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# THE ART OF DRUG SYNTHESIS

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Edited by  
**Douglas S. Johnson**  
**Jie Jack Li**  
Pfizer Global Research and Development



**WILEY-INTERSCIENCE**  
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# THE ART OF DRUG SYNTHESIS





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# FOREWORD

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The discovery of efficacious new human therapeutic agents is one of humanity's most vital tasks. It is an enormously demanding activity that requires creativity, a vast range of scientific knowledge, and great persistence. It is also an exceedingly expensive activity. In an ideal world, no education would be complete without some exposure to the ways in which new medicines are discovered and developed. For those young people interested in science or medicine, such knowledge is arguably mandatory.

In this book, Douglas Johnson, Jie Jack Li, and their colleagues present a glimpse into the realities and demands of drug discovery. It is both penetrating and authoritative. The intended audience, practitioners and students of medicinal and synthetic chemistry, can gain perspective, wisdom, and valuable factual knowledge from this volume. The first two chapters of the book provide a clear view of the many complexities of drug discovery, the numerous stringent requirements that any potential therapeutic molecule must meet, the challenges and approaches involved in finding molecular structures that "hit" a biological target, and the many facets of chemical synthesis that connect initial small-scale laboratory synthesis with the evolution of a process for successful commercial production. The remaining 15 chapters provide a wealth of interesting synthetic chemistry as applied to the real world of the molecular medicine of cancer, infectious, cardiovascular, and metabolic diseases. At the same time, each of these chapters illuminates the way in which a first-generation therapeutic agent is refined and improved by the application of medicinal chemistry to the discovery of second- and third-generation medicines.

The authors have produced a valuable work for which they deserve much credit. It is another step in the odyssey of drug finders; a hardy breed that accepts the high-risk nature of their prospecting task, the uncertainties at the frontier, and the need for good fortune, as well as focus and sustained hard work. My ability to predict the future is no better than that of others, but I think it is possible that a highly productive age of medicinal discovery lies ahead, for three reasons: (1) the discovery of numerous important new targets for effective disease therapy, (2) the increasing power of high-throughput screening and bio-target structure-guided drug design in identifying lead molecules, and (3) the ever-increasing sophistication of synthetic and computational chemistry.

E. J. COREY



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# PREFACE

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Our first book on drug synthesis, *Contemporary Drug Synthesis*, was published in 2004 and was well received by the chemistry community. Due to time and space constraints, we only covered 14 classes of top-selling drugs, leaving many important drugs out. In preparing *The Art of Drug Synthesis*, the second volume in our series on “*Drug Synthesis*,” we have enlisted 16 chemists in both medicinal and process chemistry, encompassing nine pharmaceutical companies. Some authors were even intimately involved with the discovery of the drugs that they reviewed. Their perspectives are invaluable to the reader with regard to the drug discovery process.

In Chapter 1, John Lowe details “The Role of Medicinal Chemistry in Drug Discovery” in the twenty first century. The overview should prove invaluable to novice medicinal chemists and process chemists who are interested in appreciating what medicinal chemists do. In Chapter 2, Neal Anderson summarizes his experience in process chemistry. The perspectives provide a great insight for medicinal chemists who are not familiar with what process chemistry entails. Their contributions afford a big picture of both medicinal chemistry and process chemistry, where most of the readers are employed. Following two introductory chapters, the remainder of the book is divided into three major therapeutic areas: I. Cancer and Infectious Diseases (five chapters); II. Cardiovascular and Metabolic Diseases (six chapters); and III. Central Nervous System Diseases (four chapters).

We are grateful to Susan Hagen and Derek Pflum at Pfizer, and Professor John Montgomery of the University of Michigan and his students Ryan Baxter, Christa Chrovian, and Hasnain A. Malik for proofreading portions of the manuscript. Jared Milbank helped in collating the subject index.

We welcome your critique.

DOUGLAS S. JOHNSON  
JIE JACK LI

*Ann Arbor, Michigan*  
*April 2007*





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# THE ROLE OF MEDICINAL CHEMISTRY IN DRUG DISCOVERY

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John A. Lowe, III

## 1.1 INTRODUCTION

This volume represents the efforts of the many chemists whose ability to master both synthetic and medicinal chemistry enabled them to discover a new drug. Medicinal chemistry, like synthetic chemistry, comprises both art and science. It requires a comprehensive mind to collect and synthesize mountains of data, chemical and biological. It requires the instinct to select the right direction to pursue, and the intellect to plan and execute the strategy that leads to the desired compound. Most of all, it requires a balance of creativity and perseverance in the face of overwhelming odds to reach the goal that very few achieve—a successfully marketed drug.

The tools of medicinal chemistry have changed dramatically over the past few decades, and continue to change today. Most medicinal chemists learn how to use these tools by trial and error once they enter the pharmaceutical industry, a process that can take many years. Medicinal chemists continue to redefine their role in the drug discovery process, as the industry struggles to find a successful paradigm to fulfill the high expectations for delivering new drugs. But it is clear that however this new paradigm works out, synthetic and medicinal chemistry will continue to play a crucial role. As the chapters in this volume make clear, drugs must be successfully synthesized as the first step in their discovery. Medicinal chemistry consists of designing and synthesizing new compounds, followed by evaluation of biological testing results and generation of a new hypothesis as the basis for further compound design and synthesis. This chapter will discuss the role of both synthetic and medicinal chemistry in the drug discovery process in preparation for the chapters that follow on the syntheses of marketed drugs.

## 1.2 HURDLES IN THE DRUG DISCOVERY PROCESS

Although the tools of medicinal chemistry may have improved considerably (as discussed below), the hurdles to discovering a new drug have outpaced this improvement, accounting to a certain extent for the dearth of newly marketed drugs. Discussion of some of these hurdles, such as external pressures brought on by the public media and the stock market, lies outside the scope of this review. Instead, we will discuss those aspects of drug discovery under the control of the scientists involved.

One of the first challenges for the medicinal chemist assigned to a new project is to read the biology literature pertaining to its rationale. Interacting with biology colleagues and understanding the results from biological assays are critical to developing new hypotheses and program directions. Given the increasing complexity of current biological assays, more information is available, but incorporating it into chemistry planning requires more extensive biological understanding. This complexity applies to both the primary *in vitro* assay for the biological target thought to be linked to clinical efficacy, as well as selectivity assays for undesired off-target *in vitro* activities. Some of the same considerations apply to the increasingly sophisticated assays for other aspects of drug discovery, such as ADME (absorption, distribution, metabolism, and elimination) and safety, as summarized in Table 1.1.

The reader is referred to an excellent overview of the biology behind these assays, and their deployment in a typical drug discovery program (Lin et al., 2003). The tools for addressing each of these hurdles fall into two categories, *in silico* modeling and structure-based drug design, which are covered in Sections 1.3.1 and 1.3.2. Obviously, the final hurdle is *in vivo* efficacy and safety data, which generally determine a compound's suitability for advancement to clinical evaluation.

TABLE 1.1. Important Considerations for the Medicinal Chemists

In Vitro Target	In Vitro ADME <sup>a</sup>	Physical Properties	In Vivo	Safety
Primary assay	Microsomal stability (rat, human)	Rule-of-Five	Functional	Ames test
Whole cell assay	Hepatocyte stability (rat, human)	In silico ADME <sup>a</sup> (see Section 1.3.1)	Behavioral animal models (efficacy)	Micronucleus test
Functional assay	P450 substrate	Solubility	PK/PD <sup>c</sup>	HERG <sup>d</sup> IC <sub>50</sub>
Selectivity assays	P450 inhibitor  Permeability  Transporter efflux (e.g., P-gp <sup>b</sup> ) Protein binding	Crystallinity (mp, stable polymorph)		P450 induction  Broad ligand screening Others (depending on project)

<sup>a</sup>Absorption, distribution, metabolism, and elimination; <sup>b</sup>P-glycoprotein; <sup>c</sup>Pharmacokinetics/pharmacodynamics; <sup>d</sup>Concentration for 50% inhibition of the function of the delayed rectifier K<sup>+</sup> channel encoded by the *human ether a-go-go related-gene* (HERG).

## 1.3 THE TOOLS OF MEDICINAL CHEMISTRY

### 1.3.1 In Silico Modeling

To overcome the many hurdles to discovering a new drug, medicinal chemists must focus on synthesizing compounds with drug-like properties. One of the first tools developed to help chemists design more drug-like molecules takes advantage of an area totally under the chemist's control—the physical properties of the compounds being designed. These are the rules developed by Chris Lipinski, sometimes referred to as the “Rule-of-Five” (Ro5), which describe the attributes drug-like molecules generally possess that chemists should try to emulate (Lipinski et al., 2001). The Ro5 states that drug-like molecules tend to exhibit four important properties, each related to the number 5 (molecular weight <500; cLogP, a measure of lipophilicity, <5; H-bond donors <5; and H-bond acceptors <10). The Ro5 can be applied all the way from library design in the earliest stages of drug discovery to the final fine-tuning process that leads to the compound selected for development. Correlating microsomal instability and/or absorption/efflux with Ro5 properties can also provide insight about the property most important for gaining improvement in these areas.

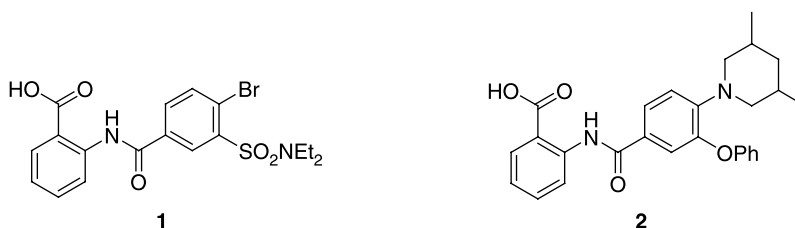
As is the case with any good model, the Ro5 is based on data, in this case from hundreds of marketed drugs. Using more specific data, models to address each of the hurdles in the drug discovery process have been developed (for comprehensive reviews, see Beresford et al., 2004; van de Waterbeemd and Gifford, 2003; Winkler, 2004). These include models of solubility (Cheng and Merz, 2003; Hou et al., 2004; Liu and So, 2001), absorption/permeability (Bergstroem, 2005; Stenberg et al., 2002), oral bioavailability (Stoner et al., 2004), brain penetration (Abbott, 2004; Clark, 2003) and P450 interaction (de Graaf et al., 2005). More recently, the solution of X-ray crystal structures of the P450 enzymes 3A4 (Tickle et al., 2005) and 2D6 (Rowland et al., 2006) should enable application of structure-based drug design (see below) to help minimize interactions with these metabolic enzymes. Models for safety issues, such as genotoxicity (Snyder et al., 2004) and HERG (*human ether a-go-go related-gene*) interaction (which can lead to cardiovascular side effects due to QT prolongation) (Aronov, 2005; Vaz and Rampe, 2005) are also being developed. Although this profusion of in silico models offers considerable potential for overcoming hurdles in the drug discovery process, the models are only as good as the data used to build them, and often the best models are those built for a single project using data from only the compounds prepared for that specific project.

The models described above can be used, alone or in combination with structure-based drug design (see Section 1.3.2), to screen real or virtual libraries of compounds as an integral part of the design process. These improvements in library design, coupled with more efficient library synthesis and screening, provide value in both time and cost savings. The move towards using this library technology has been accelerated by the availability of a new resource for library generation: outsourcing (Goodnow, 2001). Contract research organizations (CROs) in the United States or offshore provide numerous synthetic services such as synthesis of literature standards, templates and monomers for library preparation, and synthesis of libraries (D'Ambra, 2003). These capabilities can relieve in-house medicinal chemists of much of the routine synthetic chemistry so they can focus on design and synthesis to enable new structure-activity relationships (SAR) directions. For an overview of the process as it fits together for the successful discovery of new drugs, see Lombardino and Lowe, 2004.

### 1.3.2 Structure-Based Drug Design (SBDD)

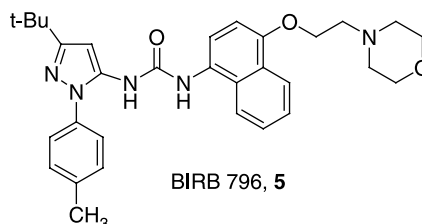
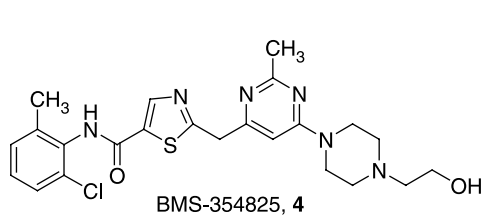
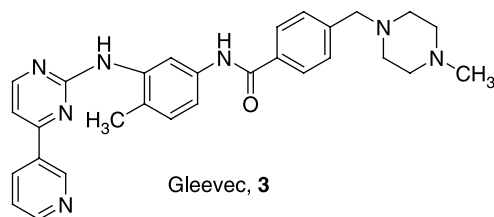
Progress in SBDD has been steady over the past two decades such that it has become a generally accepted strategy in medicinal chemistry, transforming the way medicinal chemists decide how to pursue their series' SAR. Although obtaining X-ray crystallographic data for SBDD was achieved early on, it has taken many years to learn how to interpret, and not over-interpret, this data. Structural information on the protein target provided by X-ray crystallography offers the greatest structural resolution for docking proposed ligands, but other spectroscopic techniques, such as nuclear magnetic resonance (NMR), have demonstrated their utility as well. X-ray crystallography, however, is generally restricted to analysing soluble proteins such as enzymes. Also required is a ready source of large quantities of the target protein for crystallization, as is often the case for proteins obtained from microorganisms grown in culture.

Bacterial proteins are an ideal starting point for SBDD, as in the case of the  $\beta$ -ketoacyl carrier protein synthase III (FabH), the target for a recent SBDD-based approach (Nie et al., 2005). FabH catalyzes the initiation of fatty acid biosynthesis, and a combination of X-ray data along with structures of substrates and known inhibitors led to selection of a screening library to provide a starting point for one recent study. Following screening, co-crystallization of selected inhibitors then guided the addition of functionality to take advantage of interactions with the enzyme visualized by X-ray and docking studies. A 50-fold improvement in enzyme inhibitory potency was realized in going from structure **1** to **2**, accounted for by amino acid side-chain movements revealed by X-ray co-crystal structures of both compounds with the enzyme. Although much remains to be learned so that these side-chain movements can be predicted and exploited for new compound design, the study nonetheless provides a successful example of the implementation of SBDD in drug design.

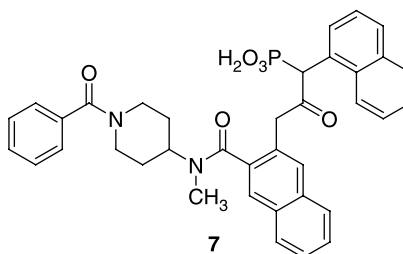
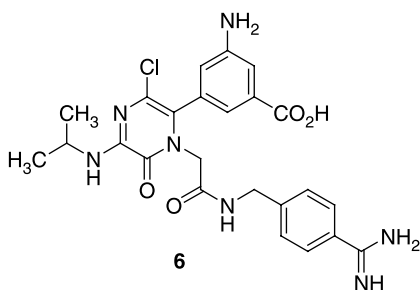


Although human proteins are more challenging to obtain in sufficient quantity for crystallization, modeling based on X-ray crystal structures has been successfully applied to many human targets. Probably the best-known efforts have been in the kinase area in search of anticancer drugs, which has been reviewed recently (Ghosh et al., 2001). For example, X-ray crystallographic data revealed important aspects of the binding of the anticancer drug Gleevec (**3**) to its target, the Bcr-Abl kinase, including the role of the pendant piperazine group, added originally to improve solubility, and the requirement for binding to an inactive conformation of the enzyme (Schindler et al., 2000). Combined with studies of the mutations responsible for Gleevec-resistant variants of Bcr-Abl, these studies enabled design of a new compound, BMS-354825 (**4**), active against most of these resistant mutants (Shah et al., 2004). More recently, non-ATP binding site inhibitors have been discovered and modeled by SBDD. For example, SBDD helped to characterize a new class of p38 kinase inhibitors that bind to a previously unobserved conformation of the enzyme that is incompatible with ATP binding (Pargellis et al., 2002). Insights from

SBDD then guided design of a picomolar p38 kinase inhibitor based on binding to this site, BIRB 796 (**5**).

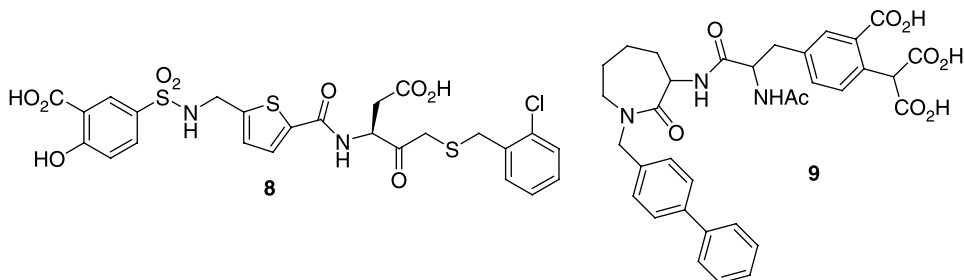


SBDD approaches to other soluble proteins have produced inhibitors of the tissue factor VIIa complex (Parlow et al., 2003) and cathepsin G (Greco et al., 2002). In the case of factor VIIa inhibitors, X-ray data provided information for both designing a new scaffold for inhibitors and for simultaneously improving binding affinity and selectivity over thrombin. Compound **6** from this work was advanced to clinical trials based on its potency and selectivity for factor VIIa inhibition. The cathepsin G inhibitor program revealed a novel binding mode for an alpha-keto phosphonate to the enzyme's oxyanion hole and active site lysine, as well as an opportunity to extend groups into a vacant binding site to improve potency. The result was a nearly 100-fold increase in inhibition following an SAR study of this direction using the amide group in compound **7**.

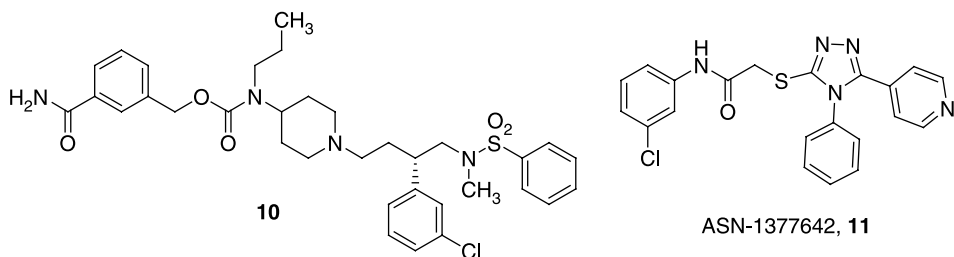


Another spectroscopic technique that has been widely applied to drug design is nuclear magnetic resonance (NMR) spectroscopy (Homans, 2004). Both X-ray crystallography and NMR can be used to take advantage of the opportunity to screen fragments, small molecules with minimal enzyme affinity, but which can be linked together with structural information to form potent inhibitors (Erlanson et al., 2004). For example, a recent approach to caspase inhibitors generated its lead structure by tethering an aspartyl moiety to a salicylic acid group; an X-ray co-crystal structure of the most potent compound **8** was found to mimic most of the interactions of the known peptidic caspase inhibitors

(Choong et al., 2002). Another example explored replacement of the phosphate group found in most Src SH2 domain inhibitors with various heteroatom-containing groups by soaking fragments into a large crystal and obtaining X-ray data, leading to the 5 nM malonate-based inhibitor **9** (Lesuisse et al., 2002).



For proteins that are not water soluble, such as membrane proteins, techniques that depend on crystallization are very challenging. Homology modeling is an alternative that can be applied to transmembrane proteins such as the G-protein-coupled receptors (GPCRs), which are the target of many marketed drugs. Based on X-ray data for a prototype member of this family of proteins, bovine rhodopsin, a number of homology models for therapeutically relevant GPCRs have been built. In the case of the chemokine GPCR CCR5, a target for AIDS drugs, a homology model afforded an appreciation of the role of aromatic interactions and H-bonds involved in binding antagonists (Xu et al., 2004). A three-dimensional QSAR model was next developed based on a library of potent antagonists, and then combined with the homology model to confirm important interactions and indicate directions for new compound design, resulting in compound **10**, a subnanomolar CCR5 antagonist. A more sophisticated approach based on docking of virtual compounds to a homology model for the neurokinin NK-1 receptor for the neurotransmitter peptide substance P has revealed structurally novel antagonists (Evers and Klebe, 2004). The most potent of these, ASN-1377642 (**11**), overlaps nicely with CP-96,345, the literature NK-1 receptor antagonist on which the pharmacophore used for virtual screening was based. Similar combinations of SBDD-based technology are providing insights for new compound design in numerous areas of medicinal chemistry.



## 1.4 THE ROLE OF SYNTHETIC CHEMISTRY IN DRUG DISCOVERY

Some may ask why anything needs to be said about synthetic chemistry as a tool for drug discovery; after all, it is common to hear that “we can make anything.” On the other hand, we can only carry out biological evaluation of compounds that have been synthesized.



Once the evaluation of biological activity and physical properties has been used to design new targets, a suitable synthetic route must be developed. However, considerations of what can be readily prepared factor into design much earlier. Chemists typically recognize familiar structural features for which they know a feasible synthetic route as they analyze data and properties. Design is guided by what can be readily made, especially what can be prepared as a library of compounds, so that work can begin immediately toward initiating the next round of biological testing.

Although there will always be limitations to what can be synthesized based on our imperfect knowledge, recent developments in two areas have facilitated the chemist's job: analysis/purification and synthetic methodology. In the first area, routine high-field NMR instruments allow <sup>1</sup>H-NMR and <sup>13</sup>C-NMR characterization of small amounts (<10 mg) of organic compounds. Liquid-chromatography/mass spectroscopy (LCMS) and other rapid analytical techniques, combined with medium- and high-pressure chromatography, allow for ready separation of reaction mixtures. New technologies such as reactor chips and miniaturization, supercritical fluids and ionic fluid reaction solvents, and chiral separation techniques will continue to improve synthetic capabilities.

In the second area, two recent advances have transformed synthetic methodology: transition-metal catalyzed cross-coupling reactions (Nicolaou et al., 2005) and olefin-metathesis technology (Grubbs, 2004). The formation of carbon-carbon bonds is probably the most fundamental reaction in synthetic chemistry. For the first several decades of the twentieth century, this reaction depended primarily on displacement of electrophilic leaving groups by enolate anions (or enamines) or addition of organometallic (e.g., Grignard) reagents. The advent of palladium-catalyzed coupling of more stable derivatives, such as olefins and acetylenes, boronic acids/esters, and tin or zinc compounds changed this simple picture. At the same time, the development of air-stable catalysts for producing complex carbon frameworks by metathesis of olefins expanded the chemist's repertoire. These methods allow much greater flexibility and tolerance for sensitive functional groups, enabling construction of more complicated, highly functionalized carbon frameworks.

Assembling this methodology, along with that developed over the previous century, into library-enabled synthesis allows the preparation of the large numbers of compounds favored for today's search for lead compounds using high-throughput screening (HTS) and in lead compound follow-up. Combinatorial chemistry was initially facilitated by developments in robotic handling technology and, for solid-phase synthesis, by Merrifield peptide synthesis. Both solution-phase (Selway and Terret, 1996) and solid-phase (Ley and Baxendale, 2002) parallel syntheses allow generation of large chemical libraries. The emphasis on these new technologies, combined with the cross-coupling and olefin metathesis synthetic methodologies, facilitates the synthesis of new classes of compounds with complex carbon frameworks. Their emergence as lead series and the ensuing follow-up are largely the result of their preponderance in the collection of compounds screened. In other words, it can be argued that synthetic methodology creates the chemical space that is available for screening and hence influences in a very profound way the medicines available to mankind. As the syntheses in the succeeding chapters make clear, synthetic chemistry plays a significant role alongside medicinal chemistry in the drug discovery process.

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# PROCESS RESEARCH: HOW MUCH? HOW SOON?

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Neal G. Anderson

## 2.1 INTRODUCTION

When one treats 1,2,3-trichloropropane with alkali and a little water the reaction is violent; there is a tendency to deposit the reaction product, the raw materials and the apparatus on the ceiling and the attending chemist. I solved this by setting up duplicate 12-liter flasks, each equipped with double reflux condensers and surrounding each with a half dozen large tubs. In practice, when the reaction took off I would flee through the door or window and battle the eruption with water from a garden hose. The contents flying from the flasks were deflected by the ceiling and collected under water in the tubs. I used towels to wring out the contents that separated, shipping the lower layer to [the client]. They complained of solids suspended in the liquid, but accepted the product and ordered more. I increased the number of flasks to four, doubled the number of wash tubs, and completed the new order.

They ordered a 55 gallon drum [of the product]. At best, with myself as chemist and supervisor, I could make a gallon a day, arriving home with skin and lungs saturated with 2,3-dichloropropene. I needed help. An advertisement in the local newspaper resulted in an interview with a former producer of illicit spirits named Preacher who had just done penance at the local penitentiary. He listened carefully and approved of my method of production, which he said might be improved with copper coils. Immediately he began to enlarge our production room by removing a wall, putting in an extra table, and increasing the number of washtubs and reaction set-ups. It was amazing to see Preacher in action (I gave him encouragement through the window); he would walk up the aisles from set-up to set-up putting in first the caustic then the water, then fastening the rubber stoppers and condenser, then using the hose. At this stage the room was a swirling mass of steam and 2,3-dichloropropene. We made a vast amount of material and shipped the complete order to [the client]—on schedule.

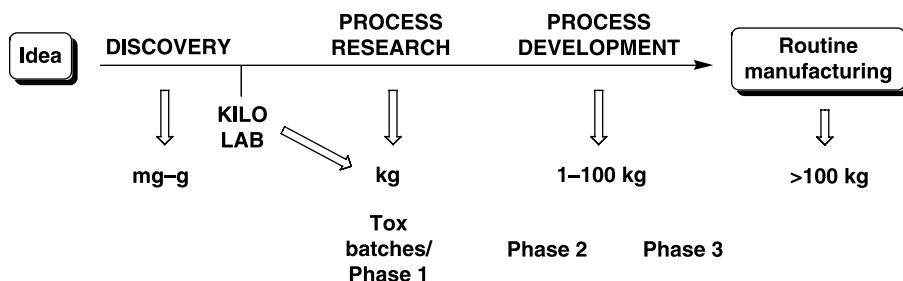
(Max Gergel, 1979)

Chemical process research and development has greatly evolved over the past six decades, and a number of resources are available (Anderson, 2000; Blaser and Schmidt, 2004; Cabri and Di Fabio, 2000; Collins et al., 1997; Gadamasetti, 1999; Lednicer, 1998; McConville, 2002; Rao, 2004; Repic, 1998; Weissermel and Arpe, 1997). In the above account of scale-up in the early 1950s, as described by the head of Columbia Organics, safety considerations, in-process controls, purification, and analyses were essentially nonexistent. Today we are concerned not only for containing the product in the process equipment, but also for keeping contaminants out of the batch. Today, such an operation would be conducted only after safety hazard analysis, selection of suitable reactors and protective personnel equipment (PPE), successful small-scale runs in the laboratory (use-tests), development of critical in-process controls, and thorough analyses of the product from the small runs. Then the process would be detailed in a log sheet or batch record, which would be approved by management. After completing the large-scale run, the product would be analyzed and its quality documented. Despite the changes that have evolved over the decades, it is important to note that both earlier and current processes have a key feature in common: delivery must be on time.

In the continuum that is drug development, timeliness is crucial. Delaying the introduction of a drug by six months may reduce the lifetime profits by 50% (Ritter, 2002). As a drug candidate moves closer to launch, more material is required, and more resources (expensive starting materials, attention of personnel, and so on) must be invested (Fig. 2.1). Timely process research and development (R&D) can avoid costly surprises that delay drug introduction. Because fewer than 10% of all drug candidates progress from pilot plant scale-up to successful launch (Mullin, 2006), people are justifiably cautious about investing time and money too early into process R&D.

Effective chemical process R&D speeds a drug to market. In the discovery laboratory, paying attention to the practices of process research is likely to improve yields of laboratory reactions, reproduce small-scale runs more easily, and scale up to 100 + g runs more efficiently. Observations may lead to better processes in later development, for example, by minimizing byproducts, easing work-ups and purification, and by detecting polymorphs.

Scale-up from grams to 100 g and more may lead to unexpected problems. Safe operations are essential to minimize risk during scale-up: with scale-up there is always increased liability from accidents, including injury to personnel, loss of equipment, delay of key deliveries, damage to a company's reputation, and more. Some companies require that safety hazard assessments be completed before any process is run in a pilot plant; others require safety hazard assessments before a process is scaled up to greater than a given threshold amount. Testing for such assessments may be conducted on



**Figure 2.1.** Batch sizes for compounds during drug development.