Sustainable Processes

Green Chemistry & Green Engineering

VTU Engineering supports process industry as a process design and consulting partner in the sign of chemical industry renovation towards sustainable products and processes. VTU Engineering wants to act as a qualified interface for those companies that want to follow the path of green innovation.

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The path of Green Chemistry.

In 1998 the American chemists Paul Anastas and John Warner published the essay "Green Chemistry: Theory and Practice”. They described in 12 points the characteristics that a chemical synthesis should present to be defined "sustainable" [1]. Originally thought as a

R&D philosophy for pharmaceutical applications, Green Chemistry has developed into a powerful tool for the technological renewal of the entire chemical industry.

Table 1: The 12 Principles of Green Chemistry of Anastas and Wagner, adapted from the "Green Chemistry Pocket Guide" -American Chemical Society Green Chemistry Institute [2].

1.	Prevent Waste formation
2.	Pursue Atom Economy The products of a chemical reaction should have molecular weight as close as possible to the sum of the molecular weights of the reactants.
3.	Select new synthesis routes to be less hazardous than the established ones.
4.	Synthetize new molecules that present no risks for humans or the environment.
5.	Use solvents that present no risks for humans or the environment
6.	Pursue Energy Efficiency.
7.	Use renewable feedstocks
8.	Reduce the formation of derivatives and by products. e.g. Avoid group protection by better regio and stereo selectivity
9.	Select preferably (bio-)catalytic reactions towards stoichiometric ones
10.	Design new molecules considering future degradation. Use a „cradle to grave“ approach to reduce waste accumulation.
11.	Perform real-time analyses to prevent Pollution E.g. Monitoring the correct evolution of the chemical reaction and/or measuring pollutant concentration in the environment for a rapid intervention in case of anomalies.
12.	Pursue „Inherent Benign Chemistry“ to prevent accidents Reduce the risk of chemicals or conditions that could cause events such as explosion, fire, accidental release.

The increasingly stringent environmental regulations, an market oriented to more sustainable products (and productions), the lower work-costs of emerging countries: these are the non-trivial challenges that the European Industry must manage today. While Europe has already lost the struggle for inexpensive commodity chemicals against Eastern Countries, the present moment is about the future in the production of fine chemicals. The 12 principles of Green Chemistry can be used to establish new synthetic routes, but also to improve existing productions, guaranteeing a technological advantage both from economic and environmental points of view . Making Green Chemistry can in fact increase competitiveness, in spite of being less easy than the traditional chemistry. This has been already demonstrated by an increasing number European chemical companies who tried first the "Green path".

VTU Engineering has been a privileged observer of this renovation effort, partnering as engineering consultant some of the pioneering projects which challenged the "traditional approach": Green Chemistry in fact is about changing the old paradigm of industrial innovation.

Most of the work of rethinking a chemical synthesis, as usual, takes place within the R&D functions of the “technology-owner company”, by developing new synthetic routes or rethinking the existing ones on the light of the principles listed in Table 1. However, the industrial success of a new process depends indeed on the capability of translating the laboratory intuition into a sound, reliable, full-scale production plant.

The great challenge introduced by Green Chemistry is to ensure technological and economic feasibility, but also to enhance environmental sustainability at the same time. In many cases, Green Chemistry aims at offering an alternative drop-in process for a product which must compete with an established, well-known technology. Normally, the time-to-market of a new product in chemistry is in the order of a decade: however, the present environmental emergency, together with the market volatility, urge to achieve a faster innovation. Environmental attention, economic constraints and fast industrialization require to rethink not only the way to do Chemistry innovation, but also how Engineering implements it in industry [3].

A specific engineering “touch” is needed to tackle the new challenges of the Green approach. This is not yet a codified practice, but it can be defined as the "Green Engineering", or the engineering at the service of Green Chemistry. This is what VTUEngineering has learned in these years, noticing how the typical engineer’s tools can become really useful also in the very first stages of innovation: engineering should not merely follow the ideation of new green routes, but has the capability to contribute to their success.

The very application of the 12 principles requires that that Process Engineering "comes to the laboratory”: Green Chemistry promotes in fact a proactive and highly interdisciplinary exchange between chemists, biologists, biotechnologists and engineers.

The following paragraphs will show how the broad and consolidated process expertise of VTU-Engineering can be used for green innovation, and how well-established engineering tools can adapt and give support to the special needs of early stage process development.

In facts, the industrial success of a new process is bound to the presence of a reliable technical partner who guarantees technological and economic feasibility from the very first moment and shortens the time to industrialization.

Bio-based Processes

The advances in green chemistry are often bio-based, starting with the use of renewable raw materials, and transforming it by means of designed microorganisms into valuable substances such as primary (e.g. amino acids) or secondary metabolites (e.g. antibiotics) or proteins (e.g. enzymes). Modern genetic engineering allows the expression of enzymes in large quantities, which are often improved in their catalytic properties in order to increase the activity or stability and thus the efficiency or the regio- or stereoselectivity (and thus the yield). Whole metabolic pathways can also be expressed and improved in the microorganisms, allowing these microscopic “bio-reactors” to produce chemicals which were before derived from oil (e.g. succinic acid) [3]. Bio-processes are intrinsically Green, as the principal solvent is Water, and the process conditions are as mild as “environment”, with ambient pressure and temperature rarely higher than 40°C: a quite different approach from traditional “stoichiometric” chemistry. Still, in terms of process engineering, bio-based chemistry involves several challenges:

- <u>Processing renewable raw materials (e.g. straw) and ensuring availability of cheap feedstock.</u> Renewables are subject to seasonality and should not overlap with food industry (glucose may derive from non-edible cellulose, but also from potato starch). Therefore the location and the scale of a renewable based plant become of paramount importance for the plant feasibility..

• Managing the fermentation of the microorganisms: The cells can grow under aerobic, microaerobic or anaerobic conditions. Refined process control must be performed for batch and continuous processes. In some cases, the product is separated off during the fermentation. Sterile technology and process control are the key to success.]

• Harvest to separate the cells and product purification. The product can be intracellular, secreted into the supernatant, or can be the cell itself. Before the cells are separated, specific pretreatments (e.g. Permeabilization) can be advantageous for biotransformation, cell disruption or pasteurization. The products are then recovered using various methods, e.g. Chromatography, extraction or selective crystallization. Bioprocesses require “exotic” unit operations, as they are not part of traditional (oil & gas derived) technology and are very little standardized, requiring extensive pilot experimentation and tailored equipment design.

VTU Engineering has a consolidated approach derived from a long lasting experience with biotechnological pharmaceutical processes: these engineering tools are hence adapted to the special needs of large scale, “green” fermentations.

An early example with VTU engineering involvement is the cephalosporin production [4] at Sandoz in Frankfurt, which includes the fermentation of Acremonium chrysogenum, the isolation of the secondary metabolite cephalsoporin C and its biocatalytic processing to produce 7-aminocephalosporanic acid (7-ACA). For this purpose, the enzymes D amino acid oxidase and glutaryl-7-ACA acylase were fermented, isolated and immobilized. In the meantime there are also improved penicillin G acylases that are used very efficiently for the final linkage with side chains and have successfully displaced environmentally harmful chemical syntheses.

More recently, VTU Engineering has contributed to the revamping of very large fermenters (>200 cubic meters) for the production of intermediates for biodegradable plastics in Italy.

These two examples are quite distant from each other: one product is a high added value API, the other a commodity chemical. Still, the same engineering tools and know-how were applied, adapting the approach to guarantee purity on one side, economic performance on the other.

The contribution of VTU Engineering to bio-processing extends also to the process development. In fact, VTU has its own technical center in Graz, where such processes can be developed. There are close collaborations with Graz University of Technology and the Austrian Center of Industrial Biotechnology (ACIB). VTU Engineering was involved in the establishment of a similar technical center in Aachen (AVT centre) [5].

Promotion of energy efficiency

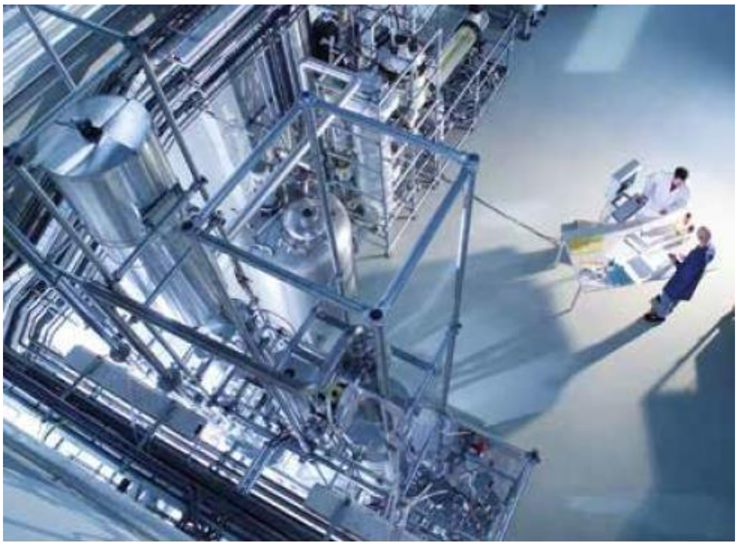
The promotion of energy efficiency, as required by the 6th point of Table 1, is a real challenge for a chemist, who develops and evaluates alternative syntheses on a gram scale in the laboratory. The engineering tools of predictive modeling (with analysis of energy flows and optimization) and process simulation are helpful here. These instruments are already available for a first concept study in order to obtain information about the energy requirement, the environmental impact and the economic framework of the synthesis to be developed. This means that important points can already be made proactively in the R&D phase (e.g. evaluation of alternative separation processes to increase yield at lower costs), which are advantageous in industrial implementation.

An approximate forecast of the future performance of the plant also allows the research to be guided by setting the so-called SMART goals (Specific, Measurable, Achievable, Relevant, Timebound) and guiding the resources in the most effective direction.

Analysis and monitoring of process parameters

Real-time analyses of process parameters allow prompt interventions, e.g. to to meet the requirements of fermentations (cultivation conditions, controlled feeding), to reduce by-product formation and to increase the yield. The effects of relevant measurement and manipulated variables are determined during development, so that optimal and robust strategies for monitoring the process parameters can be implemented in the system.

VTU Engineering successfully uses the combination of Quality by Design (QbD) and Process Analytical Techniques (PAT). In the QbD, a test matrix is specified for relevant measured or manipulated variables, which is statistically evaluated with PAT and used to make predictions. For example, the influences and weighting of the process variables determine and validate reaction time, yield, by-product formation and quality. QbD and PAT have found widespread use in the pharmaceutical field because they make an important contribution to accelerating and rationalizing expensive experimental campaigns. However, they can be used in any context and can be used to analyze and improve existing processes, even outside the pharmaceutical field.



Process engineers do have the sufficient tools to meet the challenges of green chemistry. Still, to meet the short time-to-market requirements of Green Chemistry, these tools should be applied in advance. In the usual project planning (divided into: R&D-phase, Piloting, Engineering and Plant building and commissioning) engineers enter the project when much time (and money) have been already spent. By adapting the engineering approach to become more lean and flexible to deal with preliminary data and ongoing research, Engineers can provide valuable support the Scientists in development of the new green routes, keeping an eye on the future plant and the need of ensuring competitive costs. After the final definition of the production strategy, the project can resume the EPCM order, in which know-how, experience and responsibility are the key factors.

Green engineering

VTU Engineering has always been characterized by its specialist knowledge, the experience of its technicians and the responsibility in the management of its projects. A large number of branch offices make it possible to contact the customer on site and act as a recognized partner in the implementation of projects.

Particular attention is now paid to the area of Green Chemistry, for which there are only a few companies that can competently support companies in their transition to a more sustainable production. VTU Engineering sees itself as the leading provider of "Green Engineering" services.

VTU Engineering maintains many contacts with universities that can be used to support projects. New targeted recruitment programs have led to reinforcement with engineers and PhD employees from R&D organizations, particularly in the areas of piloting, biorefineries, QbD / PAT and optimization to meet the technological shift towards Green Chemistry. Employees are encouraged by refresher courses on the latest technologies, covering topics that space from 4.0 control to industrial fermentation.

With such a team, VTU Engineering is ready to tackle the challenge of achieving a green and sustainable chemical industry.

In the service of the process industry

VTU Engineering combines specialist knowledge with creativity, which results from a multidisciplinary approach to solving procedural issues from process selection to commissioning. VTU Engineering offers its customers EPCM services:

- Tracking and management of all engineering tasks
- Support from the conception of the project idea to the start of production
- Attention to the specific needs of the customer
- Consulting activities not only for new projects, but also in the optimization and renovation of existing plants.

The company has been certified according to the DIN ISO 9001 standard since 1998 and has the SCC (Safety Certificate for Contractors) certificate for the chemical sector. For special problems of its customers, VTU Engineering is able to offer specific solutions that are developed ad hoc. In recent years, VTU Engineering has been able to refer to numerous and important references from the chemical-pharmaceutical sector (Boehringer Ingel-

heim, BDI-BioEnergy, Biotest AG, Borealis, Chemische Fabrik Karl Bucher, Hermann Bantleon GmbH, Octapharma, OMV, Roche, Sandoz, Takeda , Teva).

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