PHARMACEUTICALS, LARGE-SCALE SYNTHESIS

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 providing the need to carry out the synthesis of the drug candidate on a larger scale. The first portion of this chapter 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.

The second portion of this chapter 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 authors are 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 a unique solution to this particular synthesis. To some extent, they reflect the culture, philosophy, raw materials, equipment, and synthetic tools available during this period of time (1990–1996) as well as the initiatives 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, quality control, quality assurance, engineers, and plant operations. Furthermore, the development of a drug candidate requires collaboration with pharmaceutics for formulation studies, drug metabolism and pharmacokinetics, toxicology, clinical, purchasing, and marketing. Outsourcing specialists, working in concert with purchasing, also play a key role in the 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 time consuming 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 multikilogram 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 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 the 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- to 2000-L reactors. The scale-up factor from the laboratory to the pilot plant is quite large (1 to 200 or more), and particular emphasis is placed on detailed safety analysis of the 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 (FDA).

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.

Route Selection. When considering the merits of alternate 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 8-step linear synthesis, in which each step has an 85% yield, results in a 27% overall yield (Case I) (Fig. 2). However, if the eight steps can be divided into two 3-step converging pathways leading into 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 125%, 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 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 any 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 that material losses occur. In many cases, putting the major components to the molecule together can also simplify the regulatory filing requirements because these intermediates may be classified as starting materials under current FDA guidelines.

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 of 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 justified economically.

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 as well as natural sources has made this a more viable option in recent years. In the event that the 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, chiral templates, and chiral catalysts to produce enantiomerically enriched drug substances, and this area of research continues to be at the forefront of organic chemistry.

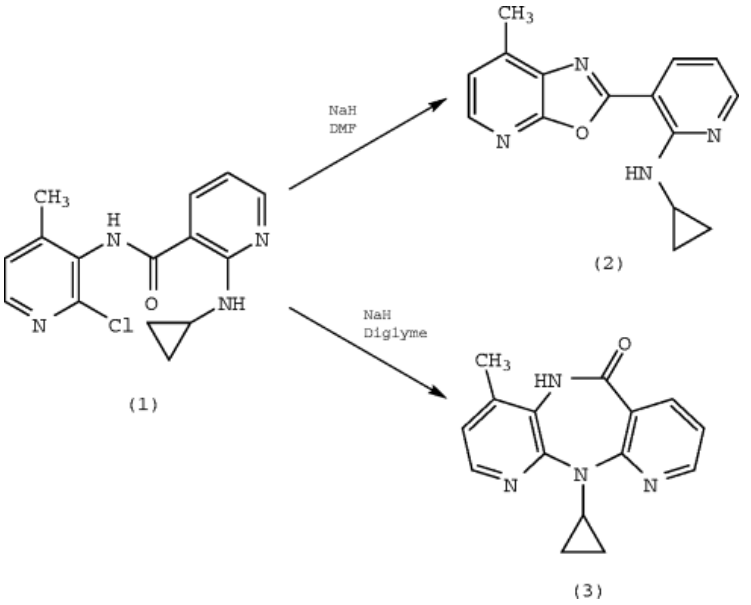
Regardless of the approach that is used to introduce the stereogenic center into the molecule, a significant cost is incurred in achieving this objective. For this reason, it is important to introduce the chiral component later in the synthesis and employ the principles of convergent synthesis (Section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

2.3. Bench-Scale Experimentation. To scale up a chemical process to pilot or commercial-scale operations, a significant laboratory effort is required to define the operating ranges of the critical process parameters. A critical process parameter is any process variable that may potentially affect the product quality 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. Experimental design is often used for the evaluation of critical process parameters to minimize the total laboratory effort (4). This technique is equally important in identifying interdependent process parameters that can have a synergistic impact on product yield and quality. In-process controls (IPCs) are also defined during this phase of the development process. All of these bench-scale activities help to provide a better understanding of the capabilities and limitations of the process and are discussed in further detail in this section.

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 (5).

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 regio control 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**) (eq. 1) proceeded by the desired reaction pathway (6). 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 to stabilize the transition state of the desired product.



(1)

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 (7) handling large quantities of these materials. 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 (8). 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 (9) and can present permitting issues if adequate environmental containment capabilities are not incorporated in 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.

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 range for a pilot or production facility that employs a silicone-based heat transfer system is $-20-180^{\circ}C$. 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 $10^{\circ}C$ will generally double the reaction rate. However, this will also increase the potential for by-product formation that could adversely impact both product yield and quality. The optimal temperature range is typically a balance between these three dependent variables.

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 in cases in which the raw material costs are low. However, in cases where raw materials of high cost and 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 because of unforeseen circumstances. This information is also important in evaluation of this variable as a potential critical process parameter for the process risk assessment.

Reaction Stoichiometry and Order of Addition. Reaction rates, product yields, and by-product formation can often be effectively managed by the selection of the 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 become of 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.

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 drug product and thus the bioavailability of the product. 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 is dependent on the rate of cooling. Generally, 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 further 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 as well as bioavailability characteristics as a result of the differences in surface area between the different crystalline forms, specification of the polymorphic form is recommended for FDA submission. Products such as ranitidine (10), lorazepam (11), and natamycin (12) 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 stability or bioavailability issues, seeding techniques can be used to control the crystallization selectivity of a specific polymorph.

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. For this reason, these discussions are restricted to issues associated with batch operations. From a procedural perspective, batch operations more closely resemble 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.

Heating and Cooling. A pilot plant is generally outfitted with multipurpose vessels that can obtain an operating temperature range of -20 to $+150^{\circ}$C. Broader temperature ranges can be obtained with silicone-based heat-transfer fluids such as Syltherm. Temperatures lower than -20°C are sometimes 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 control the reactor contents effectively. In general, from a 250-mL flask to a 100-L reactor, the surface area vs. 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 (13):

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

where T is the temperature of the vessel in $^{\circ}$C, 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^{-1} C^{-1}), kF is the heat surface, and C is the heat capacity of the reaction vessel with contents.

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 is dependent on the viscosities of the individual phases. Liquid-solid mixtures also require greater agitation to maintain homogeneity. 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.

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 alternate 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 the transfers become 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.

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 with 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 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 effect particle size reduction and 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 been used for both batch and continuous drying operations on a more limited basis.

Whenever possible, particle size distribution is controlled by crystallization parameters such as agitation and cooling rate. Once the solid material has been isolated and dried, particle size reduction can be achieved by various milling techniques. The particle size requirements as well as the physical properties of the solid dictate the type of milling equipment used for a specific application. The particle size requirements are usually defined during drug formulation development and impact the bioavailability of the drug candidate. Some of the physical properties of the solid that can affect the selection of milling equipment and conditions include hardness, crystal morphology, and thermal stability. The stability of the solid is a critical issue with regard to milling operations because of the energy applied by the milling equipment. Fluid impact mills, such as jet mills, are one type of milling equipment that is used in both development and commercial applications. These mills promote particle size reduction through high speed particle-to-particle collisions. In contrast, impact mills, such as hammer and pin mills, impart particle size reduction by particle-to-mill surface as well as particle-to-particle collisions. These units are also used routinely in pilot and production environments. Other milling techniques such as compression milling and

particle size classification can also be applied, depending on the particle size specifications and the physical properties of the solid.

Safety. When transferring processes from the laboratory to the pilot plant, it is important to identify and address potential safety issues as early as possible in the transfer process. Typically, calorimetry studies and process hazard reviews are carried out to meet this requirement. Calorimetry experiments can assist in the identification and quantification of reaction exotherms associated with the process. This information can then be used to determine the capability of the pilot equipment to control the reaction.

Process hazard reviews are conducted to identify potential hazards that could occur as a result of operational failures such as loss of power or cooling capacity. The process hazard review is conducted subsequent to the calorimetry studies to obtain the benefit of this additional information in the assessment of risk. The compatibility of the pilot plant electrical classification with the process solvents, reagents, and solids is also evaluated as part of this process. Predictive evaluations are often made during the process hazard review by using information obtained from reactions carried out using similar reaction conditions and raw materials. In addition, the pilot plant materials of construction should also be evaluated against the reaction conditions that are to be employed as part of the scope of the review process.

Because these drug candidates have potential biological activity, precautions should be taken to limit worker exposure during scale-up operations. Personal protective equipment requirements and adequate containment and ventilation provisions should also be defined as part of the safety review process. Often this assessment can be difficult because the material produced from the pilot plant will be used for toxicology evaluation purposes. In these cases, structure-activity relationship evaluations with regard to the relative toxicity of the compound may be appropriate to estimate the extent of risk.

2.5. Commercial-Scale Operations. The commercial implementation of a new process is primarily dependent on three factors: (*1*) the quality of the information obtained from laboratory and piloting efforts, (*2*) the effective transfer of the knowledge gained from these efforts, and (*3*) the ability to match the process requirements with the production capabilities. The production capabilities may be new and/or existing but in all cases should incorporate the effective utilization of existing assets while meeting the process requirements. Fortunately, the scale-up factor from the pilot plant to commercial operations is usually 1 to 20 or less, so that pilot information can be easily transferred to commercial practice. Likewise, the information transfer can be facilitated by the participation of production personnel in process development scale-up operations. The issues of equipment requirements, implementation of in-process controls, and validation requirements, as well as safety and environmental matters related to commercial production, are addressed in this section.

Identification of Processing Equipment Requirements. When transferring processes from pilot to commercial-scale operations, a comparative analysis is usually made between the equipment used in the pilot operation with the proposed commercial facility. Process flow diagrams (PFDs) that include material balances from pilot plant experiments can facilitate this analysis. Specifications and requirements for agitation, filtration, drying, and milling devices are

established based on experimental results that support these specifications and are documented.

Vent treatment requirements are also established during the evaluation of the process equipment requirements. The compatibility of the existing vent gas treatment system is evaluated against the process information obtained from the pilot runs and the existing environmental permit constraints. Permissible levels of venting are then established based on this assessment and the design requirements are documented.

Process streams from pilot plant experiments are usually retained to evaluate the compatibility of various types of materials of construction. Mass balance information is often sufficient to determine these requirements based on pH, halide content, solvents used, and process temperature. Corrosion testing of pilot plant process streams through the use of electrochemical techniques is often recommended. These results are compiled and documented along with the specifications for the materials of construction.

The process requirements for both temperature and pressure should also be evaluated against the production equipment capabilities as part of the production equipment assessment. Normal operating conditions are used as a base case, but upset conditions should also be included as part of the evaluation. If venting is chosen to control unintended reactions, vent sizing calculations must be performed and peripheral equipment selected as needed. Experiments and simulations to determine consequences of unintended reactions and the interpretation of these experiments are documented as part of the production process safety review.

The ignition prevention requirements for the process must also be defined based on electrical classification of solvents used in the process as well as the ignition characteristics of dry powders used in the process. Preferably, dry powder characteristics such as minimum ignition energy and temperature can be established based on testing of the solid materials. However, dry powder characteristics may also be estimated based on experience with similar materials. Experiments to establish ignition characteristics and the interpretation of experimental results should also be documented as part of the production process safety review.

In-Process Controls. In-process controls (IPCs) are used in both pilot and commercial operations to confirm that the process is in control and that the reactions and unit operations have been carried out to their expected completion point. Other process control points such as pH measurement, reactor content volume, distillation end points, filter cake washings, and drying end points are often considered to be critical process parameters that are also incorporated into IPCs. In pilot operations, numerous IPCs are taken to establish benchmarks for various process parameters, such as reaction time, drying time, distillation end points, and many other process variables. In a production environment, these benchmarks have been established and fewer IPCs are typically used to control the process. It is important when transferring a process from the pilot plant to review, identify, and separate the IPCs that were used only to establish process benchmarks in the pilot operations from those IPCs that would be appropriate for routine commercial operations. The appropriate commercial IPCs should then be documented and incorporated into the production procedure. This is

important because the New Drug Application (NDA) will define the IPCs in the Chemistry, Manufacturing, and Controls (CMC) section of the submission, and the elimination of an unnecessary control at this point can be quite time consuming.

Validation. The purpose of a validation program is to establish documented evidence that provides a high degree of assurance that specified processes consistently produce product that meet predetermined specifications and quality attributes. The validation program ensures that all systems, instruments, and equipment that impact the quality or integrity of the product have been validated.

The validation program is composed of several different elements and is designed to ensure that all validation requirements are addressed. General validation requirements for each of these elements are outlined in a master plan. Descriptions of the various validation elements are as follows:

Equipment/Systems Qualification. Qualification of the equipment in which the product is manufactured, the support services, and computer systems supporting the process.

Process Validation. Validation of the manufacturing process through the execution of production batches to establish that all product performance criteria have been met.

Cleaning Validation. Validation of the cleaning procedures used to clean the product from production equipment.

Method Validation. Validation of the analytical methods used to support the process validation, cleaning validation, inprocess testing, and release testing of the product.

All FDA-regulated products should be validated. Validation of each product is performed in a phased approach, encompassing all of the elements mentioned. The typical sequence for these activities is shown in Fig. 3.

In addition to validating these elements, several support programs must be in place to ensure that, once validated, manufacturing processes will be maintained in a validated state on an ongoing basis. These programs include calibration, preventive maintenance (PM), personnel training, and change control. The *personnel training* program should be designed so that all operational procedures and requirements are defined and communicated. It is also important that documentation of the training activities is completed and readily retrievable.

The *calibration* program ensures that instruments associated with manufacturing processes are calibrated and maintained. Instruments in the facility are typically classified as either critical, noncritical, or reference. Those instruments that are deemed either critical or noncritical are typically calibrated using NIST or other applicable standards on a routine basis.

A *preventive maintenance* (PM) program should be in place to support the ongoing qualification requirements for all production and support facilities. The objective of the program is to ensure that preventive maintenance requirements for the equipment are carried out throughout the operational life of the equipment. The PM requirements are established using the equipment manufacturer's recommendations and any additional requirements established by the operation site.

A *change control* program is used to regulate the alteration of systems and changes to processes. The program should outline the methods to be followed when a system, process, or equipment change is proposed. The change control program ensures that proposed changes are reviewed and approved by the quality unit and other appropriate departmental representatives before initiating changes. The program should also ensure implemented changes are reviewed before use in manufacturing. It is through this review that any required testing and documentation is defined to verify that the proposed change is acceptable and that the equipment remains in a validated state. The review also ensures that governing regulatory issues for the affected process/operation are addressed.

Validation should be performed in accordance with preapproved written protocols. The execution of the approved validation protocol will generate documentation that supports the intended use of the equipment and demonstrates compliance with current good manufacturing practices (cGMPs). A validation package that contains all documentation relevant to the validation study should be prepared at the completion of each protocol. The validation package should include the summary report that documents the results, observations, and conclusions from the implementation of the protocol, a copy of the protocol, and completed data sheets corresponding to each section of the protocol. The combination of the summary report and the protocol with completed attachments serves as a permanent document of the validation study.

Chemical Safety in Production. Before scaling the process from the pilot plant to commercial scale, a process hazard review is performed based on the additional data obtained during the pilot campaign. This review should include the evaluation of reaction calorimetry data, powder ignitability, and the results of the acute and chronic toxicity testing of all raw materials, intermediates, and the product. The battery of toxicity testing can include mutagenicity, teratogenicity, and carcinogenicity; acute dermal and ocular irritation testing results; absorption routes for raw materials, intermediates, and products; and potential sensitizers in the process. Antidotes to acutely toxic materials should also be identified as part of this evaluation. Personnel protective equipment such as gloves, goggles, and protective garments should also be reevaluated at this point based on experience gained from pilot plant operations. Any industrial hygiene sampling data obtained from various operations during the pilot studies should also be included in this evaluation.

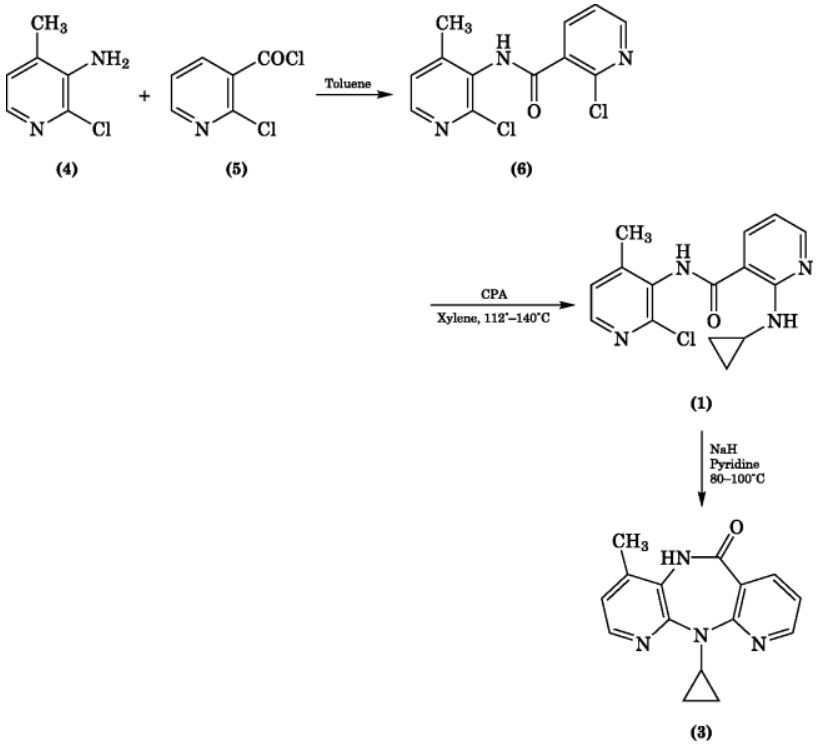
Environmental Controls in Production. Environmental permit requirements should be evaluated based on the commercial-scale material balance and new equipment specifications. Testing requirements for environmental evaluation should include acute fish and invertebrate toxicity for raw materials, intermediates, and products; biodegradation of raw materials, intermediates, and products; microbial growth inhibition of raw materials, intermediates, and products; water coefficients (KOW) and water solubility for raw materials, intermediates, and products; and waste treatability test results. Particular emphasis should be placed on the evaluation of the compatibility of the new process waste streams with the existing waste-treatment systems. If any process waste streams require off-site disposal into regulated hazardous waste landfills, leaching experiments may also be required.

3. Nevirapine

3.1. Background. In 1986 Boehringer Ingelheim Pharmaceuticals initiated an antiviral HIV research program that focused on the identification of potential nonnucleosidic reverse transcriptase inhibitors with the specific intent to develop an AIDS drug with reduced adverse side effects. A high throughput screening method was established using AZT as a standard. Promising candidates were screened for mammalian DNA polymerase as well as other enzymes and receptors. Nine months after the first lead compound was identified, nevirapine (**3**) was approved as a development candidate.

The nevirapine clinical program focused on both single and combination drug therapies. Clinical results indicated that this material not only was effective in the treatment of HIV-related illness but also was found to be well tolerated and safe. Boehringer Ingelheim submitted an NDA (New Drug Application) in February 1996 and the new AIDS drug was approved in July 1996.

3.2. Evolution of the Nevirapine Synthesis. *Medicinal Chemistry Synthetic Route.* The initial nevirapine synthesis developed by the Medicinal Chemistry Group entailed the condensation of 2-chloro-3-amino-4-methylpyridine (CAPIC, **4**) with 2-chloronicotinoylchloride (**5**), to give the 2,2′-dihaloamide (**6**). Treatment of (**6**) with four equivalents of cyclopropylamine in xylene at 120–140°C under autogenous pressure produced the 2′-alkylamino adduct (**1**) followed by ring closure with sodium hydride in pyridine at 80–100°C, to give nevirapine (**3**), as shown in eq. 2.



(2)

The basic synthetic strategy developed during this phase of drug development was quite sound and provided an excellent starting point for future process development efforts. The synthesis exhibited significant elements of convergence, starting with two functionalized pyridine precursors, which were only three chemical steps away from the target molecule. However, technical barriers existed that impeded the ability to meet the short-term API requirements for toxicology and clinical supplies, and additional process issues would need to be addressed to obtain a commercially viable synthesis from this point in the nevirapine process development. The most critical short-term issue was with the ability to obtain significant quantities of raw materials to meet the bulk active needs to support the drug evaluation efforts.

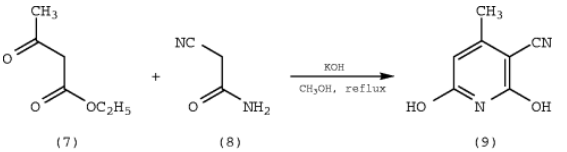
The 2-chloronicotinoylchloride (**5**) was easily prepared from 2-chloronicotinic acid, which was commercially available in multi-ton quantities. The most significant initial concern was with the ability to obtain pilot-scale quantities of CAPIC (**4**). Gram quantities of this material were initially obtained by the reduction of 2-chloro-4-methyl-3-nitropyridine. Small quantities of this material were initially obtained from laboratory supply houses, but significant scale-up quantities were not commercially available.

Attempts were made to nitrate both 2-hydroxy-4-methylpyridine and 2-amino-4-methylpyridine, which are commercially available, by conventional synthetic methods (14). However, the major product from both of these reactions was the 5-nitro adduct, with less than 30% of the desired 3-nitro isomer present in the reaction mixture. The yield of the desired isomer was improved to 82% by adding the nitric acid/sulfuric acid premix to the respective substrates at 0–5°C, followed by heating at 60–80°C for 1 h (15). However, the physical separation of the products proved to be industrially impractical because of the similarity in physical properties of the respective isomers.

Based on the information obtained from these experiences, the initial nitration approach was abandoned. The thrust of chemical and process development activities was redirected toward the development of a CAPIC process that could, as a minimum requirement, be scaled up to produce pilot plant quantities of this raw material to support, toxicology, formulation, and clinical studies.

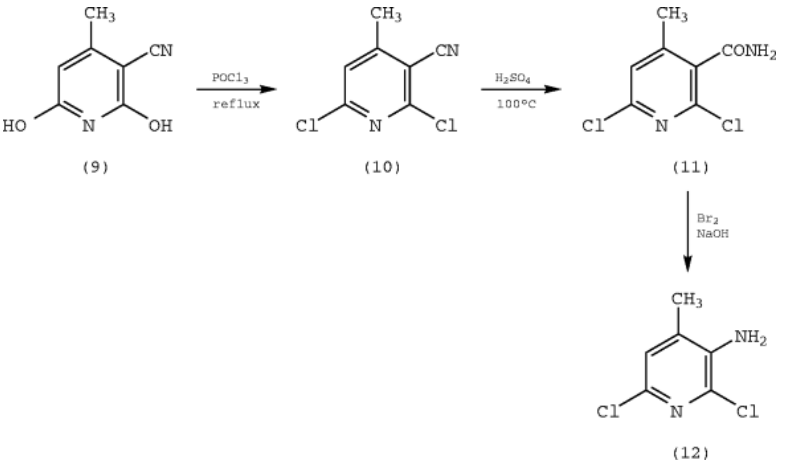
Chemical Development and Pilot Plant Scale-Up. Having benefited from the experience gained during the development of the nevirapine medicinal chemistry route, chemical development technical efforts initially shifted to the identification and evaluation of synthetic alternatives for the preparation of CAPIC. As previously stated, 2-chloro-3-nitro-4-methylpyridine could be readily converted to CAPIC by catalytic reduction. However, the ability to obtain significant quantities of this material was problematical because of the lack of reaction selectivity. Alternative approaches to the introduction of the 3-amino group were examined and found to be quite promising. Functionalized nicotinonitriles have been produced in high yield from readily available acyclic precursors by the Guareschi-Thorpe condensation (16). The 3-cyano substituent could be readily converted to the corresponding amine by hydrolysis to the amide followed by a Hofmann rearrangement (17). A process for the preparation of 2,6-dihydroxy-4-methyl-3-cyanopyridine (**9**) through use of this method was identified, which employed ethyl acetoacetate (**7**) and cyanoacetamide (**8**) as relatively inexpensive and readily available raw materials (18) (eq. 3). Further investigation revealed

that (**9**) is commercially available in multi-ton quantities.



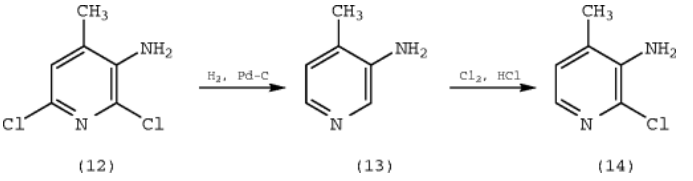
92% Yield (3)

Conditions were established to chlorinate this intermediate by use of phosphorous oxychloride, to give 2,6-dichloro-4-methyl-3-cyanopyridine (**10**), followed by acid hydrolysis of the 3-cyano substituent and conversion to the amine under Hofmann rearrangement conditions (eq. 4).



(4)

Efforts to selectively remove the 6-chloro substituent from either (**10**), (**11**), or (**12**) were unsuccessful. However, removal of both chlorine atoms by catalytic dechlorination (19) followed by selective rechlorination in the 2-position gave the desired product, as shown in eq. 5 (20).

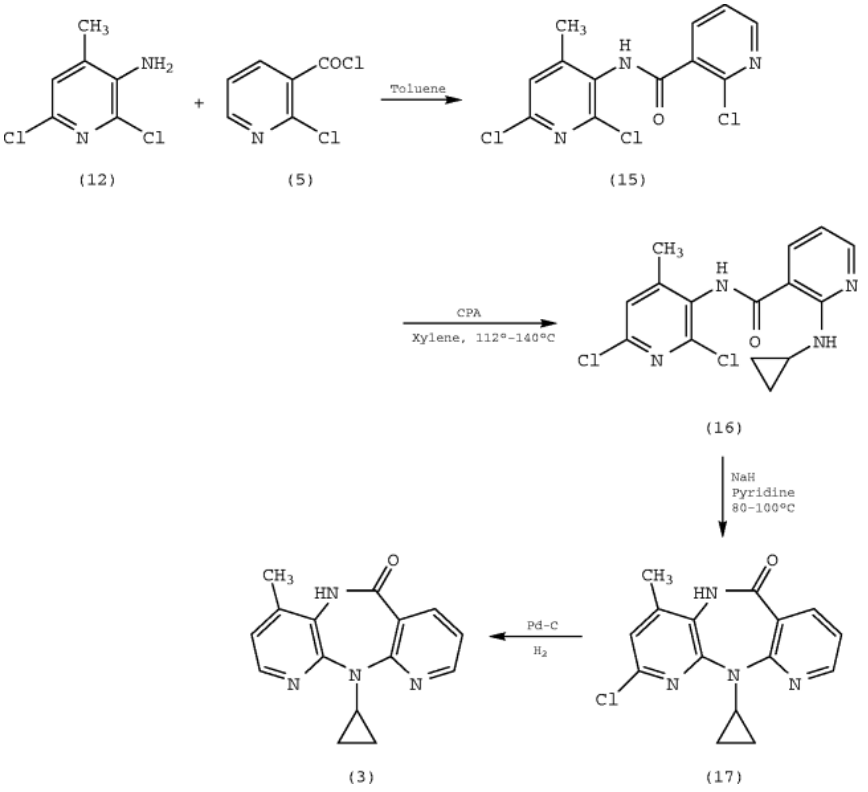


(5)

This method was used to produce the nevirapine API requirements through Phase III clinical trials as well as for commercial launch and production. Although this synthetic approach lacked atom economy with respect to the removal and addition of chlorine atoms, it provided the opportunity to meetthe short-term API supply needs and established a synthetic strategy upon which further development activities would benefit. It should also be noted that all process steps from the commercially available raw material 2,6-dihydroxy-4-methyl-

3-cyanopyridine (**9**) are carried out in aqueous media, making this option also environmentally attractive.

An alternative synthetic option was also examined that would eliminate the dechlorination/rechlorination process steps for the preparation of CAPIC, which is shown in eq. 6. In this approach the chloride was removed in the last chemical step from (**17**), eliminating the dechlorination of (**12**) and selective rechlorination of (**13**). Although this option provided significant synthesis advantages over the existing process, this alternative method produced a different impurity profile from that of the original process (eq. 2). For this reason, revalidation of the API impurity profile, toxicology, and other pharmacological and regulatory issues would be required. Because this option was identified late in the chemical development process, it was decided that the potential process benefits would be more than offset by the additional efforts required to requalify the alternative process, and this option was eliminated from further commercial consideration.



(6)

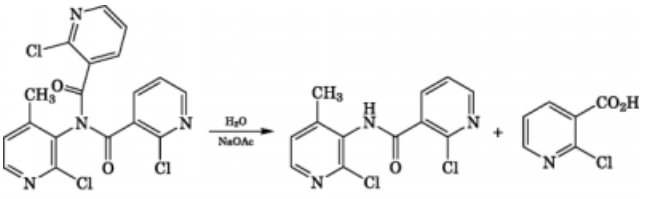
Process Development and Pilot Plant Scale-Up. The nevirapine process scheme used during chemical development (eq. 2) provided the basis on which to begin process development studies, with the objective of defining reaction conditions that would allow production to be carried out on a routine commercial basis. In this process, the basic elements of the molecule are introduced with the condensation of CAPIC (**4**) and 2-chloroniconinoylchloride (**5**). Using FDA guidelines (21) for defining the starting point in the synthesis for regulatory purposes,

CAPIC was considered a raw material in the synthesis. This provided the opportunity to implement further CAPIC process improvements in the preparation of CAPIC after the product launch with limited regulatory impact. With this in mind, priority was given to the condensation ring closure and purification steps that were filed in the New Drug Application (NDA).

In the manufacture of CAPIC, the reaction conditions were found to be quite acceptable for commercial operations, with minimal process modifications required to maximize the reactor utilization. However, reaction selectivity problems were encountered with Step 4 during pilot runs that had not been observed in previous work. An alternative set of reaction conditions was established that employed hydrochloric acid and hydrogen peroxide to selectively chlorinate the 2-position of (**13**). Process research established that a very narrow temperature range is required for this step, and the reaction temperature is controlled by the rate of addition of the hydrogen peroxide.

The condensation reaction required significant process development modifications from the procedure used to produce the initial drug development requirements. 2-Chloronicotinoylchloride (**5**) was prepared *in situ* during medicinal and chemical development runs by adding 2-chloronicotinic acid to a 5 molar excess of thionyl chloride as a neat reaction mixture. Upon completion of the reaction, excess thionyl chloride was removed by distillation. The residue was then redissolved in toluene, followed by the addition of CAPIC in toluene and sodium carbonate to neutralize the excess HCl liberated from the condensation. An alternative procedure was developed with the use of a 10% molar excess of thionyl chloride in toluene to produce (**5**). The excess thionyl chloride was removed by distillation and to the resulting mixture was added to the CAPIC/toluene solution, to give (**14**).

The work-up conditions for the condensation step (eq. 6) were also modified to accommodate commercial operations. Sodium carbonate was used in the initial chemical development pilot plant batches to absorb the by-product HCl from the reaction. The quantities of carbon dioxide produced from the neutralization made this approach impractical in a commercial plant. To complicate matters, the amide bond formed during the condensation was subject to hydrolysis under strongly acidic conditions. Solid sodium acetate was added to the reaction mixture as a buffer to address this issue. A significant quantity of the diacetylation product (**18**) was also detected in the reaction mixture before work-up. However, this material rapidly hydrolyzes to the condensation product (**6**) and 2-chloronicotinic acid upon exposure to water (eq. 7).

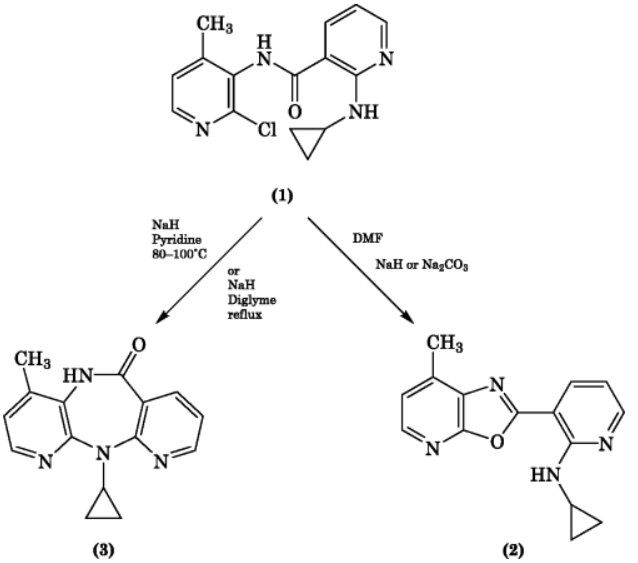


(18) (6) (19) (7)

The use of cyclopropylamine for the preparation of (**1**) (eq. 6) also presented a significant process optimization opportunity. In the initial pilot studies, four

molar equivalents of cyclopropylamine (CPA) were used in the reaction medium. Although CPA appears to be a simple building block, it is rather expensive on a per kilogram basis and represents a significant cost contribution to the overall drug substance. One mole of CPA was initially used to absorb the by-product HCl from the reaction. Calcium oxide was found to be a much more cost-effective substitution as a neutralizing agent. To efficiently remove the calcium salts before further processing, a centrifugation step was added to the work-up. However, even with calcium oxide present, a 2.5 molar excess of cyclopropylamine was still required to carry the reaction to completion. Efforts to telescope this operation into the ring-closure step were successful and (**1**) was treated as a non-isolated intermediate in process development pilot runs as well as on a commercial scale after removal of the calcium salts. Reaction temperature profile studies of this step indicated that the cyclopropylamine addition reaction occurred between 125°C and 145°C. However, a significant exothermic side reaction was observed above 145°C. Although this side reaction was not observed in any pilot trials, redundant cooling and ventilation systems were installed to pilot and commercial equipment to ensure safe operation of this process step.

One of the most critical issues to be addressed from these development activities concerned the specific reaction conditions employed in the final cyclization step (eq. 8). The medicinal chemistry route used pyridine as the reaction solvent medium and sodium hydride as the base. It was later recognized from solvent screening studies that the reaction pathway for the ring closure was solvent dependent. When dimethylformamide (DMF) was used as the solvent, an alternate cyclization pathway was observed (eq. 8). The oxazolo[5,4-]pyridine (**2**) is the exclusive product under these conditions. This product arises from the displacement of the chlorine atom by the amide carbonyl oxygen. A 2.8 molar excess of sodium hydride is required to carry the reaction to completion. The first mole of sodium hydride is consumed with the deprotonation of the more acidic amide protone.



(8)

If a base of insufficient strength is used in this reaction, the ring closure to the oxazol (**2**) primarily occurs. Although no industrially practical substitute could be found for sodium hydride as a reagent base, diglyme was found to be an effective alternative solvent to promote the conversion of (**1**) to nevirapine (**3**). This was accomplished through an effective collaboration between members of the respective chemical and process development teams. Because of the low autoignition temperature of diglyme, significant equipment modifications were required to upgrade the pilot and production facilities to meet the more stringent electrical code requirements.

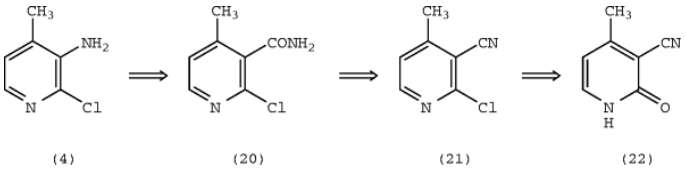
One issue with the use of sodium hydride as a reagent in pilot and commercial operations is the storage and handling requirements for this material. Sodium hydride is typically obtained commercially as a 60% amalgam in mineral oil to stabilize the reagent. In the nevirapine process, the mineral oil tends to agglomerate with the product upon precipitation from the reaction mixture. An intermediate purification step was developed through use of DMF as a crystallization medium. The crude product was dissolved in hot DMF followed by charcoal treatment to absorb the residual mineral oil associated with the product. The charcoal was then removed by filtration followed by evaporative crystallization of the product. A final aqueous crystallization was carried out to remove residual quantities of DMF from the product by acidification with hydrochloric acid followed by treatment with caustic to precipitate the product.

Commercial Production and Process Optimization. On February 23, 1996, Boehringer Ingelheim Pharmaceuticals submitted the NDA for nevirapine to the FDA. Production of the nevirapine API launch batches began within weeks after the submission. The company received regulatory approval for the product in July of that same year. A priority review of the NDA was initiated by the Agency based on the nature of the drug indication. Because of the accelerated drug development timeline, the procedure used in the final process development piloting campaign was transferred to the production unit virtually unchanged. Only minor modifications to the existing production equipment were made to address electrical code requirements.

As previously noted, having developed a relatively converging synthesis for nevirapine provided the opportunity to define CAPIC as a raw material rather than a registered intermediate in the process. This in turn provided Boehringer Ingelheim with the flexibility to manage the CAPIC manufacturing requirements more effectively. This can be a particularly important issue with new product launches in general, given the high level of uncertainty in initial market forecasts.

As it turned out, nevirapine was well received in the marketplace as an effective AIDS treatment and post-launch sales consistently exceeded the market projections. With this rapid growth came an increasing awareness of the need to improve the synthesis of CAPIC (**4**) to meet the growing drug substance demands. The linear nature of the CAPIC synthesis as well as the lack of atom economy in the method were recognized as the major process deficiencies. A retrosynthetic analysis of (**4**) (eq. 9) was carried out to evaluate alternative options for the preparation of this material. The goal of this effort was to limit the number of chemical transformations in the synthesis by constructing a pyridine ring with the optimal functionalization from acyclic precursors. The

conditions used in the existing commercial process to introduce the amino group in the 4-position by the hydrolysis and Hofmann rearrangement appeared to be an effective approach. The 2-chloro- 3-cyano-4-picoline (**21**) could be readily obtained from 3-cyano-4-methyl-2-pyridone (**22**) by chlorination with phosphorous oxychloride.



(9)

Research efforts were directed toward the evaluation of options for the preparation of (**22**) from commercially available starting materials. Several approaches were examined, all with the common feature to use a Knovenagel condensation reaction to establish the desired regiochemistry for the target molecule.

Option 1 22, as shown in Fig. 4, employs acetone and 2-cyanoethyl acetate (**23**) in the initial Knovenagel condensation. The resulting α-β-unsaturated cyanoacetate (**24**) is reacted with DMF-acetal to produce (**25**). The ring-closure step was conducted under Pinner reaction conditions, to give ethyl 2-chloro-4-methylnicotinate (**26**), which is converted to (**4**) in three steps. However, low yields were observed in the ring-closure steps in this route. An alternative approach (23) was examined using an alternative synthetic approach (Option 2). In this procedure, acetone was reacted with malononitrile (**27**), to produce (**28**), followed by reaction with trimethylorthoformate, to give a mixture of (**29**) and (**30**). Although (**30**) is the predominant product from this reaction, both compounds are readily converted to (**22**) upon treatment with sulfuric acid. Low yields observed in the formulation step led to the development of Option 3. In this procedure, the formulation step is avoided by using a protected β-ketoaldehyde (**31**) in the Knovenagel condensation with malononitrile (**27**). The protected β-ketoaldehyde (**31**) is prepared from acetone, methylformate, and sodium methoxide, and is readily available in commercial quantities. The Knovenagel intermediate (**30**) was converted into (**22**) under acidic reaction conditions. Upon completion of an economic evaluation of these procedures, Option 3 (24) was selected for commercialization.

Other efforts to improve the commercial nevirapine process have been primarily driven by equipment modifications rather than amendments to the chemical process.

3.3. Summary. The FDA approval of nevirapine for the treatment of AIDS was granted less than seven years after the submission of the IND. During this period of time, many technical and regulatory barriers were overcome to bring this product to the marketplace. From a process development perspective, the challenge, as always, is in ensuring the uninterrupted supply of bulk active drug substance in support of the overall drug development effort without sacrificing the ability to deliver a commercially viable chemical process. Although these issues represent a common theme in most drug development case studies, the accelerated pace of the nevirapine project significantly magnified the complexity of the drug development effort. Fortunately, the major elements of the original

synthesis remained intact throughout the various phases of process development and provided the opportunity to conduct these activities in parallel with minimal regulatory impact.

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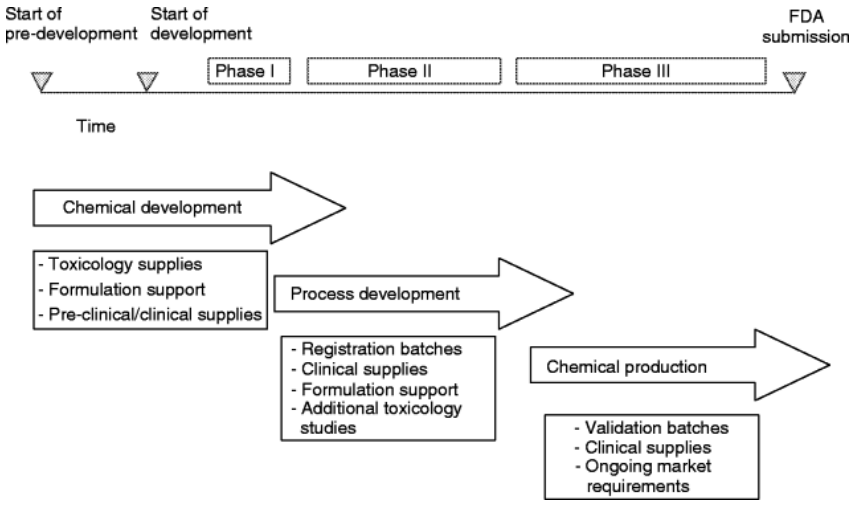

Fig. 1. Large-scale synthesis requirements for drug.

Fig. 2. Eight-steps linear synthesis.

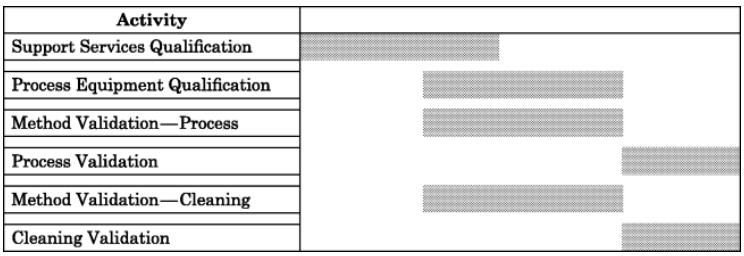

Fig. 3. Validation sequence.

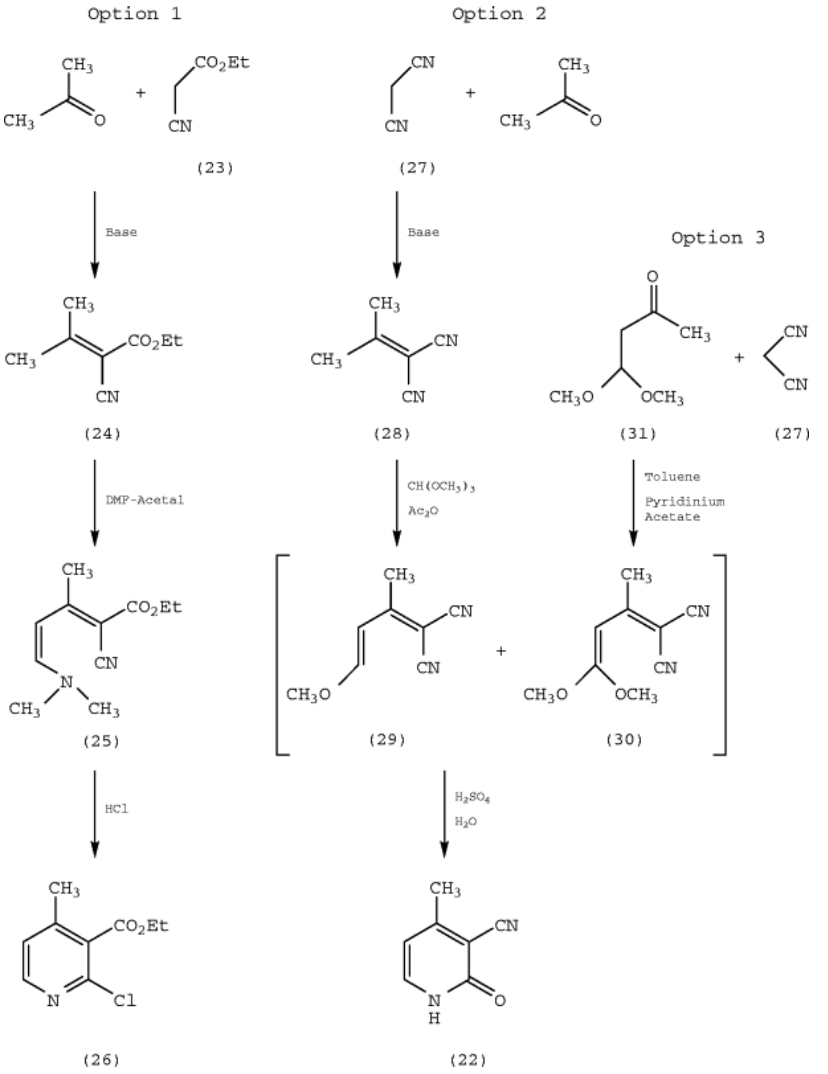

Fig. 4. Option 1 for preparation (**22**).