



## A Perspective on Chemistry and Society

A Column on the Occasion of the 75<sup>th</sup> Anniversary of CHIMIA

Idorsia Pharmaceuticals Ltd.

### Organic Chemistry: At the Core of Idorsia's Business

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**Stefan Abele** received his PhD in chemistry at the ETH Zurich (Prof. D. Seebach) in 1999. He joined Carbogen-Amcis where he held positions of growing responsibility in R&D and GMP manufacturing of Drug Substances. In 2006, he set up a fully integrated Chemistry Process R&D department at Actelion where he received the 2015 Sandmeyer

Award<sup>[1]</sup> with his teams. Since the inception of Idorsia in 2017, Stefan is responsible for drug substance R&D and manufacturing from the preclinical phase to launch and commercial supplies. As Head of Chemical Development and Commercial Manufacturing (CDCM) he is part of the Idorsia Leadership Team.

'Organic Chemistry – Where Now?', the title of a review by Prof. D. Seebach in 1990<sup>[2]</sup> has not lost its rigor and relevance. Over the last decades, there has been a stunning array of innovations in fields like photo-redox chemistry, electrochemistry, flow chemistry, C-H activation, as well as gene technology and molecular biology. These advances have brought forth new solutions to some key global challenges like new drugs for devastating diseases, new materials for batteries, and catalysts for green technologies. Simultaneously, the resources and energy required to produce target molecules are more and more under scrutiny driven by the need to develop sustainable and environmentally benign processes. Moreover, cost pressure from health systems and the need to deliver affordable drugs have increased. More than ever organic chemists are pivotal players to solve these challenges. Advanced chemistry combined with state-of-the-art manufacturing technology are key capabilities that remain the undisputed strength of our innovation-oriented society. The following perspective highlights the impact and significance of organic chemistry at Idorsia, with a focus on process chemistry and manufacturing, embedded both in the Swiss science ecosystem and a global supply network.

### Idorsia – Small Molecules and Organic Chemistry

Idorsia Pharmaceuticals Ltd started operations after demerging from Actelion<sup>[3]</sup> following its acquisition by Johnson & Johnson in 2017. In addition to over 650 highly skilled employees, a rich early-stage pipeline was transferred to Idorsia. Over just four years, the clinical pipeline has progressed and six compounds are now in late-stage development. We expect two product launches in major markets in the first half of 2022, subject to regulatory approval. With now over 1'000 professionals, Idorsia covers all disciplines required for drug discovery and development ranging from Molecular Biology, Biochemistry, Structural Biology, Research Information Management and Modelling, Pharmacology, to Medicinal Chemistry, and Chemistry Process R&D.

At Idorsia, it's a strategic choice to focus on small molecules, and the design and synthesis of small molecules of increasing complexity is the turf of organic chemists. This particular 'Idorsia DNA' is promulgated publicly by the founder and CEO, Jean-Paul Clozel, who is convinced that small molecule drugs will remain well-poised to treat many diseases where there is an unmet need, whilst also fulfilling important criteria such as ease of administration and affordability.<sup>[4]</sup> The percentage of new molecular entities approved by the FDA that were small molecules was between 70–75% over the last five years.<sup>[5]</sup> Idorsia's clear focus allows for a differentiation from peer companies who are betting on diversifying into large molecules like biologics, oligonucleotides, or peptides. Our focus on small molecules is an asset for attracting highly talented organic chemists amidst global competition. Medicinal chemists are the 'drug hunters', equipped with state-of-the-art technologies, including artificial intelligence tools to more quickly design and identify molecules for further preclinical development. Process chemists, the 'process hunters', then begin to design and develop innovative, scalable, robust and cost-efficient processes. From finding the right molecule as part of drug discovery to synthesizing and physically delivering the drug substance at every step of the development and commercialization lifecycle, chemistry is indeed at the core of our company, and contributes significantly to each of Idorsia's five strategic priorities (Fig. 1). The process chemists' additional privilege and motivation are to have a sizable impact on the Cost of Goods by developing new chemical routes for the drug substance, which can ultimately translate into higher profits for the company.

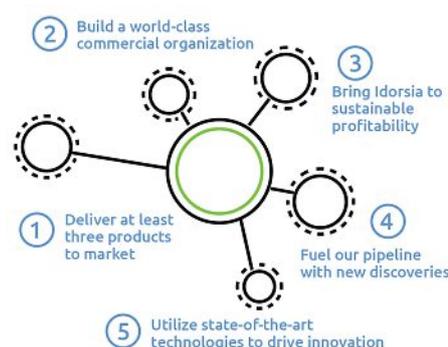


Fig. 1. Organic Chemistry plays a key role in each of Idorsia's five strategic priorities.

### Chemical Development and Commercial Manufacturing

At Idorsia, our highly productive Discovery unit produces an average of two candidates per year for entry-into-human studies. Together with the large number of late-stage assets, this creates formidable challenges for our two teams of chemists who play crucial roles in delivering high-quality drug substance: the Process R&D team and the Development and Manufacturing team (Fig. 2).



Fig. 2. Chemical Development and Commercial Manufacturing at Idorsia: Drug substance from grams to tons, from discovery to market.

The Process R&D chemists have the great challenge and opportunity to present innovative solutions to intricate synthesis problems. They are scouting for new chemical routes that allow for an expeditious and safe production of first kilogram quantities (produced in-house in the non-GMP kilo lab) for toxicology studies and formulation trials. In addition, process chemists are designing and developing so-called ‘2nd generation routes’ for the late-stage clinical assets that qualify for registration, validation and future commercial large-scale manufacturing. They also bolster our company’s intellectual property by filing process patent applications.

Sharing the results of Process R&D with the scientific community is an added benefit to our work, beyond the pride we take in helping to bring new treatments to patients in need. In addition to the genuine motivation of sharing and gauging our own research in a peer-reviewed setting, Idorsia is able to attract talented chemists by spotlighting the quality of science at Idorsia. Ultimately, publishing is used more and more as a tool to secure freedom-to-operate.<sup>[6]</sup> Organic chemistry is at the core of these activities, with a broad skill set required, ranging from keeping abreast of recent new methodologies published in literature to producing multi-kg amounts in a small plant. Deep knowledge in thermokinetics, mass-transfer phenomena, process safety, and a holistic view of the scalability and feasibility on the larger scale is essential. Concepts like Quality by Design (QbD) are applied to develop robust crystallization protocols for the drug substance, supported by online analytical tools. Physical attributes of the drug substance such as particle size and density are critical parameters for the successful formulation of the final drug product.

In parallel, the Development and Manufacturing chemists have the challenge to scale up organic chemical reactions in a highly regulated cGMP environment. At Idorsia, we manage GMP manufacturing through a global network of suppliers, called Contract Manufacturing Organizations (CMO). It is essential to ensure a seamless transfer of knowledge from the first kilobatches to final commercial batches. The know-how accumulated during the process development and non-GMP production serves as a basis for the first outsourced GMP batch. This is followed by process development, scale-up, registration, and validation of the manufacture of commercial supplies in line with cGMP and regulatory guidelines. An additional role of the Development and Manufacturing chemists includes the coordination of further functions, including formulation and drug product development, Quality Control, Quality Assurance, packaging and distribution, clinical trial supply, and Regulatory Affairs, all of which make up Chemistry Manufacturing & Controls (CMC). Thorough process understanding is primordial in controlling impurities and securing consistent quality of the API (Active Pharmaceutical Ingredient)

at scale and over time. In the end, the CMC data accumulated during development are an important part of the dossiers filed with health authorities to seek market approval.

Identifying and selecting the right partner companies for these activities<sup>[7]</sup> are key to both supply security and to reach the financial goals for our Cost of Goods. The success of outsourced API manufacturing is built on trustful supplier relationships, recognizing the added value of in-time delivery and enhanced process know-how. CMO performance is monitored with emphasis on quality, timelines, and cost efficiency. This is best realized by visits and on-site audits to control the cGMP status. Relying on external suppliers is associated with risks that need proper mitigation to secure the supply chain, as witnessed during the COVID-19 pandemics when our industry was under particular scrutiny for vaccine shortages.

### Supply Chain in the Headlines

The convoluted supply chain for mRNA and other vaccines has ruthlessly revealed bottlenecks, be it a shortage of glass vials or filter aids, custom-made nanolipids, delayed shipments or the sheer lack of enough manufacturing capabilities and trained staff. A further backlog and surge of demand in 2021 has created significant shortages and delays in logistics, as well as some massive increases of the costs of commodities such as solvents. The supply chain for a small molecule API comprising several registered starting materials and half a dozen steps to produce the final API is not trivial. Not only must the quality of all intermediates, solvents and reagents be guaranteed, but we must also ensure the timely availability of the ingredients and raw materials to deliver enough API for the patients enrolled in clinical studies or, after approval, for the commercial supply. Several levers are used to set-up and nurture a resilient supply chain of API, such as dual sourcing or stockpiling strategic intermediates for expedited manufacture of API. Purely local sourcing of complex APIs is challenging for two reasons: first, for commercial large-scale supply, the higher costs of western CMOs could lead to a negative business case. Second, since a decade, it proves more and more difficult to secure enough capacity in European CMOs. Additionally, large pharma companies are increasingly outsourcing API manufacturing. CMOs in India and China are offering a larger volume and flexibility of capacity. However, accelerated by the lessons learnt by shortages of drugs during the pandemic, there is a general trend for onshoring, or repatriation of at least parts of API production. This will inevitably come with a price increase that has to be absorbed by all market players.<sup>[8]</sup> China is forcefully implementing its environmental regulations and the recent shortage of coal and gas has led to the sudden closure of whole industrial parks.<sup>[9]</sup> This is a trend with two benefits: first, running environmentally benign processes in all parts of the world is a boon for our planet. Second, the onshoring of manufacturing and R&D into European countries will require many well-trained chemists and engineers: a bright outlook for young scientists!

### Manufacturing in Switzerland

Gratifyingly, the Swiss CMO landscape is reacting to the increased demand of their services with – for local standards – massive CAPEX investments. Over the next few years, five large Swiss CMOs are investing over CHF 1 billion into plant extensions.<sup>[10,11]</sup> While raising their profiles as drivers of innovation, they will also benefit from a stable socio-economic, innovation-friendly environment. Whereas countries like the US have very few manufacturing capabilities left, Europe has maintained higher levels of manufacturing in countries like Italy, Spain, Germany, and Switzerland. The impact of manufacturing cannot be underestimated: it attracts large-scale investments, requires a skilled workforce, is based on adjacent disciplines

like civil engineering, craftsmen, electronics, and spurs the development of efficient and 'green' processes that can be run profitably in high-cost countries. And, it is the biggest asset in reducing dependency on other countries for the supply of life-saving drugs.

### Swiss Chemistry Ecosystem

Idorsia is well embedded in the Swiss chemistry ecosystem. Some of the most renowned global institutes and universities are located in Switzerland. There is a strong organic chemistry heritage: several Nobel prizes in Organic Chemistry have been awarded to chemists from the ETH, the universities of Zurich and Basel. The Basel region, where three countries meet, with its strong chemistry and pharma history is preparing for the next wave of investments. Idorsia is in close vicinity to the Switzerland Innovation Park Basel Area,<sup>[12]</sup> which is being built to create several thousand work spaces for scientists, further strengthening Basel's role as science hub and magnet for talent from across the globe. Idorsia is profiting from this vivid and highly productive local environment on several levels: by attracting the best scientists and tapping into the global talent pool; and by exchanging perspectives with the exceptionally high density and quality of scientific peers from neighboring companies. The Swiss Chemical Society and its flagship journal *CHIMIA* play an active role in strengthening the Swiss chemical science community. Idorsia is proud of our role in this community. Through activities such as maintaining close relationships with nearby universities, hosting students and training apprentices, we hope to further the growth of future co-workers in organic chemistry.

### Conclusion

Organic chemistry, with its impact on the efficiency of drug development, on manufacturing costs and on the reduction of our ecological footprint, is at the heart of the biopharmaceuticals industry. It is an essential discipline for companies like Idorsia to find, develop and manufacture new drugs for the benefit of patients. It will be interesting to see which innovations from organic chemistry will unfold to master future challenges: 'Organic Chemistry – What's Next?'

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