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# Sustainable route design for pharmaceuticals

## Why, how and when

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**ABSTRACT:** Process technology appears to get increasing attention in the whole process of pharmaceutical development. Although the contribution of an efficient manufacturing process to the success and profit of a large pharmaceutical appears small, this contribution is significant when it comes to sustainable manufacturing. Here an efficient process helps to lower environmental impact at the site of production and allows production beyond the patent life of a product. The design and scale-up of a sustainable process comprises route design, use of state-of-the-art chemical methods and also state-of-the-art process technology such as continuous manufacturing by intensified processes. DSM has developed a set of competences in these fields. Examples and metrics related to the sustainability of the described processes are given.

### MANUFACTURING OF PHARMACEUTICALS – HOW SIGNIFICANT?

The pharmaceutical industry is among the most innovative branches when it comes to inventing and developing new chemical lead structures to supply us with ever better, more selective medicines, with less side effects and more convenient forms of application. How important are manufacturing costs of active pharmaceutical ingredients (APIs)? Given the enormous development costs of drugs which are often in the range of \$ 500-1000 M€ per launched drug, manufacturing costs of APIs appear negligible. According to a study of Drug Discovery Today (1) the share of API cost of the total manufacturing price of a drug can be as much as 10-12 percent, but varies from product to product with a minimum of 0,5 percent. Indeed, this figure seems small. For block busters this number translates into manufacturing cost of \$ 5-120 Mio per year.

Contract manufacturing of API's has, however, developed into a competitive price driven business where small cost advantages can translate into significant changes of a market share. In these cases, reducing manufacturing costs while adhering to high standards of quality and reliability matters a lot!

### MANUFACTURING OF PHARMACEUTICALS - HOW SUSTAINABLE?

The World Commission on Environment and Development defines sustainability as "forms of progress that meet the needs of the present without compromising the ability of future generations to meet their needs".

A manufacturer will not only strive to "meet the needs of the present", but first of all, do this in a way that will keep its organization alive and in business – by staying competitive. Prices of pharmaceuticals, production safety, waste and non-competitive syntheses show that the manufacturing of pharmaceuticals has to change to become more sustainable. – Both, routes and the process technology employed in API synthesis, can contribute a lot to reach this goal.

Contract manufacturing organizations such as the Pharmaceutical Products division of DSM are judged and selected by their ability to develop scalable, efficient and sustainable syntheses within short time. Therefore we have developed a set of competences allowing us to meet these needs. In the following an overview of these competences is given. It contains route selection, employing cutting-edge chemical transformations and up-to date process technology. These elements are closely related: A given route with a specific set of reagents will work best in a specific reaction environment tailored to the needs of a reaction (temperature, time, pressure) as starting materials are converted into products.

### HOW TO MEASURE THE EFFICIENCY OF A SYNTHESIS

Several concepts to judge the efficiency of a synthesis have been suggested: the E factor (2) (the mass ratio of waste to desired product) or the atom efficiency (3). Lately the pharmaceutical industry has proposed a more detailed concept (4), the PMI

(Process mass intensity), that takes the kind of chemicals (reagents, aqueous or organic) into account. All concepts reflect the beneficial effects of e.g. recycling, and all concepts are useful in guiding the direction of route development and in monitoring the progress of the chemical development towards higher efficiency. Life cycle assessment (LCA) represents a more general concept, which identifies the material, energy and waste flows associated with a process to determine environmental impacts and potential improvements. One of the applied methods (IPCC GWP 100a) was developed by the UN Intergovernmental Panel on Climate Change (IPCC) and is analyzing the global warming potential expressed as kg CO<sub>2</sub> equivalents (5). Thus the sustainability of two manufacturing processes is compared based on a life cycle assessment.

In the following we shall elucidate our approach and highlight some results:

## ROUTE SELECTION AND CHEMISTRY

In preclinical or early clinical phases the chemical route leading to the active ingredient can still be changed. Here a thorough analysis of opportunities using catalytic or biocatalytic methods helps to pave the way for an efficient large-scale synthesis. An increasing number of manufacturers of pharmaceuticals therefore ask for support in identifying sustainable lower cost manufacturing routes that bring an additional benefit in terms of blocking IP. At DSM we therefore recently launched our InnoSyn™ services that address the increasing demand for identification and development of sustainable manufacturing routes based on a flexible business model and dedicated interdisciplinary teams of experts in biocatalysis, organic synthesis, homogeneous catalysis and continuous chemistry using microreactors. This integration of expertises leads to unbiased choices and better manufacturing processes as exemplified in the below examples.

### EXAMPLE: FROM A 7 TO A 3 STEP SYNTHESIS BY COMBINING BIO- AND COPPER CATALYSIS

Heterocyclic amino acids are important building blocks for pharmaceuticals. One specific example is (S)-2,3-dihydro-1H-indole-2-carboxylic acid which is used as a key intermediate for various drugs (6). Until now the intermediate was produced at ton scale using a seven step process based on a Fischer indole synthesis followed by classical resolution as shown in Figure 1. This process was developed during the supply of clinical trial material for a specific drug. Over the life time of this drug, cost

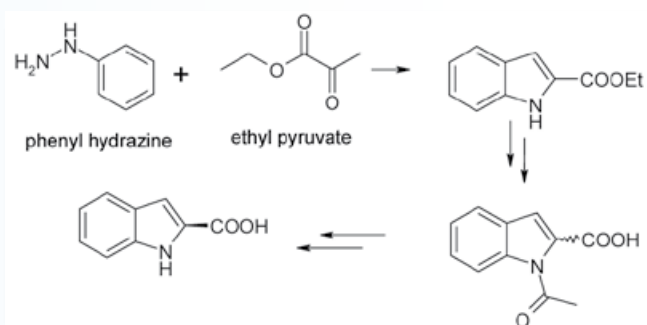


Figure 1. Process for the production of (S)-2,3-dihydro-1H-indole-2-carboxylic acid.

reduction as well as additional IP barriers became more important to our customer to secure a strong market position beyond patent expiry.

Within the DSM InnoSyn team a route scouting was therefore executed that identified a manufacturing route which can deliver the desired product in a three step synthesis from a cheap starting material as shown in Figure 2.

The challenge of this route is a) to have access to an enzyme with appropriate properties translating into appropriate cost and product quality and b) to be able to efficiently perform the C-N bond formation at high yield w/o the need for further intermediate isolation. Looking at the challenges it is obvious that the combined enzymatic as well as metal catalysis expertise is required to address various challenges. The enzymatic step might look trivial without looking for example at equilibrium positions.

These dictate that the reaction needs to be performed at >10 percent NH<sub>3</sub> and pH >10 which are quite extreme for enzymes that usually unfold/precipitate under such conditions. Indeed using standard phenylalanine ammonia lyases the enzymes not only rapidly lose activity but are also extremely inhibited by the substrate as shown in Figure 3 for the phenylalanine ammonia lyase (PAL) from *R.glutinis*.

One approach to address this limitation would be to improve the enzyme features via enzyme engineering which is an approach applied for several of our enzymatic processes which are, for example, based on designed pharmaPLEs®, hydroxynitrilases, PenG-acylases, dehydrogenases or aldolases. In the case for the desired phenylalanine lyase we turned to our network of enzyme suppliers and identified together with Verenium (former Diversa) a suitable enzyme. Cloning of this enzyme in one of our proprietary pluGbug® expression organisms and using a cheap but robust enzyme formulation yielded a robust and efficient enzymatic step which provided the product at >90 percent yield at >95% ee.

Next was the development of the ring closure of the ortho-halogenated phenylalanine (Figure 4).

*N*-arylation reactions have been typically known as the Ullmann reaction (or condensation) using stoichiometric amounts of copper. In the last decade these have been replaced by palladium-phosphine catalysts or copper catalysis. Thanks to its cost effectiveness we relied on copper catalysis for this ring closure (7), also stimulated by literature reports where amino acids were used to accelerate *N*-arylation procedures (8).

A range of experiments were performed in order to optimize the ring closure process. Most critical requirements to this extent are:

1. no solvent switch after the enzymatic reaction (ring closure should be performed in (the presence of) water).
2. high yield of the desired compound.
3. no racemisation of the stereogenic centre.

Initial experiments using the 2-bromophenylalanine revealed already a very high yielding ring closure in water, using only 0.01 mol% of CuCl as catalyst copper (T = 95°C) and fortunately no racemisation (while control experiments in NMP revealed a decrease in e.e.).

The more cost effective 2-chlorophenylalanine gives 78 percent yield of ring closed product at full conversion using 4 mol% of copper chloride. Careful examination revealed the formation of a dimeric compound – an unprecedented

*intermolecular N*-arylation of the product with the 2-chlorophenylalanine – which could be suppressed by the addition of 1,2-functionalised bases. Again no racemization took place using these conditions.

Removal of traces of copper and other impurities by pH switches, filtration and crystallization techniques delivered the (S)-2,3-dihydro-1H-indole-2-carboxylic acid as white solid.

A comparison of the old and new process was done based on a life cycle assessment (LCA) which identifies the material, energy and waste flows associated with both processes to determine environmental impacts and potential improvements. One of the applied methods (IPCC GWP 100a) was developed by the UN Intergovernmental Panel on Climate Change (IPCC) and is analyzing the global warming potential expressed as kg CO<sub>2</sub> equivalents. The result of this analysis is shown in Figure 5 which shows that the targeted and realized cost advantage goes in hand with a significant improvement of the environmental impact of the recently introduced process.

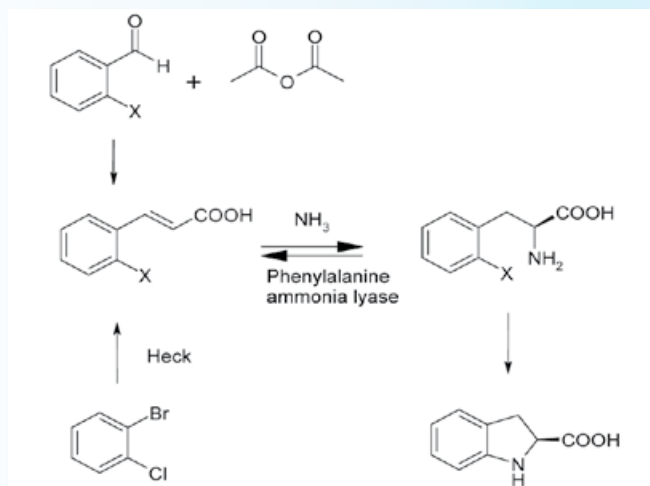


Figure 2. New 3-step chemo-enzymatic route for production of (S)-2,3-dihydro-1H-indole-2-carboxylic acid.

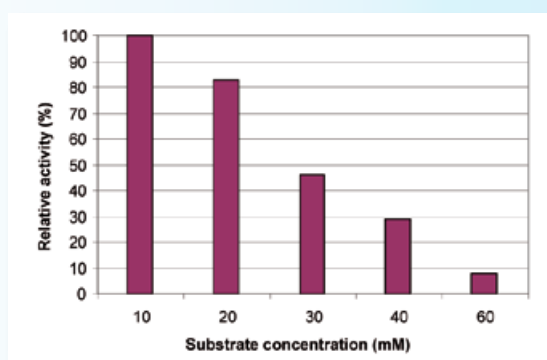


Figure 3. Strongly reduced enzyme activity at increasing substrate concentration of PAL from *R. glutinis*.

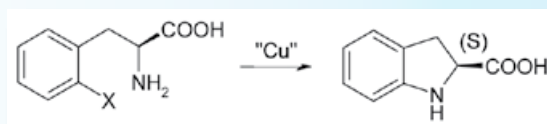


Figure 4. Copper-catalyzed ring closure reaction – in water.

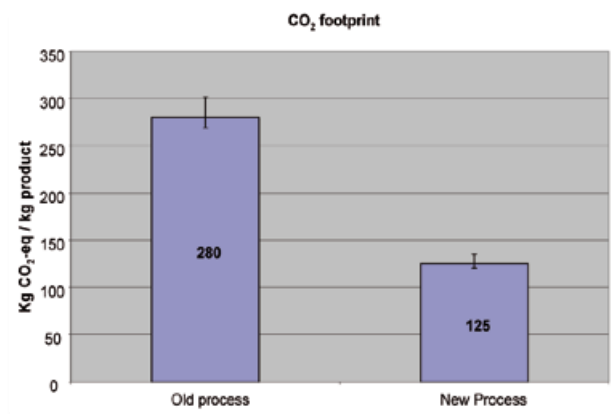


Figure 5. LCA of the old and new process for production of (S)-2,3-dihydro-1H-indole-2-carboxylic acid using the IPCC GWP 100a method.

## PROCESS TECHNOLOGY

Even if the starting materials and reagents entering the synthesis of an active pharmaceutical ingredient are fixed, there is still a possibility to improve on the efficiency of this synthesis while still meeting all quality requirements. Forward-looking filing of a manufacturing method with the authorities gives room for continuous improvement of a given synthesis without changing the chemistry.

**EXAMPLE: NITRATE ESTER FORMATION:  
A MESS OR A HIGHLY ATTRACTIVE STEP?**

Nitrations and nitrate ester formations are widespread in organic synthesis. Nitro groups are either part of the structure of an API or are used as versatile functional groups transformed in subsequent steps of a synthesis. Every large scale production of such a compound has to account for the highly reactive nitrating agent – usually nitric acid or a mixture of nitric and sulfuric acid, the energy content of the product, and for the waste created by such a process. Conventional nitrate ester syntheses focus on solving the safety issues related to nitrations: The heat of reaction, even more so the heat of a potential decomposition, are diluted by diluting the reaction mixture; the danger of spontaneous decomposition is reduced by lowering the reaction temperature and by careful removal of potential autocatalysts of decomposition, e.g. nitrous oxides.

In our case the nitrate ester formation had to proceed selectively: of 2 identical hydroxy groups only one should be nitrated. The problem is solved by extracting the mono-nitrated product once it is formed into an organic solvent to inhibit further nitration or even decomposition. Figure 6 depicts the reaction scheme. Any apparatus capable of handling this reaction has to simultaneously mix the reagents remove the reaction heat and extract the product. No doubt, one can do such a nitration in a safe way in a conventional vessel – but there is a high price to pay: usually such a process has a low space-time yield translating into high installation costs, and it produces a lot of waste. So, during process development we investigated options to improve on the safety and the sustainability of this process by running it in a continuous plant. Recently we have described how to take this nitration process into a continuously operated pilot installation (9) and subsequently into a full scale plant (10). Next to the improved safety performance, we could also considerably reduce the "E-value" of the process.

Figure 7 describes the change in the E factor of the nitration step as we developed the process from batch-wise to continuous operation and further optimized the continuous process.

## CONCLUSION

Green chemistry is on the agenda of all chemical and pharmaceutical companies. The observed high E-factors of current processes in the fine chemicals industry still indicate significant room for improvement. The required improvements will have to come from the application of advanced synthesis methods. Combinations of Biocatalysis, homogeneous catalysis and state-of-the-art process technology have been proven on large scale and for many different reactions. Biocatalysis exerts a strong positive impact on sustainability which goes hand in hand with significant cost savings. Route scouting capabilities are crucial to identify opportunities and take advantage of the potential that the combination of bio- and chemocatalysis with process technology offers. The examples discussed above demonstrate that we are well on our way to implement an increasing number of sustainable first and second generation processes. In the future, we will therefore see shorter and greener routes for production of pharmaceuticals and their intermediates based on these technologies.

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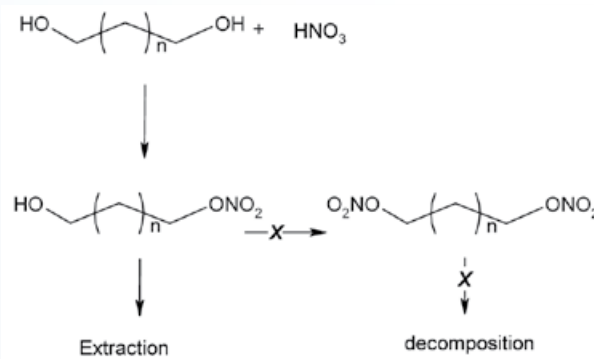


Figure 6. Selective nitration of a diol.

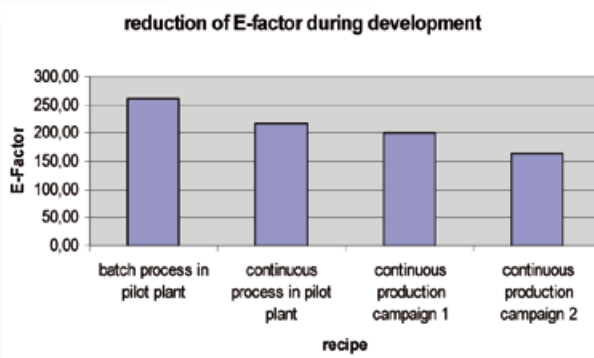


Figure 7. Reduction in E factor in the course of process development.