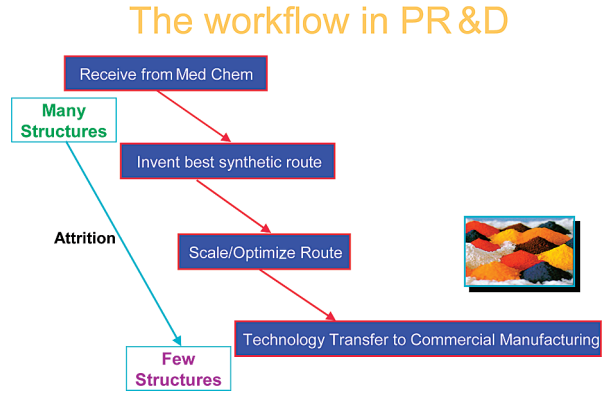
ACCOUNTS
of chemical research

Chemical Process Research and Development in the 21st Century: Challenges, Strategies, and Solutions from a Pharmaceutical Industry Perspective

HANS-JÜRGEN FEDERSEL*
Global Process R&D, AstraZeneca, 151 85 Södertälje, Sweden

RECEIVED ON DECEMBER 5, 2008

CONSPECTUS



In process research and development (PR&D), the generation and manipulation of small-molecule drugs ranges from bench-scale (laboratory) chemistry to pilot plant manufacture to commercial production. A broad range of disciplines, including process chemistry (organic synthesis), analytical chemistry, process engineering (mass and heat transfer, unit operations), process safety (chemical risk assessment), regulatory compliance, and plant operation, must be effectively applied. In the critical handover between medicinal chemistry and PR&D, compound production is typically scaled up from a few hundred grams to several kilograms. Can the methodologies applied to the former also satisfy the technical, safety, and scalability aspects that come into play in the latter? Occasionally, the transition might occur smoothly, but more often the situation is the opposite: much work and resources must be invested to design a process that is feasible for manufacturing on pilot scale and, eventually, for commercial production.

Authentic examples provide enlightening illustrations of dos and don'ts for developing syntheses designed for round-flask operation into production-scale processes. Factors that are easily underestimated or even neglected in the laboratory, such as method robustness, chemical hazards, safety concerns, environmental impact, availability of starting materials and building blocks in bulk quantities, intellectual property (IP) issues, and the final cost of the product, will come into play and need to be addressed appropriately. The decision on which route will be the best for further development is a crucial event and should come into focus early on the R&D timeline. In addition to scientific and technical concerns, the parameter of speed has come to the forefront in the pharmaceutical arena. Although historically the drug industry has tolerated a total time investment of far more than 10 years from idea to market, the current worldwide paradigm requires a reduction to under 10 years for the specific segment covering preclinical development through launch. This change puts enormous pressure on the entire organization, and the implication for PR&D is that the time allowed for conducting route design and scale-up has shrunk accordingly. Furthermore, molecular complexity has become extremely challenging in many instances, and demand steadily grows for process understanding and knowledge generation about low-level byproduct, which often must be controlled even at trace concentrations to meet regulatory specifications (especially in the case of potentially genotoxic impurities). In this Account, we paint a broad picture of the technical challenges the PR&D community is grappling with today, focusing on what measures have been taken over the years to create more efficiency and effectiveness.

Introduction

The design and development of syntheses and processes for making small molecule drugs on scale has experienced considerable attention over recent decades and is now regarded as a core capability in the pharmaceutical industry, requiring high scientific and technical skills.[1] It is now fully integrated in the value chain operating in

Published on the Web 04/01/2009 www.pubs.acs.org/acr
10.1021/ar800257v CCC: $40.75

pharma R&D (Figure 1) that starts with an idea of how a disease might be addressed and ends with the launch of a novel drug several years later.[2]

The mission of a PR&D organization can be characterized by at least two areas of responsibility. These are comprised of (i) the design and development of scalable processes that fulfill criteria such as being short and atom-efficient, cost-effective, technically robust, and environmentally considerate and (ii) the manufacture of active pharmaceutical ingredients (APIs) to support drug projects from around the time of candidate drug (CD) nomination and throughout the entire remaining R&D phase of a project. Besides these core accountabilities, PR&D has the task to deliver a comprehensive documentation describing the production method and how it was derived, as part of the CMC (chemistry manufacturing and control) section of regulatory files. Finally, in many companies PR&D retains the responsibility for the entire life cycle management of the commercial processes, which involves performance monitoring and the replacement of "old" synthetic and process technologies with novel ones. The focus of this Account is to address specific problems and challenges currently facing PR&D and how they are addressed to enable the manufacture of the desired compounds using safe and effective production methods.

When Does It All Begin?

In the "classical" approach to developing new drugs, the functions operated in isolation rather than involving the teams from other departments. Such a business model was seen as sufficiently effective, inasmuch as the pressure on shortening time lines was rather low. Spending 15 years taking an idea through to market launch was seen to be the norm, rather than something that could be improved. As productivity in the pharma industry has come into the limelight during the past decade, this paradigm has been strongly challenged and today a common driver across the business is to arrange the workflow in such a way that the sequence of activities is much faster; <10 years from start of preclinical documentation to filing for regulatory approval and launch is an achievable target in most disease areas.

This change in the operating mode has affected PR&D a great deal, because the supply of the required APIs is compressed over a shorter time span, which requires a more expedient scale-up and manufacture. Experience shows that the delivery of the first batch of a new chemical entity (NCE) on scale, normally meaning 1−5 kg, is on the critical path as this material will have to support extended toxicological and formulation studies, alongside phase I trials in humans (healthy

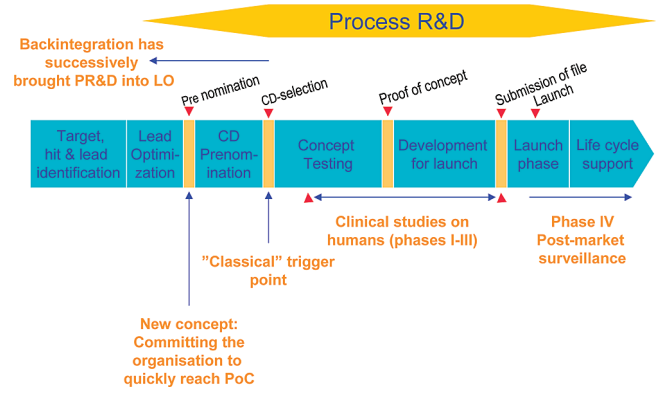


FIGURE 1. Overview of the value chain in pharmaceutical R&D with special emphasis on the interface with process R&D. Key activities on the timeline are indicated alongside critical milestones and trigger points.

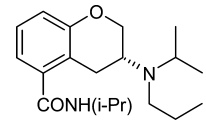
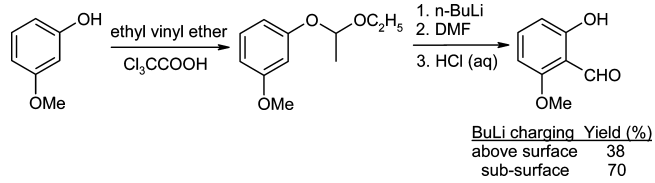


FIGURE 2. Ebalzotan, a molecule posing considerable challenge for manufacturing on large scale.

volunteers). The main reasons for this is that the compound has only been made on laboratory scale (few hundred grams) up to this point, which, considering the fact that not only the target molecule but also some of the synthetic intermediates are novel, means that there is no precedence on how to best ensure successful production. Moving fast at this early stage of PR&D work means high risk-taking. The reason being that the big step progressing chemistry from laboratory to plant scale is conducted at a point when there is still relatively poor knowledge about key features of the process (that is, kinetics, critical parameters, workup procedures, byproduct formation, and conditions for crystallization and isolation). An illustration to this effect and at the same time a hard-learned lesson is offered by the ebalzotan case (Figure 2). This molecule, chosen as a candidate in the early 1990s, showed selective $5HT_{1A}$-agonistic properties and a promising pharmacological profile, which lead to its development as an antidepressant (later discontinued due to side effects in healthy volunteers). PR&D involvement did not start until the compound selection had been made, and the request was to prepare a first batch on a scale of about 1 kg in the shortest possible time. Given this minimal lead-time and being faced with a medicinal chemistry sequence of 13 linear steps, the opportunities for neither a major redesign of the route nor finding the time to conduct a detailed scrutiny of the methods from a large-scale operability perspective were simply available. Starting the production with provisional batch sheets and solving problems as they occurred (there were many of

SCHEME 1. Formylation Chemistry: The Way in Which the Lithiating Agent Is Added Has a Dramatic Effect on the Isolated Yield[a]



BuLi charging	Yield (%)
above surface	38
sub-surface	70

[a] Abbreviations: DMF, *N*,*N*-dimethylformamide.

them!), the result was that after 5 months of hard work the material finally isolated did not mount to more than 80 g (0.25% overall yield).[1g,3] With this catastrophic outcome, an amount delivered that was far less than expected and considerably later than planned, virtually the entire project came to a halt. To mention but one example from this tour de force where the outcome in the pilot plant was substantially below the yield achieved in laboratory experiments, the Li-mediated formylation constituting the first step provides a good illustration (Scheme 1). Based on the laboratory findings, the first version of the pilot plant method demanded the addition of BuLi (hexane solution) to be conducted in such a way that the feed stream was entering the vessel (600 L) above the surface of the reaction solution. Using this procedure, the yield shrunk to half of the expected, generating only 38% of the desired aldehyde compared with >70% obtained in laboratory runs. This meant that more material had to be processed in this step and, furthermore, that the purity profile deteriorated, which proved to have a negative impact later in the process. In subsequent studies, the poor result was traced back to the formation of local hot spots in the reaction mixture, and the solution devised to avoid this from happening was to redesign the charging device allowing the BuLi reagent to enter beneath the surface of the process solution. This trivial change ensured a much more efficient dispersion of the reagent in the bulk of the solution, which avoided formation of byproduct.

Because time is of the essence in this early phase, a way to tackle the situation is to initiate the necessary activities earlier. This front-loading concept has been in operation in AstraZeneca's PR&D organization for several years, and the results achieved are unambiguous: The successful delivery of the first batch in pilot quantities is off the critical time line.[4] Proper management of the interface between medicinal chemistry and PR&D is a key to ascertain this outcome and builds to a large extent on the creation of an environment that allows a free flow of information. This way, the contacts can be pushed back into the earlier stages of lead optimization (LO), where there is still uncertainty about the exact structural features characterizing the potential CD (Figure 3). However, enough

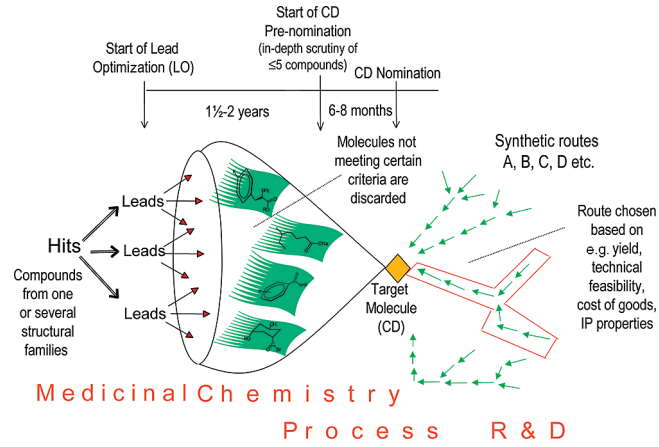


FIGURE 3. The medicinal chemistry–process R&D interface. Opportunities for efficiency gains, especially in speed of delivery of first batch on scale by front-loading work into LO and prenomination phases.

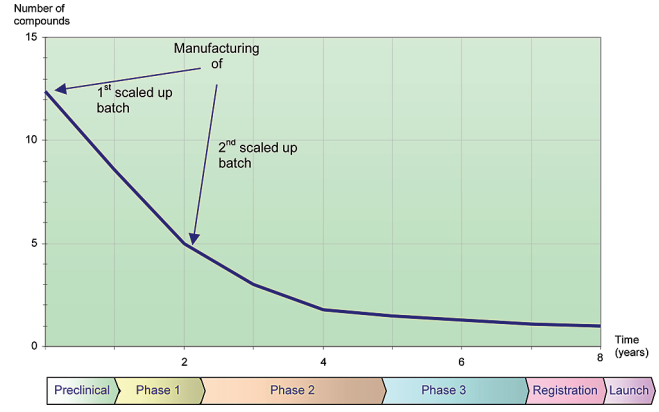


FIGURE 4. Attrition is the worst enemy to the development of new drugs, and in the phase from preclinical through first studies in humans, a statistical average of 2 out of 3 projects are terminated. (Source: Centre for Medicines Research International 2006/2007, Pharmaceutical R&D Factbook).

can be gained from these early interactions that will enable a trained process chemist to decide when to initiate his own activities such as experimental work, ordering of starting materials, applying technical feasibility studies, looking for alternative synthetic routes, assessing reaction hazards, and so on. The change in working model thus described has reduced the average time lag from CD nomination (Figure 1) until availability of the disired compound from typically >$^1/_2$ year to a few weeks.[2d,5] It is important to stress that the chemical processes applied in this early stage of a drug project are not in a fully developed and optimized state. At this point, where the attrition is extremely high with on the average 2 out of 3 molecules being lost (Figure 4), mainly because of toxicity in animals and for DMPK reasons (drug metabolism and pharmacokinetics),[2d] a process that meets critical safety, health, and environment (SHE) criteria and guarantees that the API can be manufactured to the right quality attributes is good

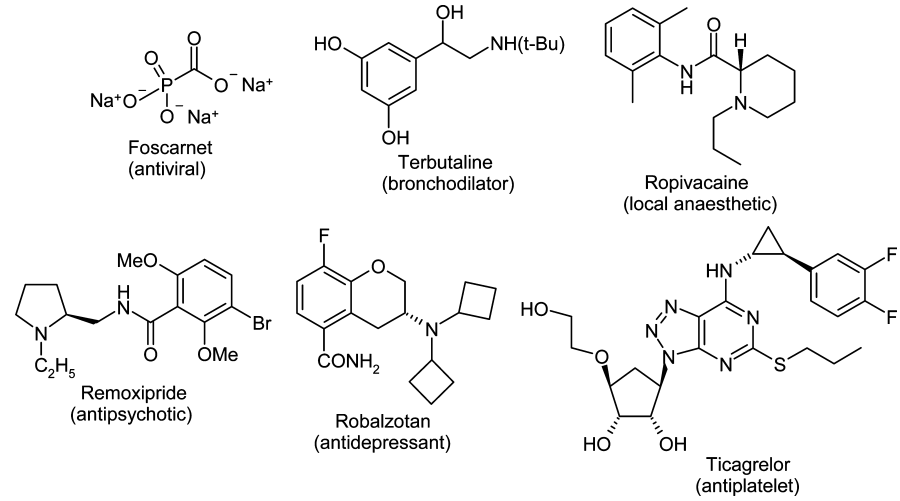


FIGURE 5. Structural diversity as exemplified by drug molecules from the AstraZeneca portfolio.

enough. The high failure rate results in only 1 of 3 compounds having to be produced a second time, and hence, it is more rewarding to focus efforts on surviving projects rather than spending on those that are close to becoming discontinued. A question immediately comes to the fore: how to pick the winners? In a constrained environment (money and people), a mechanism that would identify projects standing the highest chance of success would present an enormous asset. An in-depth cross-functional analysis on, for example, a disease area portfolio level or on individual projects will map threats and risks on one hand and compare them with opportunities, as represented by the disciplines involved. Combining these data and rating their relative importance will provide at least some guidance on which projects to prioritize when allocating resources, with the caveat that this "cherry-picking" exercise can never offer a 100%-guarantee that the right choice has been made. For PR&D, listening to customers and various experts will, ultimately, exert a strong influence on which work should be front-loaded and which can be deferred to a later start.

Making Molecules: An Expanding Toolbox

The space describing the universe of small drug molecules (typically with molecular weight <1000 Da) shows a wide variation, with new architectures being continuously added (Figure 5). To successfully address the challenging task of assembling these often highly complex compounds, it is essential to have access to methodologies capable of achieving the synthetic transformations required. In an effort to describe the as is situation within the pharmaceutical industry, a mapping analysis was recently undertaken by three major drug companies in the UK (GlaxoSmithKline, Pfizer, and AstraZeneca) of what specific reaction types had been used to

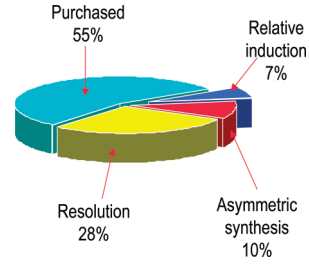
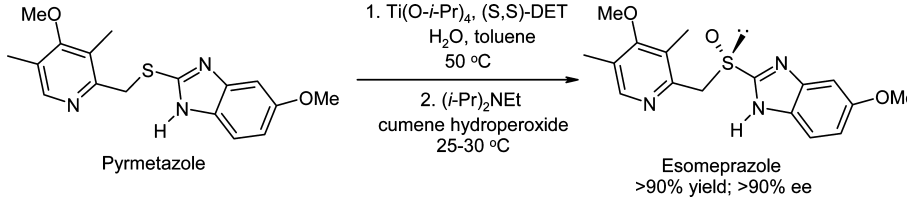


FIGURE 6. Source of stereogenic centers as found in a cross-pharma survey[6] analyzing a combined portfolio of 69 chiral molecules.

prepare a number of drug candidates.[6] The survey covered 128 synthetic sequences, representing in total 1039 discrete transformations. From this, the average number of stages per synthesis was found to be just above 8, with a spread in the actual numbers from 2 to >15. Unsurprisingly, no single reaction category is entirely dominant, and the highest score was achieved by what has been described as heteroatom alkylation and arylation with 19%. Other areas occupying relatively high prevalence were deprotections (15%), acylations (12%), C−C bond formations (11%), and interconversions of functional groups (10%).

A further lesson established by this investigation was the ways in which stereogenic centers were installed[7] in the 54% of the cohort of molecules that displayed chirality (Figure 6). Thus, the conclusion is that in a pharmaceutical industry scenario >50% of the cases will rely on supply of the required stereochemically defined building blocks from external sources. With the wealth of both simple and more sophisticated enantiomerically pure compounds available commercially, many of them in bulk, and new ones being continuously added, this state of the art should not come as a big surprise. It might seem more unexpected that "classical" resolution (28%) still assumes a very important position. The rea-

SCHEME 2. En route to Nexium, One of the Most Significant Drugs: The Bulk Production of the Active Ingredient Is Conducted via an Asymmetric Ti-Catalyzed Sulfoxidation, Operating with Turnover Numbers of 4−16 and Turnover Frequencies of 3−12 h^{-1}



son for this resides in the vast experience gathered from applying this technology over many decades and its reputation as a robust, reliable, and scale-up friendly methodology. Asymmetric synthesis, enjoying high attention and prestige in academia, is only applied in one out of 10 cases; a fact largely attributed to the dominating perception that design of catalytic processes is complex, hugely effort consuming, and tedious with uncertain outcome.[5] A further contributing factor is the high attrition of drug projects in the early parts of the pipeline (Figure 4), leading to a reluctance to invest in the design and development of such processes. Notwithstanding, today's access to a whole host of catalytic procedures, be they organometallic or enzymatic, with high specificity and capability to conduct selective transformations (oxidations, reductions, bond formations) robustly and at large scale has brought this whole area to the forefront. Thus, transition metal catalyzed stereoselective synthesis has, for example, been amply demonstrated and validated in numerous production scale processes,[8] the largest of which is the herbicide (*S*)-metolachlor[9] with an annual manufacturing volume >10 000 t. From the pharmaceutical sector, esomeprazole (active ingredient in AstraZeneca's antiulcer drug Nexium) constitutes an excellent example where a Ti-catalyzed asymmetric sulfide oxidation is carried out on a scale of 100 t per annum (Scheme 2).[1g,10]

Continuous Improvement: Adapting to Challenging Times

The intense drive to reduce cost in virtually all areas that the entire pharmaceutical industry is being faced with today will require new working practices. For PR&D, this means that efforts will be invested only to an extent where critical API deliveries or crucial route discovery/development work will not be jeopardized. This approach is in line with the management principles of lean six sigma.[11] Instead of devoting efforts on non-value-adding activities or even on what rightly can be characterized as waste,[12] the focus should be to support innovation by giving priority to work that helps develop a product or a process more quickly, with better quality, and spending less resources. A visualization of these fundamental principles applied to the workflow in our PR&D organization is provided by the speed−quality−cost triangle (Figure 7).[2d] This model offers guidance on where to concentrate efforts as the project is progressed along the time axis. Starting with *speed*, focusing on this parameter will ensure faster cycle times, which going forward eventually brings *quality* into the limelight as an element to underpin a better pipeline of emerging drugs. Finally, when the critical proof-of-concept stage is successfully passed, *cost* will get most of the attention by virtue of its direct link to the creation of a leaner organization.

The cost component is partly being addressed via the application of lean methodologies and the current trend of extensive outsourcing into countries with low PR&D/manufacturing cost. In the quality area, traditional approaches (rigorous analytical control) are now increasingly complemented by the concept of process analytical technology (PAT).[13] Speed, as the first area to concentrate on when a new project is initiated, will most likely impact the whole portfolio of drug candidates as they appear through the pipeline. A feature closely linked to this parameter is the complexity presented by the target molecule, which should not be understood purely in terms of structural challenges but also as the assessment of the number of chemical stages required to make the product. Therefore, estimating the workload created by an entire portfolio of new drugs has to be done on the basis of counting the discrete number of steps rather than the amount of individual projects, an insight often overlooked that has direct implica-

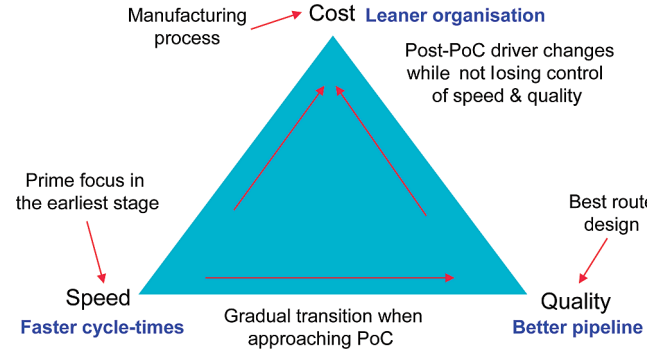
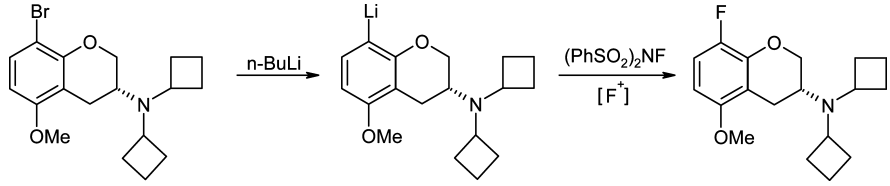


FIGURE 7. Using the speed−quality−cost triangle as guidance for where to put main efforts as drug projects progress along the R&D timeline.

SCHEME 3. An Electrophilic Fluorination on a Substituted Chroman Moiety, Using $(PhSO_2)_2NF$ (NFSi) as Source of F^+, a Reagent That Contributes with Just 7% of Its Molecular Weight



tions on resource allocation. Scrutinizing a particular synthesis from start to finish should, however, not stop at this point but include a thorough investigation of "classical" parameters such as yield per step, whether the route is linear or convergent, dilution in process streams, materials throughput, and foreseeable issues with scalability. The latter is particularly crucial when the plan is to operate on larger scale, because it is absolutely necessary to take hazards and safety aspects into serious account to avoid unacceptable risks to staff and the environment.

En Route to Green Processes

Is it possible to apply an entirely objective judgment when trying to assess the quality of chemical processes? The answer to this question is most probably no, but attempts have been made to offer a rational approach to the assessment of routes. Thus, under the acronym SELECT, a cross pharma industry group in the UK has listed a number of parameters, safety, environmental, legal, economics, control, and throughput, each specified by a number of subcriteria that ultimately will reveal strengths and weaknesses of a chosen process and provide guidance on where changes are required to improve on existing procedures.[14] With new and improved tools becoming available, for example, in the form of novel catalysts or innovative reactor designs, processes that previously were seen as "best in class" can become obsolete or outdated. Not least, the green chemistry paradigm has played an important role in changing people's minds and thoughts on how chemical processes should be constructed in the future. The foundation of green chemistry[15] rests on 12 general principles, for example, elimination of waste, atom economy,[16] reduction of risk, minimization of energy consumption, renewable raw materials, catalysis, and biodegradability. More recently, this concept has been further expanded and refined into the context of sustainability, which, besides including the "classical" green features, operates broadly under the definition of "meeting the needs of the current generation while preserving the ability of future generations to meet their needs".[17] When one analyzes sustainability, three areas can be defined, environmental, economic, and societal, against which any action or change should be assessed. Thus, if an activity is advancing just one of these areas, it will not be seen as something that has an overall positive impact on sustainability. This raises complicated questions where the consequences of short- vs long-term and regional vs global decisions have to be addressed.

Introducing a fluorine substituent in an intermediate en route to the antidepressant robalzotan[18] (Figure 5) provides a nice example of a chemistry that is far from being atom efficient. Thus, only a tiny fraction of the molecular weight (7%) of the reagent NFSi is utilized when making the product (Scheme 3). Aiming for a more optimized procedure that avoids technically complex fluorination technology (severe risk of corrosion), a starting material with the F-substituent in place was identified as a much more effective strategy. In a promising attempt to capture "downside" features of this sort as well as provide an overall assessment of the way in which a given molecule is synthesized, a numerical tool focusing on structural intricacy has been designed that allows a revealing side-by-side comparison of different approaches.[19]

When the elegance (or lack thereof) in a synthetic route is discussed, the total number of steps required often constitutes the measure of quality. The translation of a synthesis to a process will, however, not always show the same outcome in the sense that fewer steps, by default, will create a more effective and efficient production method. Instead, technical aspects come to the fore exemplified by the number of unit operations and solvent swaps required, the level of dilution during reactions and workup, demands on materials of construction, need for special (nonstandard) equipment, and the amount of the final material that can be produced at maximum (optimum) capacity in a given reactor setup. Initiatives directed toward improvements in the processing area at large have been branded process intensification, and one technology that has received much attention recently is reactors operating under continuous flow mode.[20] Moving into systems of this kind will inevitably bring in a new aspect to pharmaceutical production, where the tradition has been strongly in favor of running batch-wise. However, the current view supported by experimental evidence is that continuous processing is an option in only 10−20% of the reactions normally applied in

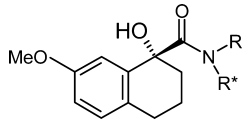


FIGURE 8. Chiral tetralin-substituted α-hydroxy carboxamides, a class of pharmacologically active molecules.

fine chemicals and drug manufacture, and hence, both approaches will be evaluated case by case.

The Big Leap: Taking Syntheses to Scale

When scale up of chemical transformations is considered, a number of aspects need to be addressed as outlined above. An effective way is to establish mechanisms allowing PR&D to interact as early as seems sensible with groups in medicinal chemistry. The gains obtained by this collaborative approach are illustrated by an authentic case,[21] where the task was to produce 2 kg of a novel API. Thus, during the LO phase, several potential candidate molecules were identified that, besides being chiral, shared a common structural motif in the form of an α-hydroxy amide moiety (Figure 8). In a first step, 300 g of each of a small number of compounds was required in order to conduct further preclinical investigations that, finally, would yield one CD. A synthetic strategy was conceived in medicinal chemistry where a linear sequence led to a racemic α-hydroxy carboxylic acid, which, subsequently, had to be resolved using preparative chromatography after transforming the acid to the corresponding amide using an enantiomerically pure amine (Scheme 4). Acknowledging that some of the steps operate at impressive yields (90%), being forced to apply yet another chromatographic purification of a complex reaction mixture further upstream and saving the stereoisomer separation to the very final stage offering only 25% yield made this process seem very unattractive. The overall yield of barely 2%, in combination with high cost and limited bulk availability of the chiral amines of interest, prompted a focused search for alternatives.

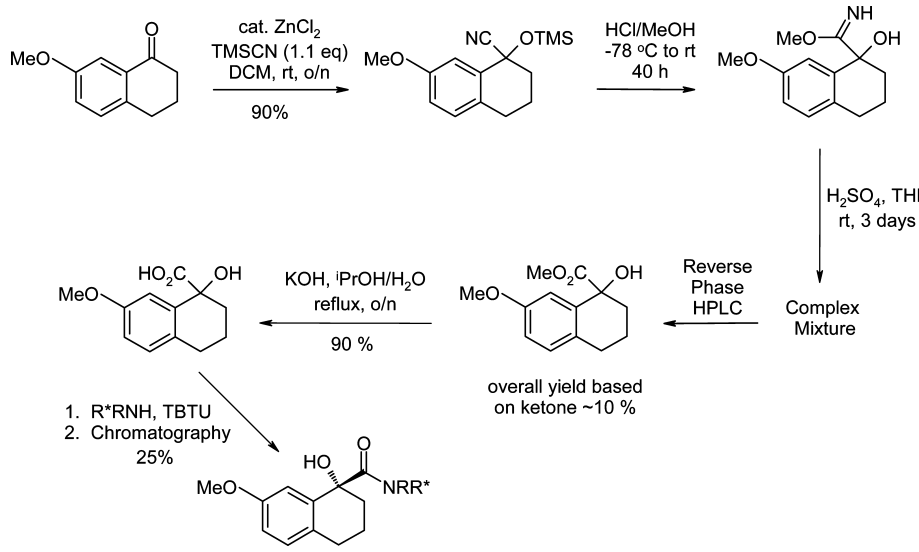
Several options were identified for how to handle the deliveries, and these fell into three main categories: (i) the medicinal chemistry route is scaled up as is; (ii) the medicinal chemistry route is modified; (iii) an entirely novel sequence is designed. The first of these was ruled out on the basis of very long projected manufacturing times, a judgment that a chromatographic isolation of the wanted enantiomer would not be workable, and fears regarding the timely supply of the chiral amine. In the second scenario looking at the bottlenecks of the synthesis, there was a perception that improving on the nitrile hydrolysis was entirely feasible. Moreover, an opportunity was seen to conduct the resolution at the stage of the penultimate intermediate constituted by the hydroxy ester, which would avoid chromatography. A possibility was identified to perform the first step in the sequence, generation of the cyanohydrin, in an asymmetric fashion. The downside of this idea was, however, that at the time only limited precedence was available indicating that such a reaction should be successful with ketones. Moving to the final category, conducting a brainstorm exercise to address how this class of target molecules could be accessed resulted in the identification of what was characterized as a winning route (Scheme 5).

Interestingly, the starting material (7-methoxy-1-tetralone) is identical to the one used by medicinal chemistry, but then the routes diverged. In the novel process, carbon-chain extension was effected by a Wittig reaction where a phosphonium ylide is added to the keto function. The nonisolated exocyclic olefin was then subjected to an oxidation under "classical" Sharpless conditions, where an Os-based dihydroquinidine catalyst results in an asymmetric dihydroxylation across the double bond in good to excellent yields, installing the correct stereochemistry at C-1. A smooth Pt-catalyzed oxidation using O_2 present in the atmosphere rendered the α-hydroxy acid as final intermediate, which after coupling with the pertinent amine afforded the end product as the desired antipode in an overall yield ranging from 42−55%. The method was still a linear sequence, but with fewer steps than the original method and transformations that all operate at very high chemical (>70%) and stereochemical yields (>98% ee). A key feature is the absence of chromatography, which in itself is enormously time-saving. When a side-by-side comparison of the two routes (Chart 1) looking at some key parameters such as total working time spent, staff resource, and amounts needed of starting material (tetralone) and chiral amine is conducted, it is clearly evident that a change in process is extremely beneficial in all aspects. Specifically, the dramatic decrease in requirement for supply of tetralone should be noted, where the original need is reduced by >90%. The lesson provided by this example is that being open to and considering alternative solutions to a problem right at the start is a worthwhile approach, where PR&D can make a significant contribution.

Intellectual Properties: A Key Interface

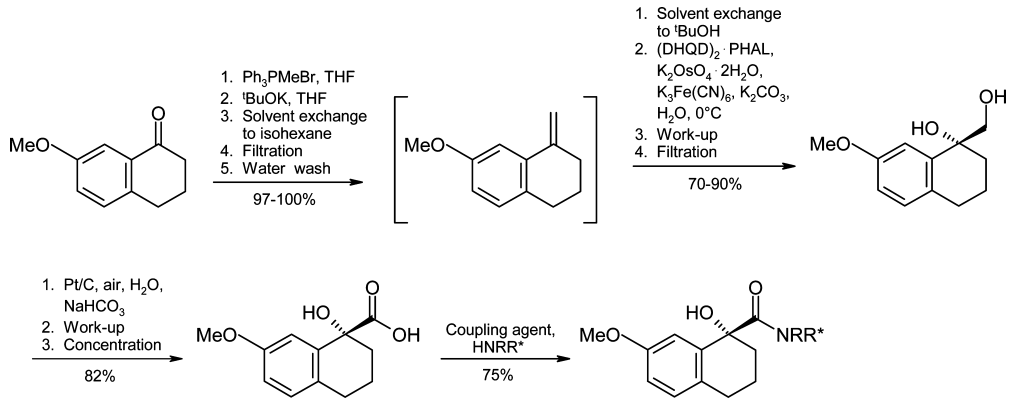
The design and development of processes for synthesizing novel molecules is, as already alluded to, a highly innovative activity. This means that results generated during these endeavors will represent intellectual properties (IPs) to varying degrees and value for the owner and, hence, might merit being patented. In the context of pharmaceutical products, the

SCHEME 4. Entry into the Family of Chiral α-Hydroxy Carboxamides Using a Synthetic Route Devised by Medicinal Chemistry (Route A), Requiring Two Chromatographic Stages, One for Chemical Purification of an Intermediate and One for Separation of Optical Antipodes[a]



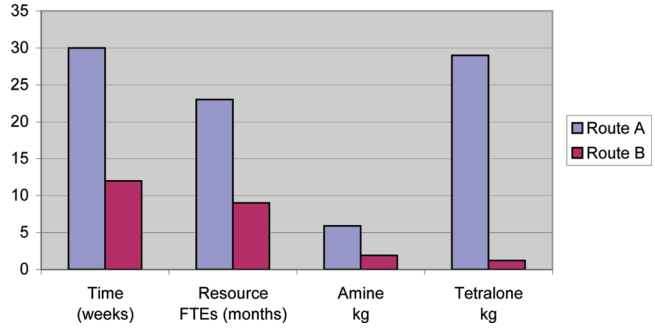
[a] Abbreviations: TMSCN, trimethylsilyl cyanide; TBTU, *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate.

SCHEME 5. A Significantly Improved Process (Route B) for Making α-Hydroxy Carboxamides Based on an Asymmetric Dihydroxylation Protocol[a]



[a] Abbreviations: (DHQD)$_2$·PHAL, hydroquinidine 1,4-phthalazinediyl diether.

CHART 1. Side-by-Side Comparison between Routes A and B (Schemes 4 and 5) of a Number of Process Attributes Leading to 2 kg of a Single Enantiomer of α-Hydroxy Carboxamides



IP protection aims at covering various aspects of the drug, for example, the structure of the active ingredient, the formulation, and the medical indication for which it is intended to be used.[22] The value in protecting processes has been heavily debated, and the views on pros and cons go in different directions depending on circumstances. Many claim that revealing the details of a manufacturing process in a patent disclosure will only trigger competitors to find loopholes allowing them to go outside the claims. Others say that a patented process gives you control of how to make the compound in question and will prevent a third party from claiming the rights to it, which if they did would exclude you from practicing the invention (i.e., the process). Features of processes that are patentable would be, for example, the order that the individual steps are conducted, the specific reaction conditions, and the use of a particular catalyst or solvent. Advantages over prior art that need to be proven to gain patent rights can be exemplified by improved yields, improved chemo-, stereo-, or regi-

oselectivity, reduced formation of byproduct, reduction in effluent streams or energy usage, or telescoping of several steps (one-pot protocol).

If full ownership represents one aspect of IP, then freedom to operate is another, where an invention is made publicly available (e.g., published in a journal), which guarantees everyone the access as no one can claim the rights to it. This approach is seeing an increased use in the process arena, a development that has been driven by the insight that policing abuse or infringement of IP is an exceedingly hard task. Revealing that someone has copied a molecule is relatively straightforward. In contrast, to successfully claim that the process for making a particular compound uses patented methods and procedures or proceeds via patented intermediates is very difficult, if not impossible. Nonetheless, for ethical pharmaceutical companies, it is crucial to prevent generic manufacturers from conducting illegal competition during the time of patent validity, and considerable efforts are devoted to enforce the law in this respect.

Conclusions and Outlook

In today's pharmaceutical industry where the speed of developing new drugs has become a key concern, process R&D is increasingly finding itself standing in the limelight. This has led to a challenge of old working principles and a demand for continuous improvement and increased efficiency. The balanced frontloading of work prior to the traditional starting point at CD nomination has generated a strong momentum, which has resulted in taking the delivery of the first API campaign at scale off the critical path. Chemical processes operated at this point will be far from the performance expected of a fully commercially viable method, however, without compromising on the safety aspects. The full implementation of quality by design (QbD)[23] and lean six sigma philosophy, coupled with application of new and innovative technologies, promises to further increase the capability of PR&D to successfully respond to forthcoming demands.

The author expresses his deep appreciation to colleagues, past and present, in Astra and AstraZeneca, who have been instrumental to the successful progression of the work reported in this Account. A special gratitude is due to Dr. David Ennis, Process R&D Avlon/Charnwood, for providing details regarding the chiral α-hydroxy carboxamide case story.

BIOGRAPHICAL INFORMATION

Hans-Jürgen Federsel, born 1949 in Säter, Sweden, has devoted his entire professional career to the field of process R&D. He has occupied different positions in Astra and AstraZeneca, both as a scientist and manager, leading to his current roles as Director of Science and Senior Principal Scientist. Alongside, he has pursued a deep involvement with academia that brought him an associate professorship in organic chemistry at the Royal Institute of Technology, Stockholm, Sweden. For a more comprehensive bio, see Acc. Chem. Res. 2007, 40 (12), 1377.

FOOTNOTES

*To whom correspondence should be addressed. E-mail: hans-jurgen.federsel@astrazeneca.com. Telephone: +46 8 553 270 63. Fax: +46 8 553 242 76.

REFERENCES

1 (a) Repič, O. *Principles of Process Research and Chemical Development in the Pharmaceutical Industry*; Wiley and Sons: New York, 1998. (b) *Process Chemistry in the Pharmaceutical Industry*; Gadamasetti, K. G., Ed.; Marcel Dekker: New York, 1999. (c) Anderson, N. G. *Practical Process Research & Development*; Academic Press: San Diego, CA, 2000. (d) Cabri, W.; DiFabio, R. *From Bench to Market: The Evolution of Chemical Synthesis*; Oxford University Press: Oxford, U.K., 2000. (e) *From Bench to Pilot Plant. Process Research in the Pharmaceutical Industry*; Nafissi, M.; Ragan, J. A., DeVries, K. M., Eds.; American Chemical Society: Washington, DC, 2002. (f) Federsel, H.-J. Start small, think big - The art of process R&D. *Nat. Rev. Drug Discovery* **2001**, *1* (12), 1013. (g) Federsel, H.-J. Logistics of process R&D: Transforming laboratory methods to manufacturing scale. *Nat. Rev. Drug Discovery* **2003**, *2* (8), 654–664. (h) Lipton, M. F.; Barrett, A. G. M., Guest Editors, Process Chemistry, *Chem. Rev.* **2006**, *106* (7), 2581−3027. (i) Rao, C. S. *The Chemistry of Process Development in Fine Chemical & Pharmaceutical Industry*, 2nd ed.; Wiley & Asian Books Private Ltd.: Chichester and New Delhi, 2006. (j) *Process Chemistry in the Pharmaceutical Industry, Vol. 2, Challenges in an Ever Changing Climate*; Gadamasetti, K.; Braish, T. F., Eds.; CRC Press: Boca Raton, FL, 2008. (k) *Org. Process Res. Dev.*; Laird, T., Ed.;this journal is entirely devoted to publishing work from the process R&D arena since 1997; see journal homepage http://pubs.acs.org/journal/oprdfk/.

2 (a) Federsel, H.-J. The integration of process R&D in drug discovery - Challenges and opportunities. *Comb. Chem. High Throughput Screening* **2006**, *9* (2), 79–86. (b) *Comprehensive Medicinal Chemistry II, Vol. 2, Strategy and Drug Research*; Moos, W. H., Ed.; Elsevier: Oxford, U.K., 2007. (c) Woodcock, J.; Woosley, R. The FDA critical path initiative and its influence on new drug development. *Annu. Rev. Med.* **2008**, *59*, 1–12. (d) Federsel, H.-J. Handing over the baton: Connecting medicinal chemistry with process R&D. *Drug News Perspect.* **2008**, *21* (4), 193–199.

3 Federsel, H.-J. Development of a process for a chiral aminochroman antidepressant: A case story. *Org. Process Res. Dev.* **2000**, *4* (5), 362–369.

4 (a) Federsel, H.-J. Drug discoverers - you need us. *Drug Discovery Today* **2001**, *6* (8), 397–398. (b) Federsel, H.-J. The role of process R&D in drug discovery - Evolution of an interface. *Chim. Oggi/Chem. Today* **2004**, *22* (3/4), 9–12. (c) Potoski, J. Timely synthetic support for medicinal chemists. *Drug Discovery Today* **2005**, *10* (2), 115–120.

5 Federsel, H.-J. In search of sustainability: Process R&D in light of current pharmaceutical industry challenges. *Drug Discovery Today* **2006**, *11* (21/22), 966–974.

6 Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. Analysis of the reactions used for the preparation of drug candidate molecules. *Org. Biomol. Chem.* **2006**, *4* (12), 2337–2347.

7 (a) Federsel, H.-J. Drug chirality - scale-up manufacturing, and control. *CHEMTECH* **1993**, *23* (12), 24–33. (b) Federsel, H.-J. Facing chirality in the 21st century: Approaching the challenges in the pharmaceutical industry. *Chirality* **2003**, *15* (S1), S128−S142. (c) Federsel, H.-J. Searching for scalable processes: Addressing the challenge in times of increasing complexity. *Curr. Opin. Drug Discovery Dev.* **2003**, *6* (6), 838–847. (d) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Kesseler, M.; Stürmer, R.; Zelinski, T. Industrial methods for the production of optically active intermediates. *Angew. Chem., Int. Ed.* **2004**, *43* (7), 788–824. (e) Federsel, H.-J. Chiral Drug Discovery and Development - From Concept Stage to Market Launch. *Comprehensive Medicinal Chemistry II, Vol. 2, Strategy and Drug Research*; Moos, W. H., Ed.; Elsevier: Oxford, U.K., 2007; Chapter 2.17, pp 713−736.

8 (a) Blaser, H.-U.; Spindler, F.; Studer, M. Enantioselective catalysis in fine chemicals production. *Appl. Catal. A* **2001**, *221* (1−2), 119–143. . (b) Federsel, H.-J. Asymmetry on large scale: The roadmap to stereoselective processes. *Nat. Rev. Drug Discovery* **2005**, *4* (8), 685–697. (c) *Asymmetric Catalysis on Industrial Scale. Challenges, Approaches and Solutions*; Blaser, H.-U., Schmidt, E., Eds.; Wiley-VCH: Weinheim, Germany, 2004. (d) Blaser, H.-U.; Pugin, B.; Spindler, F. Progress in enantioselective catalysis assessed from an industrial

point of view. *J. Mol. Catal. A: Chem.* **2005**, *231* (1−2), 1–20. (e) Federsel, H.-J. Stereoselective Synthesis of Drugs — An Industrial Perspective. In *Chirality in Drug Research*; Francotte, E., Lindner, W., Eds.; Wiley-VCH: Weinheim, Germany, 2006; Chapter 2, pp 29−65.

9 (a) Blaser, H.-U. The chiral switch of (*S*)-metolachlor: A personal account of an industrial odyssey in asymmetric catalysis. *Adv. Synth. Catal.* **2002**, *344* (1), 17–31. (b) Blaser, H.-U.; Hanreich, R.; Schneider, H.-D.; Spindler, F.; Steinacher, B. The chiral switch of metolachlor: The development of a large-scale enantioselective catalytic process. *Asymmetric Catalysis on Industrial Scale. Challenges, Approaches and Solutions*; Blaser, H.-U., Schmidt, E., Eds.; Wiley-VCH: Weinheim, Germany, 2004, pp 55−70.

10 (a) Federsel, H.-J.; Larsson, M. An Innovative Asymmetric Sulfide Oxidation: The Process Development History Behind the New Antiulcer Agent Esomeprazole. *Asymmetric Catalysis on Industrial Scale. Challenges, Approaches and Solutions*; Blaser, H.-U., Schmidt, E., Eds.; Wiley-VCH: Weinheim, Germany, 2004, pp 413−436. (b) Seenivasaperumal, M.; Federsel, H.-J.; Ertan, A.; Szabó, K. J. Factors influencing the selectivity in asymmetric oxidation of sulfides attached to nitrogen containing heterocycles. *Chem. Commun.* **2007**, 2187–2189. . (c) Seenivasaperumal, M.; Federsel, H.-J.; Szabó, K. J. Mechanism of the asymmetric sulfoxidation in the esomeprazole process. Effects of the imidazole backbone for the enantioselection. *Adv. Synth. Catal.* **2009**, in press.

11 George, M.; Rowlands, D.; Kastle, B. *What is lean six sigma*? McGraw-Hill: New York, 2004.

12 Sewing, A.; Winchester, T.; Carnell, P.; Hampton, D.; Keighley, W. Helping science to succeed: Improving processes in R&D. *Drug Discovery Today* **2008**, *13* (5/6), 227–233.

13 Romañach, R. J. Research initiatives to support science-based pharmaceutical manufacturing. *Pharm. Technol. Eur.* **2007**, *19* (10), 47–51.

14 Butters, M.; Catterick, D.; Craig, A.; Curzons, A.; Dale, D.; Gillmore, A.; Green, S. P.; Marziano, I.; Sherlock, J.-P.; White, W. Critical assessment of pharmaceutical processes - A rationale for changing the synthetic route. *Chem. Rev.* **2006**, *106* (7), 3002–3027.

15 Anastas, P. T.; Kirchhoff, M. M. Origins, current status, and future challenges of green chemistry. *Acc. Chem. Res.* **2002**, *35* (9), 686–694.

16 (a) Trost, B. M. The atom economy - a search for synthetic efficiency. *Science* **1991**, *254* (5037), 1471–1477. (b) Trost, B. M. On inventing reactions for atom economy. *Acc. Chem. Res.* **2002**, *35* (9), 695–705.

17 (a) Anastas, P. T.; Zimmerman, J. B. The twelve principles of green engineering as a foundation for sustainability. In *Sustainability Science and Engineering Volume 1: Defining principles*; Abraham, M. A., Ed.; Elsevier: Amsterdam, 2006; Vol 1, Chapter 2, pp 11−32. (b) Mours, M. SusChem: From vision to action. *ChemSusChem* **2008**, *1* (1/2), 59–62.

18 Federsel, H.-J.; Sveno, A. To overcome the hurdles: coping with the synthesis of robalzotan, a complex chroman antidepressant. *Process Chemistry in the Pharmaceutical Industry, Vol. 2, Challenges in an Ever Changing Climate*; Gadamasetti, K.; Braish, T. F., Eds.; CRC Press: Boca Raton, FL, 2008; Chapter 7, pp 111−135.

19 Fuchs, P. L. Increase in intricacy - a tool for evaluating organic syntheses. *Tetrahedron* **2001**, *57* (32), 6855–6875.

20 Wiles, C.; Watts, P. Continuous flow reactors, a tool for the modern synthetic chemist. *Eur. J. Org. Chem.* **2008**, 1655–1671.

21 Ainge, D.; Ennis, D.; Gidlund, M.; Stefinovic, M.; Vaz, L.-M. Rapid development of an enantioselective synthesis of (*R*)-1-hydroxy-7-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid. *Org. Process Res. Dev.* **2003**, *7* (2), 198–201.

22 Grubb, P. W. *Patents for Chemicals, Pharmaceuticals and Biotechnology: Fundamentals of Global Law, Practice and Strategy*; Oxford University Press: Oxford, U.K., 2005.

23 Seibert, K. D.; Sethuraman, S.; Mitchell, J. D.; Griffiths, K. L.; McGarvey, B. The use of routine process capability for the determination of process parameter criticality in small-molecule API synthesis. *J. Pharm. Innovation* **2008**, *3*, 105–112.