



**From Molecules**   
*to Medicine*



# **A journey** *through the research and development of new drugs*

Thousands of people in Bayer's research and development around the globe are dedicated to finding innovative active ingredients for prescription medicines. We focus on therapeutic areas with a high unmet medical need, areas that require further innovation despite the progress that has been made – as for example in cancer therapy.

## **Extensive research for the benefit of the patient**

It takes about 12 to 15 years to develop a new drug. Pharmaceutical companies today invest an average of more than two billion euros from the discovery of a new active ingredient until the product is ready for the market, including the cost of the many potential medicines that do not make it through the drug development process. Highly qualified scientists from a variety of disciplines work on filtering out a suitable active ingredient from an enormous number of compounds. Tens of thousands of compounds are rigorously studied in numerous laboratory tests and the best ones further optimized.

The optimum drug candidate, who meets all criteria necessary regarding efficacy, safety and developability, is finally selected to be tested in humans. In clinical development, only one out of ten drug candidates are then successful and submitted for approval to the regulatory authorities. If a drug is finally approved, this is a great success. A new drug therapy is now available for many patients.

With this brochure, we cordially invite you to join us on a tour through our research and development departments to gain an insight into the work of our scientists. In ten chapters you can follow a new drug as it develops from a molecule to a medicine.



**Dr. Joerg Moeller**

Head of Pharmaceuticals  
Research & Development  
Bayer AG

## **Medicines help**

*save lives, overcome diseases, and  
improve patients' quality of life. Bayer  
invests considerable resources in the  
research and development of new drugs.*





## Finding the right *approach*



*Scientists need to have very precise knowledge of the biochemical processes that take place in the body and how these are changed by a disease.*

## Target Discovery

The development of every drug begins with the search for a target on which the drug can act. The scientists focus their attention on the signaling pathways of cells which control all the body's major functions. Understanding these biochemical processes in the body can yield valuable clues as to how a disease can be combated. This is because the signaling cascades involve proteins that can be potential sites of action for drugs.

These target sites are usually receptors – cellular binding sites for hormones and other messengers – or enzymes, which are responsible for the chemical transformation of substances in the body. Drugs either switch these proteins off or enhance their function. However, only few protein molecules are suitable as targets for drugs. It is a difficult and complex task to detect them among the countless proteins that are produced by the body.

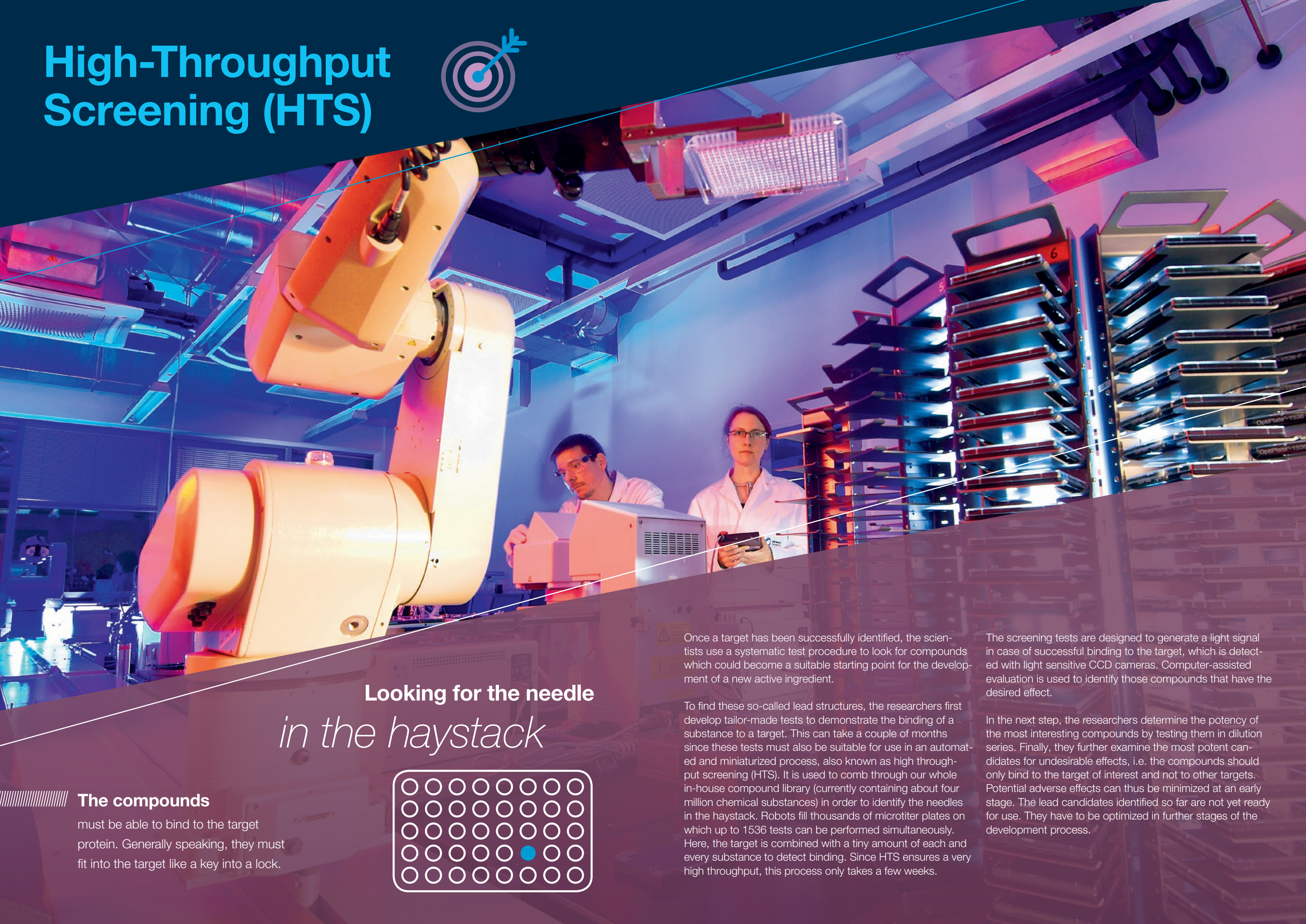
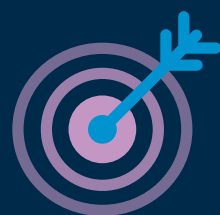
Proteins that might be playing a significant role in the course of a disease can be identified by expression profiling that detects changes in messenger RNA (mRNA) implicating their role in the disease. The scientists use RNA interference to establish whether these proteins are suitable as drug targets.

This method makes it possible to switch off individual genes by the targeted degradation of their mRNA. As mRNAs code for proteins, any target protein can be switched off in this way. If the disease-specific process at the cellular level subsequently changes, this suggests that the blocked protein might be a suitable drug target. Careful work is very important at this stage of the research process, since the quality of a target is key to the success of the subsequent work steps.





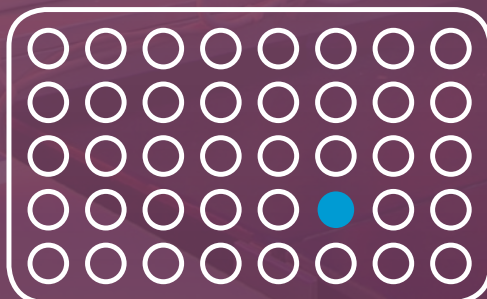
# High-Throughput Screening (HTS)



## Looking for the needle *in the haystack*

### The compounds

must be able to bind to the target protein. Generally speaking, they must fit into the target like a key into a lock.



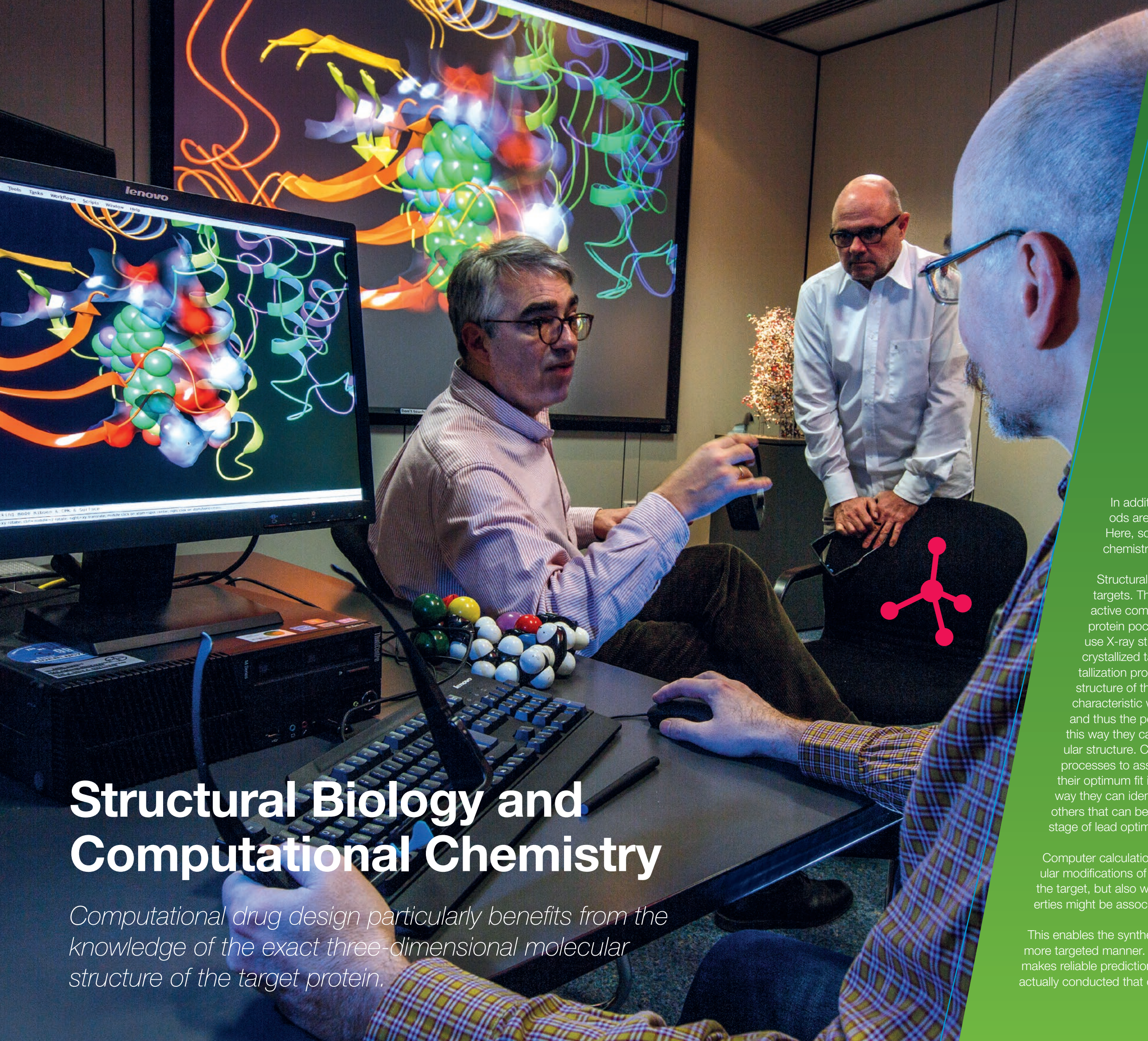
Once a target has been successfully identified, the scientists use a systematic test procedure to look for compounds which could become a suitable starting point for the development of a new active ingredient.

To find these so-called lead structures, the researchers first develop tailor-made tests to demonstrate the binding of a substance to a target. This can take a couple of months since these tests must also be suitable for use in an automated and miniaturized process, also known as high throughput screening (HTS). It is used to comb through our whole in-house compound library (currently containing about four million chemical substances) in order to identify the needles in the haystack. Robots fill thousands of microtiter plates on which up to 1536 tests can be performed simultaneously. Here, the target is combined with a tiny amount of each and every substance to detect binding. Since HTS ensures a very high throughput, this process only takes a few weeks.

The screening tests are designed to generate a light signal in case of successful binding to the target, which is detected with light sensitive CCD cameras. Computer-assisted evaluation is used to identify those compounds that have the desired effect.

In the next step, the researchers determine the potency of the most interesting compounds by testing them in dilution series. Finally, they further examine the most potent candidates for undesirable effects, i.e. the compounds should only bind to the target of interest and not to other targets. Potential adverse effects can thus be minimized at an early stage. The lead candidates identified so far are not yet ready for use. They have to be optimized in further stages of the development process.





## Modeling molecules



In addition to compound screening, computer-based methods are used to find and develop suitable drug candidates. Here, scientists from structural biology and computational chemistry work hand in hand.

Structural biologists determine the molecular properties of the targets. They investigate the position of pockets to which the active compounds can bind and the interaction between these protein pockets and the active substance. For this purpose they use X-ray structural analysis, which only can be performed on crystallized target proteins. However, the generally lengthy crystallization process does not succeed with every protein. The lattice structure of the crystallized protein diffracts the X-ray beam in a characteristic way. Structural biologists can read the electron density and thus the position of the atoms from the diffraction pattern. In this way they can draw conclusions on the three-dimensional molecular structure. Computational chemists use computerized screening processes to assess millions of substances from a virtual library for their optimum fit into the binding pocket of the target protein. In this way they can identify molecules that have not yet been synthesized and others that can be purchased from external vendors. The subsequent stage of lead optimization also benefits from computational chemistry.

Computer calculations can thus be used not only to predict which molecular modifications of a substance are likely to improve its binding affinity to the target, but also which physiochemical, pharmacokinetic or toxic properties might be associated with a proposed structural transformation.

This enables the synthetic chemists to do their work in the laboratory in a more targeted manner. However, the natural flexibility of protein structures makes reliable predictions difficult – ultimately, it is always the experiment actually conducted that counts.

# Structural Biology and Computational Chemistry

*Computational drug design particularly benefits from the knowledge of the exact three-dimensional molecular structure of the target protein.*



# Medical Chemistry

The compounds identified up to now do not yet have all the necessary properties of an active ingredient. In addition to having the desired effect, a substance must meet other criteria. If possible, it should bind only to the target and not to other molecules in the body to minimize adverse effects. It must not break down before it has a chance to have its effect, and it must be sufficiently soluble in water to get into the body at all.

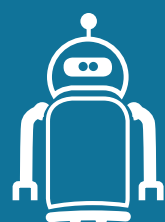
In the next stage of lead structure optimization, scientists from a variety of functions closely collaborate, step by step, to find the best-possible substance. Medicinal Chemistry is one of the functions that contributes to the required fine tuning.

In order to create molecules with such properties, chemists vary the lead candidates by adding or removing various

chemical groups or by modifying the molecular structure. But when they improve one desired property of a molecule, this sometimes worsens others. So, they systematically create hundreds or even thousands of different variations. These are then further screened to filter out candidates that are most likely to meet the requirements.

This process is supported by computer simulations which are provided by the colleagues from Computational Chemistry. The improved lead compounds are then subjected to repeated biological tests. These give the medicinal chemists ideas for further optimization steps.

## Finding *the optimum*



At this stage the substances might be compared with key blanks that can be inserted into the lock, but not turned. Medicinal chemistry gives them the finishing they need.







# Pharmacology and Toxicology

Pharmacologists, toxicologists, and other functions work hand in hand with the chemists to test the activity of the newly synthesized active ingredients in experiments.

Pharmacology investigates the desirable as well as unwanted effects to elucidate in detail how a living organism reacts to the active substance. Pharmacologists investigate whether the already established ability of the active ingredient to bind to the target molecule has a physiological effect in the living organism and is therefore able to have an actual impact on the disease. They also investigate how the active ingredient is absorbed, distributed, metabolized and excreted in the body. It can happen that an active compound is prematurely broken down in the stomach or liver and never reaches its true destination, or even that metabolism converts it into a toxic substance. Such knowledge is indispensable for developing a form of administration. Toxicologists investigate whether a substance is toxic and whether it could cause changes to genetic material, be harmful to embryos or cause cancer. Pharmacologists and toxicologists determine what is known as the therapeutic window. This is the span between the minimum dose at which a therapeutic effect becomes just visible and the maximum dose at which there is no toxic effect.

The scientists in Pharmacology and Toxicology use computer programs – in silico – to simulate processes, test active compounds in test tubes or Petri dishes – in vitro – on cell and tissue cultures or with bacteria, and finally in animal experiments – in vivo – to understand the complex interactions that take place in an entire organism. These studies are required by law and are governed by strict guidelines and state controls.

The alternating process of chemical optimization and laboratory testing usually takes several years. Once a suitable compound has been found, it is filed for patent protection and clinical testing can begin.

## Understanding effects



// Simulation



// In Vitro



// In Vitro





## Packaging the active *substance*



# Pharmaceutical Technology

An active ingredient still has a long way to go before it becomes a drug. Galenics is the science that turns an active ingredient into a safe, ready-to-use product that can be dosed as required.

Factors to be considered in the development of a suitable form of administration – be it a tablet, an ointment or a patch – include patient acceptance and the specific requirements of the active ingredient. Inactive ingredients which can make up most of a drug's volume serve as carriers for the active compound. Microcrystalline cellulose or mannitol, for example, is used in tablets, while water-oil emulsions are used in ointments.

The administration form also influences a drug's therapeutic effect. It determines how the active ingredient enters the body, where and in what dosage it is released, and the time it takes to be absorbed. For example, compounds that need to be released into the body slowly and continuously can be incorporated into additives that are not readily soluble. Active ingredients that would not survive passage through the liver are transported via a patch or injection directly into the blood circulation. In addition, the mode of administration must ensure that the patient will be able to dose the drug safely and handle it easily.

Galenics experts are also responsible for a drug's storage safety. They ensure that the active ingredient's content remains constant, the product remains chemically stable throughout its shelf life, and that it maintains its purity.

Another requirement is that the formulation can be manufactured on an industrial scale. Beginning with a prototype it on a laboratory scale, the next step is to increase scale in several steps at the test facility. Finally the scientists reach large-scale production. The newly developed drug formulation is initially used and tested in clinical trials before it can reach the market as an approved drug.

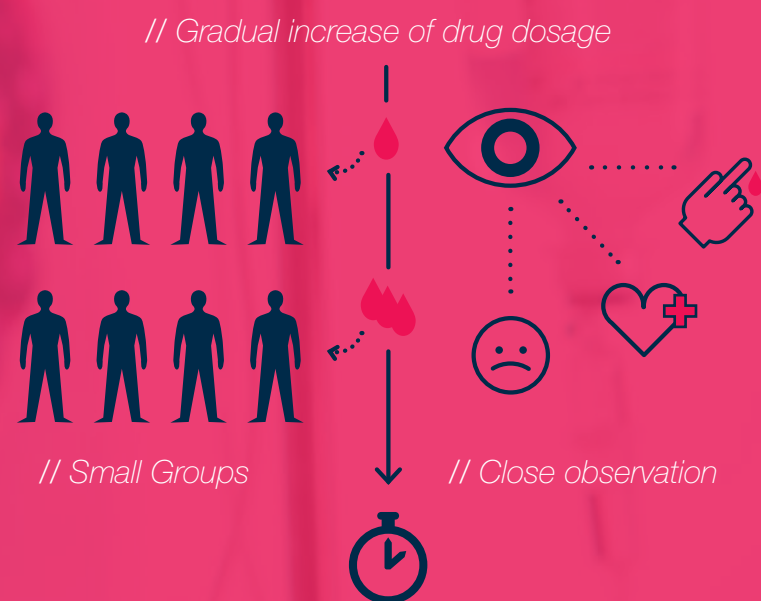


*The active ingredient has to be incorporated into a suitable form of administration so that it can be transported to the part of the body where it is needed.*



## Testing

# tolerability



Phase I-clinical trials are the first stage at which physicians study the active ingredient in humans. Studies with healthy volunteers are usually conducted at study centers operated by the drug's manufacturer, while Phase I studies with new drug candidates for cancer therapies already include patients at independent hospitals. Quite a small number of volunteers are initially given a very small quantity of the active ingredient. The dose is then gradually increased in different volunteers until the maximum tolerable dose has been identified. In this process, physicians monitor blood parameters and other vital signs such as blood pressure, heart rate and ECG to determine side effects.

They use blood, urine and stool samples to determine how a compound is absorbed, distributed, metabolized and excreted by the human body. In further studies, the physicians monitor interactions with other drugs or nutritional substances. Finally, they investigate how the new medication can be most effectively administered — a prerequisite for enabling the pharmacists to find a final formulation for the active ingredient.

The participants are comprehensively briefed beforehand about the planned study and possible risks. They give their written consent to participate, but can later revoke it at any time. They receive an expense allowance for their participation. All clinical trials involving humans are governed by strict scientific and ethical principles. A study protocol describes what is to be studied, how the trial is to be conducted, and why it is necessary. These study protocols have to be approved by the regulatory authority and an independent ethics commission. If a drug proves to be well tolerated in Phase I, it will then be tested in the now following Phases II and III on patients who are suffering from the respective disease.



## Clinical Development Phase I

// At this stage doctors test the safety and tolerability of the active ingredient as well as the way it affects the body. These studies are usually conducted on small groups of volunteers.



# Investigating *efficacy and safety*



Independent hospitals or physicians' practices in many countries are involved in these phases of clinical development. There the drug candidate is tested in two steps. Between 100 and 500 patients initially take part in Phase II studies. In Phase III, investigators test the drug on as many as several thousand patients. They examine whether the tested drug candidate is effective and, if so, to what degree, as well as which dosage is optimal for treatment and how often adverse events appear. Here, too, patients must give their consent to take part in the study.

The physicians compare the new active ingredient with an established form of therapy or with placebos – an inactive substance containing no medication – to exclude any distortion of the clinical results as far as possible. The patients are assigned by lots to one group or the other. They do not know which group they belong to, because their expectations might

influence the results. If neither the physicians nor the study participants know which preparation is being used, the study is called double-blind study. Only after the study is completed all participants are informed about their respective treatment group.

The physicians taking part in a clinical trial meticulously document the treatments, measurements and results, and pass the data on to the pharmaceutical manufacturer in anonymized form. The manufacturer uses sophisticated database systems to handle and statistically analyze the enormous volume of data. The interpretation of the data ultimately shows whether the results are medically relevant and it is worthwhile applying for the drug's approval. Clinical development brings a logistically extremely complex, lengthy and cost-intensive process to a close. The trials, which take on average eight years, account for most of a drug's total development costs.

## Clinical Development Phase II and III



// In Phase II and III clinical trials, large patient groups are studied by physicians to determine the efficacy and safety of the new drug candidate.



*The dossier with the results from chemical-pharmaceutical, toxicological and clinical trials may sometimes amount to capacities of more than 13 GB or 500.000 pages.*

**Putting**

*it all together*



# Regulatory Affairs

Drugs may only be launched if they have been given regulatory approval. The Regulatory Affairs department is responsible for preparing this final step of drug development. This department compiles the dossier that is submitted to the regulatory authorities and is their contact office.

The documentation submitted to a regulatory agency by the pharmaceutical company contains all the data from chemical-pharmaceutical, toxicological and clinical trials generated during the development and test phases. The regulatory agency reviews the documentation to see whether it provides sufficient evidence to prove the efficacy, safety and quality of the drug for the proposed indication.

Regulatory Affairs is also involved earlier, during a drug's development process. They ensure that, wherever possible, all the necessary steps for approval are considered already at an early stage. Indeed, most drugs achieve approval in this way, although in some cases it is subject to conditions, e.g. restricting the number of indications or requiring warning notices.

As a rule, pharmaceutical companies strive to market their products worldwide. To do so, they require approval for each individual country. This is granted in Germany by the Federal Institute for Drugs and Medical Devices (BfArM), in the USA by the Food and Drug Administration (FDA). In the European Union, the EMA (European Medicines Agency) is responsible for central approval, which is valid for all member states. Pharmaceutical manufacturers usually first apply for approval in the USA and Europe. If it is granted there, they also apply in the remaining countries. Often the assessment of the EMA and/or FDA is taken into consideration in the review by the other health authorities.

Approval marks the successful completion of a long journey. After a long research and development process and an approval process which also takes about one year (depending on the country), it can also take between three to five years until the drug is finally available to patients all over the world.



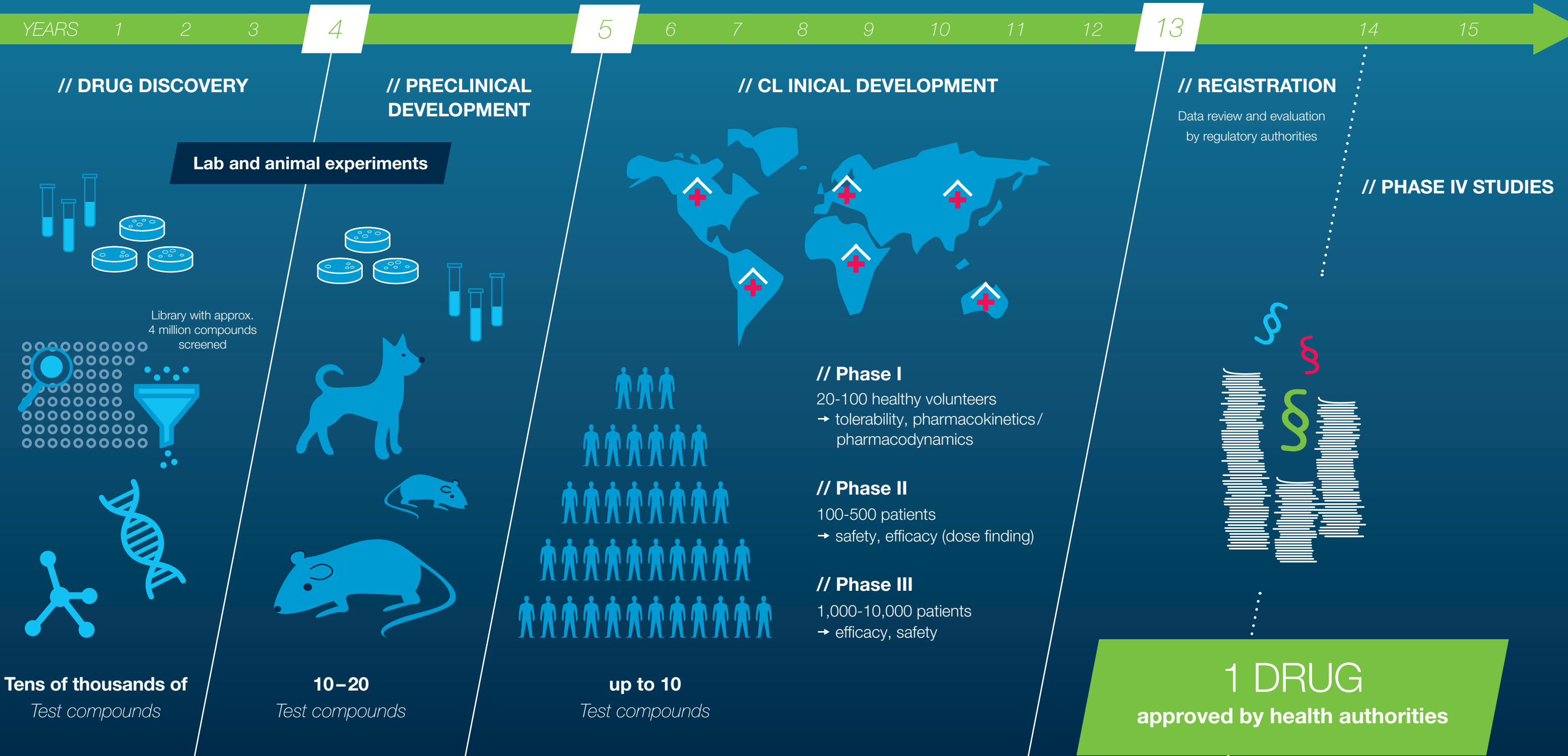
# The process of drug development

Pharmaceutical companies today invest an average of more than two billion euros from the discovery of a new active ingredient until the product is ready for the market, including the cost of the many potential medicines that do not make it through the drug development process. For the individual project, the probability of success from research to market approval is often less than 1%.

////  
Bayer invests more than 2 billion euros per year in the research and development of drugs.

////  
More than 7,500 employees work in Pharmaceuticals R&D at Bayer worldwide.

Developing a new drug  
can take 12 to 15 years





# Test your knowledge

## Quiz

3

*What do structural biologists actually do?*

- a. They determine the molecular make-up of the target experimentally and clarify whether there are any binding sites for a drug.
- b. Using special databases, they decode the genetic data of patients.
- c. With the aid of robots, they mix active ingredients together which they then make available to chemists for further tests.

4

*Do lead compounds already qualify as active ingredients?*

- a. No, they need to be tested in many more experiments first.
- b. Yes, they directly attack the source of the problem in the body and have a rapid effect.
- c. Lead compounds are active ingredients if they cause no side effects in patients.

7

*How are new drugs being tested in humans?*

- a. Often, they are tested on healthy subjects first to minimize any risks, which could be life-threatening to an ill person.
- b. If the drug has passed through all the necessary preclinical processes, it can be duplicated and given to pharmacies.
- c. New drugs are always tested first on ill people. This ensures their efficiency one hundred percent.

8

*How are the efficacy and safety of a new drug product ensured?*

- a. The patients who are given the new drug are quarantined for two weeks.
- b. Robots are used as trial subjects to test the efficiency of new drug products.
- c. In Phase II and III clinical studies, doctors test the efficacy and safety of the new drug product in large patient groups. Independent hospitals or medical practices in many countries take part.

1

*How do you actually start searching for a new drug?*

- a. Patients are first given a contrast medium to locate the source of the problem in the body.
- b. A target is sought in the body on which a drug can act.
- c. Patients have to complete questionnaires which lead to suitable medication.

2

*What takes scientists into a library in the second stage of development?*

- a. Scientists search for suitable formulations for the new active ingredient in the current literature.
- b. Past development results are archived in a research library. They are used as starting point for the new drug.
- c. The in-house substance library is searched for potential lead candidates. Over four million substances are screened.

5

*Once identified, can patients use the new active ingredient immediately for treatment?*

- a. No, if administered the body will react with major circulatory problems.
- b. No, before they can be used for treatment, the body's response to the new drug has to be tested and observed in preclinical development first.
- c. Yes, but in order not to weaken the body too much, they are given in greatly diluted form.

6

*Why does an active ingredient have to be "packaged"?*

- a. In their raw state, active ingredients are invisible, which is why they are enriched with vitamins and trace elements, coated and hence made larger.
- b. An active ingredient must be mixed with water and immediately packaged. Only in this way can it exert its effect in the body.
- c. The active ingredient must be packaged in a suitable dosage form. This influences the effect of the drug.

9

*Do drug products always have the same effect?*

- a. Yes, drug products are developed in such a way that they adapt to the patients' genetics.
- b. No, the effect of a drug may often depend on hereditary factors. The relationship between genetic predisposition and the response to a drug is therefore increasingly also being studied in the course of drug development.
- c. No, the effect of a drug is largely influenced by the psychological condition of the patient.

10

*Is the marketing authorization for a drug world-wide?*

- a. No, world-wide marketing authorization only applies if the product was developed in Germany.
- b. No, marketing authorization must be applied for in every country in which the product is to be used.
- c. Yes, if one country issues marketing authorization for a product, the remaining licensing authorities world-wide follow suit.





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