Reshoring fine chemical and pharmaceutical productions

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ABSTRACT

Keywords:
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Prolonged shortage of active pharmaceutical ingredients (APIs) in many countries that do not produce critically important APIs requires urgent reshoring of said fine chemical productions. The situation is even worsened by now frequent disruption of the global supply chains, first during the COVID-19 crisis and subsequently with the ongoing Red Sea crisis. In this study, we first outline the main economic and policy aspects emerging from selected cases of API production reshoring to Europe. Hence, broadening the analysis to include selected cases in China and India, we investigate the industrial uptake of continuous manufacturing in fine chemicals production. Following said concrete analysis of the concrete situation, the study concludes with three main findings.

1. Introduction

The word "reshoring" is economics jargon indicating the act of relocating back to western Europe, Japan or North America countries productions "offshored" since the early 1990s to companies chiefly based in China and India. "Offshoring" of productions was driven by the low cost of labor and income tax, less restrictive environmental regulations, and special incentives granted for investment in special economic zones, often with refunding of reinvested share of profits. Following a first modest increase in reshoring from China to the United States of America (USA) in the early 2010s due to increasing shipping and labor cost,[1] the COVID-19 crisis caused prolonged disruption of global supply chains causing shortage of a number of highly important products, including medicines and semiconductor chips.[2] India, for example, in early 2020 banned the export of hydroxycholoroquine, acetaminophen (paracetamol) and other 14 active pharmaceutical ingredients (APIs), aggravating a drug scarcity that in Europe had seen a 20-fold increase in recorded shortages (the number of shortages notifications) between 2000 and 2018, and 12-fold since 2008.[3] Shortage of APIs and formulated drugs, however, continued also after the end of the COVID-19 crisis. By late 2023, for example, in response to a shortage of liquid Ibuprofen, authorities in the USA were forced to temporarily allow manufacturers to produce and distribute non-approved antipyretic and anti-inflammatory drugs.[4]

Suddenly many governments in Europe and North America called for reshoring API production. Until the mid-1990s, western Europe countries, the USA and Japan produced 90% of the world's APIs.[5] Yet, in 2017 China alone was producing about 40% of the global production of pharmaceutical ingredients.[5] In France, for example, the government announced in June 2020 its intention to reshore production of acetaminophen (tradename "paracetamol", whose sales during the health crisis were rationed) "within three years".[6] In the USA, a 2021 analysis of the country's manufacturing base for APIs for essential medicines and the top 100 generic drugs revealed that more than 80% of APIs for essential medicines had no domestic manufacturing source.[7]

In general, benefiting from all the aforementioned advantages, manufacturing companies that outsourced productions in the early days of the second grand globalization in the early 1990s are reluctant relocating back home productions, be they microelectronics, clothing and automotive productions.[8] As shown in the following, Austria already repatriated penicillin production, and France is near to successful relocation of acetaminophen production.[9] From the manufacturing technology viewpoint, chemists and chemical engineers have long suggested that successful reshoring goes through industry's adoption of digitally controlled, efficient continuous manufacturing (CM) in fluidic reactors.[10] CM employing homogeneous and heterogeneous catalysis,[11] in other words, would ensure the required economic competitiveness. The higher yields, much smaller size ("footprint"), and larger mass and heat transfer in fluidic reactors would lower inasmuch the cost of the "production campaigns", as to allow repatriation of fine chemicals production in countries where the cost of labor and energy is far higher than in Asian countries.

In this study, we first outline the main economic and policy aspects emerging from selected cases of API production reshoring to Europe. Hence, broadening the analysis to include selected cases in China and India, we investigate the industrial uptake of CM in fine chemicals production. Following said concrete analysis of the concrete situation,[12] the account concludes with three main findings and forecasts that will hopefully assist industry's practitioners and researchers alike.

2. Results and discussion

2.1 Economic and policy aspects

Meeting with other European industrialists and managers at the first edition of the first "European Industry Day" held in Brussels in 2017, the head of a fine chemical company based in Belgium recounted why they decided to locate a new production in the USA:

> "Thirty years ago, the European fine chemical industry was the world leader with 33% market share. Today it has less than 15%... Minafin recently developed an innovative process to make a petrochemical ingredient from agricultural waste. Because it required a new operating permit, 12-18 months would have been requested to gain approval in Europe, after contradictory risk assessments and painful design adjustments by the State administration. Minafin

> chose the US where it only required 9 months to get permit approval, and to build and commission the unit for regular production. The investment cost saving was 2 M€ on a total of 7 M€ and the reduction of the time-to-market was close to 18 months."[13]

The manager went ahead explaining how overly complex regulation "complicated by individual gold-plated adaptations by the Member States is a millstone around the neck of the chemical small and medium enterprises, hampering their synergetic development across the EU territory".[13]

An indirect proof that overregulation and slow and uncertain authorization times were amid the main drivers responsible for Europe's decline in fine chemical productions is given by the case of Switzerland. The European country is home to a florid and diversified fine chemical industry, regardless of strict environmental regulations, high labor cost and significant income tax rates. Switzerland indeed hosts some 250 chemical, pharmaceutical and life science companies. With exports of CHF 130.87 billion and imports of CHF 54.9 billion in 2021, these companies chiefly make pharmaceuticals ("over-the-counter" drugs, patented or generic), APIs, vitamins, flavours and fragrances, crop protection agents, specialty and fine chemicals, eventually contributing 50% of Swiss exports.[14] In brief, balanced regulation, large and prolonged investments in new industrial plants and new technology, enabled Switzerland to go from a chemical and pharmaceutical industry accounting for 1.2% of national value added in 1980, to 8.7% by 2021.[15] The country, furthermore, hosts a large number of highly qualified chemists and chemical engineers shaped by chemistry and engineering schools of renown international standing.

Regardless of labor cost largely increased in the last fifteen years (2008-2023), pharmaceutical and fine chemical companies continue to benefit from producing APIs and fine chemicals in India and China. Hence, governments willing to relocate production of vital APIs have only two options: either to nationalize the pharmaceutical industry;[16] or pay private companies to relocate production.

Figure 1. New fermentation reactors for the production of penicillin in Kundl, Austria. [Reproduced with kind permission, from Ref.18].

For instance, aware that the country was relying on imports from China for its entire yearly demand and consumption of the amoxicillin (an antibiotic), the Austrian government in 2019 paid €50 million in subsidies to a large fine chemical and pharmaceutical company based in Switzerland to build a state-of-the-art fermentation facility.[17] Production of amoxicillin in the mountain town of Kundl eventually started in late 2023. The plant focuses on penicillin products including semisynthetic derivatives such as amoxicillin and ampicillin.[18] In detail, it comprises 10 reactors (Figure 1) having the capacity to produce a minimum 4,000 tonnes of amoxicillin per year, enough to supply all of EU countries' demand.

In the meanwhile, shortage of acetaminophen in France extended to late 2022 and early 2023, leading the government to ban the internet sales of all paracetamol-based medicines.[19] The country actually was the last one in Europe to host production of acetaminophen before in 2008 a large chemical company closed its 43-employee factory in Roussillon. Noting that by then China and India-based manufacturers produced already about 115,000 tonnes of paracetamol per year (equivalent to about 70 per cent of the global market), the director of the Roussillion plant told the press in 2008 that since there had not been "a major issue with imported paracetamol" pharmaceutical companies were "no longer willing to pay a premium for the decades-long record of contamination-free shipments provided by European manufacturers".[20]

Reshored acetaminophen production in France will take place in the same factory closed in 2008 using a new synthetic route "with an environmental footprint a fifth to a 10th that of other paracetamol factories in the world".[21] In early 2023 the research and development work was reported to be complete and building of the production unit about to start. The plant will have a production capacity of 15,000 t/y and is expected to start production "by the end of 2025".[22] Insight from a manager of the engineering company building the plant is instructive:

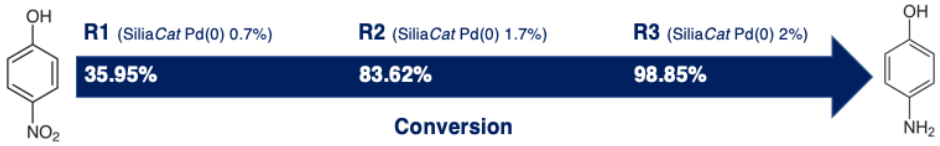
> "This plant is being built at an existing chemicals facility and can hence benefit from the utilities, laboratories, logistics and other services available on-site (water, steam, power, etc.). On the engineering front it's a complex operation, because it has to be built in a constrained setting, partly reusing existing buildings. The production unit itself has to be raised to an elevation of 40 m, as it is a gravity-flow process. There are also nearly 250 main equipment items to manage – and qualify, about 13 km of pipework, and 1,500 sensors to control the facility. Liquid effluent will be fully recovered, treated and reinjected into the process. The set-up is instructive from a financial standpoint too, as it combines support from the State (via the "France Relance" recovery plan) with the participation of UPSA laboratories and Sanofi."[23]

As in the case of Austria's amoxicillin plant, therefore, success in reshoring the production of paracetamol was due to the government financing construction of the new plants. In the words of the company's head of fine chemicals and pharmaceutical ingredients manufacturer, "the cost of the paracetamol project is about €100 million, of which almost a third is financed by the state. Without this, we would never have done it".[24] Similarly, the €28 million cost of another project aimed to start in Toulouse a new CM factory producing 4,000 t acetaminophen per year since early 2025 benefits from public funds provided by the regional government;[25] and also by the joint ownership of the company from the same local government as a shareholder.[26]

2.2 Continuous manufacturing

The new continuous process for continuously manufacturing acetaminophen lowers the cost of the most widely used production process based on nitration of phenol with the formation of *p*-nitrophenol followed by hydrogenation and acetylation.[27] The latter process suffers from a low yield of phenol nitration reaction. The CM process avoids the high pressures and long reaction times of the conventional

hydrogenation step, while nitration is carried out continuously with the substrate dissolved in environmentally friendly ethanol leading to far higher regioselectivity in favor of the *para* compound (>80% *vs.* 66% of the batch process).[27] The use of a sol-gel catalyst[28] comprised of a glassy organosilica matrix entrapping 5-6 nm Pd(0) nanoparticles (well suited for use in continuous flow processes)[29] in the hydrogenation of *p*-nitrophenol in three reactors of increasing capacity placed in series, allows very low catalytic loads under relatively mild reaction conditions. In detail, pumping the substrate at 12 mL/min rate in three consecutive reactors of 0.1, 0.15, and 0.4 L employing H_2 pressurized at low and decreasing pressure (20, 12, and 5 bar) and increasing temperature (100, 110, and 130 °C) affords nearly full conversion (98.85%) of *p*-nitrophenol to *p*-aminophenol (Scheme 1) with a remarkable productivity of 3.7 kg/L/day.[27]



Scheme 1. Consecutive hydrogenation of *p*-nitrophenol to *p*-aminophenol mediated by Silia*Cat* Pd (0) in three consecutive reactors of increasing size. [Adapted from Ref.27, with kind permission].

Finally, contrary to highly pyrophoric conventional Pd/C catalyst, the organosilica sol-gel catalyst is not pyrophoric and does not require excluding air from reactions.[30] Hence, its use eliminates the risk of spontaneous ignition of the catalyst cake after hydrogenation, providing a key technical advantage when considering the industrial upscale of *p*-nitrophenol hydrogenation using pressurized H_2 under flow as reducing agent. Self-ignition of spent Pd/C catalyst after hydrogenation reactions, indeed, is *always* observed with alcoholic solvents.[31]

By late 2023, a large pharmaceutical company producing numerous acetaminophen-based medicines acquired a capital stake in the French company willing to produce the API via said continuous manufacturing process.[25] The plant should be located in Toulouse with production expected in early 2025.[32] "This mode of construction and the implementation of new technologies" said Lecomte-Norrand presenting the process at a conference in 2023, "is the only way to make the relocated production profitable".[33] In other words, CM using heterogeneously (and homogeneously) catalyzed processes emerges as the key technology enabling to re-shore the productions of APIs.[11]

Doubts and skepticisism still abound. For instance, economic analysts in 2020 ascribed the slow industrial uptake of CM to "the lack financial incentives"[34] remarking also "the large investment needed to establish new facilities capable of CM".[34] Three years later, an industry's analyst writing on a highly read pharmaceutical technology magazine similarly reported that CM "builds on hype"[35] and that adoption remains "gradual".[35]

Between late 2019 and early 2020, however, a company manufacturing agrochemicals in China first replaced six batch reactors of 3,000 L each with a single flow reactor in silicon carbide capable to process 10,000 tonnes per year, and then three batch reactors of 6,000 L each with another such flow reactor coupled to a tube reactor.[36] Now, instead of 8 h of reaction time per batch, the flow system requires just several s of residence time for diazotization, and several min for the hydrolysis step instead of 4 h, occupying one-tenth the area of the original batch process and requiring *30 fewer workers*. Finally, the new flow reactor system allowed a solid waste reduction of 75%. As a result, the payback period for the investment in new CM technology was less than 20 months.[36]

Similarly, another China-based API manufacturer uses numerous flow reactors in SiC with a 2,000 t/a throughput at its factories for the production of "a bevy of active pharmaceutical ingredients".[37]

The company is world's fourth-largest specialty generic producer. Analogous excellent results have been recorded in many countries. In Japan, in 2020 a API manufacturer specializing in peptides replaced two 6,000 L reactors with a single industrial flow reactor (also in SiC) doubling from 250 to 500 t/a the production rate and also eliminating worker exposure risk.[38]

Accordingly, manufacturers of CM equipment and research companies specializing in CM of fine chemicals are being regularly acquired by larger chemical and chemical engineering companies. In early 2022, for example, a large China-based API manufacturer acquired a pioneering flow chemistry technology based in the USA.[39] One year later, the subsidiary of a large Japanese glass company acquired the manufacturer of the aforementioned flow systems using SiC flow reactors,[40] after it had already purchased another pioneering flow chemistry company in Great Britain in 2020.[41]

Furthermore, it is enough to change a parameter such as making sharper a corner of the heart-shaped unit of the aforementioned 2,000 or 10,000 t/a microfluidic flow reactors in SiC to achieve remarkable further improvements for instance in the mass transfer performance due the enhanced rapidity with which bubbles are broken into two or more sub-bubbles, enhancing the mixing of the two phases.[42]

The reason for which most fine chemical and API manufacturers resist the uptake of CM is due to the fact that they do not wish to lose the substantial amount of capital invested (and most often depreciated) in multi-purpose and multi-product plant (MPP) in existing batch manufacturing facilities, whose core consists of stirred stainless steel and glass-lined batch reactors equipped with reflux condensers and feed systems.[43] Even if multi-purpose CM production units can be easily installed in existing facilities, freeing most of the space occupied by MPPs, when adopting a CM reactor the latter should be abandoned. CM furthermore extends to crystallization and filtration, as shown for example as early as of 2015 by the aspirin synthesis and isolation in pure form at >60 g/h combining a continuous oscillatory baffled crystallizer with a continuous filtration unit.[44] Again, even if the continuous crystallization and filtration process can be easily transferred to industrial production, product purification and isolation units at existing MPPs should be dismantled.

Most generics manufacturers, furthermore, argue that the slim margins of the business do not justify investment to replace plants that most often have already depreciated, and lament a lack

of published "business cases" showing that CM is truly "cost effective over time".[45]

The production process improvements, however, are so large that no matter how risk-adverse the fine chemical industry can be, the shift to CM scale production of chemicals for the pharmaceutical, specialty, and fine chemical production is inevitable. For example, an API manufacturer based in India in 2023 commercialized methyl salicylate made by a fine chemical company using flow chemistry technology.[46] The company reported even in its investor relation that CM of the product occurs with a considerable reduction in production time, a 3-time capacity expansion and cost savings of 7%.[46]

For "generics" (off-patent medicines) Europe, North America and many other countries and regions of the world today heavily depend on imports from India and China. In EU countries, current 74% dependency in terms of APIs and precursors, more than doubled since the 1980s (Table 1).

Table 1. European dependency on imported APIs from the 1970s till 2020. [Source: IQVIA, 2020].

Years	Percent of dependency (%)
1970s-80s	30-40
1990s-2000s	60-70
Today (2020s)	70-80

However, for on-patent ("innovative") medicines, 64% of APIs are still manufactured in Europe, and only 11% in both China and India combined.[47] Another key outcome of the survey carried out by the data company appointed by the European Fine Chemicals Groups (an association of leading fine chemicals companies based in Europe) to investigate the situation of API manufacturing in Europe in 2019-20 is that 53% of the 52 surveyed companies were already operating "flow chemistry" as the second main technology used to produce APIs or pharmaceutical intermediates.[47] In other words, not only European companies were retaining production of highly profitable APIs and medicines still "on-patent", but most of them were already using flow chemistry to manufacture the API or certain intermediates.

2.3 Lower waste, higher profits

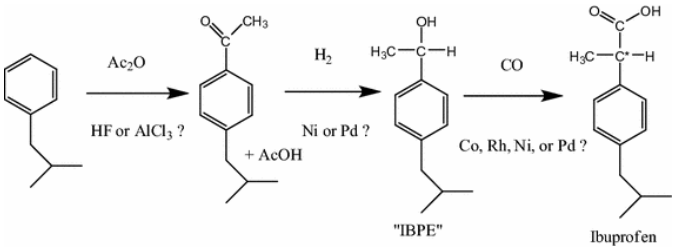
Reviewing the state of the art of green chemistry in the fine chemicals and pharmaceutical industries, in 2013 Pagliaro and Ciriminna extended to chemicals manufacturing a simple yet powerful equation borrowed from quality management (Eq.1):[48]

$$C = C_i + \text{PONC} \qquad (1)$$

According to Eq.1 the cost of a chemical production process (C), includes the intrinsic process cost (C_i) plus the price of nonconformity (PONC) of producing unwanted byproducts (waste). In this view, quality is achieved through prevention eliminating PONC, and the standard of environmental quality is Zero Emissions. In other words, waste produced in a chemical production equates to the financial measure (PONC) to assess quality at work at manufacturing and service companies introduced by Crosby in the early 1960s.[49]

Remarkably, recounting the history of the BHC Ibuprofen process eventually commercialized at a plant in Texas in 1992,[50] its co-inventor Murphy has explained that many economic human and cultural factors and motivations "including the 'Quality Movement' of the 1980s and its focus on waste avoidance"[51] actually drove the early industrial "green chemistry" inventions in the chemical industry.

Classified as a nonsteroidal anti-inflammatory drug, Ibuprofen is widely used across the world to treat symptoms in chronic diseases like rheumatoid arthritis and osteoarthritis, and to alleviate pain during migraines, menstrual cramps, and fever. Available both in solid and liquid drug formulations (currently in serious shortage in North American and in many European countries),[4] Ibuprofen had $1.43 billion global sales in 2023.[52] Conceived in 1984 by Murphy and co-workers,[53] the BHC Ibuprofen Process is one of the earliest and well-known industrial examples of green chemistry in action, having its roots in the decades-long evolution of industrial methods for making acetic acid and its derivatives. As put it by Murphy, the most strategically crucial part of the Ibuprofen synthetic scheme from a technical and environmental perspective was (and is) the Pd-catalyzed final carbonylation step (Scheme 2).[50]



Scheme 2. General synthetic strategy for "profen" drugs developed by Murphy at Celanase in 1984. IBPE stands for 1-(4-isobutylphenyl)ethanol. [Reproduced from Ref.50, with kind permission]

Murphy has suggested that green chemistry actually originated in the oil refining, commodity chemical, and consumer products chemical industry sectors from a long and complex series of international evolutionary developments in the 1970s and even earlier.[51,50] In brief, industrial and academic research chemists in many countries worked at the development of new synthetic routes aimed at preventing waste, long before "green chemistry" was formally introduced in the early 1990s.[51,50]

Showing evidence of the practical relevance of Eq.1, a highly atom-efficient process minimizes waste (PONC) and makes a chemical production profitable even in Europe or in North America. Indeed, Ibubrofen continues to be produced both in Bishop, Texas, and in Germany using Murphy's process,[54] whereas to meet the increasing demand, the company in 2017 announced construction of a new plant in Germany and increased production capacity at the facility in Texas.[55]

Remarkably and in agreement with this viewpoint, Linthorst has recently discussed how the 1979 Convention on Long-Range Transboundary Air Pollution (LRTAP) of the United Nations, entered into force in 1983, whose key policy principle was "pollution prevention", impacted knowledge production within the chemical sciences in western Europe and the USA as well.[56]

Less than a decade later came the work of Sheldon who in the late 1980s introduced the E(nvironmental) Factor, namely the ratio between the mass of waste and that of the desired industrial product ($kg_{waste}/kg_{product}$).[57] Perhaps not surprisingly, prior to join the academy in 1991, Sheldon had worked in the chemical industry for two decades, where he became concerned with the production of waste - which implies costs for a commercial process – and showed that the amount of waste per kg product for fine chemicals and APIs was regularly very high. Recounting the origins of the E factor concept three decades later Sheldon

explained how the cost of disposing of the waste obtained in the manufacture of a pharmaceutical intermediate was rapidly approaching the selling price of the product:

> "In the early 1980's my attention was drawn to the problem of waste in the (fine) chemicals industry by the closure of a phloroglucinol plant at Océ Andeno . The plant was shut down because the cost of disposing of the waste was rapidly approaching the selling price of the product. The process generated ca. 40 kg of solid waste containing $Cr_2(SO_4)_3$, NH_4Cl, $FeCl_2$ and $KHSO_4$ for every kg of phloroglucinol. Based on a subsequent inventarisation of the amount of waste formed in processes for the manufacture of other fine chemicals and pharmaceutical intermediates and some bulk chemicals, it soon became clear that tens of kgs waste per kg product was no exception in the fine chemicals industry".[58]

Noting how it was "abundantly clear from the phloroglucinol, and other examples, that the major source of waste is the application of antiquated technologies involving the use of stoichiometric quantities of mainly inorganic reagents in the form of oxidants, reductants, and acids and bases",[59] he concluded that the solution was self-evident: "substitution of these antiquated stoichiometric methodologies with greener catalytic alternatives".[59]

2.4 Barriers to market entry

Conventionally, the main barriers to market entry in the fine chemicals and API manufacturing market included high plant costs and regulatory hurdles. CM coupled to catalysis dramatically lowers both the capital expenditure cost (CapEx) required to start producing fine chemicals. Hence, the barriers to market entry that for about a century prevented new competitors from entering the fine chemicals industrial sector are now significantly lower. As mentioned above, fine chemicals and API manufacturers based in Europe synthesize highly valued "on patent" APIs relying on CM as their second most used technology.[47] Getting to regulation, several national and international regulators have long approved guidelines, standards and related programs to enable the adoption of CM, including the "ICH guideline Q13 on continuous manufacturing of drug substances and drug products".[60] The guideline is applicable to CM for new products as well as to the conversion of batch manufacturing to CM for existing products. On the other hand, the cases of acetaminophen production expected to debut in France, and that of Ibuprofen still manufactured in the USA and in Germany, show evidence that green chemistry synthetic routes allow the profitable manufacturing of "off patent", but critically important, APIs also in countries where the costs of labor and energy are significantly higher than in China or in India.

Chemical companies compete for customers based on product price, quality and speed of delivery (Table 2).

Table 2. Key aspects used by any customer companies to select a chemical ingredient supplier.

Parameter	Relevance
Product price	Very high
Speed of delivery	High
Quality	Very high

CM using catalytic processes lowers production costs, accelerates production rate, and affords highly pure (high quality) products. Furthermore, it allows easier production scale-up (or scale-down) in response to fluctuating market demand (emergencies, demand slow down, etc.).

The CM technology is now mature. For comparison, one of the first SiC reactor with 80 t/y capacity was commercialized in 2006. In 2011, the same company commercialized already a complete CM unit equipped with a reactor of 3,500 t/y capacity.[61] Now reactors with a 10,000 t/y capacity similar to those installed at the fine chemical company in China producing agrochemical at a fraction of previous cost are regularly commercialized.[37] Aware of said advances, fine chemicals and pharmaceutical companies now regularly purchase complete "turn-key" CM plants also in Europe.[62] In other words, the "valley of the death" of the innovation process (Figure 2) during which lack of revenue from sales results in consumption of the initial funding capital, has long been overcome.[63]

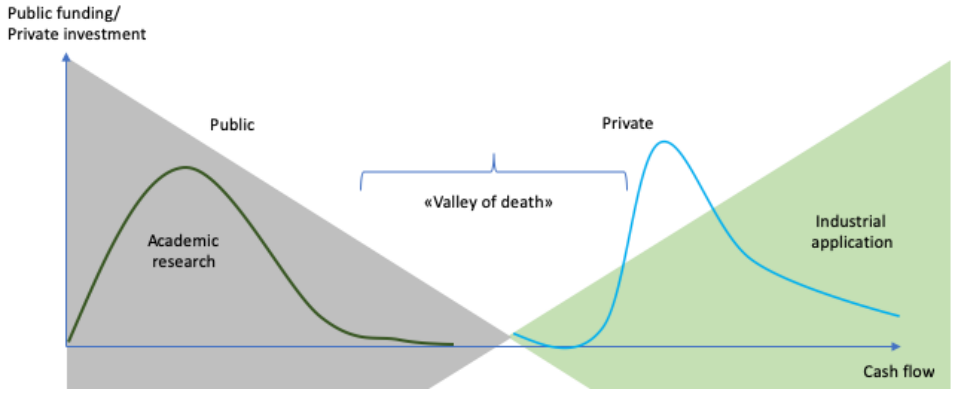


Figure 2. The "valley of the death" bridging the main moments of the innovation process (discovery and industrial application).

Besides unwillingness to replace depreciated and expensive MPPs, another barrier to CM widespread adoption is the common shortage of young research chemists and chemical engineers with practically useful knowledge of CM.[64] Writing about the industrial uptake of green chemistry and CM, we have often suggested to look at what industry *does*, rather than what it *says*.[65] For example, as recently noted by a widely read industrial chemistry magazine, "an indicator of the technology's maturity status is recent job offers from the pharmaceutical industry, where skills in flow chemistry are often required".[66]

On the other hand, a global shortage of young chemists and chemical engineers skillful in CM (and in catalysis) points to

widespread failure of universities to shape the researchers and technologists with said competences, regardless of chemical industry's pleas going back to the early 2000s. For example in Germany, chemical engineers from the world's largest chemical company writing in 2002 in *Chemical Engineering & Technology* emphasized the need for chemical engineering faculty "to place emphasis on teaching students modern, relevant engineering knowledge and methodological and systematic skills".[67] Twenty years later, namely not in the early 2000s, when the technology was in its early days, lack of adequate training in flow chemistry was reported even in world's leading countries in terms of chemistry research and advanced education such as Great Britain[68] and Switzerland.[69]

Clearly, flow chemistry equipment needs to enter university research and teaching laboratories.[69] Furthermore, flow chemistry and catalysis education based on a unified approach[70] should be included in the organic chemistry teaching curriculum, so that students are no longer educated to believe that synthetic organic chemistry in industry is the same thing as going from a heated reaction flask to a heated pot.

3. Conclusions

In summary, the prolonged shortage of numerous critically relevant pharmaceutical ingredients in Europe, North America, Australia and many other countries that no longer produce them requires urgent reshoring of said fine chemical productions. Disruption of the global pharmaceutical supply chains during the COVID-19 crisis,[71] and more recently the ongoing geopolitical crisis that forces large container ships to avoid navigating the Red Sea and cross the Suez channel,[72] makes the situation even worse (at least in Europe).

Consisting of a concrete analysis of the concrete situation this study on reshoring of fine chemical and pharmaceutical productions, a fundamental premise to the analysis was highlighted by Pollak in 2011.[73] Globally comprised of 2,000-3,000 companies, the fine chemical industry includes amid the top 20 largest companies 17 firms that are divisions of large chemical or pharmaceutical companies, and "only three pure players".[73] Furthermore, nine of the top 20 largest companies in 2011 were headquartered in Europe. The industry in 2023 had $200 billion global revenue, and is forecasted to grow at least at 5% annual growth rate for years to come.[74]

Three main conclusions emerge from this study.

First, successful reshoring requires the active involvement of national governments. The cases of Austria and France where the production of critically important APIs has restarted (penicillin in Austria),[18] or is about to restart (acetaminophen in France),[23,25] show evidence that governments need to cover at least one third of the investment required for private companies to relocate production.

Second, continuous manufacturing via (homogeneously or heterogeneously) catalyzed processes in fluidic reactors will be widely used to reshore the production of APIs. Early examples are the forthcoming production of acetaminophen in France using a CM process,[33] nearly concomitant with the restart of production at the refurbished Roussillon's plant.[23] Already widely used in Europe to manufacture on-patent ("innovative") APIs,[47] the technology is being quickly adopted also by fine chemical companies in China,[36,37] and to a lower extent also in India[46] to manufacture off-patent APIs, agrochemicals and other fine chemicals.

Third, substantially lowering the capital and operating expenses,[11] CM coupled to advanced catalysis enables market entry to new competing companies in the highly attractive (large, rapidly growing and highly remunerative) $200 billion fine chemicals industry.[74]

Finally, reshoring fine chemical productions, including those of APIs, will not harm the wealthy fine chemical industries in India and China. Both Asian countries have a huge and young population whose advanced and rapidly growing economies intrinsically create a large and increasing demand of fine chemicals from widely different industrial segments (construction, nutraceutical, microelectronics, health, cosmetic, personal care, paintings, batteries, food and beverage, paper etc.). After more than three decades on focusing on export, China's economy, relying on a highly skilled workforce and advanced technology, is currently being reformed to boost domestic demand and unleash the enormous potential of said demand.[75]

In India ($2.9 trillion gross domestic product in 2019 *vs.* $14.3 trillion for China), the country's market size is a fraction (1-2 per cent of the population earning $15 per day in 2019) of China's (25 percent of the population earning $15 per day in 2019), and the country's economy will continue to heavily rely on export.[76] Yet, the economy is growing at such rate (9.05% gross domestic product growth in 2021, 7.0% in 2022 and 7.2% in 2023)[77] that a significant fraction of the overall fine chemicals and APIs manufactured in India will soon be adsorbed by domestic market demand.

In conclusions, the fine chemical industry's products include, but are not limited to, APIs. Pharmaceutical ingredients are amid the most profitable products of the industry, but many of the concepts and findings of this study chiefly discussing APIs can be applied to other fine chemicals. For example, recently another fine chemical production has been reshored to the USA, that of 1,3,5-trichlorobenzene, a critical material for military needs that until recently was available only from Asia.[78] Further supporting our conclusions, a fine chemical company in Texas first developed the batch route obtaining a high-purity product. Then, the company started work to convert the batch process to a CM process, eventually developing a manufacturing process "that is both commercially viable and meets the stringent environmental regulations"[79] of the USA.

Acknowledgments

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Notes

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