

Active ingredients with great potential

They are the "high potentials" of the medical world. Highly potent active ingredients are substances that take full effect even in extremely small doses. Special safety measures are therefore required for their manufacture. Using advanced technologies, Bayer researchers in Chemical Development have made their production areas safer and significantly more efficient – from synthesis in the laboratory through to multi-kilogram production.



The purity law: Adam Mikolasch uses a continuous tube system that transports the highly potent active ingredient through a dust-free and hermetically sealed environment to final packaging.

Highly potent active ingredients (HPAI) are highly effective and often highly selective substances that have been developed to treat life-threatening diseases. The therapeutic doses of such active ingredients are often only one-hundredth of the dosage of conventional headache pills. "Improved optimization processes

and state-of-the-art screening technologies enable us today to find and develop drug candidates that are significantly more effective and selective and thus take effect already at a low dose," explains Dr. Timo Flessner, Head of Chemical Development at Bayer HealthCare in Wuppertal. Medical researchers are therefore increas-

ingly turning their attention to HPAs for cancer treatments but also some cardiovascular drugs, and this segment of the drug market is growing continuously. "Highly potent active substances make up an increasing share of the chemical compounds in Bayer's pharmaceuticals pipeline today," says Flessner. A special

technical infrastructure is however mandatory for the manufacture and handling of HPAs. "It is precisely because they are so highly potent that we were forced to adapt our production technologies," adds Mathias Berwe, Head of HPAI Production at Bayer HealthCare in Wuppertal. The reason is that even micro amounts in the air can negatively impact the health of employees handling these substances on a daily basis. "We have to be particularly diligent about protecting our team against these highly potent active substances throughout all production and handling steps," adds Dr. Ralf Wischnat, Head of Scale-Up & Processing in Chemical Development at Bayer HealthCare.

One milestone in the series of associated investments is the HPAI technical lab in Wuppertal. It encompasses both laboratories that produce only a few grams of the active ingredients, and facilities for producing several kilograms. "The new equipment enables us to handle the active ingredients in a closed system.

Production challenges: HPAs need special safety measures

That reduces contamination to a minimum, which in turn significantly shortens the cleaning times in the technical laboratories," says Wischnat. "And especially in the early phase of development, any time we can save is valuable."

Strict industrial hygiene standards are applied right from the start of development of any chemical process. "Just one milligram of a highly potent active ingredient can contaminate 1,000 cubic meters of air," reports Berwe. The HPAs are therefore produced inside a glove box. In this hermetically sealed space, employees use integrated gloves to manipulate the substances. The pressure inside is below the room pressure, meaning that even the minutest particles cannot escape.

"If fairly large quantities of an active substance are required, we switch over to a pilot plant. Here, we manufacture product by the kilogram based on advanced production processes and ensure substance supply all the way through to drug approval," explains Wischnat. Bayer specialists from Research, Development and Production work together closely on such



Emergency preparedness: Mathias Berwe and Dr. Ralf Wischnat (top photo, left to right) inspect the plant at the technical lab in Wuppertal prior to manufacturing a new active ingredient. Wearing a protective suit with respirator, Adam Mikolasch (photo below) makes preparations to take a sample.

projects: combined with Process Engineering colleagues, the chemical process development experts scale up the synthesis process, making sure that they find the optimum input quantities and conditions such as pressure, temperature and reaction time. The inputs are fed in a dust-free and hermetically sealed environment to the plant, where chemical conversion and processing take place. The wet, target product ends up in a drier, which converts it into a crystalline powder. "After a drug is approved, we then transfer the process to the final production plant with the help of our colleagues at Product Supply," says Wischnat.

Active ingredient production in a hermetic system

To remove the pure drug substance safely, a continuous tube system is used which

was developed in partnership with an external company. It transports the active ingredient directly into the final packaging unit without any contamination whatsoever. "The investment now allows us to support all steps of the process, from laboratory processing to market introduction of the HPAs. For certain active ingredients we also use Chemical Development's pilot plant to ensure a long-term supply of products for the market," summarizes Flessner.

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