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From Lab to Production: Event Series on Insights into Process Chemistry

Urs Brändli[a], Jan Cvengros[b], Stefan Hildbrand[c], Niklaus Künzle[d], and Maurus Marty[e]

Correspondence: [a]Dottikon Exclusive Synthesis AG, P.O. Box, CH-5605 Dottikon, E-mail: urs.braendli@dottikon.com; [b]Department of Chemistry and Applied Biosciences, ETH Zurich, Vladimir-Prelog-Weg 2, CH-8093 Zurich, E-mail: cvengros@chem.ethz.ch; [c]F. Hoffmann-La Roche Ltd, Process Chemistry & Catalysis, CH-4070 Basel, E-mail: stefan.hildbrand@roche.com; [d]Lonza AG, Lonzastrasse, CH-3930 Visp, E-mail: niklaus.kuenzle@lonza.com; [e]dsm-firmenich Ltd, Hauptstrasse 4, CH-4334 Sisseln, E-mail: maurus.marty@dsm-firmenich.com

Abstract: As process chemistry is rarely included in university curricula, experts from Swiss companies pass on their experience to students at various levels.

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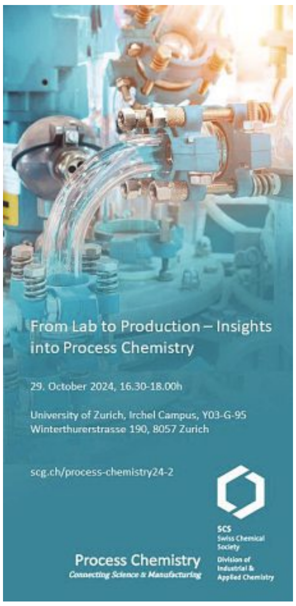
Despite the importance of the chemical industry in Switzerland, courses on process chemistry at Swiss universities are rather scarce.[1] The individual cases typically focus only on certain aspects and challenges related to chemical synthesis on an industrial scale. Students, therefore, do not have an opportunity to grasp the overall complexity of transforming the chemical reaction discovered in a minuscule flask into a robust process reliably running in a manufacturing environment. Being aware of this deficit in the chemistry education, the Division of Industrial and Applied Chemistry (DIAC) of the Swiss Chemical Society[2] launched three years ago a series of events aimed at depicting the world of process chemistry to university students and provide them with a deep insight into this fascinating field. Each event consists of three parts: (1) overview and insights into process chemistry; (2) a case study from industry; and (3) Q&A-session followed by an aperitif for further discussions and networking. The 7th event took place at the University of Zurich on October 29, 2024, and around one hundred chemistry students, doctoral and postdoctoral candidates had a chance to hear about process chemistry directly from experts active in this field and discuss with them at the subsequent aperitif (Fig. 1). This article provides a small appetizer for those who may feel intrigued about process chemistry.



At the event, the DIAC representatives focused on providing a general picture of what challenges a process chemist may encounter and emphasizing the differences of running a chemical reaction in a round-bottom-flask compared to running it in a large-scale reactor. A layman reader of this article, who is used to cooking for a group of friends or a family could think of being asked to prepare a delicious dish of equal quality for a hundred or even a thousand guests. Every single operation needs to be carried out differently. The development of a process suitable for a large-scale production occurs at multiple levels. It is important to recognize that the selection of suitable starting materials, reagents, and solvents becomes considerably constrained when financial, safety, and environmental considerations are taken into account. The industrial example presented was based on the work of various teams of process chemists in the '*Development of the Commercial Manufacturing Process for Ipatasertib*' which won the Sandmeyer Award 2020 and was published in *CHIMIA*.[3] This article gives a nice overview of the challenges of this working field.

Fig. 1. DIAC event at University of Zurich (Credit: DIAC).

In this column, we focus on the general aspects of performing chemical reactions in the industry. It is important to emphasize that the scale of such processes is determined by the demand and the nature of the target molecules, whereas the scale is multikilogram- to multiton-quantities per production campaign.

It is typically no problem to find a suitable flask in the lab to set up a reaction with a volume ranging from millilitres to litres. Any operation with such equipment, *e.g.* moving, installing, filling, emptying, or stirring, can be carried out without significant consumption of time or manpower. Even fast cooling or heating are easy to manage. It is also not a big deal, when such a flask breaks or can't be properly washed and reused. Process chemists work only during research activities and in early route-finding with round bottom flasks. During development, they are using jacketed reaction vessels with overhead mechanical stirrers and bottom outlets to mimic production environment (Fig. 2). On a manufacturing scale, permanently installed multipurpose reactors are used which of course cannot be freely moved or turned upside down (Fig. 3). The transfer of solid and liquid chemicals into and out of the reactor relies on different techniques using various additional devices (*e.g.* storage tanks, pipes, pumps, powder transfer systems, receivers, *etc*). Since most of the reactions release heat and the relative specific cooling surface decreases with increasing reactor volume a close look on a sufficient dissipation of the

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Fig. 2. A typical lab reactor setup for process chemists (Credit: DIAC).

Fig. 3. Multipurpose production reactors at DOTTIKON (Credit: Anja Wille/DES).

produced heat must be taken. Acquiring basic safety data is key, followed by a risk analysis to define and implement measures to minimize risks for each scale-up step. Process safety always comes first!

Naturally, production of chemicals for commercial use is always associated with financial aspects, which are typically neglected in the research lab. Highly likely, any doctoral students would not be able to provide the overall price of the reactants in their flask. As a matter of fact, it would be surprising if the opposite were the case. Quite a contrast to industrial processes in which a reactor is filled with chemicals costing hundreds of thousands Swiss francs. You can't afford to run a process, which is not robust enough to guarantee a successful outcome. In order to maximize the efficiency of the chemical transformation, additional parameters such as space time yield (STY) have to be considered, which have only little relevance for laboratory experiments. STY describes the amount of product (m_P) formed within the residence time τ in a reactor with volume V_R:

$$STY = \frac{m_{\mathrm{P}}}{\tau \cdot V_{\mathrm{R}}} \qquad (1)$$

The environmental and sustainability aspects of chemical reactions are also becoming increasingly important in the academic environment, although the environmental concerns usually end as soon as the reaction waste reaches the disposal container. Not in industry. Treatment of every substance required for the reaction or purification needs to be considered and thus reduction of the amount of chemicals or their parts, which are not being incorporated into the structure of the target molecule is a strategic goal. In this regard, the process mass intensity (PMI) is an important parameter, which might be considered as a mass for 'greenness' of the processes as it compares the total mass of materials m_{TOT} used to produce a given mass of product m_P.

$$PMI = \frac{m_{\mathrm{TOT}}}{m_{\mathrm{P}}} \qquad (2)$$

PMI accounts for all chemicals used in the process including not only the reactants or reagents but also solvents and other substances involved in the reaction or purification. Significant efforts are dedicated to design processes with low PMI values, whereas the best scenario would be achieved with PMI = 1. Those involved in the development tend to follow the hierarchy of measures to implement necessary changes which is: (1) AVOID, (2) REDUCE, (3) RECYCLE, (4) REUSE.

The reader might be overwhelmed by the variety of aspects that a process chemist must be aware of. There is no need to be worried, as the development of industrial chemical processes is a teamwork bringing experts from various fields together. Other team members are *e.g.* analytical chemists, chemical engineers, production chemists *etc*. The abovementioned event depicts also daily duties and tasks of a process chemist and demonstrates which stages the development includes. Besides a university degree in chemistry with strong skills in organic synthesis, it is mainly the passion for chemistry what young process chemists must bring with. Education works later on-the-job from senior scientists in process chemistry. With more experience more responsibility is given and development in various positions is possible. As a process chemist you pave the way to a new product and contribute to secure the supply *e.g.* for an active pharmaceutical ingredient for health, an ingredient for smell, an active ingredient for crop protection *etc.* It is a meaningful job with high impact and in Switzerland, many small to large chemical and pharmaceutical companies offer challenging jobs in this field.

Have we aroused your interest in process chemistry? Would you be interested to participate at the next event, or would you like to invite the program directors to your university or institute? Feel free to contact the Division of Industrial & Applied Chemistry.[2] Would you like to bring this topic to an audience with less knowledge of chemistry at secondary schools? The Division of Chemical Education is at your disposal (https://scg.ch/component/pages/page-chemical-education).

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