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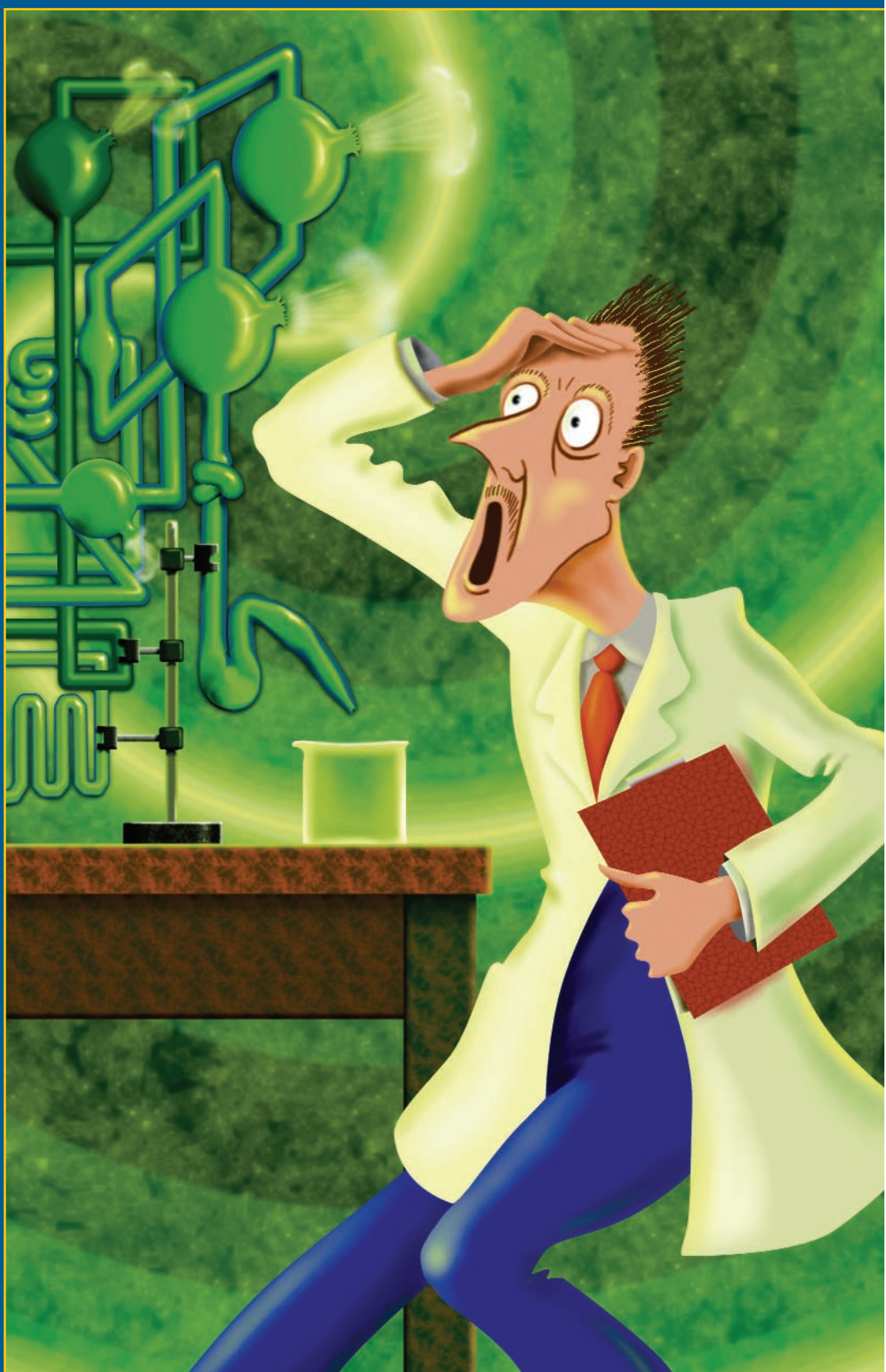

Putting partnership back into process chemistry

Recent changes in the business relationships between innovative pharma companies and their fine chemical suppliers are impairing the development of the best manufacturing processes for new active ingredients, says Dr Rob Bryant

Developing, testing and launching a new pharmaceutical product is a time-consuming and complex business. During the first 50 years of the modern pharmaceutical industry, fine chemical companies developed a successful working relationship with pharma, based on the concept of partnership. Regular contact tended to reduce problems associated with the major differences in perspective that reflect the different roles and backgrounds of the two industry sectors. The innovative pharma companies were generally happy to allow their suppliers to enjoy reasonable profits in return for sharing some of the development risks inherent in creating a new product. Over the past ten years, however, as pharma companies have found it harder to sustain the high profits enjoyed in the early years and as their supply base has continued to expand, a tougher approach to dealing with suppliers has emerged. The new generation of outsourcing executives work with a more arms-length approach, which has reduced the two sides' familiarity with one another's activities. In particular, many have little understanding of how a robust, efficient manufacturing process is created.

Chemical development	Clinical development
Discovery of API Amounts in mg	Discovery
Initial synthesis of API Amounts in gm	Preclinical
Prototype process for API Amounts in 10s-100s gm	Phase I
Registration process for API Amounts in kg	Phase II
Manufacturing route for API Amounts in 100s kg-metric tons	Phase III

Figure 1: Development of a pharmaceutical fine chemical process.

When car prototypes were made from wood and modelling clay, there was never an expectation that the ultimate production model would be built from anything other than steel. In just the same way, a medicinal synthesis for a novel drug has never been a useful guide to how an active ingredient should ultimately be produced in a full-scale plant. In neglecting this reality, modern drug companies have created a difficult business climate for the pharmaceutical fine chemical (PFC) industry and this will, in turn, create increasing problems for the innovative pharma sector unless a better mutual understanding of the needs and business dynamics of the two sides can be re-established. An important step in this process will be to recognise the vital contribution that chemical process development (CPD) makes to the eventual successful creation of an active ingredient (API) manufacturing process.

The basics

The need for material evolves during the development of a typical API (see Figure 1). Up to the preclinical stage, use of elaborate laboratory syntheses is justifiable, particularly since the candidate failure rate at this point is quite high. Beyond this stage, however, the routes used by medicinal chemists become increasingly onerous to operate, since they rarely scale-up properly and multiple iterations are needed to produce even modest amounts.

Ideally, process development should begin at the interface between preclinical and Phase I and be completed by late Phase I or early Phase II. Later improvements should only involve optimisation of the process, since more substantial modifications will inevitably create all sorts of clinical development headaches.

Responsibility for the invention of an initial synthesis and its conversion from this original method, by which small amounts of API are made into a robust production process, lies ultimately with the pharmaceutical company. However, the division of labour in creating an efficient final process varies widely, depending on the individuals and companies involved, as well as the complexity of the target API and the hazards involved in its production. Thus the effectiveness of the final production process can run the gamut from well developed and cost-efficient through to thoroughly undeveloped and overly expensive. The fact that, increasingly, too many processes of the latter type are now being operated reflects several important factors, some of the most important being:

- Increasing complexity of molecular targets and ever-growing demand for higher and higher purities (this latter requirement makes process changes difficult).
- Employment of fast synthesis methods that can identify new leads, without the need for any kind of synthetic method being developed, means that the time available to develop a good manufacturing process is more limited.
- New orthodoxy by which new leads are supposed to be launched within seven years of discovery.
- The relatively small proportion of the final product cost contributed by the API (which can be anywhere between one and twenty percent of the final selling price).
- The low importance that many pharmaceutical companies attach to the development of efficient API processes.

In an era when differentiation between rival PFC suppliers is increasingly difficult, it is an astonishing fact that this key skill of creating an efficient and robust production process is rarely advertised and too often goes unrecognised. Indeed, the primordial importance of good CPD is a discipline all too often misunderstood and undervalued. It is also of concern that many PFC producers have more limited skills in this area than

would have been the case previously. Perhaps for this reason, process development chemistry is an area of pharmaceutical fine chemistry where specialists can make a significant impact and achieve good margins.

Clinical development phase	Chemical development stage	Pharma companies – development activities		Suppliers
		Big pharma	Biotech	
Discovery	Medicinal synthesis	Analogue route definition, lead selection and lab scale synthesis		CROs and small PFC producers – often via FTE contracts
Preclinical		In-house CPD	API CPD is often outsourced	
Phase I	Prototype process	User-defined key intermediates (KIs)		Suppliers with GMP kilo-labs and pilot plants
Phase II	Registration process	Outsource KIs	Outsource API	
Phase III	Manufacturing process	Optimisation/ KI contracts	Award API contracts	PFC producers with GMP production units
Pre-launch				
Launch				

Figure 2: Chemical process development (CPD) as part of pharmaceutical product development. This table classifies activities that can be shared between sponsors (in blue) and PFC suppliers (in orange) during the overall new product development project.

Process chemistry

Transforming an initial synthetic route into a viable process takes time and skills. An attempt has been made to classify the activities that can be shared between sponsors and their PFC suppliers during the overall new product development project (see Figure 2 above).

The importance of CPD varies between projects, customers and suppliers, but certain useful generalisations can be made. During the early medicinal synthesis stage, the need for CPD is relatively restrained, unless very long syntheses are involved (when large quantities of early intermediates have to be made in order for sufficient API to come out of the final synthetic step). The supply of contract research services by CROs remains fairly buoyant because the skills required at this point are not very different from those of a medicinal chemist working in a research lab. Pharmaceutical customers, both big and small, have continued to support this sector, which represents for them a readily adjusted R&D resource. There is little commercial linkage between this early phase of activity and later stages, since the main objective is to supply modest amounts of material for lead definition. In effect, the CROs supply information rather than materials.

The prototype process

Once the structure of the new drug candidate has been defined, the need for making clinical trial materials drives the development of a prototype process, during which well-resourced companies will try to come up with a robust process for the API. Generally, this activity is simplified by defining the route as soon as possible and then outsourcing the key intermediates specific to the route. Often the synthetic routes for making these intermediates are also defined by the pharmaceutical development group. The reason given for this level of control is usually that changes to the process used will create unacceptable levels of new impurities.

This stage is the most critical for defining whether or not a good process will eventually be developed. Companies with competent chemical development skills will probably supply a reasonable template for their subcontractors. Where this is not the case, problems arise. If these prove to be sufficiently serious, process development specialists can be brought in, since there is still time for an improved process to be developed. In practice, such a service is often provided as part of the speculative development costs for winning a final production contract. Given the high fixed costs needing to be recovered, the larger PFC producers with GMP production investments often will only carry out process development under this kind of understanding – they are simply unable to justify offering a custom process development service on any other basis. In this way, customers have a tendency to consider process development as trivial because it comes 'free'. There is also a tendency for such companies to become less adept at undertaking significant process development, since their personnel and operations have become better suited to process implementation and optimisation.

A limited number of companies offer CPD as a stand-alone service, having identified the growing need for expertise in analysing a customer's process, highlighting its weaknesses and offering radical solutions within a short time-scale. The growth of the biotech sector has fuelled the demand for this type of service, as increasing numbers of pharmaceutical developers run up against insoluble scale-up and operability problems that their medicinal chemists have failed to anticipate.

Smaller pharmaceutical innovators (often referred to as biotech companies) will usually do one of two things at this stage:

•Outsource manufacture of the API to one or more subcontractors that have a combination of process development capabilities and a GMP plant.

•Continue with an indifferent process during Phase I and II clinical trials and hope to sell the package to a major company. Again, larger quantities are produced by GMP producers, who often have to persevere with very bad processes.

This second approach is clearly not a satisfactory one and the chemical manufacturing route has become a more important item on big pharma due diligence inspections as a result. Lucrative contracts have been obtained for this type of API subcontracting and the biotech sector is seen as an important developing source of revenues for the PFC industry. However, it has to be said that little companies with big products are nearly always eventually sold. The API producers will then usually lose more new business, perhaps retaining, at best, key intermediate supply contracts. This type of volatility has contributed to the downturn in producer sentiment in the past few years.

Once a product reaches late Phase II/early Phase III, 'locking into' the registration process means that major process improvements become hard to implement because of the need to carry out bridging studies, to prove material made by the new process is equivalent to that of the original one. Of course, where operability problems or costs have become a major headache, the need to redevelop the process may have to be accepted. Usually, however, even relatively poor processes are retained rather than run the risk of losing precious time and/or taking the risk of creating subsequent approval delays by process changes at this stage. Big pharma companies will source development quantities of intermediates from two or three selected companies and eventually approve one or more as suppliers for the pre-launch

build-up of material. Their own manufacturing operations will refine the API process within the tightly specified parameters set out in the registration documents and seek to ensure that the process is as efficient and reliable as possible.

During this time, a company may choose to transfer some or all of the production to a second site. This usually throws up processing issues that may not have surfaced previously. New suppliers of intermediates are often approved as part of this site transfer, because foreign subsidiaries are often happier to deal with a known local supplier. PFC companies need to accept this increasing risk as just another part of the overall challenge, while pharma companies should be aware that such late stage changes can create bad feeling among their established suppliers.

Only under exceptional circumstances will any further process development be undertaken once a registration process has been defined, since the chemical operations need to keep the Phase III production pipeline full. Sometimes formulation problems do arise that necessitate late-stage alterations in the final steps of the process, but these are usually the result of changes in the physical rather than chemical properties of the API.

Exploiting key skills

In the recent past it had always been the case that suppliers could rely on their core skills in chemistry to win additional rewards from their customers. It was usual for the cost benefits created by process improvements (that did not affect the quality of the intermediates being supplied) to be at least shared between the supplier and customer. Such improvement was often not difficult and the resulting steady stream of cost reductions, coupled with increasing demand, generally offered good rewards for the commercial risks being taken by the supplier. Sometimes the improvements allowed patents to be taken out and increased revenues and/or contract security obtained in so doing.

More recently, most large pharma sponsors have grown to better understand their suppliers' processes and costs (the need to make disclosures on the processes in greater and greater detail for regulatory purposes has made it harder to retain confidential process improvements). Most companies now insist that the rewards of improved process costs are handed back and that no intellectual property rights be retained by their subcontractors. At the same time, prices are being eroded by fierce competition for every new piece of business, with sponsors happily receiving the ensuing benefits. Further factors have also conspired to make the trading situation more difficult than before:

•A narrow, self-interested approach taken by innovative pharmaceutical companies that are knowingly undermining their supply base by emphasising cost over service, manufacturing facilities over chemical development skills and 'brawn over brain'.

•The consolidation of the fine chemical industry within large chemical and speciality chemical groups that are really only set up to take on major manufacturing projects, where profits are now closely controlled by big pharma sponsors.

•Over-investment in GMP capacity, by poorly advised companies hoping to attract business in an increasingly competitive environment, has resulted in PFC business becoming a buyer's market.

•The participation of commercially inexperienced, but increasingly technically sophisticated, competition from Asia has further extended the degree of oversupply.

•The pharmaceutical industry is increasingly 'locking out' the majority of established PFC producers by sourcing older

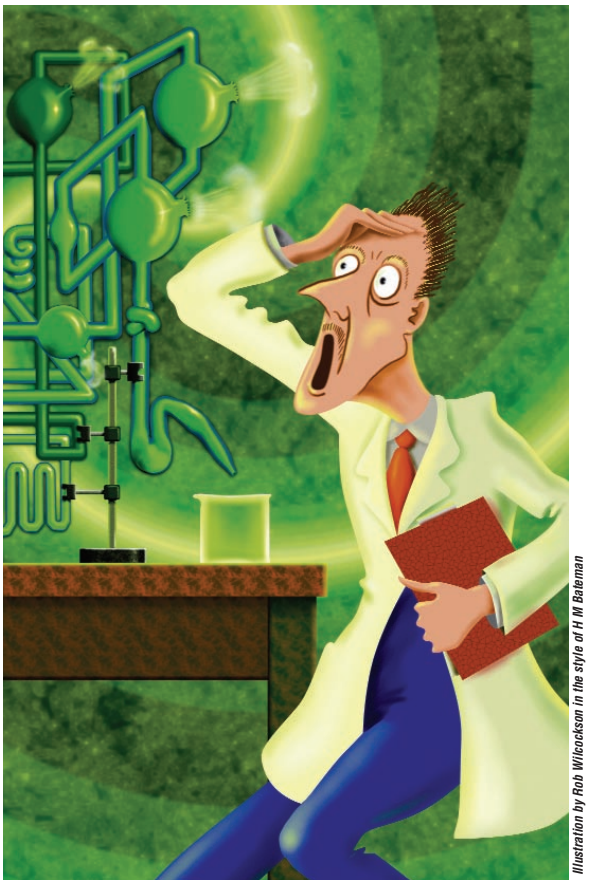

Illustration by Rob Wilcockson in the style of H M Bateman

Poor chemical processes are creating an explosive situation within the pharmaceutical industry.

Company	Location	Strengths	Chemical process development
Albany Molecular	US	Custom synthesis	Included, especially in FTE service
Carbogen (Solutia)	Switzerland	GMP pilot plant	Engineering solutions
Cambrex	US, Sweden	Full service provider	Provided as part of service
CSS	UK	Custom synthesis	GMP kilo lab
ChiroTech (Dow)	UK	Custom synthesis	Potential within group
Chemshop	The Netherlands	Custom synthesis	GMP process development
Degussa Fine Organics	UK, US, Germany	Full service provider	Provided as part of service
DSM Pharmacueticals	The Netherlands, US	Full service provider	Provided as part of service
IMI-TAMI	Israel	Custom synthesis	Additional activity
Lonza	Switzerland	Full service provider	Provided as part of service
Niels-Clausson-Kaas	Denmark	Custom synthesis	Additional activity
Onyx	UK	Custom synthesis	Included, especially in FTE service
Pharm-Eco (JM)	US	Full service provider	Provided as part of service
Regis Technologies	US	Custom synthesis	Included
Rhodia-Chirex	UK, US, France	Full service provider	Provided as part of service
SynProTec	UK	Custom manufacture	Process development specialist

Figure 3: The varied process development strengths of selected pharmaceutical fine chemical companies.

APIs and basic intermediates from Asia, while saving the 'plum' projects for their first tier suppliers.

Against this background, how is the US and European-based player going to secure new and profitable contracts?

Some success factors never change, it still being the case that dirty, difficult or dangerous processes will continue to be the source of third party contracts. However, this type of approach is increasingly difficult to operate in the over-regulated markets under discussion. But the capability to deliver good CPD is an important service that much of the competition still cannot supply, and that sponsors need more than they care to admit.

An experienced process development chemist is able to create an effective bridge between the medicinal chemist (who discovers a compound with promising activity) and the pilot plant or production operation (which produces substantial quantities of the potential API under closely defined conditions and to an acceptable level of quality – usually within a GMP environment). Most discovery companies understood the operational chasm that separates these two activities. Most successful PFC companies have been founded by ex-pharmaceutical development personnel who know about the challenges of developing new drugs.

Several factors have conspired to produce a sort of industrial amnesia on achieving rapid and effective development of good process chemistry, resulting in 'chemistry' increasingly becoming the rate-determining step in new product development:

•Transfer of outsourcing responsibility from development groups to autonomous procurement operations, resulting in a reduced collaboration between internal and external process development groups.

•Involvement of many chemical companies, whose business approach and understanding of the needs of the sponsor has led to a reduction in empathy between customers and suppliers.

•Retirement of many 'old hands' within pharma and its suppliers, who understood the importance of real partnerships in which process development was undertaken as a collaborative effort.

•Increasingly new API discovery is being carried out by small specialist companies that have neither chemical production nor chemical development resources.

The situation has been exacerbated by the creation of the bureaucratic tier system of preferred suppliers by the major pharma companies. This has led to an increasingly rigid supplier profile, in which creative process improvements by suppliers have been minimised, leading to poor motivation for the creative chemists within the PFC companies and their subsequent elimination. Over the past 5-10 years, good process chemistry has thus become harder to achieve, with a consequent tendency for poor processes being operated by default.

From this unpromising industrial landscape, however, a new generation of small PFC development companies is emerging and these, almost uniquely among companies operating in developed countries, are growing rapidly as their important services are being recognised.

Raising key issues

It would be invidious to suggest that certain companies have poor CPD skills, despite the fact that many poor processes are operated. Instead, examination of the practices of more competent firms may shed light on how high quality CPD is incorporated into a company's basic services. A review of their delivery procedures allows some reasonable generalisations to be made:

•Where early access to new compounds is possible (medicinal synthesis – prototype process), improvements can be achieved without too much difficulty. Companies offering custom synthesis have the opportunity to select realistic synthetic approaches that have good potential for subsequent scale-up. Many, however, lack the skills and/or the rewards to make the most of this opportunity.

•Where customers subcontract a developed process, there is often little opportunity to make significant changes and the supplied process has to be operated, whatever its failings might be.

•Where very significant problems arise with a process, specialist companies can sort out the weak points and rescue the project. Eventual GMP producers can also undertake such work, but only when the process transfer is at a sufficiently early stage.

Thus, delivery of good CPD can be offered in several distinct ways and achieved by different types of company, although few specialist companies exist (see Figure 3 on page 12 for examples). This seems to reflect the general belief within the pharma industry that such work is best carried out in-house. Most independent fine chemical companies will have a different view on this, and greater openness on the issue might lead to better recognition of the essential role played by companies offering their services to the pharmaceutical industry.

Litmus tests for robust manufacturing processes

- Raw materials are truly commercial (and not just bought from lab suppliers).
- Cheap bases such as caustic are used, rather than more exotic ones.
- Reaction temperatures no lower than -10°C (rare that lower temperatures really needed).
- High throughput reactions, where volume-to-weight solvent/reactant ratios fall into the range of 6-8:1.
- Use of phase transfer catalysis using cheap two phase solvent systems rather than expensive aprotic solvents.
- No examples where products are isolated by 'evaporation to dryness'.
- Aqueous extractions use isopropyl acetate, rather than ethyl acetate or diethyl ether.
- Control of crystallisations to avoid either needles or fine powders.
- No solvent drying using inorganic salts such as magnesium sulphate!
- Creation of chirality early in the synthesis, using cheap resolution methods where possible (not a final stage chiral HPLC).

The way forward

Companies in developed markets must differentiate themselves from the huge numbers of PFC companies that now offer their services to the innovative pharmaceutical industry. It has always been true that good process chemists are essential for success in this industry. However, as the basic chemical transformations required for early intermediates are increasingly being undertaken by Asian producers, companies in Europe and the US must find new ways to win profitable business. Innovative CPD remains the most challenging (and therefore the most rewarding) way in which a company can achieve prominence in the industry. As chemical targets become ever more complex, marketing such capabilities more effectively must be a core objective for those PFC companies that can really deliver this vital service. The good news is that the newer innovative pharma companies do recognise the importance of maintaining partnerships with capable fine chemical producers. This sector offers a growing market for those PFC companies that have the size and expertise to solve difficult synthetic challenges. It also offers some respite from the depressing business of being on a list of twelve potential suppliers, each of which is trying to outbid the other. Although the big pharma companies may achieve short-term benefits from this type of 'Dutch auction', such a policy will create more problems than benefits for the innovative industry in the longer term – but this is a subject for another article. SM

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