



Science For A Better Life

FROM MOLECULES TO VETERINARY MEDICINES



A journey through research and development

FROM MOLECULES TO VETERINARY MEDICINES

Like humans, animals sometimes need medicines to stay or get healthy. For over 90 years, Bayer Animal Health has invested in the research and development of new medicines to support the health of both companion animals and farm animals.

Developing a new medicine for animals is very similar to making a new medicine for humans. It requires a big investment and a long time, usually around eight to ten years. During this time, highly qualified scientists from a variety of disciplines filter through an enormous number of compounds to find a suitable active ingredient. In fact, between 5,000 and 10,000 compounds are studied, out of which only four or five potential candidates are further optimized. The best candidates from this small number are then rigorously tested in clinical studies. Ultimately, only one substance will be approved by government authorities and become available to veterinarians, farmers and pet owners.

Increasingly, people live in close proximity with animals or depend on them for animal proteins. Keeping this close relationship healthy is not just a responsibility towards animals, but it also protects humans from the transmission of disease pathogens. With this brochure, we invite you to join us on a journey to see how a molecule becomes a medicine to help animals. We hope you will share our passion for using science to keep animals healthy or treat them when they are sick – thus realizing Bayer's mission 'Science For A Better Life'.



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Pets are our companions and part of our families. We want them to stay healthy.

Introduction

BAYER CARES FOR PETS AND FARM ANIMALS

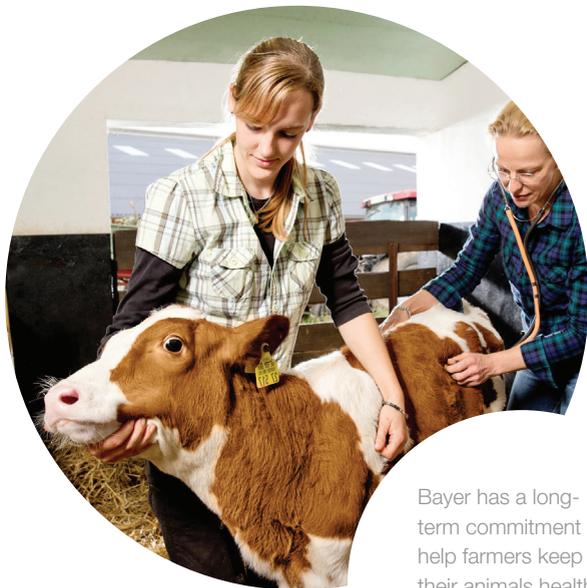
Animals are an important part of our daily lives and are essential for global public health. People and animals have a close relationship and depend on one another. It is important to keep animals healthy. Pet animals are our companions and part of our families. And farm animals are important for providing proteins that are contained in milk, eggs, meat and fish to feed the world's growing population.

Many of us have pet companions. They are part of our families and we love them. We want them to stay healthy and we want to protect them from ticks, fleas, worms and other parasites.

Often we rely on “anthelmintics” to control worms and “ecto-parasiticides” to control ticks or fleas. When a pet gets sick and has an infection, an antibiotic may be indicated.

In addition to pets, Bayer has a long-term commitment to help farmers keep their farm animals healthy and productive. The health and well-being of farm animals is vital to feed a growing world population with quality milk, eggs, meat and fish. For some diseases, there are vaccines to prevent an outbreak from starting. For other diseases, the veterinarian needs effective medicines to quickly halt the progression of sickness and restore an animal's health. This helps minimize impact to the animal and the herd, as well as the economic impact to the farmer.

This brochure outlines how new molecules are discovered and what it takes to put new medications on the veterinarian's shelf. Any new medicine is the result of a long, tenacious quest for better treatments by dedicated scientists, often veterinarians or pet-owners themselves. Chapters 1-3 describe the process of identifying compounds. Chapters 4-8 explain what is needed to develop these compounds into safe, effective medicines, often together with universities and other research partners.



Bayer has a long-term commitment to help farmers keep their animals healthy and productive.

Aside from starting the quest for new veterinary medicines from scratch, researchers can also begin with molecules that are already known for a particular therapeutic effect. For example, scientists who are looking for a new anti-infective will start with a set of molecules known for their antibiotic effects. These are modified and tested for their ability to inhibit the growth of or even better to kill bacteria that cannot be combated with current treatments, for instance.

Bayer Animal Health is uniquely positioned because we share a research platform with both our human health and plant care divisions. This means that sometimes compounds from human and plant research can be adapted for the use of animals. Because diseases in animals are sometimes similar to those in humans, and often animals and humans share pathogens leading to diseases, molecules that help humans may also help animals. This can be a basis for shared insights and for further research into the molecules for veterinary use. Another example is in the area of parasiticides and anthelmintics. Sometimes, Bayer Animal Health can also use active substances in insecticides as a starting point, or search for these in joint projects.

Many of us working at Bayer Animal Health have our own pets and farm animals. It is important to us both professionally and personally to do what we can to help veterinarians, farmers and pet owners keep animals healthy. In addition to our research, we work together with organizations, foundations and shelters around the world to help protect and care for animals. Ultimately, we care passionately for animals – following Bayer's mission 'Science For A Better Life'.



The quality of a target is key to the success of subsequent work steps.

1. *Target identification*

FINDING THE RIGHT APPROACH

The development of a new medicine begins with the search for a target on which the drug can act. To find a target, researchers must understand the biochemical processes that take place in the body and how these are changed by a disease. As these processes are often similar between animals and humans, Bayer Animal Health is able to use the results of Target Discovery conducted at Bayer Pharmaceuticals. And since certain insecticides have been proven to be safe and effective against parasites, new targets identified by Bayer Crop Science are also potentially useful to Bayer Animal Health.

Scientists focus their attention on metabolic or signaling pathways of cells that control major functions in organisms. Understanding these biochemical processes in the body can yield valuable clues for how to fight a disease, since the activity of proteins in these pathways can potentially be increased or decreased by drugs. These target sites are usually receptors – cellular binding sites for other messenger molecules – or enzymes that chemically transform substances in the body. As it turns out, only few proteins are suitable as targets for drugs, and it is a difficult and complex task to detect them among the countless other proteins in the body.

Careful work is very important at this stage of the research process, since the quality of a target is key to the success of subsequent work steps.

Once a target has been successfully identified, the scientists use a systematic test procedure to look for substances known as lead candidates, which could be a suitable starting point for a new active ingredient. These lead candidates must be able to bind well to the target protein – fitting into the target like a key into a lock.

2. Working around the clock to find a needle in the haystack

HIGH-THROUGHPUT SCREENING (HTS)

To find these potential active compounds, the researchers first develop detection tests that are matched to the respective target and are suitable for use in an automated and miniaturized process. This may take up to several months. Where possible, the tests are designed so that any successful binding of compounds and targets lights up with fluorescence and a picture is taken to capture the results.

Using these tests, robots comb through compound libraries for suitable lead candidates, a process called High-Throughput Screening or HTS. Bayer's in-house compound libraries currently contain over three million chemical substances. The robots fill thousands of microtiter plates with very small quantities of the substances,

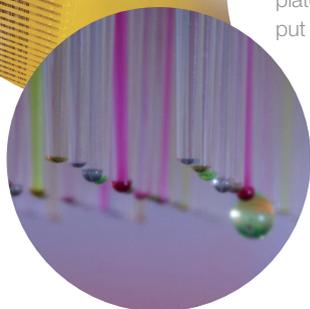
read the test results and store them in a computer which automatically identifies compounds of interest. With up to 1,536 tests per plate and a 24/7 work schedule, the robots complete this enormous task of screening in only a few weeks.

The most interesting compounds are then re-tested in a series of dilutions to identify the most potent and powerful ones, and then cross-checked for unwanted effects in a first test. These newly identified candidates are just the start. They still need to be refined and improved in further development process stages.

Some of these targets are so fundamental to life that that Bayer is able to take a unique Life-Sciences approach to research and development – combining expertise and resources in animal, human and plant research in the quest for new and better products.



Very small amounts of substances are prepared in microtiter plates for High-Throughput Screening.



In addition to compound screening, computer-based methods are used to find and develop suitable drug candidates. Computational chemistry can only be used if the exact molecular structure of the target proteins is known.

3. *Modeling molecules*

STRUCTURAL BIOLOGY / COMPUTATIONAL CHEMISTRY

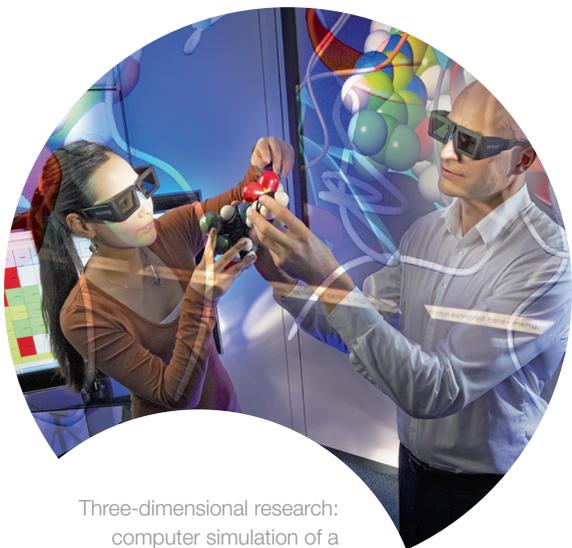
Structural biologists determine the molecular properties of the targets. They investigate the position of “pockets” that active compounds can bind to, as well as the interactions between these protein pockets and the active substance. X-ray diffraction analysis is used to check the potential. This requires the crystallization of the target proteins – a generally lengthy process which does not succeed with every protein. X-ray diffraction is a rather straightforward method to determine the position of every atom in small molecules, but it is a real challenge for proteins, which are a hundred times larger.

Computational chemists use this information to find substances that fit the binding pockets of the target proteins. They use computerized screening processes to search through virtual compound libraries and identify molecules that have not yet been synthesized. This step also helps in the next step of lead optimization.

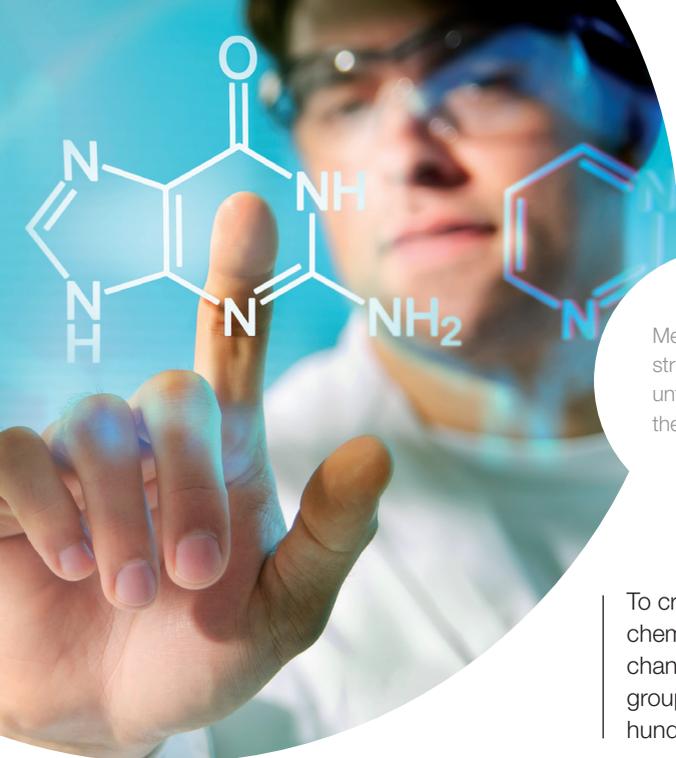
Computer calculations are used not only to predict which modifications to a molecule are likely to improve its capacity to bind to the target, but also which biophysical or toxic

properties might be associated with a structural transformation.

This enables synthetic chemists to do laboratory tests in a more targeted manner. However, the natural flexibility of protein structures make reliable predictions difficult – and ultimately, it is always the actual experiment that counts.



Three-dimensional research: computer simulation of a molecular structure provides valuable information for development of new active ingredients.



Medicinal chemists vary the structure of the lead compound until the optimal substance with the desired properties is found.

To create molecules with these properties, chemists vary the lead candidates by adding, changing, or removing various chemical groups. They first systematically create hundreds or even thousands of different

structural analogs using automated processes (automated medicinal chemistry). These molecules are then tested for their ability to kill bacteria or parasites (like ticks, fleas or worms), before a targeted

selection of these molecules are tested for their ability to cure the disease in animals. Another important aspect is the pharmacokinetic profile of the tested molecules (see more on Pharmacokinetics in Chapter 5).

The medicinal chemists take these results and create a new set of molecules, which are then tested again. The alternating process of chemical optimization and testing usually takes several years and involves the synthesis and testing of hundreds of compounds. The experience of medicinal chemists and close collaboration with a veterinarian or pharmacologist is crucial in this process, since sometimes improving one property can worsen the others. When the scientists are finally convinced they have a compound with the desired profile, the preclinical development process starts.

4. Finding the optimum

MEDICINAL CHEMISTRY

The compounds that have been identified up to this point do not yet have all the properties of an active ingredient. At this stage, they might be compared with key blanks that can be inserted into the lock, but not turned. Medicinal chemistry gives them the finishing they need to fit into the lock and open it.

It is not enough for a substance to bind: it must also meet other key criteria. For example, a substance has to be selective in binding only to its target and not to other molecules: it needs to stay in the body long enough to work, but not so long that it has a permanent impact (to avoid contamination of milk and meat); and it also must dissolve in water so that the medicine can get into the body.

5. Understanding effects

PHARMACOLOGY AND TOXICOLOGY

In the various development stages, pharmacologists and toxicologists test new active compounds. They study the desired and adverse effects of the new drug candidate to determine how it reacts in the body.



At the preclinical development stage, pharmacologists and toxicologists test the new active substances under various experimental conditions.

Pharmacology includes pharmacodynamics and pharmacokinetic studies. Pharmacodynamics investigates whether the active compound binds to its target and has the desired physiological effect: e.g. does it kill the bacteria, keep the animal free of parasites, or treat the disease? At this stage, it is important to understand what doses are needed to help the animal.

Pharmacokinetics studies the absorption, distribution, metabolism, and excretion of a molecule – in order to show that it reaches its intended destination, stays there for a sufficient amount of time to have the intended effect, and is then eliminated. A drug that stays in the animal's body for too long would not be useful for treating farm animals. With such knowledge, it is possible to select the most suitable form of administration – a pill, an ointment, a spray, a shampoo, an injection or even an impregnated collar – and to decide whether the molecule is suitable for a preferred treatment schedule such as once a day.

Toxicologists investigate whether the substance can have a negative effect on the body and whether it is capable of causing cancer, genetic mutations or damage to unborn offspring. These studies are conducted to ensure the safety of the targeted species* and to protect the safety of veterinarians, animal owners, consumers of food products and the environment. It is important to point out that these studies are required by law and are governed by strict guidelines. Bayer, like all companies developing medicines, must meet these legal requirements. All the data must then be evaluated together to answer the first key question: is the molecule safe and effective? To move past this point, the answer must always be a clear yes.

An active molecule still has a long way to go before it becomes a medicine. It must be made into a tablet, a spot-on solution, a spray, an injection or maybe even into a collar. Formulation technology is the science that turns an active ingredient into a safe, ready-to-use product.

6. Packaging the active ingredient

GALENICS

Formulation experts must figure out how to make molecules safe and convenient to give to animals. The active molecule must be made available at the intended site in sufficient concentration and for long enough. Animals are sensitive to the taste of medicines, so it is important to make sure the animal will swallow it. Ensuring that a molecule meets these criteria requires special techniques, and formulation experts in the animal health industry face unique challenges as they deal with a broad spectrum of animals, ranging from a fish to a cow.

Starting with a prototype, formulation experts then reproduce it on a laboratory scale, before moving on to larger equipment to make clinical samples, and ultimately making it on an industrial scale for the market. In each step of this process, they must demonstrate to the authorities that the quality of the product remains consistent. This means that the content, purity, color, taste and smell, as well as the timing of when the medicine is released, stays the same throughout the product's shelf life.

Bayer was the first company to pioneer the "spot-on" dermal delivery application to effectively protect animals against parasites. A small quantity is applied to the fur of the cat or dog and the droplets are distributed into the lipid layer of the skin.

Stable drug delivery systems for pets also include parasiticide collars.



7. Confirming safety and efficacy

CLINICAL DEVELOPMENT

In clinical trials, a large number of target animals are studied by veterinarians to demonstrate the safety and efficacy of the veterinary drug candidate. Independent farms or veterinary practices in several countries are involved to ensure a balanced evaluation.

Clinical development is a long, expensive and complicated process. A drug candidate with the new active ingredient is tested in two steps to identify dose safety and efficacy. In the first step, typically three to four doses are selected from a meaningful range, and are given to a limited number of target animals. These results make it possible to select the optimal therapeutic dose. This optimal dose is confirmed in repeated studies involving a larger number of animals under highly controlled laboratory conditions.

Once the safety of this final drug dose has been confirmed, the second step begins. The new veterinary drug is tested in a large number of target animals to establish its safety and efficacy under normal household or farm conditions. In all these studies, even if the animal is treated by a veterinarian, Bayer ensures that the animal's owner has been thoroughly informed and has agreed to the tests prior to the study, and that all animals are treated according to required welfare standards.

The veterinarians compare the new active ingredient with an established form of therapy or with a placebo – an inactive substance containing no medication to exclude distortion of the clinical results as far as possible. The animals are assigned by chance to one group or the other, ensuring that not even the veterinarian or farmer knows whether the animal is getting the new medicine or not. This approach is called a “blinded study”, and it ensures a fair and neutral comparison of outcomes. Only after all the data have been collected, are participants informed which treatment was given. Special procedures protect the safety of the animal in the event of unexpected or serious side-effects.

Veterinarians and owners carefully document the treatments and observations for the pharmaceutical manufacturer. During this phase, data from hundreds or thousands of animals are compiled into databases that allow statistical analysis of large data volumes.

The interpretation of the data shows whether the results are medically relevant. In other words, this data shows whether the medicine should be submitted to a government authority for regulatory approval.



A veterinarian with assistant examining a cat.

A new veterinary medicine can only be introduced to the market after approval by a regulatory authority. The Regulatory Affairs department is responsible for this final step of drug development. It compiles all the necessary data, prepares a dossier and submits it to the government authority that is authorized to approve veterinary medicines in that country. Once a new medicine has been approved, Regulatory Affairs, together with Pharmacovigilance, is also responsible for maintaining the authorization to market the product over the decades of the product life-cycle.



All data and findings are documented and compiled for preparation of the dossier.

8. *Getting a product approved for the market*

REGULATORY AFFAIRS AND PHARMACOVIGILANCE

The law of each country defines which authority is allowed to approve a veterinary medicine. In the United States this authority is the Food and Drug Administration (FDA) for pharmaceuticals, EPA for pesticides and USDA for biologicals and vaccines, while in Europe it is the European Medicines Agency (EMA) and the national authorities. World-wide approval of a drug can take three to five years and involves over 100 individual applications in many languages. Regulatory approval marks the successful completion of drug development and the authorization to finally market the product in a certain country. The Regulatory Affairs team is also responsible for keeping the dossier and package leaflet up-to-date as and when there are new developments, such as new approved uses for the product in the marketplace or when new information becomes available.

All data generated during the eight- to ten-year development process – from chemical and pharmaceutical development to toxicological and clinical studies – must be submitted to the authorities. This dossier fills several hundred files. The authority reviews this documentation to determine whether there is sufficient evidence for the efficacy, safety and quality of the drug for the proposed use. It is also this data that is summarized into user-friendly information that we can find on the package or package leaflets, to ensure the safe and effective use of the new drug.

Pharmacovigilance is the department that continually monitors the safety, quality and consistency of an approved veterinary medicine. The ongoing process ensures that the drug stays relevant for many years and continues to benefit animals.

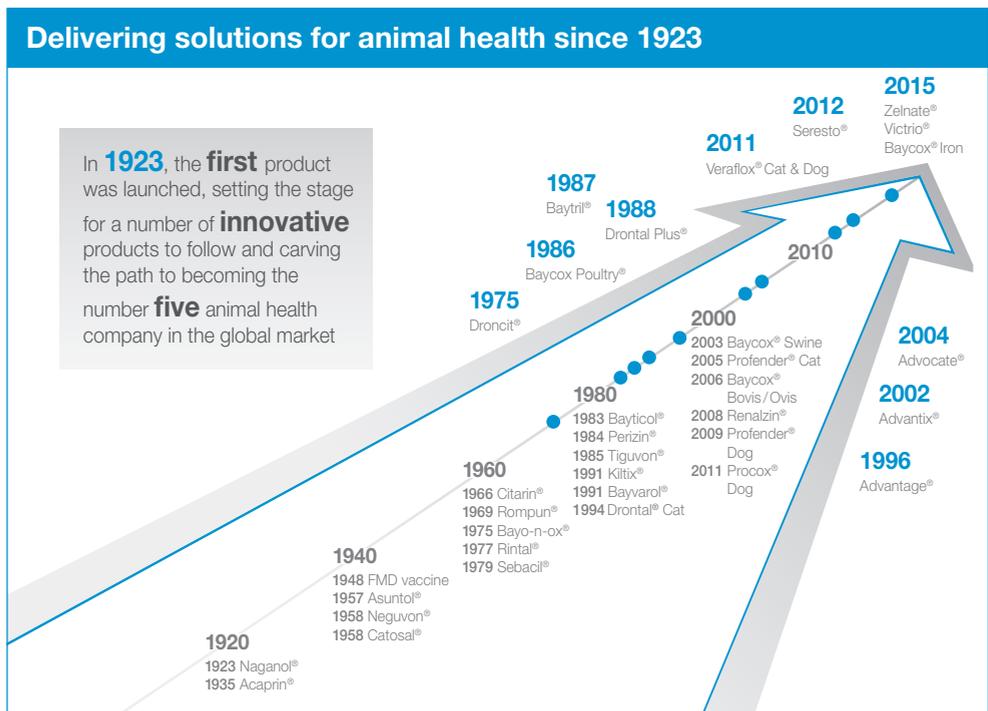
THE WORK CONTINUES

Even though medicines are available for treating and preventing infectious diseases in animals, the work of research and development continues to address new and emerging challenges. This is important to protect the animals in our lives and reduce the threat of zoonotic disease.

Scientists at Bayer Animal Health are working to find answers to tough questions. How can we help animals to be healthier and better able to withstand the threat of pathogens? What solutions can we provide farmers to help them safeguard the well-being of their animals better? How can we prevent diseases and at the same time reduce the threat of antibiotic resistant microbes, particularly in farm animals? And how can we continue to contribute to public health by keeping animals healthy?

While we search for these answers, we are also proud to partner with over 90 organizations around the world that protect and care for animals in immediate need. From helping elephants in Asia, to teaching animal welfare courses in Latin America, at Bayer we are passionate about finding new and better ways to improve the health of animals.

We hope this brochure has given you an insight into what it takes to make new medicines for animals, and helps you understand the value of each veterinary drug. As we continue to look for new and better solutions, we invite you to join us in our work to advance Bayer's mission of 'Science For A Better Life'.



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