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The Evolution of Flow Chemistry: An Opinion on Factors Driving Innovation

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Abstract: This article seeks to provide an overview of the factors within the pharmaceutical industry that have contributed to the emergence of flow chemistry over the past two decades. It highlights some of the challenges facing the industry and describes how they are being overcome by the exponential trajectory of scientific progress in the area. We identify current trends and offer a speculative glimpse into the future of drug development and manufacturing with some examples of progress being made at CARBOGEN AMCIS.

Keywords: Continuous processing · Drug substance · Flow chemistry · R&D efficiency · Scientific progress

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1. Introduction

The relentless forward march of flow chemistry technology in the pharmaceutical industry over more than two decades has been remarkable. Today, a plethora of publications, presentations and lectures demonstrating the significant advantages of flow chemistry are available to the wider chemical community.

To those closely following developments, it might appear as though the technology is on an exponential path of evolution and adoption. Evidence would strongly suggest that this is the case, but what have been the driving forces within the pharmaceutical industry that have allowed flow chemistry to become so successful and what are the new and emerging trends and environmental factors that continue to drive its adoption?

2. Forces Driving Innovation

2.1 *History*

Flow chemistry – or continuous manufacturing as it is often interchangeably referred to – was used extensively in the fine chemicals and petrochemicals sectors before it made the transition to more complex multi-step synthesis applications. The Haber-Bosch process,[1] which converts hydrogen and nitrogen to ammonia used primarily for fertilizer production, is commonly singled out as one of the earliest continuous processes. Naturally, the implementation of early continuous processes in the fertiliser and polymer industries was driven by economies of scale and narrow profit margins.

Conversely, the pharmaceutical industry has been slow to adopt new technologies to improve drug manufacturing efficiency. This is primarily because it was able to remain highly profitable throughout the twentieth century without doing so. It is also reasonable to highlight other factors, such as increased regulatory scrutiny and the potential impact of new technologies on patient safety, which have cultivated a cautious approach to technology adoption.

These economic and regulatory factors, together with some other countervailing forces discussed in this article, have contributed to an existential R&D efficiency crisis that has encouraged considerable consolidation within the industry since the turn of

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the millennium. The increasingly challenging and restrictive economic and regulatory framework has forced companies to turn their focus towards improving efficiency and sustainable innovation. Consequently, flow chemistry has rapidly emerged as a powerful tool for addressing the efficiency in complex multi-step drug manufacturing, just as its forbearer had for petrochemical and fine chemicals companies.

2.2 *Dire Circumstances*

Flow chemistry made the transition from fine chemicals to pharmaceuticals in the early 2000s – at least the term 'flow chemistry' began to appear more commonly from the mid-2000s onwards. During this period, increasing R&D expenditure and attrition rates for drug candidates at all stages of drug development were under intense scrutiny.[2]

Analysis by Scannell *et al.*[3] highlighted in 2012 that the number of new drugs brought to market per billion dollars of R&D investment had been declining exponentially when adjusted for inflation (Fig. 1). The article goes on to describe the issues confronting scientific progress. These include a progressive lowering of the regulatory risk tolerance termed the 'cautious regulator' problem, an issue of basic capital misallocation termed the 'throw money at it' problem, and the increasing effort required to produce new drugs that are better than yesterday's blockbuster termed the 'better than the Beetles' problem. The problem 'terms' used above are those used in the *Nature* article by Scannell.

Furthermore, while the number of new drug approvals (Fig. 2.) has been increasing recently, it has not been increasing at a rate concomitant with the perceived degree of technological advancement.

The soaring nominal costs of R&D led some observers to speculate that tried-and-tested business models would eventually become unprofitable if the sources of inefficiency could not be identified. Indeed, a great deal of consolidation was seen in the industry and it continues to this day. In an effort to reduce costs, some production was moved offshore[4] to take advantage of cheaper labour available in countries such as India and China; although, this did not address the underlying problem of efficiency.

Eventually, the industry was forced to search for marginal gains in efficiency across all business functions. Management and R&D structures were reorganised,[5] companies doubled-down on high throughput screening.[6] As the skill set evolved, automated and digital approaches, together with flow chemistry solutions, presented themselves to organic chemists and chemical engineers in R&D and process development departments around the world.

2.3 *The Money Problem*

While the R&D efficiency problems are very real, one of the countervailing forces in drug discovery and development that was perceived two decades ago may have been overstated. The increase in nominal R&D costs may disrupt existing business models but it does not threaten the industry as a whole.

While CPI (consumer price index) inflation reflects the increase in prices of certain goods for the average consumer, it is only a partial measure of currency devaluation. Therefore, we decided to adjust the R&D data reported by Scannell for growth in M2 money supply (M2 adjusted, Fig. 1). (M2 is a measure of the money supply that includes cash, checking deposits, and easily-convertible near money[7]). Arguably, this is a more appropriate

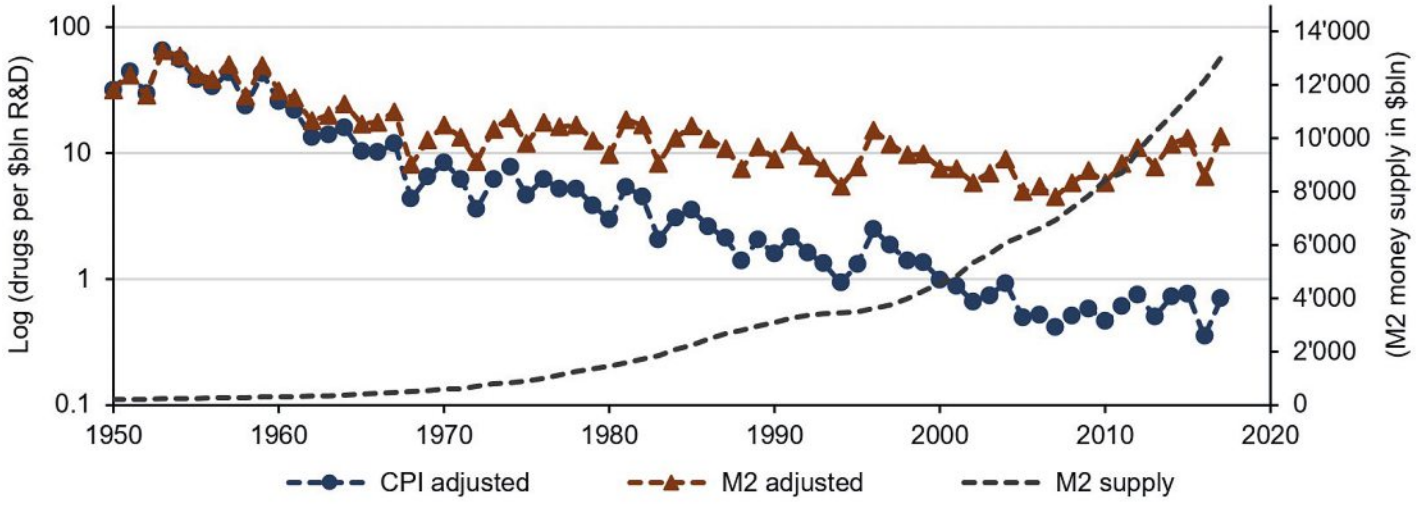

Fig. 1. Perceived pharmaceutical R&D efficiency as a function of new drugs per billion dollars R&D investment since 1950.

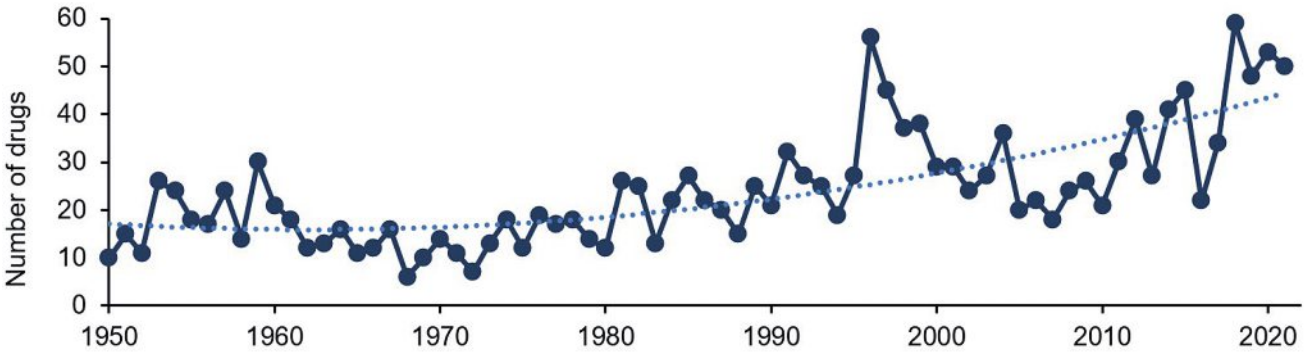

Fig. 2. Number of new drugs approved by the FDA per year since 1950.

measure of currency devaluation that more accurately reflects the nominal increase in capital availability over the years.

By this measure, R&D expenditure has not been increasing in real terms whatsoever; in fact, the number of drugs approved per billion dollars of R&D investment appears to have been relatively range bound for the past 50 years. Based on the knowledge that there is also an exponentially increasing amount of fiat currency available for R&D investment, it is unlikely that R&D costs will never become a major prohibiting factor for progress and innovation in drug discovery as was feared. Although, it may be that the drug discovery and technology innovation phase simply shifts to more agile tech and biotech start-ups that benefit from the Cantillon effect due to their proximity to capital allocators such as VC firms or governments. This appears to be true based on the trend by many big pharmaceutical companies to adopt a more mergers and acquisitions orientated business model.

Providing that academic research labs continue to receive government funding and capital continues to flow into the hands of ambitious tech and biotech entrepreneurs, drug discovery and scientific progress should proceed unabated. Undoubtedly, the past 20 years have demonstrated that spiralling nominal R&D costs have not slowed the pace of innovation; rather, the opposite seems to be the case.

2.4 *Exponential Technologies*

Necessity is the mother of invention – and every so often, a new technology or discovery has a reverberating impact on humanity. It is the nature of an exponential technology to enable change at an ever-increasing rate. As a result, today's drug development landscape looks very different from what it did just two decades ago. It might be fair to say that the pace of technological advancement was, and continues to be, grossly underestimated due to the influence of these technologies.

During this period, we have seen the completion of The Human Genome Project[8] announced in 2003 and the emergence of systems biology,[9] proteomics[10] and CRISPR technologies. Opening this 'Pandora's Box' has led to new ways of using small molecules that address biological targets previously unknown or deemed undruggable.[11] Many new binding modalities have emerged,[12] including: targeted covalent inhibitors, protein–protein interactions, RNA targeting small molecules, modified peptides and peptidomimetics, antibody–drug conjugates, and small molecules as facilitators to cell and gene therapy.

All of the advances mentioned above are underpinned by computing, probably the most significant exponential technology of the past 100 years. Specifically, the exponential increase in computational power, governed by Moore's Law, has enabled us to rapidly scale new discoveries.

The most recent exponential technology, which is arguably an emergent property of computing, is machine learning (ML) and artificial intelligence (AI). AI and ML have dramatically changed the landscape of computational biology with the appearance of AlphaFold at CASP14[13] in 2021. In a relatively short time, AlphaFold has been able to predict protein structures for the entire human genome with varying degrees of confidence. The proteome-wide AlphaFold Protein Structure Database now contains over 200 million protein structures covering 47 species.[14] Recently, it was demonstrated that end-to-end AI-powered drug discovery platforms can quickly and cost-effectively identify first-in-class hit molecules for novel targets.[15] Furthermore, these new sophisticated methods may eventually be able to decrease the attrition rate of drug candidates as they progress through the clinical trial process.

These approaches have greatly expanded the scope and importance of small molecules. Therefore, it is reasonable to expect that there will be a significant increase in drug approvals year-on-year into the coming decades. We anticipate that this increase in drug approvals will be accompanied by a corresponding build-out of on-shore manufacturing capacity within the industry to meet demand for small molecule production. We also expect high throughput experimentation to play a critical role in increasing the velocity of drug candidate synthesis. Indeed, it has already begun.

2.5 *Complexity*

Molecular complexity, however we define it, has also risen over the past decade[16] in an effort to achieve greater selectivity,[17] better solubility,[18] and higher success during early phase clinical trials.[19] This trend has been driven by the use of powerful modelling software up until recently; however, now that these methods have received an upgrade with the application of machine learning or AI-assisted approaches, this trend is likely to accelerate the move towards more complex small molecule drugs.

Consequently, it is likely that the large-scale manufacture of significantly more complex drug structures will become a bottleneck that can only be addressed with the adoption of new manufacturing technologies in the future.

2.6 *Environmental Factors*

Another factor driving change to a great degree over the past two decades has been environmental policy. Many industries, not only the pharmaceutical sector, have been rightly under increasing pressure to develop greener, more sustainable processes. This virtuous green narrative motivates companies to minimise their environmental impact even when an economic incentive is absent or if there are measurable costs associated with being more green.

As one measure, the E-factor[20] estimates the resource intensity of a given process or reaction and the wastes generated. Furthermore, in the absence of reliable and abundant green energy, a green process should also be more energy efficient. As a result, the E-factor can be expanded to include energy consumption, in terms of the mass of CO_2 or CO_2-equivalents generated[21] for any given process.

There is a recent trend towards labelling processes using a traffic light system to indicate the level of greenness. As scientists, we must be cognisant of the secondary consequences of basic labelling that lacks nuance and other ideas that originate from policy such as this one. It would be unfortunate for this to become a measure by which the fate of a project is decided, irrespective of the good it does for patients.

2.7 *Regulation*

It has certainly seemed like a slow and arduous process; however, regulation around continuous manufacturing has made a considerable leap forwards in a relatively short period of time. The final version of ICH guidance Q13: Continuous Manufacturing of Drug Substance and Drug Product will be issued in the near future, expressing the will of authorities to support this emerging technology. The Q13 guideline covers the new and unique capabilities that can be realised with continuous manufacturing that are not adequately covered in existing guidance. Notably, it addresses the definition of a batch, as part of a continuous process, and new control strategy possibilities. It also recognises the importance of sophisticated process models and the use of *in silico* experimentation that will pave the way for the implementation of more dynamic process control.

This clear commitment by regulators to align quickly with the most current technologies that are demonstrably advantageous will allow the industry to move forwards with flow chemistry processes in the highly regulated commercial environment.

Despite the clear regulatory guidance together with the abundance of published work, the number of client processes that include flow chemistry steps remains low; however, there is an increasing awareness and willingness to explore alternative flow chemistry approached when presented with an abundance of ex-

amples. Thus, CDMOs that have already developed specialised flow capabilities are themselves becoming a driving force for further adoption. This is already being reflected in the number of new filings that include flow chemistry processes.

In many cases, problems arising during initial scale-up and process safety evaluation typically performed by CDMOs is sufficient justification for the switch to flow. This pivot to an alternative approach, especially during ongoing process development, might initially lead to additional cost and development effort but will ideally lead to more robust commercial processes that will be more efficient and produce less waste.

3. Flow Chemistry – One Solution

Naturally, we maintain the position that flow chemistry and machine-assisted approaches[22] will become fundamental base-layer technologies for pharmaceutical manufacturing companies that wish to remain capable and competitive enough to produce the next wave of complex small molecules on the horizon.

As flow chemistry evolves, along with the associated digital technologies with which it is inextricably interconnected, the opportunity cost of not adopting these approaches will continue to increase. This can be nicely illustrated using the performance potential gap (Fig. 3) that shows the difference in rate of change, of revenue generating potential for example, of pro and anti-technology adoption scenarios over time.

What follows is a brief overview of how we see flow chemistry as a single solution that addresses all of the forcing factors described earlier in this article. In addition, we have included a few examples of how CGAM is embracing this new paradigm.

3.1 *Agile Manufacturing*

With an increasing demand for their services, CDMOs will naturally respond by increasing manufacturing capacity to capture more of the market. Traditionally, expansions require large investments of capex and take many months or years to plan and execute; furthermore, any indication that demand might be transitory may result in no investment whatsoever. This makes investing equally as risky as not investing at all.

This problem can be partially solved with flow chemistry technologies that provide agile manufacturing solutions ideal for a rapid and cost-effective build-out of new capacity. The small physical footprint of flow equipment and its interoperability with existing batch equipment means that it can be easily installed alongside existing infrastructure and, in addition to providing increased capacity and capabilities, it can improve the productivity of existing batch assets.

At CGAM, we have invested over CHF 19 million across our manufacturing sites in 2021 and we have significant expansions planned for our facilities over the coming years. However, in the near term, we are also focused on improving the efficiency of existing processes using flow chemistry. Both are intended to meet our projected increase in demand.

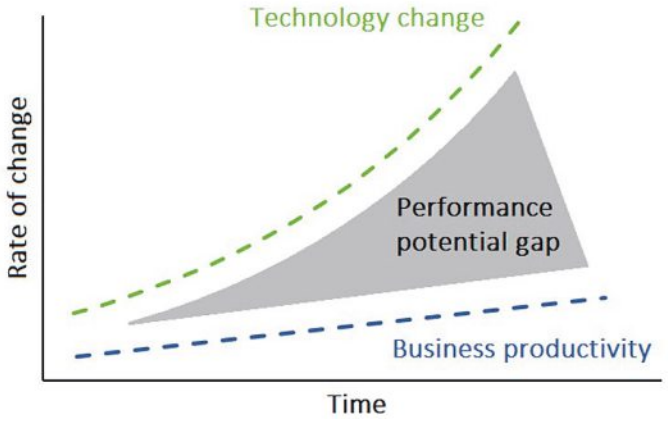

Fig. 3. The performance potential gap.

Initially, we have focused on fast reactions that require cryogenic temperatures, such as Grignard[23] or lithium base reactions,[24] which are well suited to flow. Using modular flow devices (Fig. 4) we have been able to successfully improve and accelerate the processing for several stand-alone chemical steps.

Fig. 4. Modular flow equipment for continuous reactions involving organometallic reagents.

The process development time required to take a flow process from lab to production scale can also be significantly decreased. When coupled with on-line process analytical technologies (PAT) and intelligent optimisation software, machine-learning algorithms or other AI-assisted approaches, a sufficiently automated flow chemistry platform can identify optimal process parameters in a fraction of the time compared to traditional batch methods.[25]

In our laboratories, we have taken a step in this direction for the development and validation of flow processes. Using a small lab-based flow reactor, which demonstrates equivalent heat and mass transfer characteristics to a larger production scale device, we were able to perform large DoE based optimisations and robustness studies over a period of several days rather than months. Critically, due to the equivalency of the flow reactors, we were able to directly scale from grams to kilograms with very little additional effort.

While there is still a significant amount of work required to fully automate and integrate off-line analysis and data interpretation, this high throughput experimentation approach significantly reduced the overall number of lab hours and freed up time that could be spent on more creative tasks.

3.2 *New Capabilities*

Flow chemistry can also partially address the problem of increasing molecular complexity by simply increasing the number of possible chemical reactions available to process chemists. Hazardous reactions can be used either to shorten the overall synthetic route, by replacing multiple benign steps, or to introduce complexity into molecules directly by less conventional mecha-

nisms. Unfortunately, a large proportion of hazardous reactions are beyond the reach of small or medium-size CDMOs due to the specialised equipment and knowledge needed to perform these reactions at large scale safely.

Flow chemistry provides a well-characterised and precisely controlled environment that is particularly well suited for many hazardous reactions.[26] Efficient heat and mass transfer properties reduce the likelihood of hot-spot formation and ensure that sufficient cooling capacity is available for the entire contents of the flow reactor. In addition, the accumulation of highly energetic reagents or intermediates can be limited by implementing make-and-consume approaches that reduce the active reaction volume while maintaining a high throughput of reagents. Other advantages include the strength of the flow reactor construction relative to the volume of energetic material contained within and the ability to implement a multitude of probes and sensors that can detect abnormalities and automatically shut down the process if necessary.

Furthermore, the ability to run hazardous or conventional reactions at high pressure and temperature above the boiling point of a preferred solvent expands the chemical space that can be explored across all reaction classes.

Reactions that require cryogenic temperatures, while easily obtained in the lab with the use of solid CO_2, are not always scalable due to limited cooling capacity, poor mixing or drawn-out reagent addition times. This can lead to poorer yield and increased impurity formation. As mentioned previously, we have been able to scale-up cryogenic flow processes that ensure mixing on a timeframe of 10–100 ms, allow for stoichiometric addition of reagents and provide sufficient heat transfer away from the active reaction zone. These conditions, and the degree of control over them, are invariably superior to what can be achieved in batch.

It is also worth noting that flow chemistry is compatible with other types of cooling technology, such as thermoelectric Peltier cooling devices, which are now commercially available for many applications[27] and offer further improvements in cooling efficiency.

3.3 *A Photo-Electro Renaissance*

The integration of electro and photochemical synthesis techniques into flow chemistry has led to the development of new flow devices that can now produce material at reasonable scale. The various types of electrochemical flow reactors have been reviewed in detail.[28] More recently, flow reactor design for electrochemical applications has taken a right-turn with the development of spinning-disc or spinning-cylinder reactors that can harness the mixing efficiency of Taylor vortices between electrodes.[29]

Consequently, the number of publications on flow-assisted electrochemistry and photochemistry has increased in recent years. Some notable mentions include a flow-assisted Shono oxidation for the synthesis of unnatural nazlinine analogues by Ley *et al*.[30] and the large-scale preparation of artemisinin by George *et al*.[31] A depth of literature on flow-assisted photochemistry has been well reviewed in a number of publications[32] and such processes can now realistically contribute to molecular complexity at scale.

A key, low volume intermediate for a highly potent antibody-drug conjugate (ADC) warhead being manufactured by CGAM involves a photo-oxidative cyclisation. Recently, we have been evaluating the innovative photo-vortex reactors[33] on a model system and we anticipate a 20x increase in throughput, compared to circulating falling-film reactors that are currently in use. We believe that implementing this new technology will reduce the manufacturing time for this step from several weeks to just a few days.

3.4 *Efficiency Gains*

In addition to what has already been mentioned in regards to efficiency in previous chapters, flow chemistry has been a significant benefactor of the ESG (environmental, social and corporate governance) narrative – emphasis on the E – as it offers to improve the efficiency of manufacturing processes, in terms of both energy consumption and waste.

For example, heating and cooling infrastructure accounts for a vast amount of the energy consumed. However, most commercially available cryostats have a cooling efficiency of only 50–70% at ambient temperature, depending on the exact device, and the efficiency can drop below 5% when the temperature falls below –50°C or so. Fortunately, efficient mixing in flow reactors makes it possible to perform some fast exothermic reactions at higher temperatures than what would be possible in batch. As a result, transitioning such processes from batch to flow can lead to a significant reduction in energy consumption.

In addition, some processes can be more safely performed at higher concentration or under solvent free conditions, thereby reducing raw material inputs and waste streams simultaneously. Other improvements in the upstream chemistry can often translate into gains in efficiency downstream. A notable example would be the continuous flow preparation of norketamine.[34] In batch, a thermal rearrangement in diphenyl ether is followed by a laborious down-stream extraction sequence. However, the authors were able to switch to using ethanol under super-heated flow conditions followed by direct co-crystallisation from the reaction solvent.

Such examples are numerous throughout the recent literature and as new down-stream flow technologies come online, such as continuous extraction, distillation, crystallisation, *etc*., flow chemistry will begin to offer comparable utility to traditional batch equipment.

4. Summary and Outlook

At the beginning of this article, we acknowledge that there were significant challenges confronting the pharmaceutical industry in the 2000s that led to the emergence of flow chemistry and other machine-assisted approaches in drug manufacturing. However, given the breath-taking amount of scientific progress in drug discovery and development that we have witnessed in the past 20 years we are also of the opinion that some of the countervailing forces perceived at the time may have been overstated. In particular, we believe that the exponential increase in nominal R&D expenditure is flat in real terms and does not present a counter force to drug discovery or innovation in general.

Crucially, we see flow chemistry as a suitable bridge from the analogue synthetic chemistry world to the high velocity, digital synthetic chemistry world that is increasingly interconnected with advances being made in computation-powered biology, AI and machine learning, and automation and robotics.

We predict that highly automated flow chemistry technologies will continue to evolve and become more sophisticated and that adoption will continue at an accelerating rate as the demand for small complex molecules increases in the coming decade.

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