Alan Steven

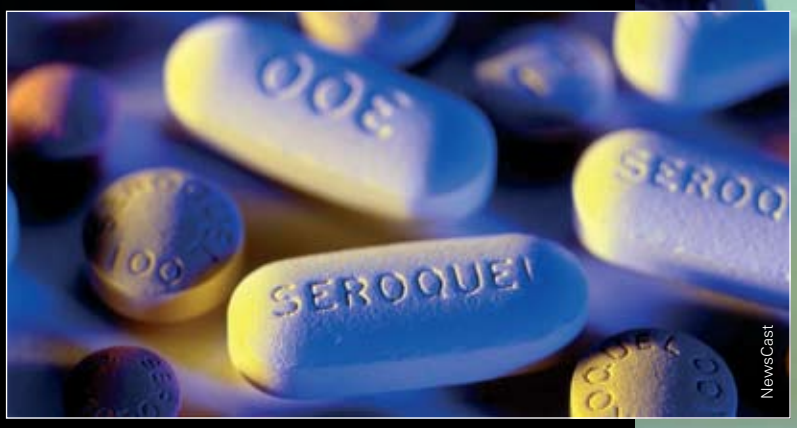
Process Chemistry

Process chemists work within the pharmaceutical industry and are a link in the chain from an initial idea to a new drug making it to the market. It generally takes at least 10 years from an idea by a medicinal chemist to a new treatment for patients – during this time, the process chemist devises the best possible method for producing the drug in large quantities. In this article, Alan Steven describes the role that the process chemist plays.

Drugs are normally compounds with the ability to promote a response from our bodies that reduces the level levels of harmful foreign bodies (such as bacteria, fungi or viruses), or re-establishes the equilibrium of a process that has previously been disturbed or is out of control.

A compound that may eventually become a drug will first be made by a medicinal chemist with some knowledge and understanding of how the compound affects the function of its target in the body, how it is likely to distribute itself in the body, and whether the body may turn it into a more toxic substance. The medicinal chemist will have modified the structure of the compound several times, improving its good characteristics and minimising the bad points such as toxicity.

Only milligram quantities of the compound will have been made thus far, however,at this stage and the assessment of its potential has only just begun. The vast majority of such compounds will ultimately not turn out to be suitable as drugs, and so they are onlycalled drug candidates at this stage.



When a patient takes a tablet, he or she is receiving a dose of a drug – the compound with the desired therapeutic effect. The tablet consists of the drug substance mixed in with other, inert (unreactive) compounds such as cellulose.

A chemist working in AstraZeneca'a research and development labs at Charnwood, Leicestershire.

Key words
drug
synthesis
toxicity

Samples from AstraZeneca's Culture Collection Bank of freeze-dried micro-organisms from around the world.

NewsCast

The process chemist

Toxicology is the study of the adverse (negative) effects of chemicals on living organisms.

It is the process chemist who must supply much larger quantities of the most promising compounds made by the medicinal chemist for the study of short- and long-term **toxicological** effects, the transformation of the actual drug substance into a tablet by pharmaceutical chemists, and, ultimately, its testing with patients in clinical trials. As a compound progresses through this phase, increasing amounts are required for these key studies, which can be delayed if there is a problem in making the compound. Someone is often waiting for more of the drug candidate, so process chemists often have little time to develop an ideal synthesis. The best route which is currently available may be fine-tuned, whilst, in the background, work on a completely new route which allows the drug candidate to be synthesised with even greater efficiency in the future may be carried out.

Synthesis is the making of compounds.

There is usually a lot of scope for improving the **synthesis** of the drug candidate. This is because medicinal chemists are less interested in the efficiency of the synthesis but need to produce large numbers of compounds for biological testing quickly. A medicinal chemist will usually choose his/her reaction conditions so as to achieve a high percentage yield, which is a measure of the efficiency of converting a starting material into a product, whilst a process chemist considers the efficiency of a reaction from a much wider perspective. For example, process chemists try to use cheap, readily available starting materials, environmentally-friendly reagents that can be disposed of cheaply, and reaction temperatures that do not require excessive amounts of energy.

A route that has been improved by the process chemist on the laboratory scale also has to be developed into a series of processes that are suitable for manufacturing the compound on a multi-kilogram scale. When a process chemist is trying to join a series of isolated reactions together into a scalable process the following questions may be asked:

- Must the product be isolated, or can it be reacted on without having to change the solvent from the preceding reaction?
- How are any byproducts from the preceding reaction going to react in the present reaction?

A developed process will use the minimum number of different operations to form the maximum number of bonds in the reaction vessel in the shortest amount of time and for the lowest cost per kilogram of drug candidate.

Bath-tub-scale chemistry

Processes should also be robust, safe, simple and reproducible. Robustness is built into the reactions by identifying all factors (e.g. temperature, stoichiometry, reaction time) that may change the outcome and establishing the values of these factors that can be tolerated before the reaction starts to misbehave or change in some way. A developed process will also be as simple as possible: ideally, its reactions can be performed by an operator in the equivalent of a bath tub with the pure product crystallising out of the reaction and later being collected by filtration. The reactions should also be reproducible – it is more important that we get the product in the same yield and with the same quality, than for the yield to fluctuate between being very high and very low. Our reactions are designed with a view to scaling them up so they can be performed in a 6000 litre vessel (or even bigger). If something goes wrong on that scale, you need an awfully big spatula to scrape the vessel out!

Process chemists are synthesising drug candidates that we all hope will ultimately improve a sick person's health when ingested. We therefore need to be able to prove exactly what a participant in a clinical trial is putting in his/her mouth to ensure the reverse is not the case due to contamination with toxic impurities. This is done by manufacturing the drug using certain good manufacturing practices that are based on good science and ethics. They include questioning where the starting materials for a reaction have come from, proving that your reaction will not be contaminated by any materials left over from the previous reaction run in your reaction vessel and establishing that your product is really what you think it is.

Fine-tuning a reaction

In order to be able to produce as pure a drug substance as possible, and to control its purity, the process chemist needs to understand the chemical reactions used, as well as any side reactions that are taking place to form impurities. Impurities that can not be detected when the reaction is performed on a small scale in the laboratory soon become an issue when a reaction is scaled up, even if they are formed in the same percentage yield as on a small scale. To get this understanding about our reactions, we need to study how fast the reaction is taking place (the kinetics) as well as how the starting material is converted into product in terms of making and breaking bonds (the mechanism). Often this understanding allows us to tune the reaction conditions so that a reaction is steered along just one of many possible paths. Let us say an unknown impurity has appeared in the drug substance during development. The process chemist will have to isolate the impurity, determine its structure using a variety of techniques (often with help from analytical colleagues), propose a mechanism for its formation, and change the reaction conditions accordingly in order to minimise its formation.

The role of the process chemist is truly one of the most rewarding in drug discovery and development. The odds of discovering a marketable drug within one's life as a medicinal chemist are very small. A chemist working in process research and development, by contrast, gets to work on more advanced projects, and so has a real chance of developing a synthesis for a drug that may ultimately save people's lives when it reaches the marketplace.

Alan Stevens is a process chemist working for the pharmaceutical company AstraZeneca.

Process chemists working in AstraZeneca's labs in Boston, USA.

Look here!

http://www.sep.org.uk/catalyst/articles/catalyst_17_1_293.pdf
An article from a previous issue of CATALYST about testing new medicines
www.abpi-careers.org.uk for more information about working in the pharmaceutical industry and the different roles which are available
http://tinyurl.com/2mkx5e
This web page allows you to access a publication from the Wellcome Trust about how drugs are developed.