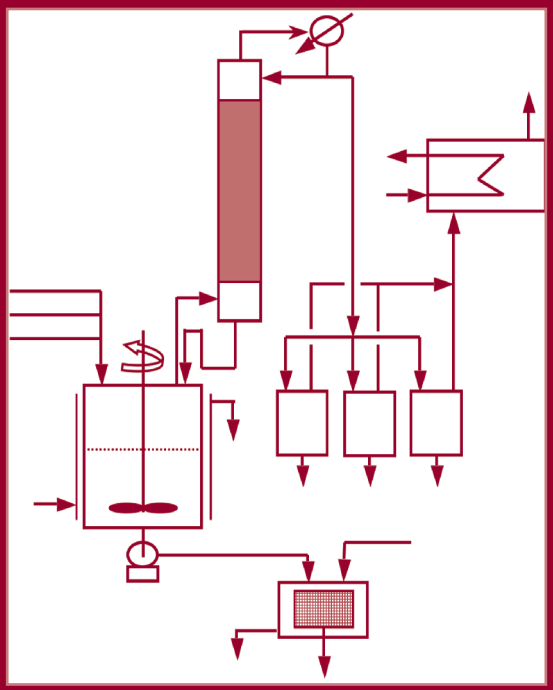
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 205

SECOND EDITION

Active Pharmaceutical Ingredients

Development, Manufacturing, and Regulation



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Preface

In the first edition of this book, I spoke of how active pharmaceutical ingredient (API) manufacturing fits within fine chemical manufacturing, describing how enormous changes during the 20th century have occurred in the pharmaceutical industry, causing equally significant changes in the bulk pharmaceutical chemical suppliers.

The intent of this second edition is to not only update what had been written earlier but also to add more definitive information on areas that require further emphasis and to expand the scope of the publication to include areas of significant importance to APIs. We have added a full chapter on biological manufacturing as well as sterile bulk manufacturing that remains a critical part of the field. We have divided the chapter on regulatory requirements into one focusing on requirements and expectations and another focusing on guidelines and strategies.

We have added full chapters on process safety, general plant safety, and environmental control. These chapters reflect the increased importance of handling the more exotic APIs being developed. These three chapters focus on better controlling the environment into which new processes enter and protecting the workers and the population that live near the plant.

In the years since the writing of the first edition, there has been and seems to continue to be a geographical shift for API manufacturing, away from the United States and particularly to India and China and other "third world" sources. This is partly due to the desire of these nations to sell APIs into the European and U.S. market and partly due to the drive for these countries to expand their presence in the world's finished pharmaceutical market itself, which requires API manufacture.

I must point out that each and every topic covered in this volume has changed in some fashion from the past and will continue to change in the future; therefore, the reader is receiving a "starting point" from which he or she must continue to follow the progress of a particular subject in order to keep current.

I wish to express my thanks to Informa for its invitation to assemble the second edition of this book and, particularly, to Sandra Beberman for her advice and continuing encouragement throughout this process.

Stanley H. Nusim

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1 Introduction

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Pharmachemical manufacturing is that branch of the fine chemical manufacturing industry directed to the manufacture of chemicals whose ultimate use will be in a final pharmaceutical dosage form, referred to as the active pharmaceutical ingredient (API). This industry segment has undergone very significant changes in much the same manner, but trailing, the pharmaceutical industry itself, from the time it emerged early in the 20th century.

Thus, we must examine what has happened in the pharmaceutical industry over this period to understand the implications for API manufacturing. This will lead us to the present time and to the goal of this book.

It is our objective to provide a reference book that speaks to those issues that need to be addressed to assure that an existing or proposed pharmachemical operation will meet its objective of supplying an API to meet a medical/market need efficiently and effectively. To better meet this objective, we have added chapters on biological manufacturing and sterile operations, as these operations have grown rapidly to a new level of importance in the API manufacturing environment.

The changes that have occurred are themselves a result of major changes that have taken place both directly and indirectly in and on the industry. These changes include company consolidations, both backward and forward integration; the increased and changed role of quality; the significant intensification of regulatory bodies worldwide; the impact of the greatly increased potency of APIs thereby reducing pharmachemical requirements and the broadening of the market worldwide.

These ideas will be discussed briefly here and touched on in depth in the subsequent chapters.

I. CONSOLIDATION AND INTEGRATION

The "pharmaceutical industry" at the turn of the 20th century was essentially the local pharmacy (or chemist as it was also known outside of the United States). The objective of the pharmachemical supplier to the local industry, at that time, was to provide all of the chemicals, including APIs, as needed by the pharmacist to formulate and compound the prescribing doctor's prescription.

Thus, the great pharmaceutical titans of today, such as Merck, were a fine chemical manufacturer providing a full variety of basic laboratory chemicals and solvents as well as the actives of the day to meet all of the formulating needs of the pharmacist. This activity was common in those early days, as well, to Pfizer, Bayer, and Sterling, among others.

The forward integration of these companies into providing the finished dosage form had by the middle of this past century become the standard rather than the exception as the medical community shifted to writing prescriptions for the local pharmacist to fill, prescribing finished dosage forms rather than the pharmacist compounding his or the doctor's own formulations.

This practice continues to this day, a major factor being the regulatory environment that was created and has grown over this past century. The need to determine the efficacy and safety of those formulated product has grown to very significant proportions during this period.

II. QUALITY

An overriding driving force in this direction, although it may never have been originally intended, has been the shift of governmental control that has been exercised by the U.S. Food and Drug Administration (FDA). A brief discussion of that change is now in order.

The initial purpose of the first Pure Food, Drug, and Cosmetics Act (Act) that was passed by Congress in the first decade of the last century was one of safety. It began by the regulation of those items of commerce that had the potential of poisoning the individual who used it if the product was contaminated. It is for this reason that the Act covered those three specific items, all lumped together although each being used for very different purposes.

The initial focus, at that time, for drugs as well as the other two types of ingested or topically applied products, was lack of contamination as determined by quality sampling and testing. In addition, and extrapolating that issue to new proposed pharmaceuticals, the key data required was the toxicity data and its ratio to the proposed dose level, the "therapeutic index." However, no data or judgment on efficacy was required for its proposed use. Its medical purpose and its ultimate use remained in the hands of the physician and the sponsoring company that promoted it.

In the middle 1950s, this changed dramatically when the Act was amended significantly. The change, driven by congressional hearings and the "thalidomide affair,"[a] now required not only more significant safety data, beyond simple toxicity but also more significantly scientific proof of efficacy. This now placed a new burden on the sponsoring company to provide unequivocal proof, to the government's satisfaction, that the addition of a new chemical entity at the dose level recommended was worthwhile to the public. The shift was due to the recognition that replacing a tried and true medications, which was widely used and its side effects well defined with a new compound with only limited experience in man, was in itself an unknown risk and therefore must be shown to be worth the risk.

This propelled the cost and the risk associated with the discovery and introduction of new chemical entities. This change was absorbed by the industry and set the stage for the next major shift in policy that came in the middle 1970s. This was the establishment of current good manufacturing practices (cGMPs) for the manufacture of pharmaceutical actives as well as the finished pharmaceutical products.

This was the next step in the focus of the FDA on the safety of the product. Up until this point, contamination (or lack thereof) was defined by the presence

[a] Thalidomide was an antinausea drug approved in Europe at that time and was before the FDA for approval in the United States. Pregnant women who were normally prone to nausea became an instant market for the new drug. However, very serious birth defects (missing limbs) were experienced in babies borne to many of the women who had taken the drug. This precipitated a worldwide reaction to review the new drug approval process. Needless to say, the drug was not approved in the United States at that time. (In recent years, it has been approved for limited special use in leprosy as well as a cancer treatment.)

(or absence) of foreign impurities not specified in the analytical protocol for the product. This was the case for either the pharmaceutical product or the API that went into the finished product. Although this could be a definitive test for a uniformly distributed contaminant, it would not necessarily find random contamination that occurred in processing or extraneous matter that could enter the system from dirty facilities or poor operating practices.

Finished goods testing, today, as it was at that time always depended upon the assumption of uniformity of product. It was this presumption that permitted the approval and release of a product based on the testing of 100 g of a 100 kg pharmachemical batch or 30 tablets of a lot of 500,000 tablets.

The concept of "cGMPs" and quality assurance became the dominant theme thereby pushing the analytical testing (quality control) into the background.

In principle, one now had to show, to have a product free of contamination, that the manufacturer produced the product in contaminant-free equipment in a clean facility, within equipment designed and tested to show consistent and reproducible product by people thoroughly trained and with full knowledge of the process. Thus, in the United States, this greatly shifted the emphasis to a more rigorous standard of "quality."

The most recent change implemented is the requirement of formal "validation" of facilities, equipment, and the process itself. This is the "proof" that the process and the facility can produce quality product on a consistent basis.

In a similar fashion, one can see the extension of the tighter regulations as they apply in the United States to Western Europe. Through the EU, they have implemented similar standards for the very same reason in Europe; additionally, many of the "third world" nations have already implemented its own GMP initiatives reemphasizing the growing uniformity in such requirements throughout the world.

All these factors are discussed more thoroughly in the appropriate chapters within this book.

III. POTENCY

A subtle change that has emerged in the methods of discovering and developing new drugs in the past decades has had significant impact on the pharmachemical industry.

In the early days, the key to drug discovery often was screening programs where laboratory-screening models were used to test new chemical entities for efficacy against specific disease candidates. Those that were effective, however, often found much of their potency diminished as the active, generally formulated into a pill, was attacked by normal body chemistry as it passed through the digestive system on its way to be absorbed into the blood and transported to the disease site. Thus, only a fraction of the orally ingested drug reached the drug target area. As a result, dose regimens for most oral drugs were 100 to 500 mg.

These dosing levels generated needs for significant quantities of actives in some cases into the millions of kilograms annually (5 billion tablets at 200 mg dose require 1 million kg of active). This resulted is significant dedicated plants for each drug active; particularly since the active was generally a complex organic molecule requiring many chemical steps to synthesize.

However, with the advent of the focus on biochemistry and the new sophistication to understanding the chemistry and biology of the body, today's

drugs are designed so as to be more potent. In addition, they can be chemically protected to limit the destruction of the drug as it passes through the body on its way to the target site. Thus, normal dosing of today's "designer" drugs are 5 to 20 mg, 10-fold less than in the past. This reduces the API need for "blockbuster" drugs by an order of magnitude (10 billion tablets at 10 mg dose requires 100,000 kg of API). This also suggests that the lesser volume products would require very small quantities of API making dedicated facilities for them very uneconomical.

These factors have refocused API manufacturing from facilities dedicated to a single API product to multiproduct manufacturing facilities. The added costs of a facility due to the more rigorous cGMPs that now apply favor these kinds of facilities where the cost can be shared by many rather than a single product.

This adds a very critical aspect to the operation because the issues of equipment clean out and turnaround particularly as the issue of cleanliness to assure that cross contamination does not occur.

IV. COMPUTER CONTROL AND AUTOMATION

This industry, like nearly all others, has seen the positive impact of the introduction of computers and automation in the manufacturing facilities. The first impact was in the automatic control systems that are used to maintain accurate and reproducible operating conditions for reaction and isolation systems. This was extended into the integration of multiple operations under computer control often eliminating or at least minimizing people intervention.

This itself caused some concerns for the FDA, which, in the past, depended on manual documentation by operators of batch procedures written and issued by people and people observing and recording all data. This was transformed to computer-recorded data and operating instructions being maintained in computer files. This generated an entire series of new issues that had to be dealt with by both the operation and the FDA. First was security to be sure that the automated instructions are safe from improper and unauthorized changes to the issue of signatures, often electronic signatures, a new concept that has become very common.

V. SUMMARY

The changes referred to above, and the changes that are to occur, without doubt, in the future, drive the need to understand where we are today and where we are going in the future. We have chosen to address the various segments and activities of a pharmachemical plant by having a focused discussion on each in the subsequent chapters.

Again, I repeat a statement from the preface. Each and every topic covered in this volume has changed from the past and will continue to change in the future; therefore, the reader is receiving a "starting point" from which he or she must continue to follow the progress to keep current.

2 Bulk Drugs: The Process Development Task

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I. INTRODUCTION

The purposes of this chapter are few and rather ambitious. The first is to provide a sound perspective of bulk drug process work to the uninitiated and the relatively new practitioner, hopefully without prejudice to the benefit that the approach herein might afford to an experienced but still restless practitioner. All work in a forest that is dense and rich in its variety; it should be regarded from a vantage now and then, and it is from such a deliberately selected vantage that the chapter unfolds.

Then there is the promotion of the power that the purposeful convergence of chemistry, microbiology, and chemical/biochemical engineering can bring to bear on the increasingly difficult task at hand: *the timely conception, development, and reduction to practice at scale of a sound process for the manufacture of a bulk drug*. In the 2000s, timely is shorthand for swift, sound encompasses safety to the environment and to people as well as amenability to various regulatory approvals, and reduction to practice at scale means that the resulting process can be used for reliable manufacture in whatever context might be first required.

> Chemistry, in the context at hand, is the aggregate of synthetic, analytical, and physical chemistry fields within what may be called the drug *process* chemistry discipline at large. The latter, while practiced for decades, has truly come into being in the 1990s, spurred mostly by the greater ascendance of the pharmaceutical industry among chemistry practitioners and by the enhanced role of the bulk drug process in the outcome of drug development. Whereas toxicology or clinical results were the exclusive causes for the demise of drug candidates, the greater difficulty in making today's more complex structures in today's regulatory milieu has for some time raised the profile of their bulk process development task as a factor in the overall outcome (1).
>
> Although first manufacture of the bulk drug is the paramount objective of the technology transfer to manufacturing, the process body of knowledge should be sturdy and complete enough to support expanded manufacture for product growth, as well as provide at least a clear sense of direction for process improvements or second-generation processing.

The above definitions conveniently describe a complex task to which considerable skills need to be applied with due deliberation and under constant managerial attention. Indeed, successful bulk drug process development, as just defined, requires that sufficient interdisciplinary and operational resources be brought together in a cohesive manner, not unlike that required by a critical mass in nuclear fission. Most often, having the resources is not enough, and their cohesiveness makes a significant difference in the degree of success, sometimes making the ultimate difference: *having or not having a new drug available when needed*.

Another sought perspective applies to the integration of the bulk drug process development task with the simultaneous drug development program at

large: toxicology, dosage form development, clinical development, and the assembly of the regulatory submissions. The latter, leading to the desired regulatory approvals as the culmination of the overall effort, has in recent years become increasingly dependent on the scope and execution of the process work for the bulk drug, which in some of its aspects has now become fastidious and greatly increased the burdens of the bulk process development task.

As the last objective, the methods of bulk drug process development will be weaved discreetly, if not seamlessly, throughout the chapter: (a) the principal issues that shape the methods, (b) the most trenchant choices confronting the process development team, and (c) some selected heuristics (i.e., empirical rules that, although lacking proof, are useful often enough) distilled from the author's experience.

> As a distinct and credible literature of process development for bulk drugs and fine chemicals has come into being and grows, statements of applicable empirical wisdom are appearing with a modicum of organization (2,3,4,5,6) and the field should one day become amenable to independent study (it is not currently taught formally anywhere). In addition, a journal focused on the field has been published since 1997 as a joint venture of the American Chemical Society and the Royal Chemical Society (7). Alas, the engineering scale-up of synthetic bulk drug processes is still badly understated, as most contributors to the new body of literature are synthetic chemists. For compounds derived from biosynthesis, however, there is a large body of biochemical engineering literature that deals in depth with the scale-up of the biosyntheses and the subsequent "downstream processing" technologies (8,9,10).

The application of the fruits of bulk drug process development to process design, technology transfer and first manufacture will be addressed in the companion chapter 3, as those activities are carried out in a distinct context that overlaps with the R&D activities. Such planes of contact will, of course, be identified in this chapter and their discussion confined to the minimum needed herein.

With regard to the scope of the chapter, it is ambitious in its aim to support the above objectives, yet modest in its depth of descriptive material, since doing justice to the latter would require a much larger volume. Instead, the author has chosen to address the fundamentals along the said objectives, while keeping the descriptive technical material spare and aimed at selected targets of the bulk drug process development task: for example, seeking thermochemical safety, scaling up, achieving the desired physicochemical attributes of the bulk drug, and capturing and applying the process know-how.

As of this writing in 2009, the process development milieu of the bulk drug industry is quite varied—from the large drug company in which all the skills are represented to the small virtual firm that contracts out the work, as well as firms that do selected process development tasks as part of their attempt to secure the eventual manufacturing business from the owner of the drug candidate. The author has not attempted to deal separately with these different environments lest the exposition of the target fundamentals get obscured by the specifics of each case. Instead, the bulk drug process development task is discussed within the continuum of a large drug company, and commentary that applies to other contexts has been inserted, hopefully in a sparing and incisive manner.

The reader should be alerted to an additional choice of the author. Although the increased regulatory expectations have deeply transformed the process development task, the paramount stance for the practitioner remains intact: *know and understand your process, reduce it to practice soundly, and operate it in a disciplined manner*. Accordingly, this and its companion chapter, aimed at the fundamentals, avoid the spectrum of the current good manufacturing practices (cGMPs) subject, which seems to have soaked so much of the energy of process practitioners throughout the bulk drug industry. However, the issues associated with the assembly of regulatory submissions [New Drug Application (NDA) and the like] and with the expectations of the subsequent approval process will be discussed as required to meet the objectives of the chapters.

Finally, the diligent reader of these two chapters, armed with the perspectives provided herein, should find that continued study of the literature can be quite fruitful. To assist in that task, a selection of references is included, most of which are cited throughout the text, with the rest cited separately as suitable reading for the studious.

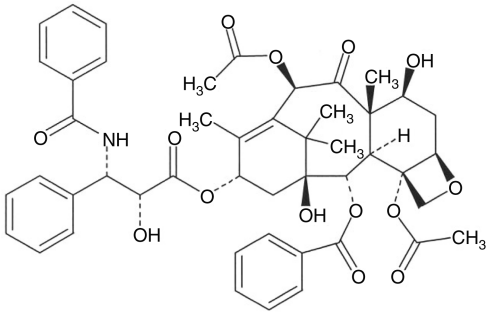
II. THE BULK DRUG PROCESS AS PART OF THE DRUG DEVELOPMENT PROGRAM

A. The Chemical Process of a Bulk Drug

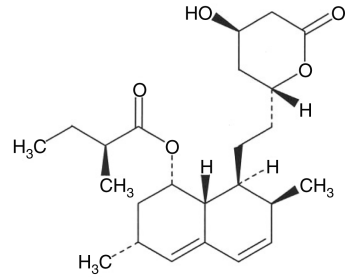
In the context of this chapter, a *bulk drug* or a *bulk drug substance* is a material—a single chemical compound with the desired biological activity—obtained in bulk form and destined for the preparation of dosage forms. The latter, when administered in a prescribed manner to the target patient, animal or plant, delivers the drug so as to elicit a desired physiological response and, in due course, the intended therapeutic or protective result. More recently, terms such as *active pharmaceutical ingredient (API)* or *bulk pharmaceutical chemical (BPC)* seem to have overtaken the usage, seemingly as the result of their adoption by regulators in the United States. Herein we will use the original term *bulk drug* (or *bulk*), as it most aptly describes the material—a drug that is obtained and characterized in bulk form. However, we will confine our scope to those compounds commonly known as *chemical entities*—drugs of relatively small molecular weight that can be characterized well by current methods of chemical and physicochemical analysis. In doing so we are excluding those macromolecules, substances, and preparations of biosynthetic origin that are collectively known as *biologicals*. The processing methods used in biologicals, albeit based on the same fundamentals, are significantly different from those applied to chemical entities, and their process development, registration and manufacture also take place in a rather different environment. In addition, organic compounds categorized as nutritionals and fine chemicals at large are not within this scope, their processing similarities with bulk drugs notwithstanding.

Bulk drugs are obtained through three chemical processing routes:

a. Extraction, recovery, and purification of the drug from biomasses of natural origin or from fermentation (Fig. 1): (*i*) paclitaxel is extracted from various *Taxus* plants, and (*ii*) lovastatin is biosynthesized in the fermentation of nutrients by *Aspergillus terreus*.
b. Semisynthesis, in which a precursor compound from a natural source or fermentation is converted to the target drug by synthetic chemical modification:



Paclitaxel – Found in *Taxus* plants.



Lovastatin – From certain microbial cultures.

FIGURE 1 Bulk drugs from natural sources: Paclitaxel (antileukemic and antitumor) and lovastatin (inhibitor of cholesterol biosynthesis) are examples of the diverse and complex structures made by plant and microbial cell biosyntheses, respectively. In most instances of such compounds having desirable biological activities, their structural and chiral complexities make chemical synthesis not competitive with isolation from biosynthesis.

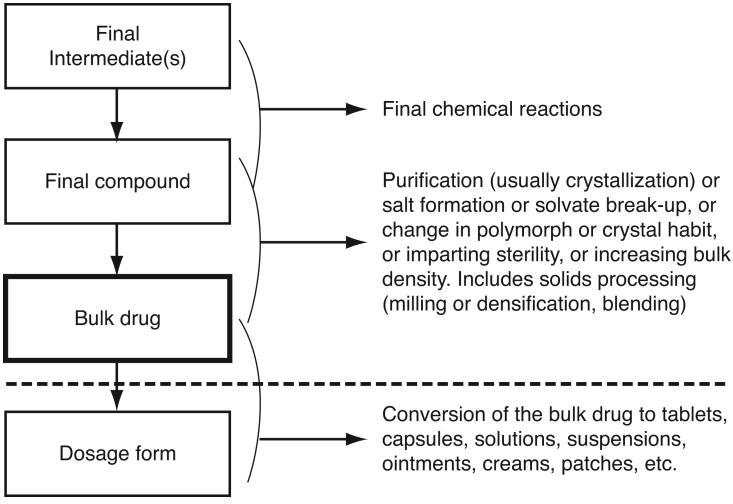


FIGURE 2 Semisynthetic bulk drugs: ampicillin (antibacterial) from penicillin G. Modifications of biosynthetic structures are often created to improve the in vivo attributes of the original compound, utilizing the biosynthesis product as the starting material containing most, if not all, of the structural complexity that provides the basic biological activity. Similarly, codeine (analgesic), although found in opium from *Papaver* plants, is most economically made by methylation of morphine, which is more efficiently isolated from opium.

(*i*) Penicillin G (from fermentation) is converted to 6-aminopenicillanic acid, which in turn is reacted with an acyl chloride to afford ampicillin, and (*ii*) natural morphine is methylated to codeine (Fig. 2). Both routes to bulk drugs take advantage of the diversity and richness of molecular

structures found in natural sources, where many important biological activities are found.

c. Total synthesis from simple starting materials or less simple intermediate compounds (Fig. 3): (A) fosfomycin from commodity chemicals and (B) lobetalol from 5-bromoacetyl salicylamide.

> In either total synthesis or semisynthesis processing, sometimes a desired synthetic transformation is best done by an enzyme. Such synthesis step, whether using a preparation of the enzyme or the host microorganism, will be considered a chemical synthesis step (a *biotransformation* or a *biocatalytic step*) and not a fermentation for biosynthesis.

Whichever of these routes is used to obtain a bulk drug constitutes the *chemical process*. Further processing of the bulk drug to obtain the dosage form constitutes the *pharmaceutical process*. This distinction is depicted in Figure 4, where simple graphical means are used in an attempt to differentiate the *bulk* character of the product of the chemical process from the *discrete* character of the product of the pharmaceutical (or *dosage form* or *secondary manufacturing*) process. The distinction also reflects their very different technology, manufacturing, and regulatory environments.

> In the current pharmaceutical parlance, the term *API* (for *active pharmaceutical ingredient*) is used most often as descriptive of the biological activity contribution.

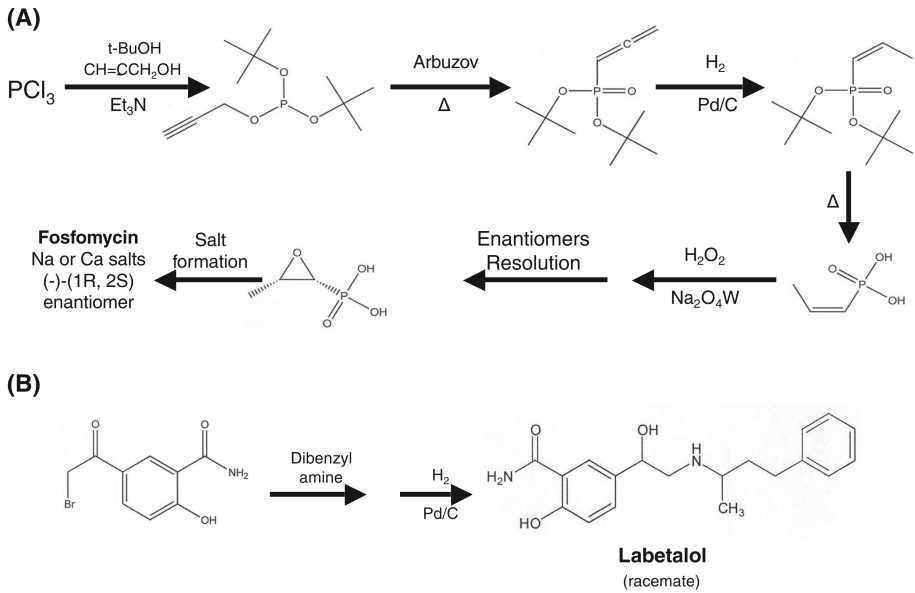


FIGURE 3 Drugs by total synthesis: Fosfomycin (antibacterial) is a good example of the manufacture of a bulk drug by total synthesis from basic chemicals, albeit the compound is of biosynthesis origin. Alternatively, and more frequently, the manufacturing process is simplified by tapping on commercially available compounds of greater structural complexity (*intermediates*), such as 5-bromoacetyl salicylamide as the starting material for lobetalol (antihypertensive). Even if the intermediate is custom made by others, the process development and manufacturing task for the drug developer is greatly simplified relative to the use of basic or building block chemicals.

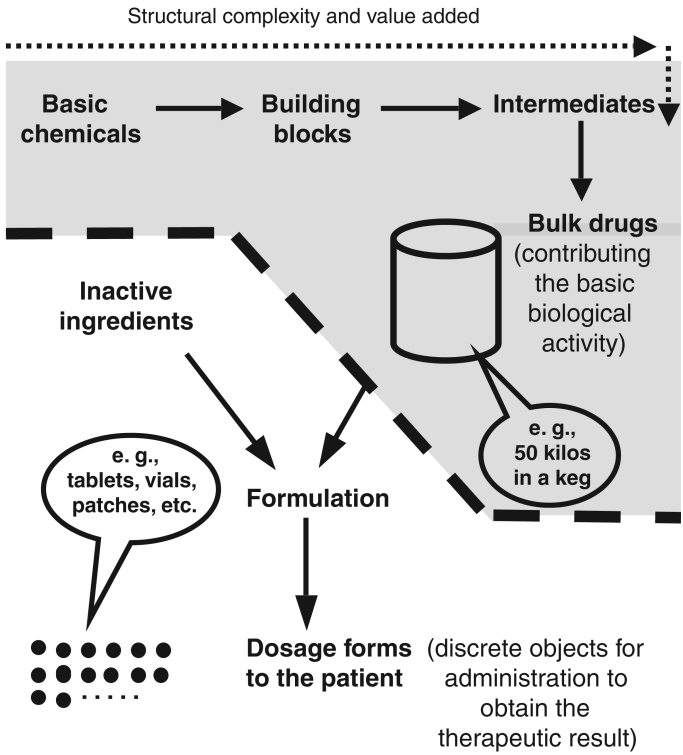


FIGURE 4 The domains of chemical (bulk drug) and pharmaceutical (dosage form) processing, with the chemical processing domain defined by the shaded area of the diagram.

Herein, however, the term *bulk drug* is used instead as descriptive of the physical and chemical character of the subject material, with its biological activity taken as obvious. Indeed, the conventional term for the other ingredients added to formulate the dosage form is still *inactive pharmaceutical ingredients*.

As we proceed, unavoidably some other terms will be used that may not be familiar to all readers. Accordingly, an effort will be made to define such terms at the point of first use, as well as to use them sparsely. For example, *unit operations* are those methods that can be found repeatedly used in chemical processing and that have a common phenomena root, their many variations notwithstanding—filtration to separate solids from an accompanying liquid, distillation to separate volatile components from a mixture, or milling to reduce the particle size of particulate solids. The organization of chemical processing on the basis of such unit operations was crucial to the development of organic chemical technology, which was originally arranged on the chemistry basis of *unit processes*, such as nitration, sulfonation, or esterification. Whereas the latter organized knowledge on a strictly descriptive basis, the unit operations approach made possible the study of processing phenomena on the basis of generalized principles from physics, chemistry, kinetics, and thermodynamics, which could then be used to undergird methods applicable in the context of any chemical process and over a wide range of scale and circumstances—hence the keystone role that unit operations played in the advent of chemical engineering as a discipline, with a practice quite distinct from that of the earlier industrial chemistry.

B. A Perspective

Process development of a bulk drug consists of three distinct tasks:

a. Preparation of the bulk drug, as needed, by the overall development effort—*the preparative task*. The scope of this task varies over a wide range, as shown in Table 1.
b. Definition and achievement of the desired physicochemical attributes of the bulk drug, as needed, by the dosage form development—*the bulk drug definition task*.
c. Acquisition and organization of a body of knowledge that describes a sound process for regulatory submissions and technology transfer to first manufacture at scale—*the body of knowledge task*.

TABLE 1 Bulk Drug Demands of the Various Drug Development Phases

Preclinical phase—initial toxicology, probes on drug bioavailability, data gathering for the IND, additional animal studies, etc.	Supplies to be delivered over 2–6 mo.	Total ~5–50 kg.
Phase I—use in humans (20–80 mostly healthy subjects) for pharmacokinetic, pharmacological, routes of administration, dose-ranging and tolerance studies. Continuing toxicology and dosage form development. All aimed at the design of phase II/III studies and defining the target dosage forms.	Supplies to be delivered over 6–12 mo.	Total ~20–100 kg.
Phase II/III—increasingly large number of patients (up to thousands) in studies for therapeutic effectiveness (initial and confirmatory), dose and regimen determination, evaluation of target populations for safety and efficacy, support of desired claims, market specific and dosage form specific studies, etc. Continuing toxicology and dosage form development, stability studies. All aimed at the assembly of the dossier.	Supplies to be delivered over 18–48 mo.	Total ~300 to >2000 kg.
Phase IV—post-approval studies for optimization of drug use, pharmacoeconomic data, morbidity and mortality data, head-to-head and concomitant drug uses, etc.	These studies are generally supplied from bulk drug made in the manufacturing operation.	

Notes:

1. The IND (Investigational New Drug) is the submission requesting the USFDA's exemption from drug shipping in interstate commerce, thus signaling the intent to initiate study in humans (or target species if a veterinary drug). Dossier is a term often used to describe the total body of knowledge on the drug candidate, from which individual submissions are assembled for filing with the various agencies, for example, the New Drug Application (NDA) to the USFDA.
2. The range of bulk drug totals reflects the wide differences among drug candidates and their programs. Issues such as drug potency and dosage regimens, low animal toxicity, length of treatment to the clinical endpoint, relative difficulty of dosage form development, number of dosage forms developed, and scope of the clinical studies are the principal factors determining the demands for bulk drug. Obviously, relatively infrequent extremes exist on both ends: from a low end for drugs such as dizocilpine, paclitaxel, and some experimental oligonucleotides to a high end for HIV protease inhibitors (high doses) and some cardiovascular drugs (clinical studies of very large scope).

Abbreviation: USFDA, United States Food and Drug Administration.

Source: Author's observations from involvement in numerous drug development programs.

However, these tasks cannot be directed to successful and timely completion unless viewed and managed as a veritable trinity, their differing demands and instantaneous urgencies notwithstanding. Drug development is a fast paced and difficult enterprise; it presents frequent junctures at which the need to focus on the most compelling task needs to be artfully balanced with other needs lest the aggregate task be compromised—all three tasks need to be completed at the same time for timely and successful product launch. Selected instances of such balancing, in which some risk is often inevitable, are discussed throughout the rest of the chapter; therein lies the crucial need for overall coordination of *each* drug's development program.

> Although various models exist, today's drug development is generally facilitated by a coordination mechanism and forum, usually in the form of a cross-functional team that drives and manages a drug candidate. The principal objectives are to have and execute: (a) a drug development plan, (b) rigorous means to closely track its execution, and (c) mechanisms to effectively respond to events and findings that invariably arise in spite of the plan. Indeed, the development of a new drug encompasses a myriad activities and objectives that are extremely cross-linked among the various disciplines contributing to the effort. Clearly, the bulk process development team needs to be well represented in the cross-functional forum throughout the drug development cycle.
>
> Success in development coordination means that, no matter which coordination model is used, there must be prompt and effective resolution of most issues and difficulties, say >90%, *at the team level*, with the rest going up to a broader and more senior team of the R&D organization (i.e., the heads of the disciplines, functions, and those above). Indeed, the direction and operation of such teams have become a distinct function (it will be referred herein as *drug coordination*) with its own set of skills and not unlike the distinct set of skills in new drug submissions and approval—the *regulatory affairs* function.

The relationships of the three basic tasks with the overall drug development program are depicted in Figure 5 in rather simple terms, whereas the specifics of each relationship will be discussed under the heading of each task. The arrows indicate the flow of materials from the preparative task and the flow of information and know-how from each task to the others and to the drug development at large.

It is also useful to depict the bulk drug process development cycle on a Cartesian coordinate plane (Fig. 6). The abscissa axis represents progress since the onset of development of a compound, and although progress along well-defined milestones is used, one might also look at the abscissa as measuring the applied technical effort or, less precisely, the extent to which the bulk drug process has been reduced to practice (e.g., kilos of bulk drug made, batches made, or versions of the process piloted). Inevitably, the abscissa scale shown herein is arbitrary, albeit deliberately selected; the experienced reader will probably readily think of an example with a more apt progress scale—thus the need to deal with the latter in terms of more distinct *stages*, which Figure 6 attempts to depict.

> Were elapsed time to be used, the distance between *phase II/III* start and the *dossier* filing milestones would be quite variable from drug to drug, as that interval depends on the scope of the clinical program and on the therapeutic target. Whereas osteoporosis, diabetes, and depression require considerable time to reach their efficacy endpoints, those for bacterial infection or pain relief, for example,

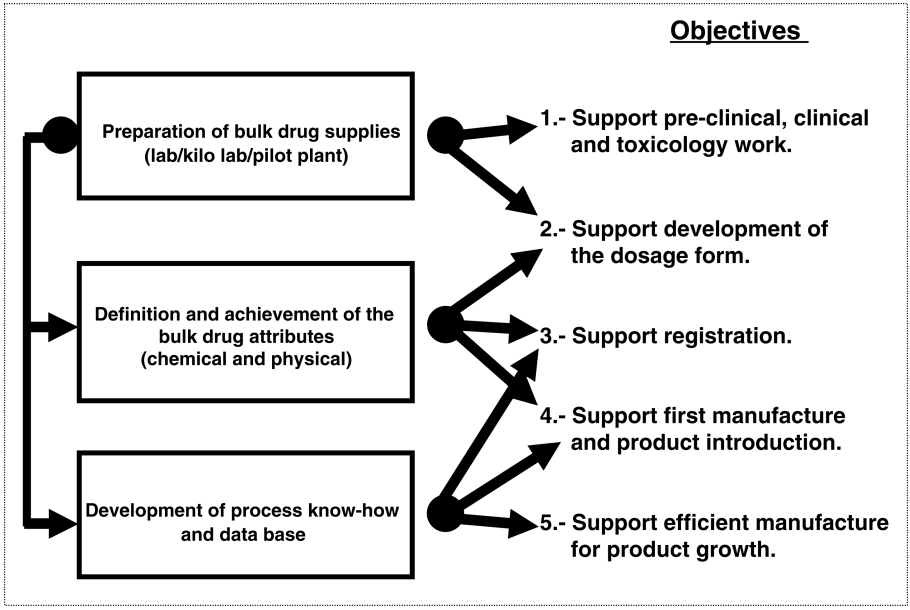


FIGURE 5 The three basic tasks of bulk drug process development. These tasks exit concurrently throughout most of the development cycle, albeit their burdens vary through the cycle. Nevertheless, managing well all three tasks as inseparable parts of a single overall endeavor is the principal managerial challenge in bulk drug process development.

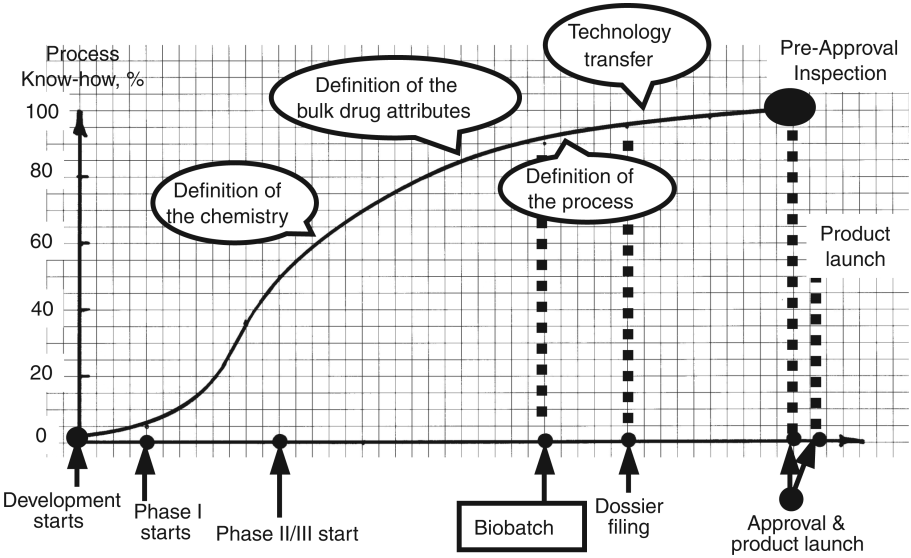


FIGURE 6 The process know-how versus applied effort plane, including the major milestones of bulk drug process development. As defined herein, 100% know-how describes the body of knowledge needed for registration and reliable first manufacture for product launch, whereas additional know-how accumulates with manufacturing experience and follow-up work that might be done for process improvements or a second generation process.

arrive much sooner. For this, and for other reasons related to the intended scope of the drug development (e.g., claims structure, schedule of filings, and multiple routes of administration), the elapsed time scale is unsuitable for the *process* know-how purposes of Figure 6. Instead, applied effort or extent of reduction to practice of the process relate directly, if not strictly in direct proportion, to the acquisition of the process know-how.

Although the *biobatch* and *preapproval inspection* prerequisites are specific to United States Food and Drug Administration (USFDA) approvals, analogous expectations are arising in other drug agencies in the major markets (more on this in chapter 3). The *biobatch* is a distinct marker in dosage form development in that it serves as the bioavailability/bioequivalence bridge to pivotal clinical studies as well as the bioavailability/bioequivalence reference for all subsequent dosage form output. As such, the biobatch reflects the process that goes into the dossier, *uses representative bulk drug* and excipients, and its size is no less than 10% of the intended manufacturing scale. *Preapproval inspection* is a methodology employed by the USFDA to ascertain, at its discretion, that the intended manufacture of dosage form and bulk drug corresponds to the processes used in the pivotal clinical studies and described in the NDA or other new drug submissions.

The ordinate axis, on the other hand, is straightforward, as it measures the fractional bulk process know-how relative to that required for regulatory approvals and for sound first manufacture. Note, therefore, that it is not being suggested that at 100% on the ordinate axis there is nothing else to be learned about the process; instead, *the 100% ordinate value merely describes the knowledge required to fulfill the said process development objectives*. Indeed, further gains in process know-how are always realized with manufacturing experience, and mature processes often differ appreciably from their first manufacture versions, by virtue of gradual improvement or from significant step changes (*second-generation processes*), although most often the seeds for such later developments are planted in the original development body of knowledge. Thus, the curve in Figure 6 describes the accumulation of know-how during four distinct phases of the process development effort:

a. The *preparative stage*, during which the effort is focused on making available kilogram amounts of the bulk drug to the preclinical, toxicology, and phase I work, usually not based on the eventual synthesis route, let alone the eventual process.

   Whereas the synthesis *route* (or *scheme*) describes the intermediate chemical structures sought to arrive at the final compound (starting materials, synthesis approach, and probable chemical reactions to use), the *process* describes how the route is implemented at a much higher level of detail (solvents, catalysts, purifications, isolations vs. straight-through, etc.).

b. The *development stage*, in which the preparative work is scaled up and the synthesis effort goes into high gear, aimed at the manufacturing route *and* process. It is in this stage that the chemical engineering effort is applied in earnest, first to support the scaled-up preparative work and then to address the scale-up issues of the manufacturing route.

   Ideally, the chemical engineering contribution starts early so as to appropriately influence the seminal choices being made by the process chemists as to route. This influence is reasonably apparent with respect to issues of thermochemical safety and probable environmental impact; yet, there is across-the-board synergy that a

chemistry/engineering dialogue can exploit. The latter is particularly true in those instances when the chemists perceive a desirable approach as not being feasible on grounds of scale-up difficulty or, more simply, because of lack of experience with some demanding processing conditions.

c. The *consolidation stage*, in which the synthesis route is fully settled and the specific process for it is defined at the level of detail that permits process design for the manufacturing plant, definition of the bulk drug attributes, and the assembly of the dossier. Also during this phase all the preliminaries for technology transfer are carried out and the stage set for first manufacture.
d. The *technology transfer stage*, in which the process is run in its first manufacturing venue, its performance established, and the bulk drug needed for product launch produced. Also during this phase the manufacturing scheme receives approval within the approval of the dossier, often after plant inspection by the approving agencies.

From the preceding definitions, a discussion of the specifics of each stage is now possible, also based on the depiction of the bulk drug process development cycle on the know-how versus the applied effort plane introduced in Figure 6. During these stage-specific discussions, the three bulk development tasks will serve as the basis and along the lines of Figure 5.

C. The Stages of Bulk Drug Process Development

1. The Preparative Stage

Although preparative work takes place throughout the process development cycle, this first stage is most aptly described as the *preparative stage*. Its focus, although not exclusively, is the preparation of limited amounts of bulk drug for assorted preclinical purposes and then is followed by first scale-up to support phase I activities, which include testing the drug in healthy subjects (humans or target animals if a veterinary drug).

Starting with bench scale equipment (up to 100 L in the so-called *kilo lab*) or pilot scale fermentors (up to 5000 L when titer is low), this early preparative work uses whatever synthetic method or fermentation conditions (the microorganism and the nutrients) are immediately available. In most cases of synthesis, the route may be a somewhat streamlined version of the discovery route or a temporary route that may or may not include parts of synthesis schemes being considered for eventual development. In most cases of biosynthesis, the microorganism is that from the discovery stage but taken from whatever stage of microbial strain improvement is amenable to scale-up from shake flasks or bench scale fermentors.

Fermentation processes at this stage are generally of very low productivity (final concentrations of the target compound of <1 g/L), making access to relatively large fermentors most helpful, including, in cases of dire need, the use of manufacturing scale units (up to 75,000 L), the poor scaled-up performance of the early stage notwithstanding. The analogy for chemical synthesis is the arduous operation of lengthy procedures in the kilo lab, the low yields notwithstanding.

Although the kilo lab will be described more fully later on, it may be said at this point that the kilo lab is a larger-scale lab, traditionally used for running preparative procedures rather than experimentation.

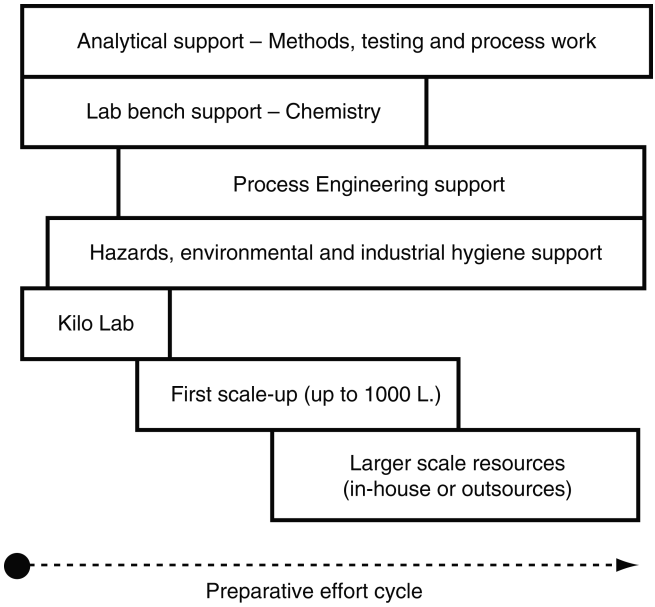


FIGURE 7 The resources for the preparative task. The need to engage larger-scale resources depends on the scope of the preparative task, which can vary widely (Table 1 and Fig. 8).

Preclinical and phase I development work is crucial in that it determines the merit of further development or, hopefully, the adjustments that need to be made to move the compound forward—thus the importance of providing the required material on time to get those answers as soon as possible. This reflects on the need for capital investment in facilities such as the kilo lab or pilot plant, and we will discuss elsewhere in this chapter the challenges of this stage of development when the preparative stage depends on *outsourcing* (the reliance on outside suppliers). Indeed, sufficient internal resources for the *preparative stage* is a clear competitive advantage, with the optimal setting providing the means—hardware and engineering skills—to swiftly overlap the kilo lab work with pilot plant work up to, say, 1000 L vessels and the appropriate auxiliaries and operating environment [safety, industrial hygiene (IH), and pollution abatement]. Figure 7 depicts this preparative environment, whereas Figure 8 complements the range of preparative scopes presented in Table 1.

Also depending on the resources of the organization, synthesis bench work may take place in search of routes that can support a manufacturing process, as the routes used during the discovery phase are largely unsuitable on the basis of projected cost, length of the synthesis cycle, commercial unavailability of starting materials, or their perceived inferiority relative to what the process chemists foresee as attractive alternatives. Clearly, the compelling wisdom of such early synthesis work needs to be balanced against the resources available and, most of all, against the empirical probability of less than 20% that a drug candidate at that stage will reach the market, as indicated by Table 2.

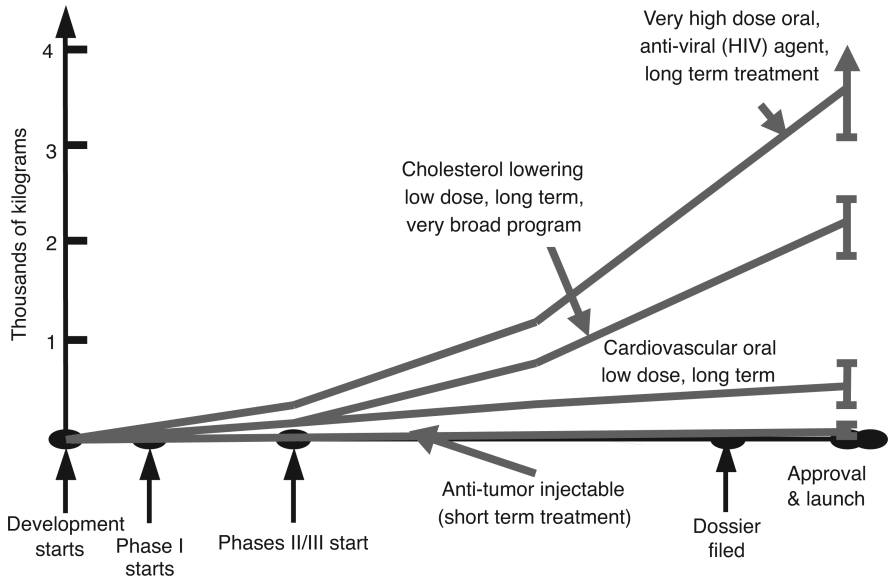


FIGURE 8 The scope of the preparative task. Some examples to illustrate the dependence of the preparative effort on drug potency, therapeutic target, and scope of the clinical effort.

TABLE 2 Best Practices Probabilities of a Drug Candidate Reaching the Market

Drug candidates in the preclinical phase	5–10%
In phase I	10–20%
In phase II	30–60%
In phase III	60–80%
Post–NDA filing	>95%

Notes:
"Best practices" refer to drug development organizations with established good records of bringing drugs to market. In particular, best practices include a high hurdle for a drug candidate to enter development or phase I.
Source: Author's assessment from assorted estimates, including those from the PhRMA Annual Report—online edition, 1997. While the figures from total compounds synthesized (or total number of biologically active compounds) have increased as the methods for generating actives improve their total output, the above figures *after entry into development* have remained largely unchanged. The above ranges probably reflect the adequacy of the tools used to assess the merit of developing an active compound and the rigor of the criteria for moving a compound forward. More recently (2005–2009), the above probabilities for drug candidates in Phase III have decreased significantly.

Whereas medicinal chemists practice organic synthesis as an indispensable tool and are largely oriented upstream (toward the domain of biological and pharmaceutical attributes of the compounds they work with), process chemists in the drug industry practice synthetic chemistry as their profession and are oriented downstream (toward the reduction to practice beyond their lab bench)—thus the usual discontinuity in synthetic route at the discovery/development boundary.

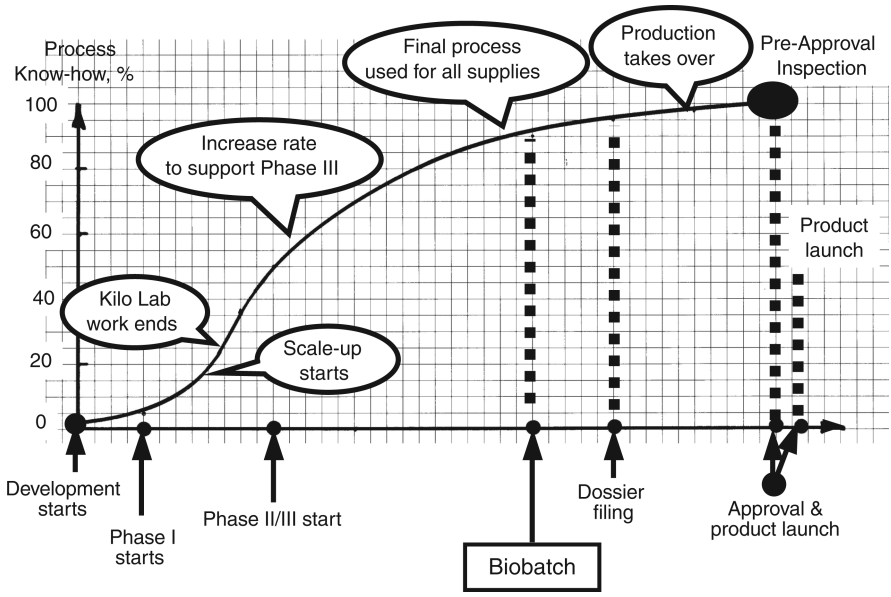


FIGURE 9 The preparative effort in the know-how versus applied effort plane. The principal preparative milestones are shown.

Although sometimes much is made about smoothing and simplifying the discovery synthetic route (eliminating isolations and purifications, shortening the processing cycle and using less expensive materials), the most desirable contribution of the process chemist is the conception of a distinctly advantageous synthesis route that can then be developed and engineered into a sound manufacturing process. Such a route would bring the advantages of fewer steps from reasonably available starting materials, environmental benevolence (or, preferably, *green chemistry*), parallel moieties that can converge into shorter synthesis cycles, stereoselectivity, and similarly decisive gains.

As a summary, Figure 9 focuses on the *preparative stage* and the rest of the preparative effort on the know-how versus applied effort plane, whereas Figure 10 depicts the materials flow from the bulk drug preparative effort at large.

2. The Development Stage

As made clear by the slope of the curve in the know-how versus applied effort plane (Fig. 6), the *development stage* comprises the most productive development effort:

a. Synthesis work at the bench scale seeks the eventual manufacturing route in earnest, preferably on more than one approach, with all promising a substantial, if not overwhelming, advantage over the current preparative procedures.

   In chemical synthesis, the route is basically driven by the structure of the target compound. Within that logic, however, the creativity of the process chemist is bounded only by the realities of starting materials availability.

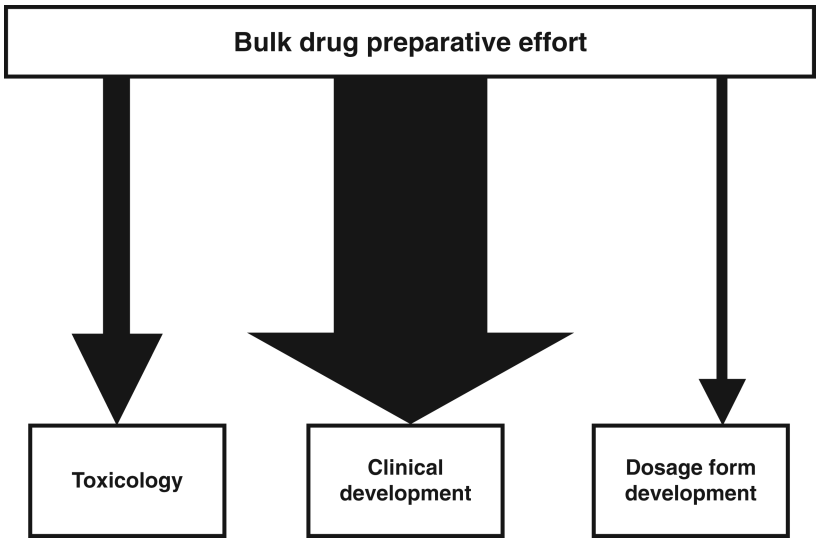


FIGURE 10 Materials flow from the bulk drug preparative effort. The width of the arrows *approximately* indicates the relative amounts of bulk drug going to the users in the overall drug development program. Examination of this figure and Figure 9 provides an equally approximate description of the bulk drug usage as a function of the development cycle.

However, examples of bulk drugs made from commodity chemicals are now few and rapidly disappearing (thiabendazole and l-methyldopa, for example), as the more complex structures of today's medicinal chemistry preclude synthesis from basic raw materials. Instead, today's process chemist must be very alert to what the fine chemicals industry offers (or could be induced to offer) by way of suitable building blocks or intermediates and the corresponding manufacturing capabilities. Such alertness, combined with creative synthesis skills, is the key to truly advantageous routes. This theme is discussed amply and in depth in some of the previous references (2,3,4,5), as well as in Saunders's compendium of selected major drugs (11). In the extreme, the total synthesis of structurally rich natural products, although rarely aimed at a manufacturing process, offers leads and inspiration to the process chemist, as well as blazes the trail with new reactions, some of which are eventually used in bulk drug syntheses (12).

> In celebrating the opportunities for the creative process chemist we should not neglect factors such as the increasing desire for environmentally benevolent chemistry (*green chemistry*) or the prevailing business model in the bulk drug industry, by which the range and scope of chemical processing has been narrowed in favor of contracting out (*outsourcing*). There is also, on management's part, the reluctance to practice hazardous chemistry (nitration, sulfonation, phosgenation, etc.), with that spectrum of processing now all but ceded to contract manufacturers.
>
> Some compounds of natural origin products have been manufactured by total synthesis when structurally simple (e.g., chloroamphenicol, fosfomycin) or when inevitable to bring a significant drug to market, as in the case of imipenem (13).

The selection of the chemical route, which is invariably made before it has been sufficiently reduced to practice, is the strategic decision, as it has the greatest potential to define the process and its overall performance—costs, reliability, environmental impact, etc. Accordingly, it is a decision that is best made with the benefit of sufficient engineering assessment, as sometimes the chemical appeal is not sufficient. Indeed, engineering assessments of capital and operating costs, environmental impact, and issues of process design and scale-up bring sharply into focus the general direction as well as the specific development actions that the route requires to become the manufacturing process. On occasion, such assessments cause reappraisal of the route that, if timely, can redirect the project to considerable advantage—to a superior variation within the same basic route or to a substantial change to a hybrid chemical scheme and, less frequently, to abandonment for another route.

> Preferably, the synthesis route is settled not late during this stage, but it is not all that rare, in the higher caliber process efforts, for that "better route" to come through and displace the prevailing route just in time to switch the scaled-up preparative work.

It is at this stage of merging chemistry and engineering efforts that the process development effort generally settles onto the right track and approaches critical mass. Process development organizations that lack the requisite engineering skills or that tap into relatively distant skills (say, from a technical resource in manufacturing) are at a marked disadvantage with respect to choosing the better process, since the said assessments are not done, are done less effectively, or are done without the criticality of mass that the occasion demands. The distant engineering skills are also far less persuasive when their assessment of the proposed synthesis is not favorable.

All seasoned practitioners of bulk drug process development know from at least one experience the very high price paid when the wrong process gets too far down the development cycle, and retreat is either unacceptable or very costly to the overall development timetable—thus the compelling need to make the fundamental choices of route, and of process approach within the route, with the full set of skills and address the key questions:

1. What will the commercial plant look like? What will its operation be like?
2. What are the probable capitals costs? How long will it take to be ready to start up?
3. What are the scale-up issues? Can they be addressed on time?
4. What is the environmental impact? Is there a good fit with the likely plant sites?

Once the bulk process team gets past this juncture with an action plan, the rest of the development stage is mostly a matter of good execution by all the disciplines involved. Although the analytical R&D function has not been mentioned up to now, its role is, of course, pervasive throughout—first in support of the early preparative work (a duty that remains with the function for the rest of the development cycle) and then in decisive and indispensable participation of the development activity at the bench and in the pilot plant.

Biosynthesis processes, which are based on fermentation processing in which the microorganism does the synthesis, face the same set of development issues but in a narrower field of options. Not only is the biosynthesis well defined and fixed by the microorganism, but alternate microorganisms with radically different pathways that could be more desirable are not that available. Chemical entities of natural origin are secondary metabolites of microorganisms or plant cells, and variations in the metabolic pathways that lead to a given secondary metabolite are relatively narrow compared with the many variations by which a compound can be made by chemical synthesis.

In this case, the development team (microbiology and biochemical engineering) aims at coaxing the organism or plant cell to be more effective. Strain mutation is a proven technique for improving the productivity of microbial biosynthesis and plant cell processes, although very few in industrial practice also seem amenable to increased productivity by manipulation of the cell lines and fermentation conditions. The microbiologist and the biochemical engineer are thus able to offer the potential for increased fermentation output by factors up to an order of magnitude or more—a potential not to be matched by increased yields from an organic synthesis. Indeed, some fermentation processes can go into manufacture at low titers with a high probability that increases will be obtained with continued development of the microbe or plant cell, as well as the fermentation conditions. Thus, variations on the biosynthesis—unlike variations on how to chemically synthesize a compound—are modest in range but not in significance to fermentation productivity (e.g., use of phenylacetic acid as a precursor in the fermentation of penicillin G) or other important aspect of the process (e.g., switching to a different *Taxus* plant from which a precursor to paclitaxel, comprising the taxane ring with all of the desired stereochemistry, could be extracted and chemically converted to paclitaxel at an advantage over the prior extraction of paclitaxel).

It is in the processing downstream of the fermentor that development possibilities become numerous, as a wide range of unit operations for concentration, purification, and isolation exist, just as wide as the processing options for recovering the desired compounds from streams (i.e., materials) issuing from chemical synthesis. This is discussed much further elsewhere in this chapter.

b. It is also in the *development* stage that the preparative work is scaled up in earnest with two purposes: (*i*) greater output of the bulk drug and (*ii*) the identification and resolution of the problems of scale attendant to the desired process. Although the latter goal requires that the desired route be at the scaled-up stage, considerable progress can be made if pieces of the desired route are scaled up before the total route is brought to the pilot plant.
c. It is also during the development scale that the definition and achievement of the desired physicochemical attributes of the bulk drug is pursued in earnest, hopefully after the dosage form development team has narrowed down the ranges for those properties after the major decision—which particular salt or the free base or the acid will be the bulk drug form of the biologically active structure. Such a decision may come late in the cycle, for

oral drugs in particular, as the search for the desired bioavailability and stability may be arduous (14).

d. Finally, it is during the *development stage*, preferably early, that the bulk development team starts its work with the appropriate downstream organization in anticipation of successful drug development, registration, and market launch. This set of activities takes place in a rather distinct track from the R&D track, often placing inordinate demands on the bulk process team, as its obligations to the drug development effort remain unaltered by the onset of its obligations to eventual technology transfer.

> There is a great deal of risk when bulk process resources are badly caught in the vise of the demands from their drug development partners and the increasing demands of technology transfer. Staffing of the bulk process team—the engineers in particular—needs to recognize that successful drug development brings with it technology transfer. Unfortunately, R&D management and the peers in the drug development program are often insensitive or oblivious to the situation, and the cross-functional coordination team needs to be indoctrinated accordingly. It is very helpful to have the downstream functions related to manufacturing participate in the coordination team and thus ensure that those demands get known, if not fully appreciated.

In summary, Figure 11 depicts the *development stage* in the now familiar know-how versus applied effort plane. It is also timely to present the full spectrum of the bulk drug development disciplines and all the activities that they carry out, including those shared with others in the corporation or with outsources, as shown in Figure 12.

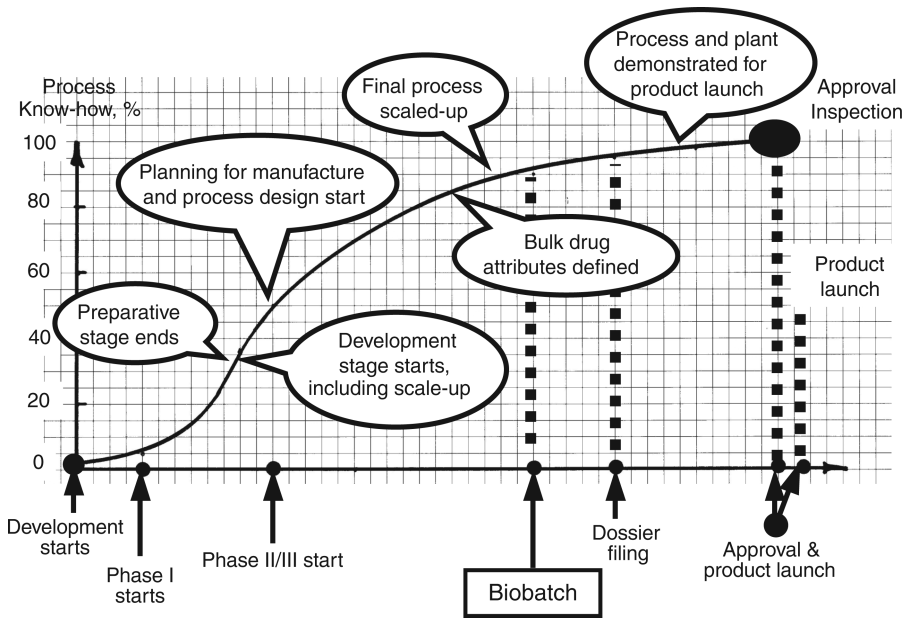


FIGURE 11 The development stage in the know-how versus applied effort plane. The principal process development milestones are shown.

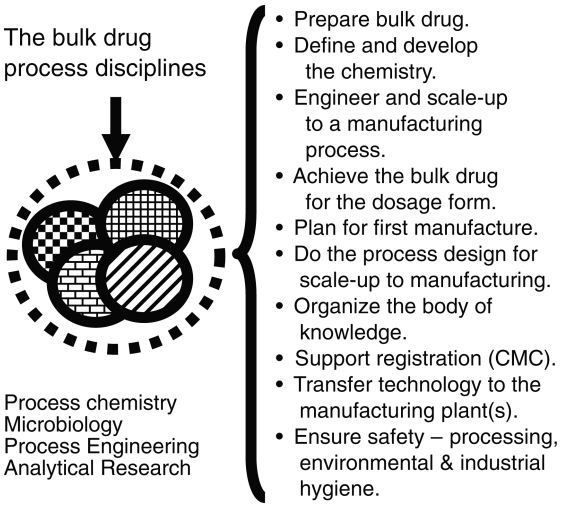


FIGURE 12 Disciplines and activities in bulk drug process development. *Abbreviation*: CMC, chemistry, manufacturing, and control.

3. The Consolidation Stage

Although it is not infrequent for a significant bulk process "loose end" to remain tenaciously loose until late in the cycle, by and large the development cycle reaches a stage at which the more difficult development work has been done, to wit:

a. The chemical synthesis route is fully defined, albeit sources and specifications of starting materials may still be under negotiation or definition.
b. The actual process based on the synthesis route is sufficiently defined, and sound pilot plant operating procedures exist or are clearly in the offing.
c. Preparative support to the drug development program, although continuing and never leisurely, is no longer threatened by uncertainties about how to prepare the bulk drug.
d. Thermochemical safety data are firm, and only updating for process changes remains to be done. All issues are being dealt with adequately in the process design of the manufacturing plant.
e. The environmental impact of the process at the site of manufacture and at large is understood and acceptable, meeting company policy objectives. Obtaining all the requisite permits is likely.
f. IH issues specific to the process are understood and being addressed adequately in the process design of the manufacturing plant.
g. The process design, and possibly plant construction, is proceeding. Uncertainties seem within the grasp of the combined development/process design effort, and work can be focused accordingly.
h. Analytical methods for in-process and bulk drug control have been largely defined and remain to be confirmed and validated. Absolute purity, impurity profile, and crystal form are settled matters.
i. The scope and approaches to the dossier are largely in hand, if not in text.

There is, of course, no suggestion of the work being completed. Far from it, the *consolidation stage* is intense in a different way than the *development stage*. A

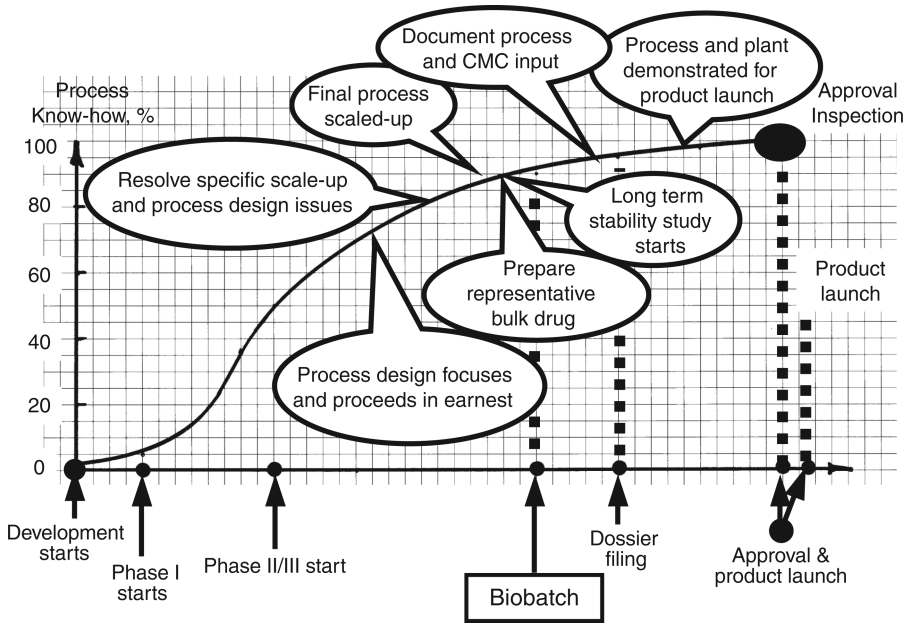


FIGURE 13 The consolidation stage in the know-how versus applied effort plane.

great deal of the work ahead is filling blanks (few if the prior work has been done well), refining pilot plant procedures, and catching up on the documentation that will support the dossier. Also, the final work on the definition and achievement of the bulk attributes needs to be done to support the final work on the dosage form side and the biobatch and stability studies that will follow.

There is also the largely increased workload in preparation for technology transfer, usually requiring frequent travel, a great deal of interaction, and the pursuit of much detail. Snags in process design and plant construction do come up, and environmental permits may require scrambling for some data.

However, the slope of the know-how curve is decreasing rapidly, as the bulk process is being implemented more than it is being developed, the loose ends notwithstanding. In summary, Figure 13 depicts the *consolidation phase* in the know-how versus applied effort plane.

4. The Technology Transfer Stage

Most of the discussion on the nature and scope of the technology transfer activity is presented in chapter 3. Nevertheless, the following seems pertinent at this point, as it relates to the technology transfer burden that the bulk process development team carries in addition to its duties on the drug development program.

a. A finite effort, even in the midst of a very difficult *development stage*, must be allocated to looking ahead to the specifics of manufacturing the bulk drug. This has been indicated in Figures 11 and 13.

b. The bulk process team needs to keep the rest of the R&D organization, its peers in the coordination team in particular, aware of this downstream task.
c. The technology transfer team needs to be well rounded—chemists or microbiologists, engineers, and analysts—and at the site of technology transfer. Staffing and briefs to do the job should be generous to decisively start up the process for product launch. No rescue missions allowed!
d. Successful technology transfer—from early planning for manufacture, process and plant design, process start-up preliminaries, and the actual demonstration that the process works in the commercial plant—rests squarely on the process body of knowledge being as complete as needed by the task and organized to effectively impart knowledge to the downstream organization.
e. Regardless of what organizational arrangement might exist, the bulk process development team needs to assume, hopefully in a collaborative understanding, a leadership role as the bringer of the know-how.
f. With the necessary adjustments, all of the preceding activities apply when transferring the process technology to contract manufacturers or licensees. More on this will be covered in section "Outsourcing in Bulk Drug Process Development."

III. FROM THE BENCH TO THE PILOT PLANT AND BEYOND

A. Process Conception and Bench-Scale Development

Except for fermentation or recovery from natural sources, all other chemical entities are obtained by chemical synthesis from organic chemicals and the process conception starts with that of the synthesis route—the scheme by which selected starting structures are converted to the target drug candidate. Factors considered by the synthetic chemistry team are as follows:

a. Starting materials that are available (or could be available) and promise an attractive route, and a wish list for such a route could be as follows:

    1. The route is direct, with few steps needed to reach the target compound.
    2. It is also convergent (two moieties can be assembled in parallel, then joined near or at the target compound), thus offering shorter synthesis cycles and higher yields.
    3. If chirality is sought, it appears attainable through enantioselective methods.
    4. Once obtained, chirality is preserved through the route.
    5. There is minimal need for blocking/deblocking.
    6. Highly hazardous materials, reactions, or intermediates are absent.
    7. An environmentally benevolent process is sought (i.e., *green chemistry*).
    8. Probable cost is appropriate to the product.
    9. The synthesis route fits nicely with existing plant running a related process.

    The relative priorities of these factors vary widely, as they are seldom all present; neither are they fully independent from each other. For example, directness of synthesis may come at the price of a very expensive reactant or would require that a very hazardous intermediate be made and perhaps isolated. Or perhaps the greenest route seems least feasible. Additionally,

the selection may be constrained by compelling demands of the drug development program: for example, the most attractive route would take longer to be ready for preparative work and development; it has to defer to the lesser route that can prepare the bulk drug now—not an uncommon juncture and decision, although it can be subsequently reversed.

Indeed, there is no established system to deliver the best or even a very good choice of synthesis route, and creativity and synthesis acumen still dominate, although obviously aided by the above and other simpler criteria, such as that of "atom economy" (how many atoms of the reactants end in the final compound?) (15). Occasionally, the choice is facilitated by a compelling case of an ideal starting material availability (e.g., a chiral intermediate that would bring all or a good deal of the target chirality with it), a selling approach that fine chemical producers exploit. Then at some point soon, the leading choice of route needs to be challenged by the various engineering assessments described in list "a" under section "The Development Stage."

Bench development of the route (or routes) of choice is pursued aggressively, ideally by both synthesis chemists and chemical engineers, with the former elucidating reaction pathways and by-products, seeking superior reaction conditions (solvents, catalysts, auxiliary chemicals, temperature, pressure, concentrations, reactant ratios, and approximate kinetics), as well as probing workup and isolation methods. The engineers work, in collaboration with the chemists, on aspects of the chemistry better suited to their skills (e.g., kinetics and thermochemistry, multiphasic reactions systems with mass transport effects that distort the chemistry, very fast reactions with selectivity issues that are sensitive to mixing, or reactions requiring concurrent separation or continuous reactors with tight control of residence time or extraordinary heat removal provisions).

Such bench development by both disciplines is what transforms a synthesis route into a process candidate for scale-up and eventual manufacture. If done concurrently—as it should be—it allows for the results to flow across the disciplinary boundary, shortening the path to a sound process derived from a sound choice of route.

b. Fermentation or natural product extraction processes, on the other hand, are not burdened by a broad range of route possibilities, as discussed in list "a" under section "The Development Stage." Bench development by microbiologists and engineers, however, is indeed rich with possibilities, to wit:

For microbial or plant cell fermentations

1. Elucidation of the pathway to the secondary metabolite
2. Nutrient, precursors, and optimization of fermentation cycle conditions (from the previous results)
3. Strain and cell line improvements with respect to productivity and robustness in fermentation
4. Data gathering to support scale-up to stirred tanks at all pilot plant scales
5. Definition of the downstream process candidate for recovery, concentration, purification, and isolation of the target product from the fermentation

For extraction of compounds from natural sources (plant or animal material)

1. Evaluation of differing sources of the compound bearing materials
2. Pretreatment conditions for successful extraction
3. Extraction or leaching conditions, solvent or extracting stream (i.e., material) selection, and separation of spent plant material
4. Definition of the process candidate for concentration, purification, and isolation
5. Data gathering to support scale-up

Most likely, both technologies eventually have to deal with relatively large volumes of cell mass or plant material waste, and bench work to address those issues is also needed.

B. Process Scale-Up

1. What Is Scale-Up?

At its simplest, scale-up is the set of processing issues that arise when the same operations take longer to execute in larger-scale equipment than at the bench scale. Although such issues do arise, they can be anticipated and in most cases avoided or largely mitigated through changes to the design and operation at the larger scale.

Much more often and less apparent, however, are the processing issues created by operating at a larger scale—*with greater dimensions and different geometries*—and thus affecting flow regimes, phase separation rates, interfacial surface areas, mass and heat transfer rates, flow patterns, heterogeneity in process streams (i.e., materials), and many other dimensionally sensitive variables and parameters. These effects are not related to a different time scale of processing events but arise instead from strictly physical effects that distort the process results from those at the small-scale baseline, including chemical outcomes. Relevant examples are as follows:

a. Reactants to a system of fast reactions cannot be mixed fast enough, and fractions of the reaction mass proceed for finite times at concentrations very different from the intended average concentration (some fractions are unduly rich in the reactant being added, while others are unduly low), resulting in a product distribution different from that predicted by the kinetics or obtained at the smaller scale.
b. Mixing in larger stirred tanks, if not adjusted properly, can result in significant differences in the composition of matter of multiphase process masses across the tank volume relative to the more uniform results in smaller tanks.
c. Rotating devices of larger diameter, such as agitators and pump impellers, as well as internal moving parts in a solids mill, will exhibit higher tip linear velocities and thus generate greater shear stresses in fluids or contribute greater energy to impacts relative to the analogous operation at the smaller scale.
d. Crystallization processes at a larger scale can suffer from unwanted nucleation as the result of heterogeneities in solvent phase composition during semibatch addition or in local temperatures upon cooling, as well as

be more prone to crystal attrition and contact nucleation from the higher tip speed of the agitators and greater energy impacts among particles.

e. Transfer rates of sparingly soluble gases into liquids in stirred tanks generally suffer with increasing scale of the tank unless provisions are made to mitigate the differences, as the gas bubble size distribution (and with it the interfacial surface area) generated by the agitator impeller is different. Hydrogenation rates observed in laboratory pressure vessels, for example, most often do not scale up to pilot scale–stirred tanks because of the extraordinary gas absorption obtained in the liquid vortex at the lab scale; the larger pilot scale tank, being equipped with baffles, does not generate a vortex and that contribution to gas absorption is not present.
f. Large process vessels lose heat less rapidly than smaller vessels at the same internal and ambient conditions and, when deliberately cooled, will cool less effectively absent a mitigating cooling provision.
g. Larger flow contacting vessels for devices for gas-liquid, vapor-liquid, solid-liquid, and liquid-liquid systems will perform less well because of maldistribution, and bypassing of the phases worsens as the cross-sectional area of the contacting vessel increases. Such scale-up requires that provisions be made with internal parts to alleviate maldistribution.
h. Flow vessels will exhibit different flow patterns and residence time distributions than smaller vessels, which need to be taken into account so as to design the larger vessel accordingly.

Indeed, carrying out a processing operation at a sufficiently larger scale often shifts the rate controlling step of the process event *from one domain to another*. As an example, in reactions in gas/liquid systems, the small scale usually permits the reactant in the gas phase to be abundantly available to the liquid phase (the rate of chemical kinetics is observed, *as the gas/liquid mass transfer is not limiting*). Whereas upon scaling up, *the gas/liquid transfer may become limiting*, and the reaction, now starved for the reactant being supplied by the gas phase, does not follow its expected kinetics. The result of such shifts may go beyond the different rates of reaction, as selectivity (and relative rates of impurities formation) may change upon lack of a reactant. Generally, chemical reaction systems that have very fast rates or that take place in multiphase systems are sensitive to the operating scale due to the intrusion of mass transfer effects upon the performance of the chemical kinetics.

The above partial list provides frequent scale-up issues that arise in bulk drug processing with consequences of lower chemical yields or, worse yet, loss of control over the impurity profile, as well as slower processing, excessive damage to microbial cells and crystalline solids, undesirable particle size distributions, and any from a wide range of assorted shortfalls in process performance.

Understanding, *predicting*, and dealing with these issues require more than a modicum of chemical engineering skills, such as fluid mechanics, mass and heat transport, the use of dimensional analysis tools and mathematical methods for the simulation of events in a new context. Absent those skills, scaling up will result in surprises, cause much less effective troubleshooting, and engender an

unwarranted fear of scaling up. Indeed, such apprehensions are now codified in arbitrary batch size ratios beyond which regulatory constraints to process change apply.

> Often enough scale-up is done much too tentatively, inserting intermediate scales that are not needed. Direct scale-up from the lab to the plant is quite feasible in a number of cases (e.g., fast liquid phase reactions with known kinetics and thermochemistry). All that is required is that the issues be understood and the proper parameters reproduced or improved at the large scale, using adjusted process conditions, as it is the set of the defining parameters what needs to be reproduced, not necessarily each process condition.
>
> Failure to understand scale-up issues equates a change in scale with a change in the process. While it is appropriate for a change in operating scale to come under the scrutiny of a well-managed change control system, there should be no assumption that it is "the process" that is being changed—a distinction that is not about semantics but about the approach to scale-up by the practitioner. This pertains in particular to operation of a pilot plant, in which scaling up and changing the process are a daily overlap that, if not practiced with a sufficient understanding of what is happening, will often befuddle the practitioner.

Yet, scale-up is inevitable, even in the relatively low-throughput environment of bulk drugs. Skillful use of the pilot plant environment, by which the preparative task and the process development scale-up coincide in time and place, is essential to a vigorous bulk development program lest the activity oscillate between the extremes of unskilled scale-up and feared scale-up. Indeed, lack of sufficient scale-up skills is a major disadvantage in bulk drug process development.

2. Tools for Scaling Up

In addition to the engineering skills and the access to the full range of supporting laboratory capabilities (bench development; in-process, analytical, and physical chemistry; microbiology), scaling up requires a variety of measurement apparatus (e.g., a compressibility cell to measure flows through beds of solids at different compression), as well as the frequent assembly of dedicated apparatus or pilot units (e.g., units to measure fouling rates of surfaces over short-term tests, small-scale centrifuges to more reliable measure centrifugation rates, leaf test units for vacuum filtration tests). It so happens that often enough some studies and measurements cannot be made in processing equipment nearly as well as they can be made in a smaller scale apparatus dedicated for the purpose at hand. The enterprising scale-up team will, in due course, assemble and accumulate such test apparatus as the needs arise.

In addition, some scale-up work needs apparatuses that are operated for preparative purposes as well, along the lines of the kilo lab, but in a flexible environment not focused exclusively on batch processing as the kilo lab is. Examples of such apparatus are fluid bed crystallizers, hydroclones for the evaluation of that method of solid/liquid separation, lyophilization cabinets with special vial sampling capabilities, and intermediate scale membrane processing assemblies. An area well suited for such testing purposes is not only highly desirable but often facilitates preparative work by processing methods not within the scope of the kilo lab. Such an area should be reasonably open for the manipulation of portable equipment, with ample walk-in hoods and tall