

Innovative process technology speeds up drug manufacture

A quicker way of making active substances

A revolution is about to happen in the pharmaceutical industry: in the foreseeable future it might be possible to make active substances not just in small batches, as has been the case up till now, but in continuous processes, like food. This could speed up the development of new active substances and make the manufacturing process more efficient. Bayer's research scientists are currently trialing this method on a substance that looks very promising for cancer treatment.

A hidden, deadly danger: organ or tissue cells divide in an uncontrolled manner and a tumor develops. In the worst case it is malignant, and the person is diagnosed with cancer. But the prospects look promising that doctors may get a better grip on the disease in the future. Here, it is not only the search for new, effective and well-tolerated drugs that plays an important role, but also the way the drug compounds are made. This is something Bayer's research scientists and engineers have been concentrating on because if the route from a promising potential active substance to actual treatment can be shortened, patients stand a better chance of rapid treatment.

It is the route now being followed by a substance provisionally named BAY 86-9766. Developed to combat cancer, it is currently undergoing clinical trials. Five steps are needed to synthesize BAY 86-9766. Each of these normally has its own manufacturing procedure defining how the raw materials and intermediate products react with each other.

Efficient drug manufacture: like a chemical assembly line

This means that the chemicals have to be crystallized, dried, analyzed and placed into interim storage four times. Only once the fifth step has been completed is the finished product ready.

Specialists refer to this process as batch production because the substances are produced in separate batches.

To date, this is the conventional way of making pharmaceutical products. But "batch production has its downside too. For example, it can be labor-intensive and demanding in terms of logistics, because the various batches and intermediate products need to be analyzed and placed in interim storage separately. This can be very time-consuming and expensive," explains Dr. Agathe Christine Mayer, a chemist and project manager at Bayer Technology Services. Many industries are now using continuous processing as one of their manufacturing techniques. The petroleum, plastics



Highly automated: in future, new drugs will be manufactured not in individual steps but continuously. Tobias Grömping (photo, right) checks the settings on a modular production container in the new INVITE research center before the production chain begins. Ahead of scale-up, Dr. Sigurd Buchholz and Dr. Christian Severins (photo, left, left to right) test the process in a small continuous active substance production plant.



and food industries mainly use highly automated plants. Raw materials go in at one end and the finished product comes out at the other – like a chemical assembly line. Experience shows that continuous processing can have many advantages. "The plants are often compact and thus occupy less space, while a high level of automation reduces the need for labor. Ideally, production capacity could adjust flexibly to demand and production times could be shortened," continues Mayer.

Entirely new technologies are vital to improving manufacturing processes in terms of sustainability and ratio-

nal use of resources. In Europe, the chemicals industry is closely involved in this approach, for example via the new INVITE research center. Experts are already discussing a paradigm shift in the way that drugs are made. "The supervisory and regulatory authorities have recently started promoting the use of continuous processes in pharmaceuticals production so that technological progress and, consequently, new drugs can reach the patient more quickly," says Dr. Gerhard Braun, Head of Process Research and Development in Chemical Development at Bayer HealthCare in Wuppertal.

An interdisciplinary team made up of chemists and engineers is now systematically applying this new technology to BAY 86-9766. "The development drug belongs to an innovative active substance class which we hope will be very effective in the fight against cancer," says Braun. Bayer believes it may have great potential to treat a wide range of cancers. It inhibits specific enzymes that are critical to the multiplication of cancer cells. BAY 86-9766 has shown promising results in clinical studies to date, and so there are real hopes that it could be ready for market launch in a few years' time.

The chemical factory of the future

History is being made in a dark green, two-story building at the Leverkusen Chempark site. It is here that the chemical production plant of the future has been operating since September 2011, when it was installed in the new INVITE (INnovation, Vlsion, TEchnology) research center, a facility in which industrial companies and academic partners are working together to develop new process technologies. The research center company is a joint venture between Bayer Technology Services GmbH and TU Dortmund University and is being supported by the regional government of North Rhine Westphalia with grants from a national economic stimulus package. One of the first projects, which makes use of INVITE's development and demonstration infrastructure, is the F3 Factory (Flexible, Fast and Future Factory). 25 organizations are working in partnership on this EU project, which aims to make chemical manufacturing more flexible. Seven leading European chemical companies are taking part in the project, which is coordinated by Bayer Technology Services. The partners hope to combine the advantages of large, optimized plants with those of smaller, more flexible plants. The idea is that, in the future, chemical factories will be built according to a modular principle. Stan-

dardized equipment modules will be assembled in containers, which in turn will be linked together to form a complete plant. INVITE is an open innovation platform for close cooperation between partners from industry and research.



Factory designers at work: in the newly opened INVITE research center, Dr. Günter Bachlechner, Head of Technology Development at Bayer Technology Services, and INVITE Managing Director Dr. Thomas Bieringer (left to right) inspect the new approach to pharmaceutical production. In future, equipment units will be assembled on a modular principle.



Technology under control: Bayer employees Ulrich Bauer and Carsten Flick (left to right) inspect one of the production units where products such as active substances for new cancer drugs will be manufactured. The work by Bayer HealthCare's experts on continuous production is a pioneering achievement.

"The five-stage process of synthesizing BAY 86-9766 is typical of the complexity of pharmaceutical substances and the associated challenges in terms of process technology," explains Dr. Sigurd Buchholz, Head of the Flow-Chemistry Competence Center at Bayer Technology Services, who together with Braun is coordinating the work relating to the continuous production of BAY 86-9766. The anti-cancer substance was selected to trial the new manufacturing method for precisely this reason. Mayer and her colleagues are currently transferring the synthesis to a continuous process. The team working on this project includes experts from Bayer HealthCare's Chemical Development department, Bayer Technology Services, and substance production specialists from the Supply Center in Wuppertal-Elberfeld.

Innovative cancer drug selected for pilot plant

"We must make sure that our design can be integrated into the current method of production and that it can reliably make enough products of the required quality at competitive costs. This is a crucial and technically demanding step in addition to all the other tasks," says Dr. Jürgen Wieschmeyer, Head of Substance Produc-

tion Operations at Bayer HealthCare in Wuppertal. Bayer's scientists are developing a conventional batch process alongside the continuous process, which will enable them to compare both methods directly and resolve any shortcomings even quicker in the future.

In the continuous plant, chemical processes take place in microreactors, block-shaped metal devices only a few cubic centimeters in volume. "You have to think of the manufacturing process as a long stream: the reagents keep flowing onwards, reacting with new substances that are fed in at certain points. By-products are removed continuously. There is never a specific intermediate product that you can hold in your hand," says Dr. Christian Severins, whose laboratory at Bayer Technology Services is being used to test the plant. If the manufacturing process is stable at laboratory scale, the process engineers will transfer it to production scale.

Bayer's research scientists are currently building a demonstration plant for the first steps of synthesis, which will produce a few kilograms per hour. "That is about the scale we would need for production later on," says Dr. Lars Frye of Bayer Technology Services, who is in charge of building the demonstration plant. This shift to

Interview



"Safety must be guaranteed"

Dr. Susanne Keitel is a pharmaceutical specialist and Director of the European Directorate for the Quality of Medicines and HealthCare (EDQM) in Strasbourg. This body, which is part of the Council of Europe, is responsible for establishing quality standards for medicines.

Why is it so difficult for the pharmaceutical industry to switch to continuous processes?

The demand for many currently authorized drugs is probably not large enough to justify the switch in economic terms. This is also due to the regulatory requirements that must be met if significant changes are made. In contrast, the food industry applies well-established procedures, for example, to test product quality during manufacture. So far the pharmaceutical industry has been rather hesitant.

What can be done to ensure that the quality of drugs is not impaired by the switch?

The requirement here is that suitable control and monitoring methods are devised and implemented for each product and process.

What are the benefits for patients?

Continuous production can cut manufacturing costs. If these cost reductions are passed on to the public health system, statutory health insurance funds and patients could save money, and this would further improve access to drugs.

The FDA in the United States is supporting the use of continuous processes in drugs manufacture. What is the attitude of European authorities?

In principle, the European authorities are open to innovative approaches to the development and production of drugs. However, another aspect which they have traditionally regarded as a priority is well-founded pharmaceutical development in which the key product and process parameters are identified and described in the marketing authorization dossier. This is the foundation for a thorough understanding of the process, which makes the development of continuous manufacturing processes easier.

Disposable fermenters accelerate the development of new biologic drugs

Medicine in a bag



Oscillating, disposable bioreactor: Dr. Uwe Langer from Biotechnology Development at Bayer HealthCare, developer Jörg Kauling, and Annette Waldhelm from Bayer Technology Services (left to right) check the product quality.

Biologics – drugs manufactured by means of biotechnological processes – are increasingly important in the fight against cancer. Examples include antibodies and other proteins produced by animal cells that have been genetically programmed for this purpose. Used as drugs in the human body, their specificity allows them to primarily attach to cancer cell structures. Once they have reached their destination, they may either destroy the cells directly or release an anti-cancer toxin.

"Finding a suitable candidate protein is a laborious process," comments Dr. Hans-Dietrich Hörlein, Head of Biotechnological Development at Bayer HealthCare in Wuppertal. Millions of different protein substances have to be tested – and, of course, manufactured before they can be tested. For decades this has been done in vessels made of stainless steel. But the old metal favorite now has a rival. Scientists working for Bayer HealthCare and Bayer Technology Services have joined forces to develop a new type of fermenter: BayShake™, a box-shaped, transparent pouch made from fiber-reinforced plastic. The main advantage of the pouch is that once production is complete it is simply replaced by a new one, saving time and money. "Steel fer-

menters have to be cleaned thoroughly each time, and the risk of residues contaminating the next production batch can never be completely ruled out," explains Dr. Berthold Bödeker, one of Dr. Hörlein's colleagues. One important aspect in the production of biologic drugs is continuous and thorough mixing of the cells. "This is why our pouches rest on powered rotating plates," explains Jörg Kauling of Bayer Technology Services. The efficiency of the mixing process is demonstrated when he adds a dye to the water. It takes just a few seconds for it to be evenly distributed.

Dr. Clive Wood, Head of Global Biologics at Bayer HealthCare, is convinced: "BayShake is the future. If we can test more candidate proteins in a shorter time, we stand a better chance of further success in the fight against diseases that have until now been very difficult or impossible to cure." Bayer has invested around EUR 35 million in a new technical center in Wuppertal to further improve the conditions for developing biologic drugs. The new building, over 20 meters high and with several thousand square meters of floor space on five stories, is scheduled to open in 2013. Then the BayShake™ fermenters will be able to show a new audience what they can do.



The heart of the new process: one approach for transferring production to a continuous procedure involves the use of microreactors, where the substance can react much faster and more efficiently (photo, left). Dr. Agathe Christine Mayer and Dr. Gerhard Braun (photo, right, left to right) first developed the production method in their automated parallel reactors in the laboratory. The process is now being transferred to a demonstration plant for active ingredient production.

larger equipment and volumes is called scale-up. "In batch processing this can be complicated. For example, in large containers the surface to volume ratio is lower, and it becomes increasingly difficult to remove the heat of reaction," explains Severins. This can dramatically increase reaction times. A small round-bottom flask can be cooled and the reaction completed within a few minutes, but in the larger reaction vessels of a conventional production line this can take several hours. In the worst-case scenario, the product has already decomposed by this time.

Innovative technology requires interdisciplinary teamwork

It is precisely for this reason that continuous processing offers great advantages. The reactors are not too large, and it is easier to remove the heat of reaction. It has been possible to use new options in the scaled-up plant as well. Several identical continuous reactors are being assembled and will run in parallel. Under the current plan, all the equipment for the BAY 86-9766 pilot plant will fit into two standard containers measuring six meters by just under two meters forty centimeters. They will be placed in the new techni-

cal facility at the INVITE research center (see box text, page 74). "If this were a batch plant, the reaction vessel alone would completely fill the container," comments Frye. Size is not a problem when it comes to the continuous plant: the heat exchangers have a volume of three liters, and a process-intensive micromixer is used for mixing.

Bayer's development scientists are facing great challenges as they are breaking new ground. Continuous processes must be monitored online, using various spectroscopic methods such as Raman, infrared and especially near-infrared spectroscopy. These techniques make it possible to measure the concentrations of the substances present without touching them. Probes in the product flow stream are the measuring points. "This allows us to monitor the progress of the reaction," says Dr. Kai Lovis, in whose laboratory the spectroscopic measurements are carried out.

Another challenge is to achieve stable continuous plant operation for weeks or months without cleaning. Some reactions produce solids that form deposits in a plant and eventually block valves or pipes. Bayer's scientists are finding answers to these challenges. "In shifting from batch to continuous processing, we are benefiting

from many ideas suggested by apparatus engineering and process management specialists. We are learning new things every day," says Buchholz.

Continuous production: new reaction paths are possible

Because it is often easier to control process parameters in continuous plants, entirely new reaction paths may now open up that in the past were inaccessible to batch production on financial and safety grounds. Thanks to the close cooperation between specialists from all parts of the Bayer world, the project team is confident that it will succeed in making continuous processes an established route in the pharmaceutical industry as well. "It's a completely new type of process development – challenging but with amazing opportunities," explains project leader Mayer.

 www.research.bayer.com/drug-manufacture
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