratory effort is required to define the operating ranges of the critical process parameters in order to scale up a chemical process into pilot or commercial-scale operations. A critical process parameter is any process variable that may potentially affect the product quality and/or yield. This information is required to prepare a process risk analysis, which is an FDA prerequisite for process validation. Process parameters that are often evaluated as part of the risk analysis include reaction temperature, solvent systems, reaction time, raw material and reagent ratios, rate and orders of addition, agitation, and reaction concentration. If catalysts are employed as part of the process, additional laboratory evaluation may also be required to further define the process limits. Process recycling of solvents and other materials must require data that define the impact on product quality as well as the limits and specifications of recyclability.

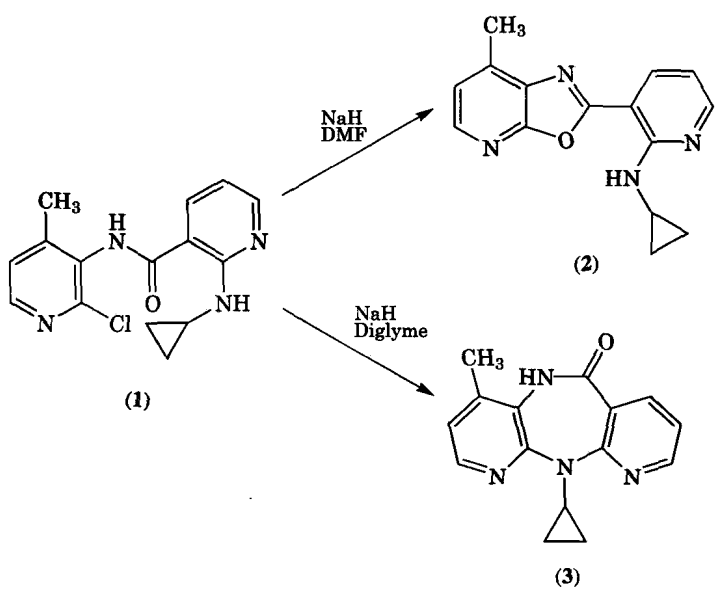
Experimental design is often used for the evaluation of critical process parameters to minimize the total laboratory effort [7]. This technique is equally important in identifying

interdependent process parameters that can have a synergistic impact on product yield and quality. In-process control (IPC) requirements are also defined during this phase of the development process. All these bench-scale activities help provide a better understanding of the capabilities and limitations of the process and are discussed in further detail in this section.

2.3.1. Selection of Reaction Solvents Solvents are generally used to promote the solubility of reagents and starting materials in a reaction mixture. Reactants in solution typically undergo conversion to product at a higher rate of reaction and are generally easier to scale up because of the elimination of mass transfer issues. For this reason, the solubility properties of the reagents and raw materials are a major consideration in the solvent selection process for scale-up. In addition, the solvent must be chemically compatible with the reagents and raw materials to avoid adverse side reactions. For example, an alcohol solvent would be a poor choice for a reaction when a strong base such as butyl lithium is being employed as a reagent. Information pertaining to the physical properties of solvents is available to assist in the solvent selection process [8].

Solvents can also be used to promote product isolation and purification. An ideal solvent system is one that exhibits high solubility with the reagents and starting materials but only limited solubility with the reaction product. Precipitation of the reaction product from the mixture can increase the reaction rate, drive reactions in equilibrium to completion, and isolate the product in the solid state to minimize the risk of undesirable side reactions. Solvents can also aid in the regiocontrol of the reaction pathway. It was found in the preparation of nevirapine (3) that when diglyme was used as the reaction solvent with sodium hydride, the ring closure of (1) (Scheme 1) proceeded by the desired reaction pathway [9]. However, when dimethyl formamide was used for this reaction, the exclusive product was the oxazolopyridine (2). In this particular case, the solvation effects may have helped stabilize the transition state of the desired product.

One of the most challenging aspects of solvent selection is the avoidance of certain classes of solvent that are routinely used in laboratory operations but are inappropriate for pilot and commercial-scale applications. Solvents such as benzene and 1,4-dioxane can present significant health risks to employees



Scheme 1.

handling large quantities of these materials [10]. Toluene is routinely used as a commercial substitute for benzene and other aromatic solvents. Likewise, solvents that promote peroxide formation such as diethyl ether and tetrahydrofuran present significant safety hazards in scale-up operations [11]. Methyl *tert*-butyl ether is a good commercial substitute for these materials. The autoignition temperature of the solvent should also be considered against the process operating conditions and electrical classifications of the equipment being used. With regard to environmental issues, several chlorinated solvents have been identified as priority pollutants [12] and can present permitting issues if adequate environmental containment capabilities are not incorporated into the scale-up facility. Although specific health, safety, and environmental issues for a given solvent can usually be addressed, it is important to evaluate the advantages of using an undesirable solvent against the additional cost and operational constraints that are imposed on the process.

2.3.2. Reaction Temperature Before conducting a reaction temperature profile experiment, it is important to understand the temperature limitations of the specific scale-up equipment that is to be used. For example, the typical operating temperature for a pilot or production facility employing a silicone-based heat transfer system ranges from −20 to 180°C. It is also important to understand the capabilities of the temperature control system used in the scale-up facility. The selected reaction temperature range must also be consistent with the accuracy and precision limits of the equipment. Given these constraints, the objective of this effort is to identify the optimal temperature range that gives the maximum conversion of starting materials to product in the shortest period of time and with the minimum amount of impurity formation. A general rule for the evaluation of reaction temperature is that increasing the reaction temperature by 10°C will double the reaction rate. However, this will also increase the potential for by-product formation, which could adversely impact both product yield and quality. The optimal temperature range is typically a balance between these three dependent variables.

2.3.3. Reaction Time In a laboratory environment, reactions are often run overnight with limited concern for the actual time requirements to complete the reaction. When selecting the reaction time for a specific process step to be scaled up, consideration should be given both to the potential reaction yield improvement and to the equipment utilization requirements. In many cases, doubling the reaction time will result in only a small percentage increase in yield. The cost of the additional equipment time can more than offset the potential yield benefit for cases in which the raw material costs are low. However, in cases where raw materials of high cost and greater chemical complexity are employed, the additional reaction time may be easily justified on an economic basis.

Consideration should also be given to the quantification of potential adverse effects from extending the reaction time beyond the optimum condition. Product decomposition and by-product formation are often observed under these circumstances. This information can be beneficial in scale-up operations when reaction times are extended beyond the specified period due to unforeseen circumstances. This information is also important in evaluation of this variable as a potential critical process parameter for the process risk assessment.

2.3.4. Reaction Stoichiometry and Order of Addition Reaction rates, product yields, and by-product formation can often be effectively managed by the selection of appropriate ratios of reactants and raw materials as well as by the rate and order of addition of these materials. A fundamental mechanistic understanding of the process is essential for the effective evaluation of these parameters. Reaction kinetic information can be beneficial in defining the limiting reagent for the reaction under evaluation. More often, the financial impact of specific raw materials will be a key driver of the overall process economics, and as a result, optimization efforts will focus on the minimization of these materials. This issue has gained increasing importance because of the chemical complexity of advanced starting materials in bulk pharmaceutical production. Likewise, a statistical design of experiments

can assist in the evaluation of multiple process parameters and also identify interactions between multiple process variables.

The minimization of by-product formation can be a particularly difficult task because of the high degree of chemical functionality in bulk pharmaceutical intermediates and products. Oligomerization reactions are a major mode of impurity formation in these types of chemical processes and can often be effectively minimized by the control of addition rates. Characterization of these impurities can also provide valuable insights into the control of these side reactions. The order and rate of addition are also frequently used to control extremely exothermic reactions. Chlorinating reagents such as thionyl chloride and phosphorous oxychloride, as well as strong bases such as butyl lithium, lithium diisopropylamide, and sodium hydride are usually added in a controlled manner to limit both heat and by-product formation in these reactions.

2.3.5. Solid-State Requirements The solid-state properties of active pharmaceutical ingredients can have a dramatic impact on critical dosage form parameters such as bioavailability and product stability. For this reason, FDA filing requirements include the definitive characterization of drug substance physical properties as part of the NDA information package. Formulation activities during the drug development process are directly linked to these parameters, and control of these physical properties during laboratory, pilot, and commercial-scale operations can be challenging.

The particle size distribution of the API can affect the dissolution rate of the formulated product and thus the drug bioavailability. Once particle size requirements have been defined from formulation studies, the process must be capable of routinely meeting these requirements. One of the ways that particle size distribution can be controlled is by the conditions under which the product is crystallized. Typically for cooling crystallizations, the particle size distribution depends on the rate of cooling. In general, smaller size particles are formed under rapid cooling conditions, whereas larger crystal growth is experienced with slower cooling rates. Milling and grinding techniques can also control particle size. However, these methods exclusively result in particle size reduction. Both the milling conditions and the solid-state characteristics of the bulk active material being charged to the mill thus determine the particle size distribution of the API. Milling parameters are discussed in more detail in Section 2.4.4.

Bulk drug products often exist in different crystalline or polymorphic forms. Because the polymorphs of a specific API can exhibit distinguishably different bulk stability properties and bioavailability characteristics as a result of the differences in surface area between the different crystalline forms, specification of the polymorphic form is typically required for FDA submission. Products such as ranitidine [13], lorazepam [14], and natamycin [15] serve as examples of APIs that exist in several different polymorphic forms. The solvent system and the crystallization conditions generally determine the specific crystallization form that is isolated. Polymorph selection for regulatory submission is usually based on the ability to reliably produce and process the material in the same crystalline form. In many cases, this is the thermodynamically most stable polymorphic form. In the event that a less stable polymorphic form is desired, because of the stability or bioavailability issues, seeding techniques can be used to control the crystallization selectivity of a specific polymorph. However, when seeding is required a seeding strategy must be developed including specifications and documentation of the seed history or genealogy.

2.4. Scale-Up from Bench to Pilot Plant

Bulk active pharmaceutical ingredients are most often produced at the pilot scale under batch-mode operations with multipurpose equipment. In contrast, continuous operations are typically reserved for high volume products that can be produced in dedicated facilities. Although there have been significant advances in the development of continuous microreactor technology in recent years (see Section 2.6) the focus of scale-up discussions in this section will be restricted to batch-scale operations. From a procedural perspective, batch operations more closely resemble

conventional bench-scale operations. However, the successful transformation of bench-scale experiments in laboratory glassware to pilot and commercial-scale operations requires a more detailed understanding of the physical issues related to scale-up, such as heating and cooling requirements, agitation, liquid–solid separation techniques, and solids handling requirements. Particular emphasis is placed on understanding the thermal requirements because this can often be the area of greatest perceived risk. This can influence the rate of by-product formation, which has an impact on both the impurity profile and the yield. Fortunately, reactions proceed by the same mechanism regardless of the scale, and problems in scale-up are typically restricted to physical parameters.

2.4.1. Heating and Cooling A pilot plant is generally outfitted with multipurpose vessels that can obtain an operating temperature range of −20 to +150°C. Broader temperature ranges can be obtained with silicone-based heat-transfer fluids. Temperatures lower than −20°C can be required in API production and can be achieved with liquid nitrogen cooling systems.

The heating and cooling capabilities of a reactor system are determined by several factors. Variables such as reactor surface area, materials of construction, the temperature of the heating and cooling media, and the heat capacity of the reactor contents contribute to the thermal properties of the reactor system. The effects of these parameters on heating and cooling are greatly magnified upon scale-up from the bench to the pilot plant. For example, a 250-mL round-bottom flask in the laboratory has a large surface area to volume ratio. As a result, the flask can be heated and cooled quickly. In comparison, the surface area to volume ratio of a 100-L glass-lined steel reactor is drastically reduced and may influence the ability to effectively control the reactor contents. In general, in transitioning from a 250-mL flask to a 100-L reactor, the surface area versus volume is reduced by a factor of 10. Likewise, the surface heat constant (k) of a stainless steel reactor is much greater than that of a laboratory reaction flask, which could result in a thermal transfer that is much more rapid than that of the laboratory experience.

This effect of heating and cooling can be calculated as follows [16]:

$$T = t_s - (t_s - t^0)e^{-kF/C} \tag{1}$$

where T is the temperature of the vessel in degree-centigrade, t^0 is t at the beginning of the heating, t_s is the temperature of the heat-exchange fluid, F is the reactor surface, k is the heat constant on the surface (kcal/m^2/h/C), F is the heat surface, and C is the heat capacity of the reaction vessel with contents.

2.4.2. Agitation The key function of agitation is to ensure homogeneity of the reactor contents. The major factors that affect reactant homogeneity are both the reactor-agitator configuration and the physical properties of the reactor contents. Miscible liquids of low viscosity, such as ethanol and water, represent mixtures with which one can easily attain homogeneity with minimal agitation. As one might expect, biphasic mixtures require more vigorous agitation than miscible solutions. The extent of the additional agitation requirement depends on the viscosities of the individual phases. Liquid–solid mixtures also require greater agitation to increase the uniform dispersion of reactor contents. In many cases, the solid is formed later in the process, resulting in different agitation requirements over the duration of the reaction.

Catalytic hydrogenations can represent some of the most challenging agitation issues. A typical hydrogenation reaction will require the dispersion of a heterogeneous catalyst and hydrogen gas throughout a specific solution containing the material that is to undergo the reduction. Hydrogenation agitators are often specifically designed to maximize the dispersion of the hydrogen gas throughout the liquid phase.

The ability to transfer heat to the reaction mixture is also a function of agitation. A typical agitation heat-transfer correlation is as follows:

$$k \propto \frac{L^{4/3}N^{2/3}}{D} \tag{2}$$

where k is the surface heat constant, L is the agitator impeller length, N is the agitator speed, and D is the vessel diameter.

2.4.3. Liquid–Solid Separations In the majority of drug syntheses, the reaction product is a solid. The isolation of the solid product from the reaction mixture is often accomplished in bench-scale operations by rotary evaporation of the volatile components of the reaction mixture, leaving a solid residue that is easily recovered. This technique is clearly not amenable to scale-up, and therefore alternative methods of solids isolation are required. Crystallization of the desired product from the reaction mixture is the most desirable approach as the first step to product isolation. Laboratory, pilot, and commercial-scale crystallizations are typically carried out by cooling, evaporative concentration, or by pH adjustment to precipitate the salt form of the product. However, the use of cosolvents to reduce the product solubility can also be effective in promoting dissolution. Typical liquid–solid slurries are manageable in the 20–30% solids range in a pilot plant or commercial operation. At higher solids concentrations transfers can become significantly more difficult.

Separation of the solid product from the liquid phase is usually accomplished at the bench scale by vacuum filtration through a single-stage filter such as a Buchner funnel. Although pilot and commercial-scale facilities are equipped with similar types of equipment, centrifugation is commonly used for liquid–solid separations. This is particularly true for commercial-scale operations. One of the major advantages of centrifuge systems is their ability to effectively remove liquid from a product cake. This can result in a significant reduction in both the product drying time requirements and the impurity content. For example, the residual solvent content of solids isolated by centrifugation is typically in the 5–10% range, whereas solids isolated by vacuum filtration can be in the 20–30% range. Measurement of filtration rates and cake compressibility at the bench scale can provide valuable insights into the commercial feasibility of the isolation conditions and the selection of appropriate equipment.

2.4.4. Drying and Solid Handling Drying operations under laboratory conditions are typically restricted to the use of vacuum ovens. Similar types of equipment are often used in pilot operations and are commonly referred to as tray dryers. These types of dryers fall into a specific FDA class of dryer systems referred to as indirect conduction heating static solid-bed dryers and are very versatile when processing wet solids that are difficult to dry. One of the drawbacks of these systems is the static nature of the drying operation that limits the ability for heat transfer to occur across the solid mass. In addition, these units are very labor intensive and can present significant industrial hygiene and validation challenges on a commercial scale. For these reasons, pilot plants are often equipped with a variety of types of dryers to make an effective transition between the laboratory and the commercial-scale operations.

The most commonly used commercial drying systems are rotary tumble dryers. This type of dryer falls into the FDA classification of indirect conduction, moving solids bed dryers. These units work well for free-flowing solids that have high volume requirements but are less effective with solids that have a tendency to agglomerate and cake while drying. Agitated drying systems such as paddle and spherical dryers are another type of solids drying system that are of the same FDA dryer class as the rotary tumble dryers. These units typically have a fixed heated surface and internal agitation to maximize heat transfer while breaking up any agglomerated solids. Agitated dryers are often outfitted with chopper attachments to the agitation system that can also affect particle size reduction and potentially avoid an additional milling step. As a result, these units can provide high-throughput drying of a variety of difficult-to-handle materials, are applicable for both pilot and commercial applications, and are commonly found in more modern installations. Fluidized bed dryers represent a second FDA classification of drying system. These units use a hot inert gas flowing at a high velocity to suspend and dry the solid in a finely divided state. This type of dryer equipment falls into the FDA classification of direct heating, dilute solids bed, and flash dryers and has