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Challenging times indeed for the pharmaceutical industry, so what can process R&D do to improve on the situation?

In search of sustainability: process R&D in light of current pharmaceutical industry challenges

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Is there a need for a paradigm shift in the pharmaceutical industry? Many researchers think so and take as examples the eroding corporate reputation, a regulatory environment that is harsher than ever, and the request for cheaper drugs from patient organizations and authorities. Process R&D, which interfaces medicinal chemistry and production, has taken on this challenge by increasing the delivery focus early on to ensure timely availability of desired compounds. The quest for lower costs of goods has forced the design of best synthetic routes that, given the molecular complexity, often lead to catalytic methodologies. Applying these methodologies will enable not only the cost element, but also the increasingly important aspects of environmental friendliness, and atom and stage efficiency, to be addressed.

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Hans-Jürgen Federsel, PhD, is a renowned specialist in the field of process R&D where he has spent his entire professional career spanning a period of 30 years. Starting off as a bench chemist in former Astra at the major Swedish site in Södertälje, he has climbed the ranks occupying positions both as line- and project-manager. After the merger that formed AstraZeneca he has been the Head of Project Management at the aforementioned location and was then appointed to a newly created role as Director of Science in Global Process R&D as of the beginning of 2004. In connection with this he was also given the prestigious title Senior Principal Scientist. Strong academic links have been further developed throughout the years after obtaining his PhD in organic Chemistry at the Royal Institute of Technology in Stockholm, which was recognized by awarding him an Associate Professorship there. His long-lasting links to this Institute have recently brought him a seat on the Board of the School of Chemical Science and Engineering. Publishing in peer reviewed journals and books, and frequent lecturing has rendered fame to his name that goes far beyond the limits of his own company, and Dr Federsel enjoys invitations from all over the world to share learning and experience from his broad knowledge base on process R&D.

From admiration to skepticism: changing views of the pharmaceutical industry

Half way into the first decade of the twenty-first century, it seems more appropriate than ever to reflect on the standing of the pharmaceutical industry: namely, its setbacks, its public image, its challenges, and also its opportunities for the future. Hardly anyone reading this review will be ignorant of the difficulties that the pharmaceutical industry is currently facing. There have always been formidable challenges in developing new drugs, but the general feeling has been that these challenges can be handled, albeit at an ever-increasing cost. So what has changed in today's environment?

It suffices to say that, on top of the constantly high attrition level for drugs under development (in aggregate, the industrial average rate of attrition measured from first trials in humans to registration seems to be locked at ~85–90% [1,2]), there is the increasing regulatory burden put up by various approving authorities and foremost by the US Food and Drug Administration (FDA) [3]. In other words, the demands to show clear evidence of efficacy without a corresponding increase in side-effects have become more stringent. Furthermore, some recent spectacular cases dealing with registered products, such as Vioxx® (rofecoxib) from Merck (http://www.merck.com) [4–7], have given evidence that, even after several years of post-launch experience in wide populations, the risk remains that accumulated safety data will show side-effect profiles that are not considered acceptable. The political dimension of these events and their possible impact on regulatory policies are currently receiving much attention [8], which ultimately might lead to the

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withdrawal of otherwise well-functioning medications, thereby rendering the relevant company with liabilities that could mount to billions of dollars. In addition, there is not much to be hoped for in the current drug pipeline, at least in the short term, as witnessed by the sharp decline in FDA approvals in 2005, which saw only 20 new products being cleared for commercial launch as compared with 36 the year before (a reduction of 45%!) [9].

Overlaid on these risks of severe setbacks are other challenging problems that must be addressed; for example, the continual price pressure exerted by government and healthcare institutions, or patient and other pressure groups, to reduce the cost of new products that are about to be introduced or are even at the post-launch stage [10–13]; and the increasing parallel import of drugs from low-cost countries and markets applying tax exemption – an opportunity that, to be honest, has been explored by the bigger pharmaceutical industries (e.g. in Puerto Rico for many years) as a means to produce drugs at a cheaper rate but to trade them at full price. The growing competition from generics producers earlier and earlier in the life cycle of a product is also an issue with which pharmaceutical producers must grapple.

Moreover, the industry is facing a productivity crisis whereby the 'new molecular entities' progressing through the pipeline must be improved from both a quantity and a quality perspective [14,15]. Now, more than ever, it is essential that nonviable molecules are discarded as early in the race as possible and that the surviving few manifest a spectrum of properties that enables them to become successful on the market. In early 2006, the FDA launched a welcome initiative (see http://www.fda.gov/bbs/topics/news/2006/NEW01296.html) that, at least in part, tries to respond to these problems with the proposed rule that investigational drugs and biologics would be exempt from strictly following cGMP regulations [16]. One of the ambitions of the FDA is to improve 'the ability to get discoveries made in the laboratory into clinical testing', which, however, does not give academics a *carte blanche* to run the entire program in the clinic with non-GMP materials but instead offers a possibility to conduct small so-called 'phase 0' studies. Another approach that has been advocated is inspired from the automotive industry and its crash testing of vehicles. In pharmaceutical companies, this harsh methodology is applied to molecules before they have even been synthesized, tested in biological systems, or administered to humans by feeding relevant data into predictive computational tools and algorithms [17].

The exhaustive list of question marks and critiques also includes concern about the frequent lack of firm links between biomedical *in vitro* data and the condition in the patient [18]. In fact, serious doubts have been raised over whether any innovation in the pharmaceutical industry generates truly novel medicines and, consequently, whether innovative power *per se* is really needed to survive [19,20]. Considering all of these factors, it seems timely to ask the following, albeit unpleasant, questions. How sustainable a business is the commercial development of drugs in today's environment [21,22]? And how much change will be required to bring this previously flourishing industry back to where it once was.

How is process R&D affected?

It is not hard to point out areas where process R&D (PR&D), in all likelihood, will have no or at most marginal influence. For example, the way to conduct clinical studies and the branding strategy and marketing efforts supporting a new drug will be rarely affected by a procedure whose main responsibility is to design viable chemical processes. There is, however, one parameter that explicitly falls under PR&D accountability – namely, the cost contribution that the active pharmaceutical ingredient (API) will make to the final formulated product.

As a bulk material and intermediate on the way to the finished medicine, the API has traditionally received relatively little attention with respect to the cost of goods (COGS); however, this situation has now been reversed. With a few exceptions (such as the field of antibiotics, with its harsh competition, high-dose regimes and many treatment alternatives), the prevailing view has been that the market would accommodate nearly any cost of the API, inasmuch as a favorable and understanding handling was expected when conducting price negotiations. In other words, expensive medicines could always count on achieving higher prices as compensation.

In a more difficult pricing environment, this approach has lost its validity and it has become essential to develop processes for manufacturing APIs that represent the ultimate in known and available technology. Given the importance of 'time to market', which remains one of the highest priorities of pharmaceutical companies, the need to meet increasingly stretched targets for speed to best route has come to the forefront in PR&D [23]. The distinction might be subtle, but 10–20 years ago it was considered satisfactory to define quickly a 'good enough' synthesis that would be fit for the purpose, but not necessarily the ultimate or best-optimized one. This approach is no longer viable, at least not as a default position. Instead, the timeliness of defining a scalable route has to go hand in hand with the requirement to select methods that represent the 'best in class' from both a synthetic and a technical aspect [24].

The economical implications that the API has on the overall cost of a drug can be better understood by considering data from industry estimates (Figure 1). From this data set, which represents the 'historical' situation in the recent past, two observations stand out.

- First, the share of the API in the COGS, which in essence accounts for the expenses of raw materials, reagents and solvents among others, is roughly a third across a whole portfolio of products, but varies substantially for individual drugs (from ~5% to 40%).
- Second, the contribution of the API to the overall manufacturing price of the formulated drug (represented as an in-house value of the product at the stage of readiness for delivery to customers) is 10–12% at its maximum value and ~0.5% at its minimum.

By using the manufacturing price – namely, the total costs that the producing company will accrue (e.g. expenditures for material, staff, depreciation and infrastructure) – as a reference point, these percentages will be less variable and insensitive to geographical area or country, where the sales price at the customer level differs more widely owing to national legislations and the construction of healthcare systems. This approach therefore allows more meaningful comparisons. Admittedly, there will be considerable cross-company variation in the calculation models applied and in how assets and depreciations are handled to derive the respective

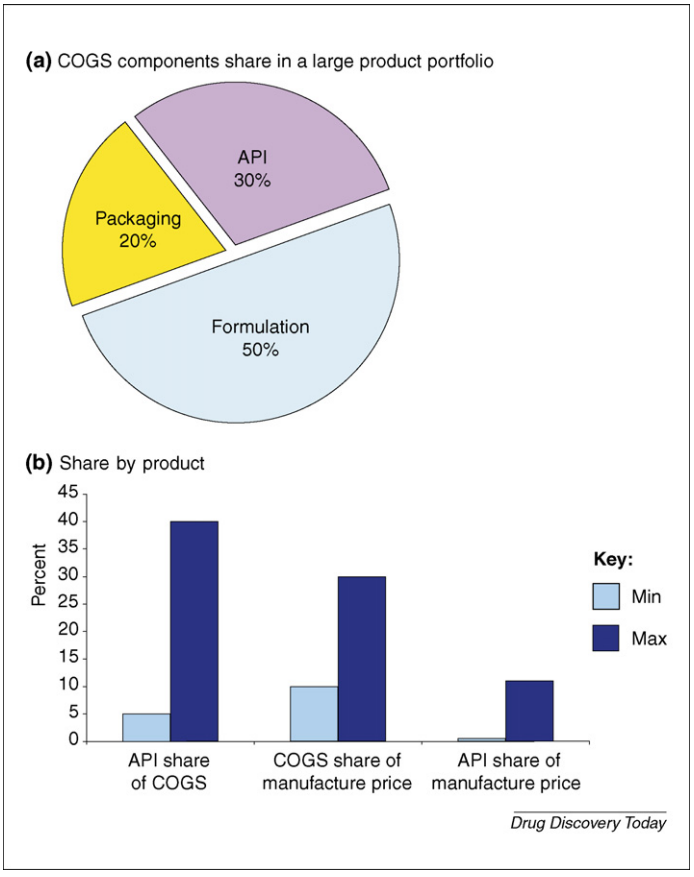

FIGURE 1

The cost basis for pharmaceutical products. (a) Pie chart visualizing average cost of goods (COGS) components in a final dosage form within a large product portfolio. **(b)** Bar chart expressing the minimum–maximum spread of share on a product-by-product basis.

manufacturing price, but what seems to be a universal trend is that, in the prevailing situation of shrinking financial margins, the proportion of the manufacturing price to which the COGS components contribute is clearly increasing. Much more sophisticated economic theory needs to be applied, however, including careful analysis of the drivers of price sensitivity, cash flow, and differences in healthcare funding structures to understand in full the pricing of new products [25].

Nonetheless, also relatively simplistic scrutiny will reveal the directions in which we are moving and will enable us to make the following conclusions. Increasing complexity on the molecular level will most probably not lead to more demanding and complicated dosage forms or result in more expensive packaging design and materials, but will generate higher costs of the API. The relative impact of API on the COGS and manufacturing price will therefore increase significantly.

In these circumstances, it is easy to see that much of the increased focus on trying to minimize the cost of the API and other contributors to the COGS is a trend that is likely to accelerate in the coming years. The directions are very clear: a process that is being developed must strive to be the best or optimal achievable in terms of quality, yield and environmental and safety standpoints, and must simultaneously reach the lowest possible cost of the API. Ways to address this far-reaching demand are discussed in the following section.

Where PR&D can make a difference

A cornerstone of PR&D departments across the pharmaceutical industry worldwide is the principle that delivery of the API in the required amount and of the right quality must never delay the progression of an R&D project. In this regard, the role of PR&D as a technical support function stands out very plainly. There is no doubt that maintaining this principle is central to the ability to progress quickly to decision points or milestones in drug projects. Inevitably, it requires good and open communication between all parties involved and smooth logistics to succeed. A few facts and observations highlight the situation that used to be – and still is – encountered at the 'classical' interface between discovery-PR&D and development.

- An especially crucial transition occurs around the time of candidate drug (CD) nomination – that is, the point in time when the formal decision is taken to develop further a given molecular entity for ultimate testing in humans – with special emphasis when going from the pre-CD state to a nominated CD, as is seen, for example, in the stepwise increase in resource demand.
- API volumes requested increase sharply, from a few grams to a few kilos.
- Limited insight into and low awareness of PR&D and its challenges in the rest of the R&D organization has hampered effective ways of working.
- The historical preference has been, almost by default, late initiation of full-blown route design work and development, mostly not beginning until a CD is about to be appointed.
- Risk averseness, often due to an unwillingness to commit to costs on the backdrop of a high uncertainty, has prevented early manufacturing from starting to target larger quantities.
- Scale-up is frequently done by poorly investigated methods, meaning that processes will be operated by nonrobust methods with a concomitant increase in risk of failure.
- With complex target molecules (APIs), projects frequently face lengthy delivery schedules, partly due to prolonged lead times (6–12 months is not uncommon) for increasingly sophisticated building blocks, and require specialist knowledge and proprietary technology.

Operating in the old-fashioned sequential manner will inevitably put delivery of the API on a critical path. There is a pronounced risk that the availability of the API could turn into a showstopper, with the knock-on effect of slowing down progression in the early stages of drug development. Delays in reaching important decision points, such as tolerability in humans or proof of concept, might be the unwanted consequence of such an approach. As long as the CD in question presents a low synthetic and technical challenge – for example, when making it requires only a few chemical steps or when analogs of known products with well-documented manufacturing procedures are involved – then the old principle of late-stage work initiation is feasible. Owing to the number of embedded drawbacks and their associated risks, however, the sustainability of this working model has been questioned [26–28]. Therefore, there seems to be a clear trend away from adhering to this 'wait-and-see' approach as the prioritized business model, because it is perceived as old-fashioned and incapable of responding to current needs [29]. The argument for adopting a more forward-looking approach is further underpinned

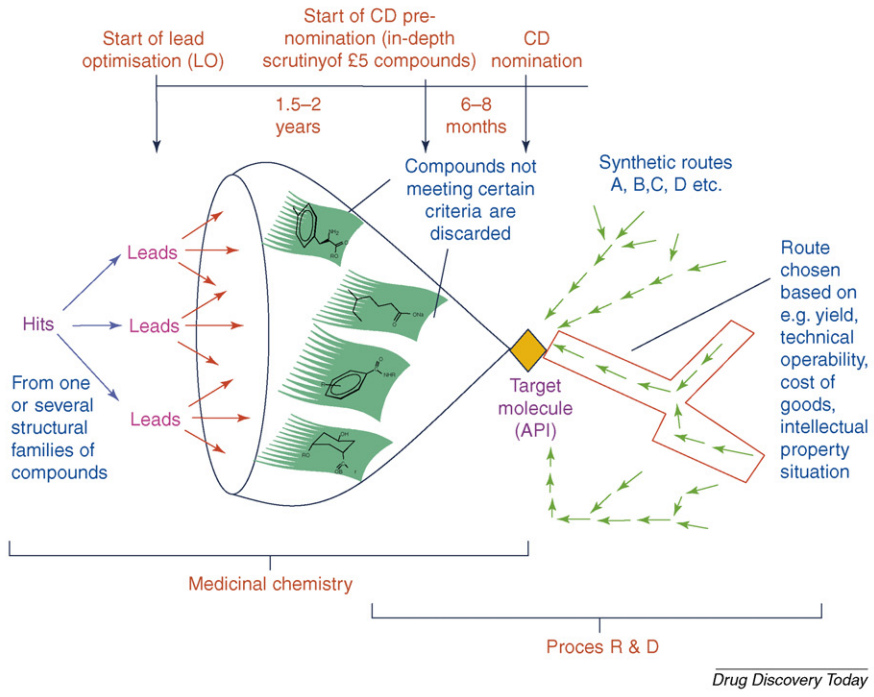

FIGURE 2

Opportunities for early overlap: back-integration of PR&D work improves the capability to achieve speedy delivery of the active pharmaceutical ingredient (API). Candidate drug (CD) nomination denotes the point in time when a decision is taken to progress a specified molecular entity with the aim to conduct trials in humans.

by the fact that, in the grand scheme of things, delaying PR&D work to save cost is not a valid path if it will slow down the progression of studies in humans.

By contrast, a different way of addressing demands and requirements in the current environment can be envisaged where the foremost ambition is, at least in theory, to put the highest priority on securing compound supply [30,31]. In practice, this should mean that once a CD nomination (or similar essential event) has been successful, the CD should be available in sufficient quantities to kick-off further pivotal studies. The principles that express this 'modern' way of operating can be summarized as follows.

- The timely delivery of a first scale-up batch is crucial, and a zero delay should be the aspiration to take this activity off the critical path.
- Lead times from CD nomination to API supply are reduced considerably, from months to weeks, as has been demonstrated in an internal AstraZeneca improvement program (http://www.astrazeneca.com).
- Risk taking is necessary to reach the goal of shortened lead times and, with a balanced approach, each project should be treated on its own merits.
- The earliest possible route design and pilot production are prerequisite to achieve the desired outcome of fastest possible supply.
- The aspiration should be to have the final (preferably equal to the best or optimum) synthetic route in place when preparing material for clinical studies in phase II, especially in priority projects where progression to crucial study readouts is expected in the shortest possible time.

The transition from the early/mid to later discovery work conducted in medicinal chemistry, together with the timely involvement of PR&D, is shown in Figure 2.

Given the intrinsic problems of forecasting the outcome of drug hunting, it is almost impossible to indicate a single unambiguous point along the timeline when PR&D should initiate its work; however, the general recommendation must be that, while waiting for experimental activities to start when the shortlist of candidate compounds comprises only a few discrete structures, it is entirely feasible to build up knowledge and initiate planning during the lead optimization phase. It is, indeed, an interesting and rewarding experience to envisage potential large-scale syntheses of the wide variety of new chemical entities that are scrutinized. Strikingly, there is a commonality in the mindset of people in medicinal chemistry and those in PR&D, because both start by adopting an approach of diversity: the former to create a differentiating set of molecular structures displaying wide ranges of properties; the latter to identify possible routes with different technical features leading to the same target. Yet in realizing this, at some point only one must be picked!

The ultimate process: dream or reality?

For professionals in PR&D, it is always a challenge to answer the question of whether the best process from all conceivable aspects has been achieved. The truth is that a simple yes or no answer depends on what kinds of success criteria or assessment parameters have been defined and at what point in time. For example, the chemical yield in a synthesis of a given product can be at a maximum using currently available methodology. This might,

however, be achievable only at the expense of a higher cost, as compared with a different route that offers a lower yield, simply because it makes use of more expensive raw materials and reagents. Similarly, the batch cycle time of a particular process might underbid all competing processes for the same target, but unfortunately render a considerably higher amount of waste streams.

Thus, the conclusion is that optimizing all foreseeable parameters, such as those mentioned above, within a given process is most probably not achievable. Consequently, a strategy must be put in place to point out which parameters to prioritize on the basis of relative impact and likelihood of success. As it turns out, moving away from stoichiometric reactions in favor of catalytic procedures is a means to address several important areas – namely, COGS, yield (both in terms of chemical and stereoisomeric outcome), length of synthetic route, product quality, work-up and/or purification, and waste generation. Thus, drivers and blockers to adopt catalysis as a prime option in route design will be described in detail in the following sections.

Factors driving catalysis

With respect to the drivers, several significant factors, some of which have been hinted at above, can be pointed out.

(i) COGS stands out as a frontline item because a considerable reduction in chemical expenditure can be expected, often with high achievable yields, in catalytic transformations.

(ii) A more benign environmental profile as a consequence of reduced usage of raw materials, solvents and reagents for the production of a given amount of product.

(iii) For a successful construction of complex molecular architectures, often the only feasible way forward is to revert to catalyzed reactions.

(iv) A perceived view of high technical level and proprietary knowledge surrounding the handling of catalysts (be they of chemo- or biocatalytic nature) and operating catalytic processes affords good chances of maintaining control and preventing generic competition.

In total, four convincing reasons for why one should aspire to rely on catalytic chemistry. Of course, all four reasons do not apply to the same extent in every case, but they will most certainly have to be considered and assessed.

Factors blocking catalysis

Conversely, there are several factors that frequently seem to be blockers, preventing one from treading the road to catalysis:

(i) Prolonged development times can be expected as a consequence of the rather time-consuming work to find the right (best) catalyst. This is largely due to the nongeneric nature of most catalysts, which often requires the optimal one to be tailor-made to fit a particular substrate, for example, in the area of asymmetric synthesis.

(ii) There are, and have been, intellectual property issues surrounding the use of some ligands, notably those called 'privileged' [32]. In many cases, these limitations have prevented commercially available catalysts from being used to their fullest extent. Instead, the design of in-house, patent-free 'competitors' is favored as a means of avoiding payments of license fees or royalties. The situation is improving considerably, however, and a scenario is now emerging where both supplier and customer see opportunities for a win–win possibility by joining forces and establishing different kinds of cross-company collaborations [33]. Nonetheless, this is still seen as a restricted area by many, with several hurdles to overcome.

(iii) Many catalysts that are used today incorporate a heavy metal component (Pd, Pt, Rh, Ru, Cu, Mn, Os, Ti and Fe are some of the more abundantly applied ones), which poses the potential risk of contaminating the product (including the API, depending on where in the sequence the organometallic step is placed). Thus, there is always the issue of defining tolerable levels of residual amounts. For very toxic metals, it is not uncommon for the regulatory demands to require a maximum content of only a few ppm and, to fulfill this criterion, rather sophisticated and validated scavenging and/or cleaning operations must be incorporated into the work-up stages of the process [34,35].

(iv) The use of enzymes or whole-cell systems remains for many an enigmatic area, showing some resemblance to black-box chemistry. Admittedly, much of the fear of involving large biomolecules in processes has now disappeared, largely triggered by numerous examples of highly efficient transformations on both small and large scales [36–41]; however, an intrinsic reluctance to commit to enzymatic catalysis is preventing the wider application that this technology deserves. As with chemo-catalysts, there is also the problem of choosing the enzyme that provides the optimum fit for purpose, but here novel methods are paving the way. Thus, directed evolution tools facilitate either random or focused mutations of the protein chain to create large arrays of new enzymes that can be screened against a given substrate to identify best performance [42,43].

(v) In general, catalysis is seen as an area requiring extensive amounts of experience to succeed, particularly when aiming at operating in asymmetric fashion. Numerous full-scale processes use catalytic chemistry, for example, in the bulk production of polymers, and much more than half of the annual amounts of chemicals produced worldwide relies on the involvement of catalysts, but the track record in the pharmaceutical industry is less impressive. This is especially true when adding up those catalysts that work asymmetrically. Thus, the global data currently available, which encompass the fine chemicals industry, indicate that only between 15 and 20 stereoselective transformations on the manufacturing scale use chemical catalysis [44]. With a growing number of industries focusing on generating chiral molecules in high stereochemical purity (which has probably been the case for the past 2–3 decades), this number is surprisingly low. It is, however, important to stress that this number is far greater if processes that are still under development are included, but the unfortunate fact is that most of these will not reach any practical commercial application, owing to the high attrition rate in pharmaceutical R&D.

(vi) With the low predictability faced in identifying the best catalyst for a given substrate, in particular in the asymmetric field, widespread opinion still questions whether an investment in the area is justifiable at all, especially considering

the risks. Even though attempts to overcome this gap have been made [45], the development of an *in silico* tool is still in its infancy; therefore, finding the right catalytic system is, by and large, a trial-and-error approach that requires time and resources. Of course, screening techniques will improve this situation, but because most intermediates (at least if they are advanced enough) in a synthetic sequence leading to an API by default represent new chemical entities, there is always the possibility that known commercial catalysts will work only suboptimally. Unless the problem can be tackled by simple process modifications, the knock-on effect is that the work will inevitably have to involve *de novo* design of catalysts and ligands, a process that no doubt will be very effort consuming.

(vii) When starting the development of a catalytic reaction, the assumption in the overwhelming majority of cases is that the resulting process will be superior to its stoichiometric (i.e. noncatalytic) counterpart. The advantages expected are, for example, higher yields, better product quality (chemical and enantiomeric purity), lower cost of the product, more efficient production and reduced waste streams. Although this is true in many cases, there are notable exceptions. Thus, manufacture of the NSAID drug substance (*S*)-naproxen by the 'classical' resolution method with incorporation of an in-built recycling-racemization loop is much more economical than the asymmetric approaches known to date. This is due to either the need for an overly expensive starting material or a lack of efficiency in the catalytic step, resulting in a stereoisomeric purity that is too low and requires extra purification steps to reach the desired quality in terms of % enantiomeric excess [46,47]. Therefore, no guarantee can be given that the outcome of an investment in a catalytic process will always be economically competitive, even if the chemistry *per se* is operating well.

Utilization of catalysts: steps in the right direction

Following on from the above lists of outspoken benefits and more or less likely risk factors that need to be taken into account when considering a strategy for designing a future process, there is absolutely no doubt that catalysis in its broadest sense will always provide an extremely powerful tool. This is not to say that every problem will be best solved by using catalytic methodology, but a good assumption is that more and more API production will be taking this approach in the future.

As a recent high-level testimony to this, the 2005 Nobel Prize in chemistry was given to Chauvin, Grubbs and Schrock in honor of their contribution to the understanding and practical development of metathesis (see The Royal Swedish Academy of Sciences: http://nobelprize.org/chemistry/laureates/2005/index.html), a wide-reaching catalytic procedure that facilitates the creation of new carbon–carbon bonds [48]. In fact, this transition-metal-catalyzed reaction has already demonstrated its utility in the pharmaceutical industry, in particular when it comes to constructing complex cyclic molecules, where it is much more effective than conventional technologies. A brilliant example of the fruition of this chemistry is found in the synthesis of BILN 2061, a new inhibitor of hepatitis C virus. Here, the metathesis reaction is used in a ring-closing mode and has lent itself to successful scale-up to generate a 15-membered macrocycle towards the end of a lengthy process [49,50] (Figure 3).

The growing importance of catalysis is further manifested in the fact that metathesis is not the first catalytic methodology to achieve a Nobel prize: in 2001, this prize was awarded to Knowles, Sharpless and Noyori for their seminal stereoselective reduction and oxidation protocols [51]. It suffices to mention here the groundbreaking process for the anti-Parkinson compound, L-Dopa, which was introduced into commercial manufacture on a multi-ton scale in the 1970s by Knowles and his team [52,53] in Monsanto – an achievement that has paved the way for many followers.

Another beautiful example showing the strength of catalysis is the expedient transformation of an activated phenol (by attaching a triflate group) to create a benzamide in the presence of a palladium(II) salt, carbon monoxide and an amine. This reaction constituted a key step in the manufacture of ebalzotan, a serotonin receptor ($5HT_{1A}$) agonist developed as an antidepressant, which, however, was never commercialized. Nonetheless, the synthesis worked impeccably and provided a real shortcut to the target compound as compared with conventional techniques [54] (Figure 4).

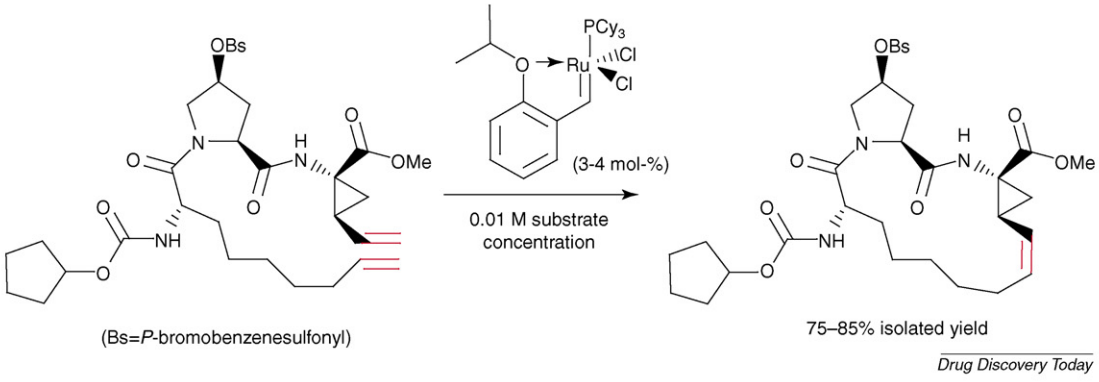

FIGURE 3

Application of a Nobel prize winning carbon–carbon bond forming method of catalysis. Ring-closing metathesis operates under catalytic conditions on large scale.

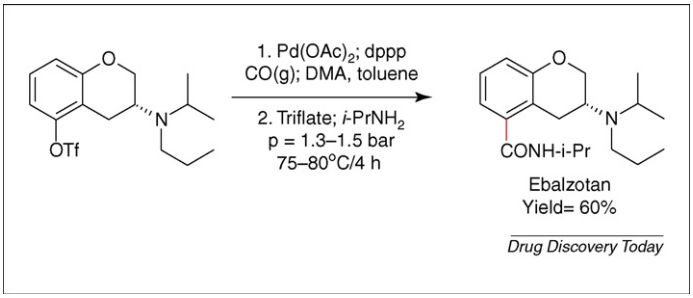

FIGURE 4

Use of a palladium(II) salt catalyst in the manufacture of ebalzotan, a serotonin receptor ($5HT_{1A}$) agonist. This Pd-catalyzed carbonylation reaction, the final step in the linear 13-stage synthesis, has been scaled-up to a 40-kg batch size.

It would be an exaggeration to claim that in themselves these examples represent ideal processes from all conceivable aspects. The message that they send, however, is that the utilization of efficacious catalytic technologies is indeed a big step in the right direction to designing processes that can be labeled 'best mode of operation'. In this respect, a few factors will clearly have a beneficial impact on the inclination to apply catalysis:

- knowledge – a basic understanding and appreciation of principles;
- experience – sharing of learning from authentic cases across companies and the scientific community;
- predictability – tools that allow the expedient selection of best mode of operation for a given transformation (i.e. which catalyst to choose for a particular substrate);
- uniqueness – the realization that there will be no better alternative to solve a specific problem;
- mindset – think catalytically.

Responding to molecular challenges in the future

Speculating about likely schemes and attempting to be visionary about the future are always risky and uncertain. If we limit ourselves to looking at the chemistry part of drug discovery and development, a picture emerges to which most pharmaceutical companies would probably agree. In fact, some of the projections refer to a reality that is already present.

Molecular features

(i) Chirality is abundantly present, not infrequently displaying multiple stereogenic centers: albeit assuming a dominating position, chiral molecules will not assume exclusivity and achrial structures will continue to play an important role.

(ii) Aromatic moieties with 'unconventional' substitution patterns and substituent combinations will increase.

(iii) Heterocycles will continue to constitute the core portion of most compounds, but in a considerably expanded repertoire of motifs and in more complex environments.

Work load

(i) Resource availability has largely reached a plateau (steady state) as a consequence of more stringent cost control and improved work processes, including availability of a diverse range of automated systems enabling increased throughput.

(ii) The inability to appreciably improve on attrition rates demands more projects to be pushed through the pipeline without spending more resources to ensure more compounds make it to market approval.

Timelines

(i) Reaching first time in humans and, further on, proof of concept and proof of principle in as short time as possible becomes key and constitutes competitive advantage.

(ii) The aspiration is to conduct the route freeze of the scaled synthetic process as early as possible, preferably when producing material for phase II clinical trials.

(iii) Minimum lead time will be expected for first API delivery at scale-up to cover needs for pivotal toxicology studies before going into humans (healthy volunteers).

Addressing these challenges

To overcome successfully, or at least address these challenges, numerous changes have to be implemented, not least in the way that the business operates: striving for more efficiency and better utilization of resources will be essential throughout the whole value chain. Focusing on the chemical issues and, in particular, on how catalytic methodologies can be used to improve the way in which molecules are being assembled, several existing techniques become apparent that are already having or will be expected to have a strong impact.

- Cross-coupling reactions (e.g. Suzuki, Buchwald-Hartwig, Stille, Sonogashira, Kumada, Hiyama, Heck and others), an effective and straightforward way to create substituted ring structures, notably arrays of interconnected cyclic moieties via formation of carbon–carbon or carbon–heteroatom bonds.
- Dynamic kinetic resolutions to use the maximum amount (theoretically 100%) of material prepared in racemic form via conversion into a single enantiomer [55–57].
- Asymmetric synthesis (both chemo- [58,59] and biocatalytic [60–63] mode) when the situation demands; for example, responding to COGS drivers and when alternatives are inferior or even non-existent.
- Metathesis, notably when applied to effect a ring-closing reaction (e.g. to create less common hetero- or macrocyclic structures); a so far relatively unexplored possibility (but see Figure 3), but more stable and versatile catalysts will support its increased utility.
- Heterogeneous catalysis of traditional style (palladium on charcoal) in situations where these are known to function, but where modification and improvement of the catalyst can broaden its scope and include new types of reactivity.

In summary, this list of capabilities tells us that a wide range of catalytic approaches are at hand and new ones continue to be developed, thereby increasing the likelihood that many given problems should find solutions building on the use of catalysis. When aiming to design a process intended for production, the properties of scalability of the reactions involved should never be neglected. A unidirectional targeting of this parameter will, however, draw attention away from other key questions. Thus, there seems to be a common misconception that many synthetic transformations are nonscalable, or at least not prone to easy scale up, when instead the more relevant criteria should be whether they

can be operated safely at a manufacturing level and perform at an acceptable cost [64].

Summary and outlook

The pharmaceutical industry is facing tough times as it is put under strong pressure from at least three aspects: the low productivity expressed by the small number of launches of new drugs per year; the spiraling cost, not only for R&D but even more for marketing and advertising the products; and the severe cost pressure to reduce prices at the level of the consumer. Therefore, it is not surprising that the entire business sector is looking at ways in which to tackle these challenges by scrutinizing all parts of the organization to see where there are possibilities for improving efficiency and effectiveness and how an increase in output can be reached.

For PR&D – a technically oriented function spanning the whole range from small-scale laboratory work to fully-fledged commercial manufacturing – this will mean focusing on certain key areas: quick process scale-up to enable fast API delivery to ensure that a speedy progression to important project milestones is made; creation of genuine process understanding as a lever to reach the best synthetic route in every case, preferably as early on as possible along the timeline; definition and establishment of streamlined working methods to obtain 'more for less' because resources (both money and people) will be limited; chemical processes that ultimately are delivered to the production units must be of the highest possible quality and well-optimized to be capable of responding to reduced COGS margins.

In addition to addressing all of these issues, it is necessary to apply, and eventually even develop, better scientific and technical tools and methods by which tomorrow's problems can be successfully solved under the projected future working climate. This will inevitably have to involve more directed approaches, in which the level of predictability will decide their utility on a case-by-case basis. In other words, technologies that can be predicted to deliver a desired outcome will be prioritized over those with a less foreseeable result. Moreover, little evidence suggests that a 'one fits all' scheme is to be expected, at least not for many years to come. Instead, the adaptation of best available methodologies to a given situation will be the rule of thumb.

A key feature in the field of synthetic chemistry is the reaction selectivity because this presents means to reduce or completely avoid the formation of side products that might require sophisticated work-up procedures for elimination. Thus, to cope with increasingly complex molecular architectures in the future, novel transformations and new reactivity need to be explored and incorporated into the arsenal of methods. Furthermore, the whole concept of catalysis will continue to flourish – both in the chemo- and bio-modes – and new approaches will broaden the scope to enable increasingly complicated problems to be addressed. One spin-off from using catalytic chemistry that rightly attracts growing public awareness is related to its perceived green chemistry properties [65–70]. Combined with the often considerably improved atom efficiency [71–73], which makes use of most (preferably all) of the atomic content in a building block or starting material when transforming it to a product, processes operating along these lines will stand much greater chances of meeting increasingly tough demands from both environmental viewpoints and a cost perspective. When we have arrived at this stage, it will thus be fully justifiable to claim that we have reached the desired state of sustainability within PR&D!

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