Process Chemistry: The Science, Business, Logic, and Logistics

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Tony Zhang was born in China and obtained his B.S. degree in chemistry from Shandong University in 1982. He came to the United States in 1983 as a CGP Fellow and joined Professor Ei-ichi Negishi's group at Purdue University, receiving his Ph.D. in 1989 on research related to palladium-catalyzed cyclization reactions. He joined Reilly Industries, Inc., in 1989 as a research chemist in the fine chemical business, working on new methodologies for the selective synthesis of pyridines and other heterocycles. In 1992, he moved to Eli Lilly as a Senior Organic Chemist in the Division of Chemical Process R&D and was promoted to Research Scientist in 1996, Senior Research Scientist in 2000, and Research Advisor in 2004. He has led multidisciplined teams engaged in the design and development of synthetic routes for new pharmaceuticals across major disease areas, including bone/metabolic diseases, CNS disorders, and oncology. He has patented, published, and lectured extensively in areas of synthetic methodology, heterocyclic chemistry, transition metal catalysis, asymmetric synthesis, and research management. Currently he is Research Fellow for the Division of Chemical Product R&D, Lilly Research Laboratories.

1. Introduction

Process Chemistry generally refers to the design and development of synthetic routes for the ultimate goal of manufacturing at commercial scale for fine chemicals and, in particular, pharmaceuticals. While some of the most efficient multistep processes have been developed and utilized in far greater scale for the production of crop-protection chemicals,[1−3] colorants, flavors, and fragrances,[4−6] publications and public disclosures (journal articles, patents, conferences, symposia, and monographs) have been dominated by chemists from the pharmaceutical industry, which has also been one of the largest sources of employment for synthetic and analytical chemists.[7] Contributing papers in this special issue of *Chemical Reviews* from leading experts in the field present a panoramic view of the state of the art of this discipline. These reviews are intended not only for practitioners in the field to learn from each other but also for chemists engaged in total synthesis, methodology development, or physical organic research to become familiar with the expectations, capabilities, constraints, and gratification involved in the design and implementation of a synthetic route for large scale. As such, this review seeks to provide an overview of the logic and logistics of synthetic design in process chemistry, highlighting those caveats not commonly found in contemporary total synthesis literature. The following sections, abundant with elegant solutions for processing chemistry problems, serve to enlighten students entering the workforce with a balanced understanding of the science and business and to inform researchers engaged in developing synthetic methodologies of the practical considerations process chemists use to make choices when designing routes for commercialization. Given the fact that process chemists in pharmaceutical companies are responsible for commercializing the most complex organic molecule portfolios and do so under considerable constraints, much of the discussion will be specific to this field, while some underlying principles are paradigmatic of process chemistry in general.

2. The Dual Goals of Process Chemistry

Process chemistry established its professional identity (ca. 1950s) with the advent of modern pharmaceuticals that required multiple-step synthesis and stringent requirements for quality of the active ingredients. Prominent among the early process chemistry examples are the elaborate synthetic routes developed for various β-lactam antibiotics,[8] many of them still being practiced at hundreds of metric ton scales. The first Gordon Research Conference on Organic Reaction and Processes in 1954 marked the adolescence of process chemistry, and its subsequent annual gathering of chemists

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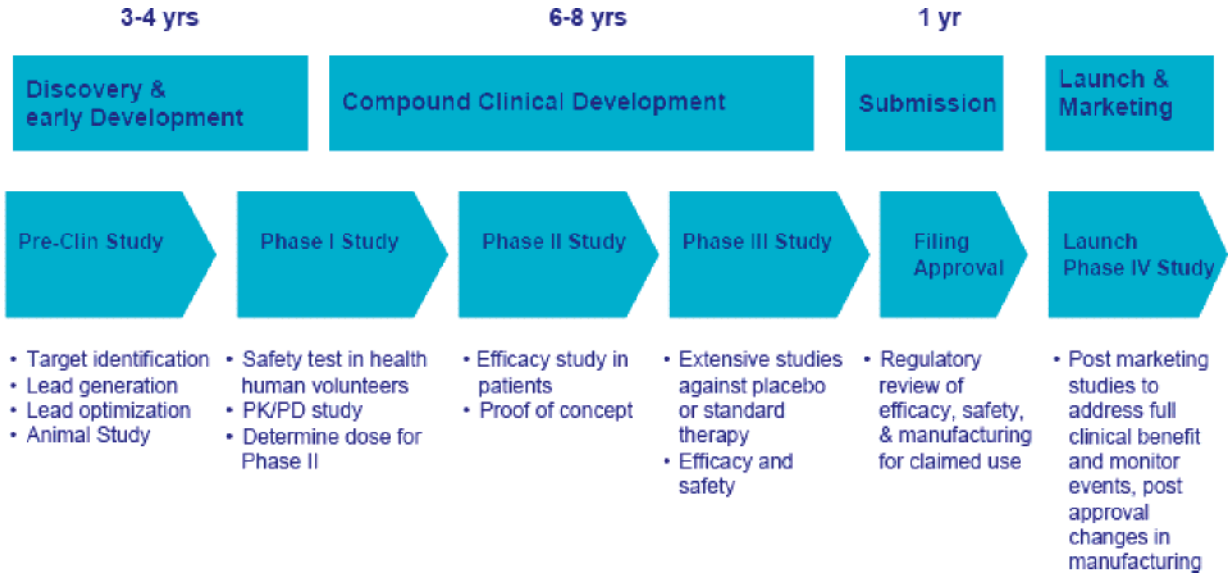

Figure 1. Prototypical drug development process.

from both academia and industry served the roles of conduit, adhesive, and lubricant to the community. Since the science, engineering, and business aspects of process development were first reviewed ca. 1990s,[9,10] several excellent monographs[11−23] dedicated to the subject have surfaced in recent years and are highly recommended reads for anybody interested in synthetic chemistry. The recent proliferation of conferences and symposia[24] dedicated to the subject signifies the coming of age for this profession. The successful launch of the journal *Organic Process Research & Development* (OPRD)[25] provides a scientific platform for the process professional to share with the rest of the world a wealth of reliable procedures, pragmatic tips, and techniques for organic chemistry.

What defines the roles of process chemists? Aren't they simply a group of chemists running reactions in a tank instead of a round-bottom flask? To appreciate the intricacies of this multidisciplined science, it is helpful to examine the development process for modern pharmaceuticals[26] (Figure 1).

It is easy to discern from Figure 1 the principal responsibility of process chemists at providing various amounts (~200 g to 2000 kg) of active pharmaceutical ingredient (API) to drive development, including formulation, toxicology, and human clinical trials. However, a salient while less conspicuous role played by process chemists is the generation of process knowledge to enable commercial production. This includes optimization and definition of process parameters and operating ranges, development and validation of analytical methods, characterization of impurities, and establishment of quality control strategies. Close collaboration with analytical chemists is essential to ensure the soundness of these tasks. Unfortunately, results from this line of research, rich in scientific content, are seldom manifested to the public, precipitating as confidential documents in the form of manufacturing batch records, process flow documents, regulatory submissions and company internal reports. However, the data generated and knowledge distilled are crucial for establishing manufacturing processes for new chemical entities with safety and robustness. These two goals, namely, providing **material** to enable clinical development and generating processing **knowledge**, set the general framework upon which process chemists balance and prioritize their research activities, appropriate with the stage of development.

From a general perspective, all of the materials produced prior to marketing are used for the ultimate purpose of knowledge generation, that is,. safety and efficacy of the drugs via toxicological testing and human clinical trials. The focus of process development chemists on knowledge generation is a business necessity so as to ensure not only that the drug substances meet safety and efficacy specifications but also that the processes of its manufacturing meet quality requirements and regulatory expectations.[27−29] Along the development timeline, several iterations of a synthetic sequence may be required to satisfy the material needs with an increasing degree of rigor for quality and greater emphasis on economics as a drug candidate progresses toward being launched. The risky nature of innovative medicine means that a great majority of the drug candidates never reach the marketplace; however, the advanced need for material and information requires that commercialization activities, including scaling up to demonstrate the soundness of the process, be carried out at risk years ahead of the anticipated approval of these drug candidates. As a result, the majority of the synthetic routes, elegant as they are, were developed for drugs that eventually fail. For the fortunate few that make it to the market, change in synthetic route post-marketing approval is a very costly endeavor. As such, getting the synthetic route right from the beginning of the drug development process and with confidence that it will remain the route of choice for the foreseeable future of the drug is the ultimate challenge for process scientists.[30]

3. The Criteria for Process Chemistry

> *In summary, we have accomplished an efficient enantioselective total synthesis of acmemycin (21.5% overall yield) in 19 steps (longest linear sequence).*

These are typical concluding remarks for a journal article celebrating the completion of a total synthesis. Multiplying the best yield from each step to arrive at an "overall" yield is the first order of business after positive structure identification of the final compound. These two criteria, namely, *overall yield* and *total number of steps*, have been universally used by chemists to gauge their achievements, especially when multiple laboratories are engaged on the same target, as is often the case. While these two measures of a typical

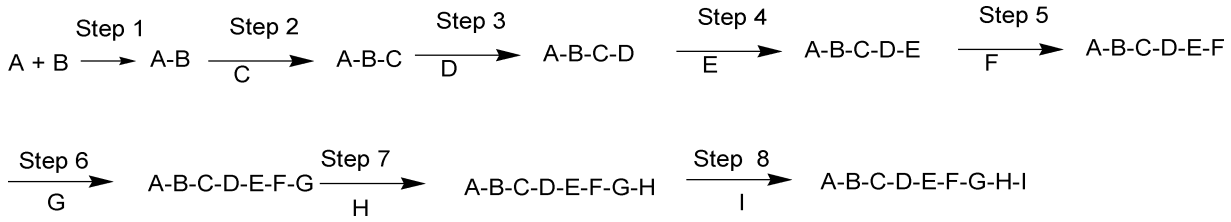

Figure 2. Linear synthesis route.

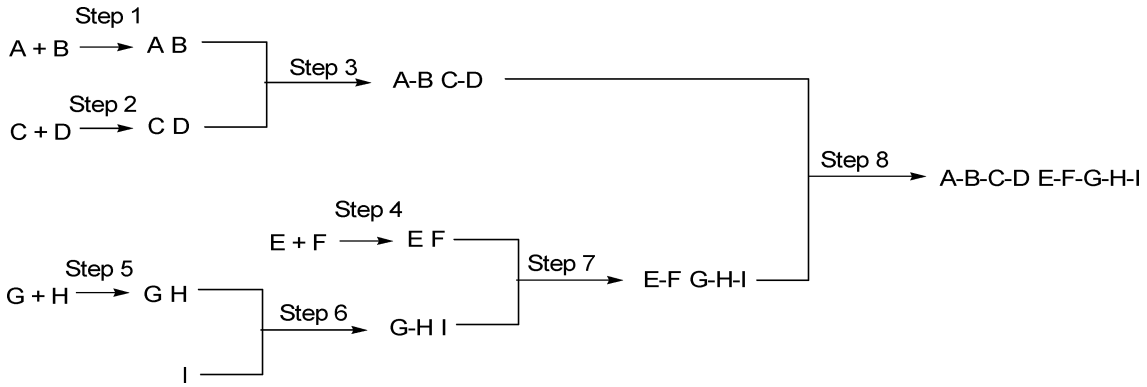

Figure 3. Convergent synthesis route.

synthesis have enjoyed wide acceptance among chemistry communities for their simplicity to understand and to quantify, their usefulness for process chemists are attenuated to a considerable degree.

First, there is ambiguity related to the definition of a step. It could be a bond forming/breaking event, a resolution of enantiomers via diastereomeric salt formation, or whatever is represented by an arrow in a synthetic scheme as long as there is space to pile up reagents sequentially. To most process chemists, it equates to the *number of isolations* in a synthetic sequence. Elimination of such an isolation does effectively reduce the step count (telescoping), with the usual consequence of decreased cycle time and solvent usage, contributed by unit operations including distillations, filtrations, crystallization, and drying. However, this practice does not necessarily improve the overall yield (vide infra) or the desirability of the synthetic route, and quite often piling steps together sacrifices additional control points for improving product quality. It is prudent for process chemists to understand each step individually before endeavoring to telescope them. Oftentimes the determining factor is the suitability of the intermediate for isolation, as governed by chemical stability, physical properties, potency and toxicity of the compound, and the need for and the ability of the isolation process to reject impurities.[31] The same can be said about the workup; not every step needs to be quenched with HCl, extracted with EtOAc, washed with $NaHCO_3$ and brine, dried over $MgSO_4$, evaporated to dryness, and purified by column chromatography over silica gel.

The second question has to do with the definition of a starting material, or where does one start to count the steps: should it be from a known compound published in the literature, from a natural product, from a material listed in a catalog, or from an item ordered from a custom manufacturer? Depending on the nature of task at hand, one must not lose the sight of the dynamic nature of starting material supply when judging a particular route by step-counting. A fundamental understanding of genealogy of specialty chemicals and the capability of the fine chemical industry is beneficial for identifying a suitable starting material from which to build upon a lasting synthetic route. It is also worth noting that the term *API* (active pharmaceutical ingredient) *starting material* in a pharmaceutical setting has regulatory implications and requires a deliberate data package to support its designation.[32]

Third, the number of steps is not an objective measure of efficiency when multiple synthetic routes are presented with different degrees of convergency. For example, consider the following two synthetic routes illustrated in Figures 2 and 3. Both schemes have the same number of steps, the only difference being the bond connecting sequence. In Figure 2, the molecule is assembled in a totally linear fashion, while the scheme in Figure 3 is highly convergent. It is inappropriate to declare that the scheme in Figure 3 is twice as efficient as that in Figure 2 because its longest linear sequence is only four steps or to conclude that both schemes are the same since they have the same number of total steps. For process chemistry purposes, the number of steps serves as one convenient surrogate for gauging task complexity, to be balanced with other important factors such as intermediate stability (crystallinity), potential for telescoping, throughput, and most importantly, the nature of the steps.

The second criterion, that is, overall yield, could be even more misleading at certain situations. An assessment of the maximum number of steps within a practical total synthesis sequence, and the importance of exercising prudence at reporting reaction yield have been presented by Hudlicky.[33] Just like the number of steps, overall yield is directly affected by the definition of the starting point. However, in a convergent situation, multiple starting points exist. For example, if one were to assume that every step in Figure 2 is 90% yield, based on the limiting substrate, the overall yield is evidently 43% (0.9^8) for this totally linear route. Perilous territory awaits as we attempt to assign the overall yield for a convergent process in Figure 3. Is it 66% (steps 5, 6, 7, and 8) as the cumulative yield of the longest linear sequence as commonly practiced? Or is it 73% (steps 1, 3, and 8), because fragment A is designated as the start of the synthesis since it contributes a majority of the molecular weight or complexity in the final product? Can one argue that overall

yield should be calculated from step 4 on because fragment F is the most expensive? Ironically, the usual method of calculating overall yield in a convergent synthesis resorts to picking a linear fragment of a whole picture, while ignoring the impact from the rest! Things get much more complicated when different versions (early or late) of convergent synthesis are to be compared. Multiplying yields from *all* steps in a synthesis to give an overall yield, whether it is convergent or not, has more integrity but tends to conceal the benefits of a convergent synthesis.

A fundamental concept taught in synthesis classes is the desirability of incorporating convergency into synthetic designs.[34] It is often erroneously interpreted that the advantage for convergency is that the overall yield is higher than that for a linear synthesis (Y^n vs Y^m, Y being the yield of an individual step, n being the longest linear sequence of a convergent synthesis, and m being the total number of steps in a linear synthesis). Convergent syntheses have many intrinsic merits, either in a process chemistry or in an academic setting, *vide infra*; a higher overall yield is not one of them. A superficial higher overall yield, obtained by ignoring the rest of the synthetic sequence away from the longest linear section, is at best misleading. For practical process chemists, overall yield and total number of steps are only two among many criteria that must be considered.

The ideal synthesis as articulated by Wender,[35] that is, where the target is made from readily available starting materials in one simple, safe, environmentally acceptable, and resource-effective operation that proceeds quickly and in quantitative yield, is a standard all chemists should strive to achieve. The difficult part is when not all of these goals are within reach, as is usually the case, how do process chemists make the tradeoff? Any attempt to answer this question usually comes with a series of qualifiers. The most frequently used criterion tends to be the percentage of manufacturing cost in the price of the product sold (COPS for cost of product sold, or COGS for cost of goods sold). However, this relative measure of cost is related to the dose strength of the drug (amount of active pharmaceutical ingredient in the dosage form, for example, a pill), the scale of production (volume), and the sale price. All of these factors are usually unknown when the comparisons need to be made, and estimates and projections tend to have a large margin of error. In addition, the impact of many important factors, for example, process safety and environmental impact, cannot be easily accounted for in current monetary terms. On the other hand, the overall cost to manufacture a kilogram of drug substance at projected scale by a particular process is a more manageable metric.

In process R&D, milestones are marked by successful scale-up at various stages of the development timeline. While very few of the route concepts that got explored in the laboratory and even those demonstrated at pilot plant scale seldom end up being installed at commercial sites due to high attrition rate, design for commercialization should always be the ultimate goal from day one. Quite often, the development timeline does not allow for the final route to be chosen to satisfy current material needs. Hence, an interim route or process is often is used to provide material for initial clinical studies. For obvious reasons, it is always most desirable to "get it right" the first time. Achieving this goal will require a holistic evaluation of various criteria, not only for the interim but for the entire duration of the route being used for production. The diagram in Figure 4 is an illustration of the facets that process scientists strive to build into their synthetic sequences.

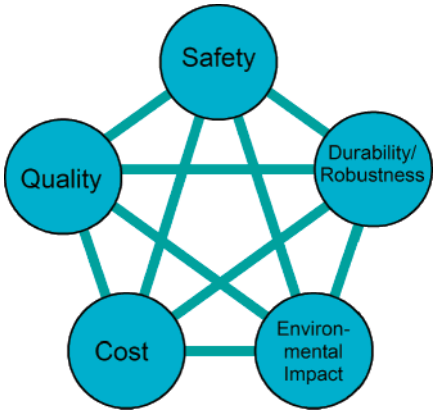

Figure 4. Major route design factors and their interactions.

Judging the fitness of a route for commercial production is a task that requires experience, intuition, foresight, and risk-taking. It demands a seamless integration of scientific considerations, engineering input, and sound business analysis. The complexity lies not only within quantifying the intangibles but also in weighting these different factors with a time variable once they are reduced to numbers. The five major criteria of safety, quality, durability, environmental impact and cost are all interrelated.

3.1. Safety

Safety is obviously the most important factor to consider when evaluating a process, and there is a wealth of information dedicated to this topic.[36−41] A run-away chemical process at large scale puts human lives and plant property at great risk, jeopardizes business timelines, and causes serious environmental damage. A thorough understanding of reaction thermodynamics and kinetics guides engineering design for better heat and mass transfer controls. In the route design stage, every effort should be made to avoid the *accumulation* of unstable or energetic intermediates. Many highly exothermic reactions and unit operations can be carried out safely through sound engineering design and the development of addition rate (dose) controlled heat management. In addition, the explosion hazard associated with static and organic dust has to be evaluated thoroughly,[42] especially for operations such filtration, drying, and milling.

Another aspect of process safety concerns the containment of potent compounds. This requires adequate protection of workers against exposure and elimination of cross-contamination between different process streams. These are also important factors to consider when deciding whether to isolate an intermediate.

3.2. Quality

The emphasis on quality for human pharmaceuticals is most prominently manifested by the fact that not only do products have to meet strict specifications but also the manufacturing processes and associated analytical methods must meet preset criteria. As such, incorporating the principles of quality by design into process design is the cornerstone for ensuring product quality and process performance.[27−29] Minimizing the introduction and generation of impurities, perfecting analytical methods for their detection, and establishing procedures such as crystallization for

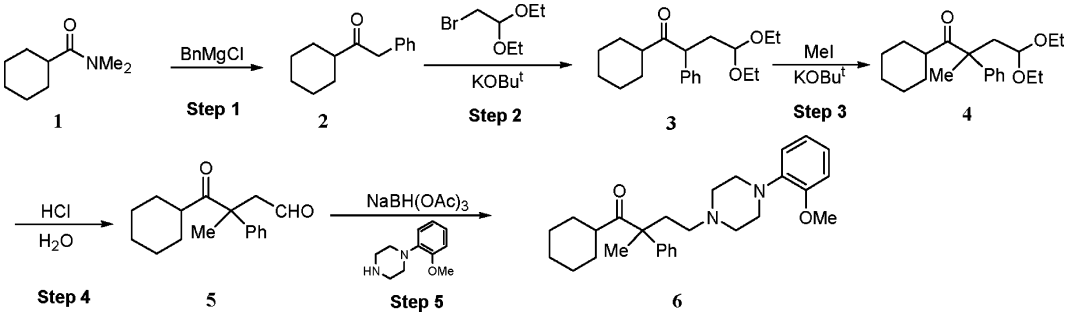

Figure 5. Original synthesis of compound **6**.

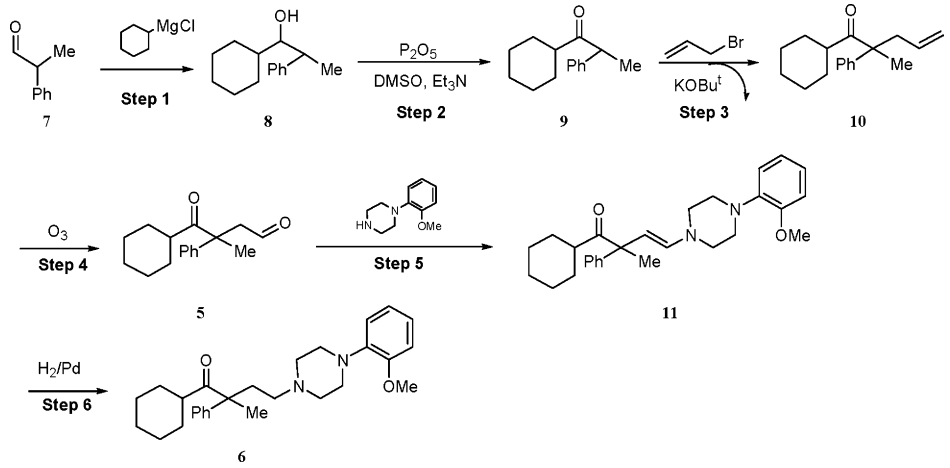

Figure 6. Improved synthesis of compound **6**.

their removal are all part of the control strategy that one must start to formulate with foresight at the synthetic route design stage. Generally, impurities (including residual starting materials, reagents, and solvents) that are the most differentiated from the desired products by physical or chemical properties are the easiest to control, which happens to be the direct reason for the necessity of a capping step in each cycle of a peptide synthesis. Fundamentally, an ideal reaction sequence is the one where each product would be inert toward reagent or starting material for this step, and only the product would be reactive in the next step. This can be illustrated by a comparison of two different synthetic routes for the synthesis of 5HT-1_A antagonist **6** (Figures 5 and 6).[43,44] For the first route, a substantial amount of bibenzyl ($PhCH_2CH_2Ph$), introduced from the Grignard reagent, along with byproduct from Grignard addition to the ketone product **2**, were the major impurities. Driving step 2 to completion risked double alkylation. Incomplete methylation from step 3 gave rise to a desmethyl impurity in the final product, which proved troublesome to remove due to its propinquity to **6**. While **6** could form a crystalline HCl salt, none of the intermediates (**2**−**5**) were solid, and thus impurities and residual starting materials were prone to be carried forward to the last step.

In the improved synthesis (Figure 6), in addition to employing only highly efficient reactions (Grignard, oxidation, and hydrogenation), an enamine intermediate **11** was introduced in step 5, which proved to be remarkably stable and crystalline, serving as a control point for all impurities hence before. All steps were much more efficient and high in throughput. Moreover, by design, all residual starting materials in every step do not participate in the subsequent step, thus preventing them from being carried over. For example, residual ketone **10** from step 4 did not take part in the enamine formation step and thus can be removed easily as a nonbasic impurity. It is noted that this route is one step longer than the previous one, a drawback easily justified by the superior product quality and process performance. More convergent routes are certainly conceptually possible, for example, via alkylation of **9** with an arylpiperidine analogue. However, it will introduce new problems associated with the use of an alkylating agent, which is prone to possess mutagenic activities, in the last step.

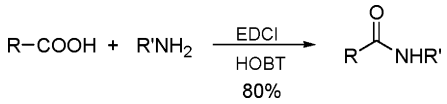

Figure 7. An amide coupling reaction.

3.3. Environmental Impact

Incorporation of green chemistry principles into synthetic route design has evolved from intuitive efforts by individuals toward an institutionalized practice among major pharmaceutical companies.[45] A time dimension is essential for evaluating the "greenness" of a process as more data emerge on the environmental impact of various chemicals. Reducing the volume of chlorinated solvents used in chemical processes will be one of the biggest challenges for the process chemists in the coming decade and represents a great opportunity for alternate methodology development, especially for oxidation reactions.

Minimizing environmental impact by a chemical process starts with an attempt to understand each step at the fundamental level, holistically. Figure 7 is a typical synthetic scheme describing a favorite amide forming reaction as it would appear in the contemporary literature. It tells the reader the starting material, product, reagents, yield and, sometimes,

Table 1. Supply and Demand of Starting Material

reason for the high price of materials	long-term pricing trend
hard to make (hazardous, special equipment, containment for toxic compounds and intermediates)	down (increase in volume demand brings incentive and justification for R&D, capital investment among third party suppliers, new chemistry and technologies)
high environmental burden	up (unable to minimize the adverse environment impact) or down (alternative, greener technologies emerge; waste recovery becomes economical)
limited natural source (precious metals)	up (demand to start command a significant market share) or flat (insignificant to affect market)
natural products (e.g., paclitaxil from yew tree bark, marine toxins from sponges)	up (depleted) or down (alternative sources developed, e.g., fermentation)
limited suppliers	down (more suppliers will emerge as demand picks up)
limited buyers	down (increased demand will induce more suppliers into the field, e.g., cephalosporins, statin side chains)
regulated substances (narcotics and chemical weapons)	up (tightening regulatory environment)
hard to transport (hazardous)	up (tightening regulations)

solvent, reaction time, and temperature. The atom economy[46] is obviously quite excellent if one chooses to ignore the molecular weight of EDCI/HOBT. What is left for readers to ponder is how much solvent is used, how the product is separated from the reaction mixture, what became of the reagent, and how the starting materials were made. It is curious that organic chemists no longer balance their chemical equations, at least for purposes of publication, perhaps due to the mutlistep nature of most synthetic schemes, despite the fact that it is simple to do and extremely useful for thorough process development. Nonetheless, whatever is charged into a reaction vessel has to come out, either as a product, as an impurity, or as waste. A great portion of process chemists' effort is directed away from this typical synthetic scheme. Mass balance analysis, the detailed account of the fate of reaction components during the process, provides a useful tool for a "mini" life cycle management and should not be limited only to the product of interest. The biggest contributor to the relatively high E-factor[47−49] for pharmaceutical production relative to petrochemical has been solvent usage, because of molecular weight and complexity. Reduction of solvent usage starts with understanding the fundamental roles solvents play in the chemical reaction, whether for solubilizing reactants, for controlling reaction rates, for facilitating heat/mass transfer, or for enabling product purification and separation. Quantitative understanding of key parameters such as solubility offers the most direct path to reducing solvent usage. As will be discussed in section 4, strategic placement of a burdensome step within a synthetic scheme can be very effective at reducing waste. Very often the greenest process is also the most cost-effective one, at least in a long run.

3.4. Cost

The cost of manufacturing an active pharmaceutical ingredient (API) by a particular route has many components. While the most obvious contributor is the cost of materials (substrates, reagents, catalysts, solvents, filtering media, and their transportation, etc.), it usually accounts for only a small (typically 20−45%) portion of the overall expense in a production setting. Conversion costs to produce API are usually the overriding factor. These include the cost of labor (operators, analysts, quality control, and other supporting personnel), capital (equipment, instruments, and facility depreciation), utilities (water, steam, electricity, nitrogen, compressed air, etc.), maintenance, waste treatment, taxes, insurance, and various overhead charges. Many of these cost categories are directly proportional to the concentration (space), duration (time), and efficiency (yield) of a process. The research and development cost for the process of interest can also be figured into this cost equation:

$$\text{cost/kg} = \text{material Cost/kg} + \text{conversion cost/kg} + \text{amortized development cost/kg} + \text{royalty payment/kg}$$

It is worthwhile noting the subtle relationship among these factors. Investment in development, either designing a new and superior route or optimizing an existing route, can have a dramatic and lasting effect on lowering the cost of production over the lifetime of a drug. However, the pressure for shortening the development cycle time to meet patients' needs and the intellectual property protection window for the medicine dictate that development activities have to conclude at a set time with discipline. While additional development will certainly improve the process, it is the project owners' responsibility to balance these factors to plan R&D investment for optimal returns. They have to decide on what data must be collected to enable registration of the process with regulatory authorities and what can be accomplished by optimization after commercial installation. More importantly, a variable of time has to be included in every consideration to reflect the dynamic nature of the business. A route decision will have a long lasting impact on overall economics. For example, when a raw material is expensive and a decision has to be made on utilizing it in the synthesis or adding a few more steps to go around it, the assessment should not only involve comparing the merits of routes based on current raw material prices but also encompass a dynamic forecast on the pricing trend based on the market's ability to equilibrate the supply and demand for these starting materials and reagents. Process chemists need to serve the role of a catalyst by lowering the activation barrier to facilitate this equilibrium (Table 1).

The dynamic landscape of material supply is evident. Commercial availability of starting materials does not need to be a strict requirement at the onset of the synthetic design. As long as economically feasible technology for preparing a starting material is within reach, the vast network of specialty chemical suppliers will rise to the challenge to make it at commercial scale, bringing in their niche technologies or raw material positions, if the drug becomes successful. On the other hand, if a staring material is "commercially" available from a catalog but there exists no economical way

to sustain its long term supply at scale, the synthetic route would only become a perilous path. From a scientific perspective, the designation of a starting material should not rely on its current commercial availability, which usually is just a manifestation of existing demands; instead, the decision should be based on how the starting material itself can be prepared and how it would fit into the overall impurity control strategy built into the downstream chemistry.[26−29,32] It is prudent to understand how the starting material is prepared by the suppliers for total life cycle management from an environmental impact perspective, for controlling entry of impurities that could potentially be carried into the final product, and for ensuring *durability* and *robustness* of the synthetic route.

Royalty payment for the freedom to operate shall also be included when evaluating the cost of a process on the occasion that a particular piece of intercultural property is patented by a third party. Without the legal freedom to practice the chemistry, commercialization of the process is at risk. This applies to the ownership of both process patents and composition of matter patents on intermediates, reagents, ligands, and catalysts. The options of designing around, licensing, or resorting to alternate technology eventually boil down to a case-by-case business decision. Underestimating the resourcefulness of process chemists has led owners of patented chemical technology to demand royalties greater than the difference between what the technology offers and what the next best alternative does, thus losing the opportunity window for commercial application. It is also a cruel business reality that most processes designed and developed for drug candidates do not end up being commercialized for launch due to attrition by less than desirable clinical or toxicological findings. The triple eclipse of patent term of the technology, production process lifetime, and technical *superiority* defines the size and value of this window of opportunity.

3.5. Durability/Robustness

While robustness (ruggedness) commonly refers to the consistency and reliability of a process to perform despite variations in process parameters, we would like to introduce the concept of durability to encompass a time factor for better reflecting the dynamic nature of the business. *Durability* measures the robustness of the entire process along its projected useful lifetime. For most total synthesis endeavors in academic laboratories, the completion of the synthesis usually means the completion of the project. It is unlikely that the same route will ever be repeated by anyone else. For process chemistry, an established commercial route is meant to be repeated many times, by different teams of people, and expected to deliver product with the same quality, consistency, and predictability in purity profiles and cycle times. An implemented synthetic route will likely last as long as the product lifetime for the innovator company because the burden for switching a registered route is quite high. A practical implication is that any route designed for commercialization shall be durable during this period of time until product patent expiration and beyond. The following are some key features of a route with high durability:

1. Starting materials have multiple synthetic sources and changing from one supplier to another will not adversely impact process performance and product quality.

2. Reagents, starting material, and solvents have a low probability of becoming unavailable due to factors such as transportation restrictions, use restrictions (e.g., chemical weapons, narcotics, etc.), environmental regulations, and natural resource depletion.

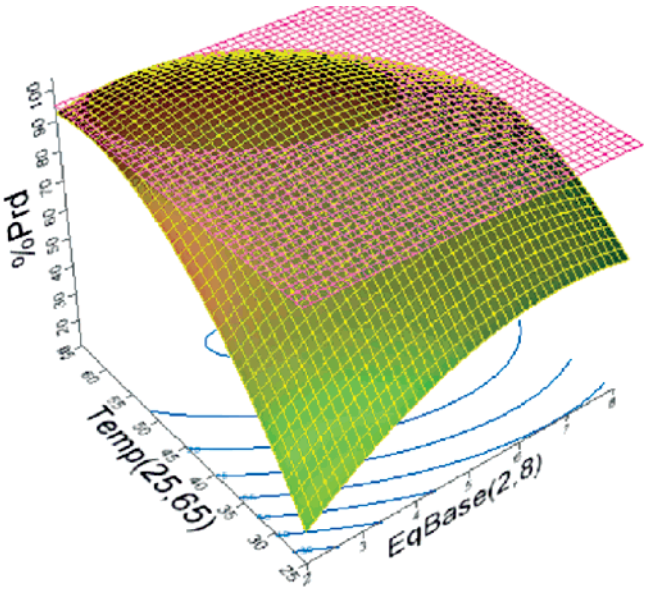

Figure 8. Definition of processing parameters by DoE.

3. The overall process has a minimal adverse impact on the environment.

4. The process can be easily scaled up or down adjusting for market demand.

5. The process is designed so that it is capable of incorporating advances in chemistry science and engineering technology without impacting product quality and purity profile.

6. The process is flexible with design features so that intermediates are stable to be shipped and stored and the process can fit into different equipment sets and sites.

7. The ultimate measure for durability is that the process will remain as the route-of-choice as long as the product is on the market.

With regard to robustness, much of the work activity is related to defining an operating space (Figure 8) for a particular process. Deviating from this defined region will result in lesser quality, lower yields, or hazardous consequences (edge of failure). The size of this operating space is often referred to as the *robustness* or *ruggedness* of the process. It is a measure of a unit operation's capacity to remain undeterred by variations in process parameters and an indication of the process' reliability during normal applications. Because operations take longer in the plant and process sequences do not always go as planned, demonstrated robustness in the laboratory provided a margin of safety against catastrophic failure at scale-up. Collection of data, aided by DoE (design of experiment)[50,51] and PAT (process analytic technology)[52−55] tools, charts the edge of failure in a multivariate fashion and is an integral part of the process chemists' responsibility to provide assurance of quality, consistency, safety, and productivity. A highly robust process also requires a smaller number of assays for forward processing decisions, thus reducing the burden on analytical resources.

An important and stringently regulated aspect of robustness is the control of impurities. Because of drug safety concerns, a change in the impurity profile among batches is a much more serious event than fluctuations in product yields.

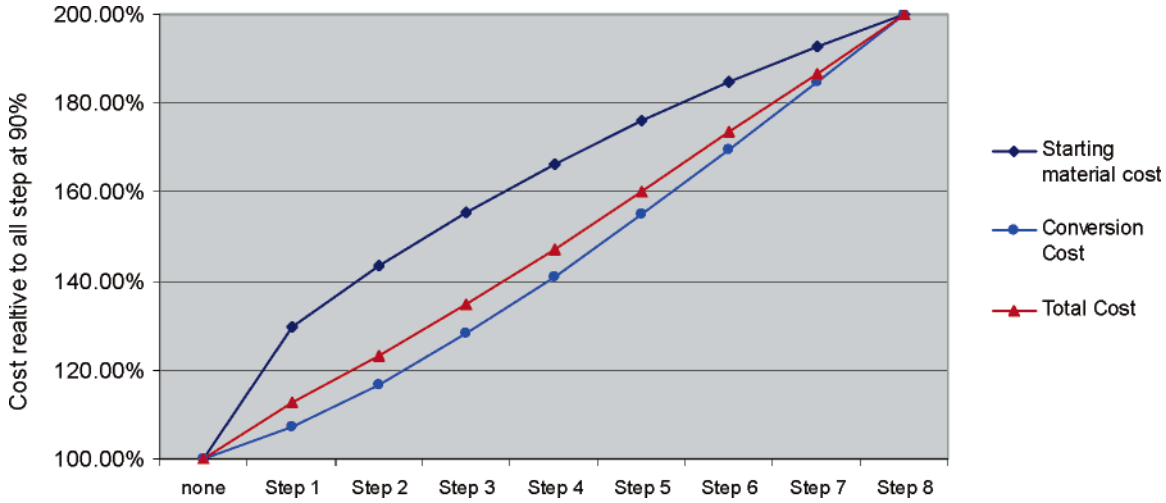

Figure 9. Effect of placement of a low-yielding step (45% vs 90%) on the overall cost.

Closely related to impurity control is crystallization process development, where the focus is on the maximum recovery of high-quality compound not only with the right chemical composition but also with desirable physical properties, that is, the control of polymorphism, crystal habits, and particle size.[56−58] These physical properties are closely related to dissolution behaviors, impurity rejection abilities, and solid form performance (e.g., filtration, milling, and formulation processing) and, as a result, are becoming increasingly important to the pharmaceutical industry.

The foundation for the robustness/ruggedness of a process lies in its operational simplicity. Too often when one problem is solved, another is introduced inconspicuously. Every operating step has to be scrupulously examined and justified for its necessity, and simpler alternatives have to be explored. In the heat of constant battles with development deadlines, one must not forget that *the solution cannot be more complicated than the problem.*

4. Logistic Concerns

4.1. Throughput

Throughput is usually measured by the unit time productivity for a given manufacturing rig (space−time yield), for example, the number of kilograms of drug substance produced by a plant module within a 24 h shift. It is the major factor governing conversion cost and is imminently dependent upon residence time (reaction and isolation), concentration, resource intensity (operators, QC and analytical personnel, equipment, and utilities), isolation methods, and hold time for bottlenecks. Unfortunately, in most synthetic literature, little attention has been given to the merits of high-throughput processes and methodologies.

Managing the relationship between the logic and logistical aspects of synthetic route design could also have a profound impact on the overall throughput. The logic of synthesis has been well defined and widely accepted in planning for the strategic bond connection/breaking sequence to assemble the molecular architecture,[34,59−62] based on functional activities of different fragments and their relationship within an entire molecular framework. This has served chemists well as guiding principles in designing the optimal pathway for synthesis. The importance of logistics, commonly understood as the planning of procurement, stockpiling, and movement of materials to enable a strategic activity, has not been recognized as much by the synthetic community, since the focus on overall yield and number of steps usually dominates the discussion. In practice, simple logistical considerations could lead to remarkable efficiency improvement with the least amount of effort. The following hypothetical examples serve to illustrate a few extreme cases.

4.2. Placement of a Low-Yielding Step

While there is really no good place for low-yielding steps, inevitably there is always one in a given synthesis. It is evident to a student of organic chemistry that a drop in the yield of a single step will impact the overall yield negatively. As presented earlier, overall yield is more objective when linear routes are compared but may be misleading as a standard to measure the desirability of a route. Taking the totally linear route in Figure 2, for example, the overall yield is 43% if every step is 90%. When a low-yielding step (45%) has to be included, the overall yield would be effectively cut in half to 21.5%, regardless of which step is the low-yielding one. A real-life example is a chiral resolution step where the theoretical maximum yield is 50%. Intuitively, one would surmise that it is preferable to carry out the resolution at the front end of the synthesis to cut loss earlier. Figure 9[63] compares the effect of placing a low-yield step at various positions in a hypothetical linear synthesis. It is evident that it is far more desirable to place an inefficient step earlier in the sequence. For example, the overall cost per kilo of the final product increases by 100% when such a transformation is performed at the last step 8, while the impact is only 13% and 23% more when it is placed at steps 1 and 2, respectively. Correspondingly, the respective increase in the E-factor is 7%, 13%, and 100% for dropping the yield to half at steps 1, 2, and 8. It is worth emphasizing that the overall yield dropped to 21.5% in all these scenarios! This underscores the fact that overall yield obtained by compounding individual step yield together is not an effective measure for judging the true efficiency of a process.

4.3. Focus of Development Effort

This analysis is helpful for prioritizing optimization efforts across the steps. The impact of improving a single step yield can be vastly different, depending on which step is being optimized, while improvement on overall yield remains the same no matter which step was optimized. As illustrated in

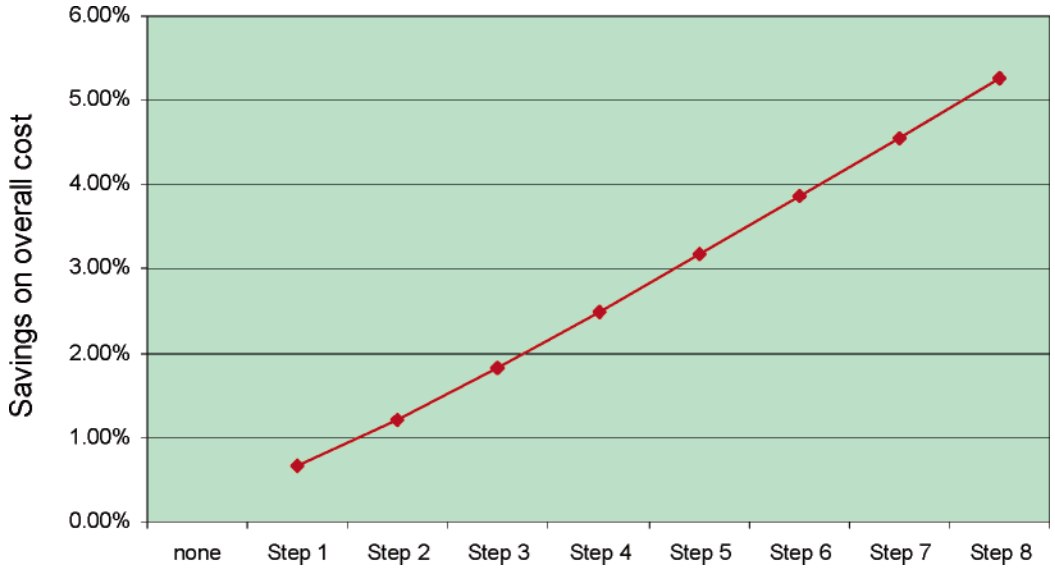

Figure 10. Effect of improving a step yield (from 90% to 95%) on the overall cost.[63]

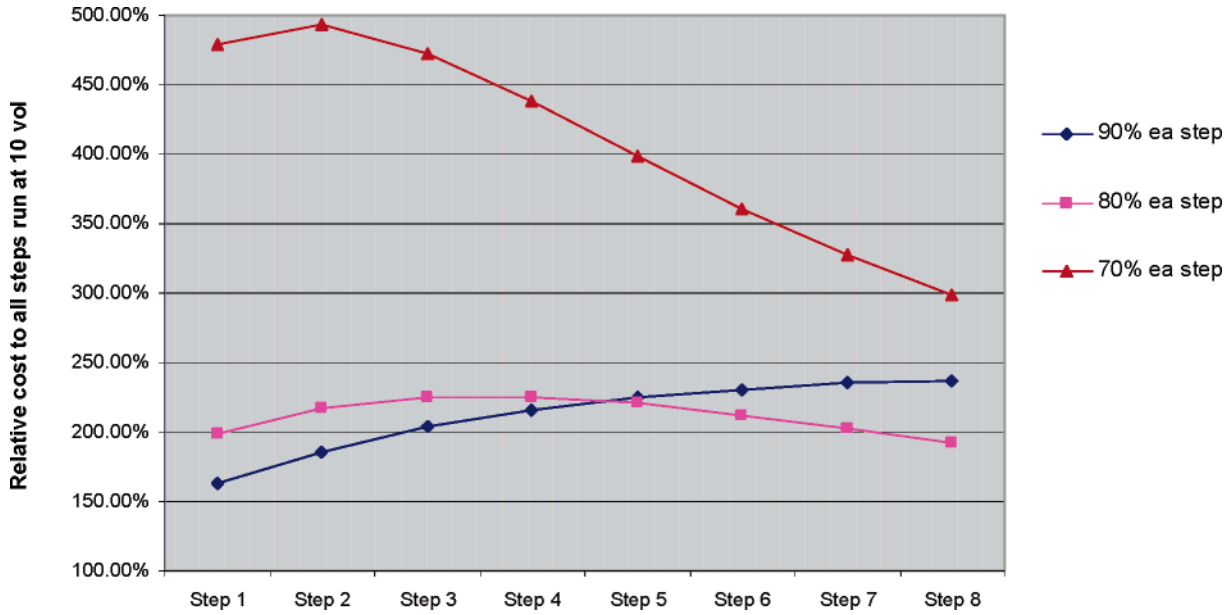

Figure 11. Effect of placement of a dilute step (10×) on overall cost.[63]

Figure 10, an improvement in yield from 90% to 95% for step 8 lowers the overall cost by more than 5%, while the same yield increase for step 1 has almost negligible effect (0.6%) on the overall cost. Again it should be noted that overall yield increases by 2% in both cases! In reality, an even more important driver for focusing development effort on the late stages of the synthetic sequence is the greater impact on final product (API) quality by these last few steps.

4.4. Placement of a Dilute Step

Similarly, the placement of a highly dilute step has an impact on the total volume of solvent used in the synthesis depending on which step. Intuitively, given a choice, process chemists tend to place a high-dilution step toward the end of the synthesis, because attrition by yield of accumulating steps would leave a smaller amount of material and hence less solvent to use at later stages. This is more or less the case as illustrated in Figure 11 by the red curve, where each step is 70% yield and placement of a dilute step (100 vs 10 kg/L) at step 1 and 8 leads an increase in total solvent usage by 370% and 200%, respectively. However, the difference is much smaller when the step yield is uniformly higher (blue and purple curves). In fact, the impact on overall solvent usage is the highest if the dilute step is placed in the middle of the synthesis when each step is at 80%. This is a manifestation of two contradicting factors interacting with each other: molecular weight and total weight processed. For the first few steps, substrates have low molecular weight but require high molar quantities; for later steps, substrates have high molecular weight but lower molar quantities. In a real situation, the freedom to place a dilute step is very limited and high dilution should be avoided to reduce solvent usage and processing cycle time. This is, nonetheless, an oversimplified model to illustrate that the consequence of placement of a dilute step is not intuitively simple. Minimization of solvent usage is often the most effective way for reducing a process's environmental footprint. Very often, the reaction concentrations are set in a rather arbitrary manner

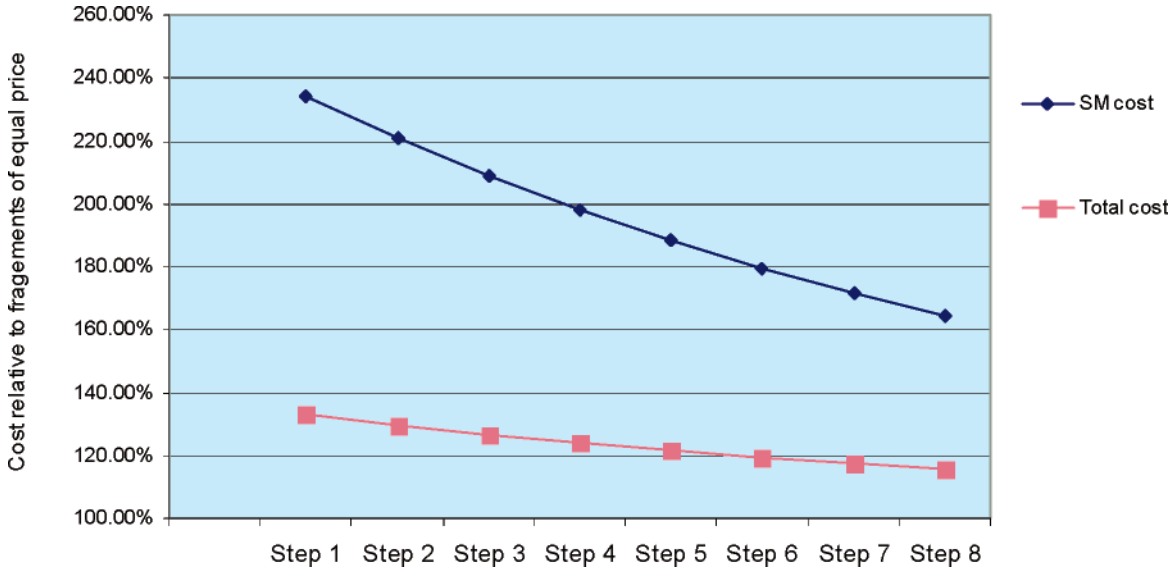

Figure 12. Effect of using an expensive reagent (10×) on overall cost.[63]

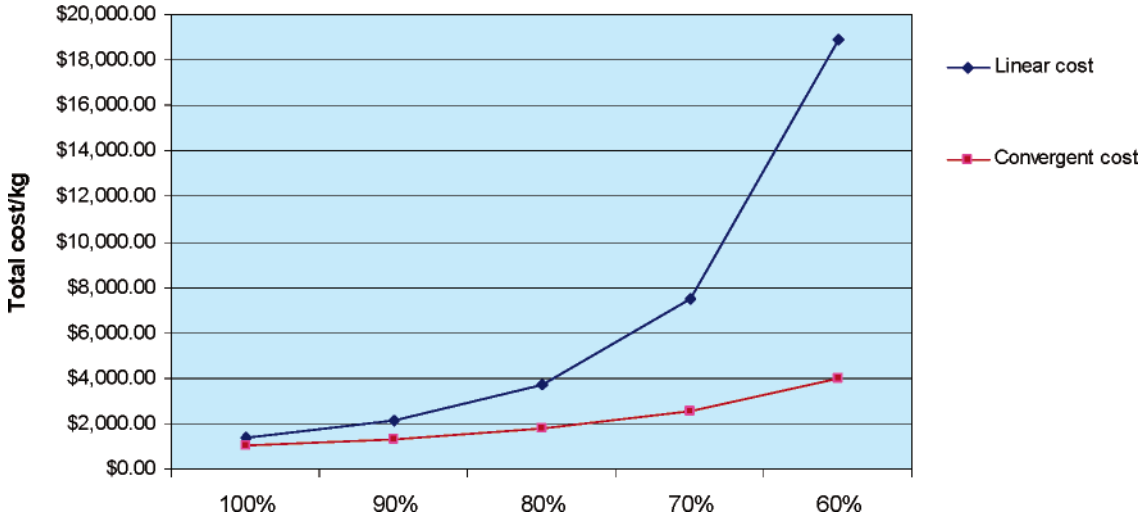

Figure 13. Cost−yield relationship for convergent and linear routes.

(say, for example, 0.5 M), rather than being guided by reaction kinetics or solubility data of the substrate, product, and impurities.

4.5. Placement of an Expensive Material/Reagent

With the same precaution, one can examine the effect of utilizing an expensive reagent (Figure 12) in a linear synthesis. The conclusion again is to use it near the end of the synthesis. In practice, however, this decision has to be made in connection with other factors to determine whether it is a viable alternative to move such an reagent toward the end, because conversion costs often outweigh the difference resulting from the change.

4.6. Differences between Convergent and Linear Routes

A convergent route (Figure 3), on the other hand, is perturbed to a lesser extent by gyrations in dilution, step yield, and reagent cost, because the alignment of the steps disperses the risk more evenly across branches of the synthetic pathway. Changes are more of a local phenomenon. For example, while a total cost per kilogram by a linear route (Figure 2) is 60% more than that by a convergent one (Figure 3) when each step is 90% in yield, the difference is a much more pronounced 200% when individual step yield drops to 70% (Figure 13). The fact that even at 100% step yield the linear one is 36% more expensive to carry out than the convergent one is a reflection of larger amount (weight) of intermediates processed by the former manner.

More importantly, a synthesis conducted in a convergent fashion generally requires shorter cycle time (from start to finish, if one allows parallel processing of fragments) and hence provides a higher throughput in comparison to a linear route. The underlying reason for this phenomenon is that in a convergent layout, the total weight of material being processed is less than that for the linear one, and consequently less solvents are consumed and less plant time is occupied. For example, the same illustration by Figure 13 would reveal that the ratio of the total weight of intermediates processed for each kilogram of product by the convergent route is about 8:1 when step yield is 70% each, while the ratio is 24 for the linear one! The larger ratio leads directly to longer processing time and thus drives up both material and conversion cost. If one compares the different journeys each fragment experiences before ending up in the final

product molecule, it becomes quite obvious that more of these fragments ride along nonproductively on the linear route than on convergent ones: they do not participate or materially contribute to the desired reaction, and riding along simply exposes them to deleterious side reactions! Better chemical selectivity is thus inherent within a convergent process because the fragments are subjected to fewer chemically transforming conditions.

Another feature inherent with convergent synthesis is that it allows parallel processing of different segments, permitting a shorter cycle time from start to finish. This logistical advantage will not only facilitate the designation and procurement of synthetic intermediates as a regulatory starting material[32] but also help to control impurities at the final steps where molecular complexity increases quickly. This is made possible by the fact that impurities generated by a final convergent assembly of molecules tend to be less similar to the desired product than those from a linear synthesis when the changes in molecular composition are more incremental in nature, thus facilitating their purge. An example is the last step (step 8) shown in Figures 2 and 3. In the linear synthesis, residual starting material (ABC-DEFGH) is very close in molecular weight to that of the product, whereas in the convergent version the two fragments (ABCD and EFGHI) are quite different from the product. A drawback to this strategy is that use of an excess of a component to drive reaction to completion is limited by cost vs a simpler fragment.

5. Conclusions

In summary, the prominent role played by process chemistry in the drug development process dictates that a holistic consideration should given to all governing factors for selecting a synthetic route. The danger of making decisions on numeric measurement has to be appreciated as it tends to oversimply the complexities of these factors in process development. A simple case in point is that 1 lb of mercury is the same as 1 L of water when all wastes are counted by weight (e.g., E-factor), while their impacts simply do not equate when released to the environment. The criteria for an ideal synthesis must be calibrated against the purpose of the endeavor. The following are some practical considerations useful for understanding the business:

1. Depending how they are defined, using the number of steps and the overall yield to judge the soundness of a particular route should be accompanied with extreme caution. As we have illustrated, two syntheses with the same number of steps and same overall yield starting from the same raw material can have vastly different economical outcomes. A key measure for the efficiency of a synthetic route intended for a production setting is no different from manufacturing efficiencies for any goods: COGS. For APIs, this means the cost per kilogram of active pharmaceutical ingredient. A major and often overlooked contributor to COGS is cycle time. While material cost (starting material, reagents, catalysts, solvent, filtering aids, etc.) is relatively easy to calculate, the impact of cycle time as part of the conversion cost on COGS is much more dynamic. Emphasizing the cycle time impact at the onset of synthetic design will have a profound effect on reducing COGS. After all, it is not the number of steps in the synthetic scheme that will determine the cycle time, it is how long it will take to execute these transformations (start to finish). One should count not only how many kilograms can be produced from a manufacturing rig within one shift but also how long this batch has been lingering in the plant, either being processed or waiting to be. The concept of unit-time productivity or space−time yield (kilograms produced per day at a set manufacturing footprint) is embedded within COGS. It is worth remembering that COGS will change with scale and time, which has been illustrated aptly by Anderson.[31]

2. A synthetic sequence with the same overall yield and number of steps can have dramatically different economic and business consequences depending on the logistic factors. Strategic placement within a synthetic scheme of steps with low yields, high dilution, or expensive reagents/conditions will have significant impact on the route efficiency, even when the overall yields and the number of total steps remain the same. Even though in practice the freedom to move steps around at will is severely limited, because synthetic operations are not totally modular, strategic placement of such undesirable steps when necessary to maximize the space−time yield shall always be part of the process chemists' consciousness.

3. The "higher" overall yield of a convergent synthesis, achieved by counting only selected steps (longest linear sequence) within the whole route, is not a sound measure for synthetic efficiency.[64] Overall yield is more meaningful when two totally linear routes are compared.

4. Convergent syntheses are preferred to linear routes due to their inherently more favorable logistical nature. A convergent process allows for the minimization of unproductive carryover of molecular fragments along the synthetic sequence; it is more robust against perturbations in the process and therefore has a shorter residence/cycle time and better selectivity. Impurities produced in a convergent process are better differentiated from products than those in a linear synthesis, facilitating their purging. Because components within the molecule are subject to fewer synthetic transformations in a convergent synthesis, chemoselectivity is intrinsically superior, and the need for protecting groups is reduced. The ability to parallel process intermediates toward a converging point is also invaluable from a project management perspective. In addition, choices for more than one intermediate as API starting material in a regulatory sense allow for efficient leveraging of third party producer's capabilities.

5. A time dimension should be considered as part of the evaluation process for the synthetic route. This is the concept of **durability**. Chemists must consider route options based not only on the current state of affairs but also on the potential for each route to be optimized, possibilities of new technology emerging, and raw material supply to be improved (or deteriorated) along with time. This dynamic evaluation in a holistic manner is aimed at selecting a synthetic route that will withstand the test of time and possess a high potential to be optimized (developability and improvability).

The importance of pharmaceutical development to the industry and society in general is well recognized, and has attracted in-depth analysis from the business community.[28] Arguably, the business environment for process chemists is changing as rapidly as the progress of chemical science. Pressure continues to increase for process chemists to reduce development cycle time as the pharmaceutical industry is being challenged on multiple fronts. Coalescing the business, engineering, and science organically is the art of process chemistry. The true beauty of this art form lies not only in

the aesthetic elegance of the synthetic design but also in its function to bring molecules of the highest quality in the most economical, robust, safe, rapid, and environmentally friendly way to the patients.

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