Europe IFAH
Representing the European Animal Health Industry

DOSSIER 02

VACCINES
Protecting our animals

Some important facts about how and why vaccines are developed

IFAH-Europe - Improving the quality of life for animals and people

Healthy livestock

Wholesome food

Animal welfare

Safe environment

Veterinary medicinal products make a significant contribution to improving the world we live in.

Animals, like people, suffer from disease and require proper care from the veterinarian, the farmer and the pet owner. Whenever possible, prevention is always better than cure. One method of preventing disease is the use of vaccines.

The mission of the animal health industry is to supply safe, efficient, and cost effective veterinary medicinal products, including vaccines, which are a safe and easy way to stimulate the body's natural defence processes to prevent disease and contribute to animal health and welfare.

Research on vaccines and on the immune system of animals is constantly evolving to provide animals with new products that prevent diseases or have other improved characteristics (such as more safety, more efficiency, or ease of administration or storage).

The manufacture and sale of medicines, including vaccines and antisera, is highly regulated to ensure that only safe and effective products of consistent quality reach the marketplace.

This brochure seeks to explain briefly these and other important aspects about vaccines and antisera and to increase understanding of a fascinating subject.

A glossary of terms is provided at the end of the brochure.

IFAH-Europe thanks the following for having provided pictures for this dossier:

The Edward Jenner museum - image on page 6
J. van Lancker S.A. - N'Dama cows on page 8
Bayer, Intervet, Merial and Virbac.

CONTENTS

GENERAL INTRODUCTION

The importance of animal medicines

The main aims of veterinary medicine are:

- To prevent animal disease;
- To treat it when it occurs;
- To ensure animal welfare;
- To ensure healthy food;
- To preserve a healthy environment;
- To foster economical livestock rearing, for food and recreation;
- To protect public health and control animal diseases which threaten people by contact or food contamination.

Vaccines play an important role in meeting these aims.

Maintaining animal health is vital, as it contributes to the welfare of both food producing and companion animals, the prosperity of farming, the safety and availability of food, and the well being of animal owners (see zoonotic diseases in box on page 5).

Healthy animals lead to a safer environment by reducing the chance of zoonotic disease (e.g. salmonella poisoning – see box), and the spread of diseases from the increase in travelling of goods, animals, and people, and by making better use of resources in feeding an increasing world population.

New diseases are constantly emerging. There is the challenge of bringing the benefits of vaccines to remote less developed areas of the world, where rural societies are often very dependent upon their animals. Research into modern technologies provides an opportunity to meet these challenges.

Reducing salmonella contamination

"Vaccines can decrease public health risk caused by salmonella in poultry products by reducing the colonisation of reproductive tissues as well as reducing faecal shedding. There is experimental and some limited field evidence that a reduced level of faecal excretion and systemic invasion of salmonella organisms in vaccinated birds will result in a reduced contamination of table eggs and the environment."

Reference: European Food Safety Authority Opinion of the Scientific Panel on Biological Hazards on a request from the Commission related to the use of vaccines for the control of salmonella in poultry. The EFSA Journal (2004) 114, 1-74.

Vaccines contribute to world health

Vaccination has profoundly influenced and improved world health, and will continue to be a fundamental tool to meeting future health challenges. It has eliminated smallpox and can control many other scourges against which no treatment exists, such as human polio, foot and mouth disease in cattle, canine distemper and rabies in man and animals.

The causes of disease

Animal diseases take many forms. They include malnutrition, infertility, stress, hereditary and congenital defects, cancers and, perhaps the most important, infections and parasitism due to micro-organisms (also called pathogens).

Vaccines and antisera are most commonly used to prevent diseases caused by pathogens such as bacteria and viruses; but they can also be used to control diseases caused by other organisms, such as fungi (ringworm) and parasitic worms.

Vaccines provide relatively long-term disease resistance in animals. Antisera treat established disease or protect animals at immediate risk from contact with infection and have a shorter duration of effect. This is explained in more detail on the following pages of this brochure.

Because prevention is always better than cure…

It is always preferable to prevent disease rather than having to resort to treatment. The consequences of disease may be transmission to other animals or people, loss of efficiency through reduced animal growth, or drop in milk production, death, etc.

Good husbandry, including efficient bio-security measures, is the most important factor in prevention of diseases in livestock. Nevertheless, animals can become ill and highly infectious diseases can spread rapidly with devastating results. Therefore vaccines are an important part of the veterinarian's toolbox.

Zoonotic diseases

Animals may sometimes have infections that are communicable to people, called ***zoonotic diseases.***

The animal may show no sign of illness if it has developed a natural resistance to the disease, but if transmitted to a human with no specific immunity against the agent, illness results.

Examples of zoonotic disease are numerous; the most famous is rabies, but there are also: Tuberculosis, ringworm, anthrax, brucellosis, leptospirosis, sarcoptic mange, salmonellosis (food poisoning), plague, echinoccocosis (tapeworms) and many more.

Veterinarians and other scientists are among the first line in the defence of public health.

HOW IT ALL STARTED

"Immunology" is the study of the body's natural defence mechanisms against disease.

Observation…

The common observation that people or animals that survived a particular disease had a better chance of resisting subsequent re-infection lay down the principles of modern immunology. Around 1000 A.D., the ancient Chinese already practiced a form of immunisation by inhaling dried powders derived from the crusts of smallpox lesions. That is well before the founders of modern vaccination: the English physician Edward Jenner (1749-1823) and the French chemist and microbiologist Louis Pasteur (1822-1895).

The first attempts to control smallpox (variola) in the early eighteenth century involved introducing the pus from a smallpox pustule into a scratch on a healthy individual (termed "**variolation**"). There was a risk that the procedure would cause the life-threatening disease and those inoculated could spread smallpox to others and start an outbreak. Catherine the Great of Russia, her family and members of her court were treated by this method in 1768 – and survived.

Tradition had it that milkmaids, who handled cows regularly, were more attractive than many of their neighbours, since they did not carry the facial scars of smallpox. It is now known that this was because they had contracted the far less serious infection from the milder virus of cowpox which was very prevalent in dairy cattle. This milder infection with the cowpox pustules had given them the immunity to cross protect against the more serious human smallpox.

Common sense…

In 1774 an English farmer, Benjamin Jesty, is recorded as having inoculated his wife and son with pus from cowpox, using an ordinary stocking needle and they later resisted a serious outbreak of smallpox.

And scientific inspiration…

News of this reached **Edward Jenner**, who studied dairy workers for some twenty years. He carried out extensive and successful tests on patients, using cowpox inoculations before publishing his results in 1798. He called the material "vaccine" (from "vacca" the Latin for cow) and the procedure "vaccination".

Edward Jenner about to vaccinate a child

Collecting blood from an immunised cow to make antiserum.

100 years later…

The next major advance in the veterinary field was in the 1870s, due to a chance observation by **Louis Pasteur**. He was working on the "chicken cholera bacillus" and he inadvertently left a flask of the organism on the bench exposed to high temperatures over the summer. When he injected 8 chickens with it, they did not get sick. Furthermore, they were protected against infection with fresh cholera bacillus, while new chickens were not.

Louis Pasteur (1822-1895)

Pasteur recognised the underlying principle that **altering the bacteria reduced their ability to cause a disease, while still giving protection when used as a vaccine**.

He also found that another way of reducing the virulence of a micro-organism is to involve the passage of the micro-organism in an unnatural host.

He demonstrated this with rabies virus from a fox by infecting an "unnatural host", the rabbit, allowing it to become ill, and then re-isolating the virus and injecting a new rabbit. Pasteur found that the variants of the virus selected by this process were less pathogenic for the fox, and could be used to prepare a "live" vaccine.

What is a vaccine?

A vaccine is made from a killed or weakened disease organism or part of it which does not cause disease when injected into the body, but stimulates the body to produce antibodies and protective cells that can combat the disease.

Discovery of antisera…

Later it was discovered that injecting the liquid part of the blood (serum) of animals, which had been in contact with a disease, into the bloodstream of other susceptible animals gave **immediate** (but temporary) **protection** against that disease. Thus the **antiserum** could be used promptly to treat disease or protect in-contact animals.

What is an antiserum?

An antiserum is made from the blood of an animal known to have antibodies to one or several diseases.

The blood is collected and the blood cells are removed. The remaining clear amber liquid contains the desired antibodies, which after further processing can be administered to another animal as a prevention or cure.

…and antibodies

Finally, science uncovered the mechanism of this protection. The micro-organism triggered the body to produce special proteins that then circulated in the body in large quantities via the bloodstream (the immune response).

These proteins bind to and counteract the disease organism and are known as **antibodies**. Each antibody is very specific to the disease that stimulated the body's immune response.

Thus, a sick or susceptible animal could be given an antiserum containing the antibodies that would neutralise the disease organism.

The animal has immediate disease protection during the few days it needs to produce its own immune reaction.

N'Dama cows

INTRODUCTION TO IMMUNITY: HOW IT WORKS

Any microscopic organism, such as a virus or bacterium, or larger creature such as an intestinal worm or biting insect, can be said to parasitise the host. These infections can often stimulate a natural defensive reaction in the animal under challenge, which is called **immunity** or an **immune response**.

Without immunity protective mechanisms, infections would make survival impossible. This is the case with AIDS patients, for whom catching a cold can be life threatening.

Immunity can be defined as the ability of an animal, man – or plant – to resist the challenge of such infections. It may occur naturally or can be induced by using vaccines or antisera. For example:

1. A species or breed of animal may be more resistant to an infection than another one ("inherited natural resistance");
2. An animal can become resistant to a disease after recovering from a first exposure to the disease ("naturally acquired immunity");
3. An animal can become resistant to a disease after exposure to the appropriate vaccine ("induced acquired immunity");
4. A foetus or newborn can be protected from disease by the protective nature of the mother's blood or first milk, also called colostrum ("passive immunity");
5. Finally, serum containing the right antibodies can be transferred to prevent or treat a particularly serious disease ("induced passive immunity").

These five types of disease protection are explained below.

1. Inherited natural resistance to disease

Certain **breeds** – or even individuals – within a species have varying degrees of resistance to diseases, which affect other breeds. As an example, local N'Dama cattle in West Africa do not become ill when infected with the blood parasites known as trypanosomes, carried by the biting tse-tse fly. These parasites make the rearing of non-indigenous cattle impossible in many parts of Africa. The local cattle breeds are genetically "adapted" to their environment and their resistance may be regarded as inherited.

2. Naturally active immunity: response to disease

The reaction of individual animals to challenge by disease organisms (pathogens) will normally result in acquired immunity, which helps the animal to resist future infections by the same pathogen. The body recognises individual components of the invading organism as "foreign".

These components (e.g. a structural protein in the membrane of a bacterium) stimulate the immune response and are called "antigens".

The animals' defensive system reacts by producing **antibodies** and **protective cells** in the blood which can neutralise the effects of the invading organisms and assist in recovery.

This is known as **active immunity**. Once established, it is reinforced by further exposure to the same pathogenic agent to maintain a high level of immunity.

3. Induced active immunity: response to vaccine

As explained earlier, naturally acquired active immunity occurs when the body is exposed to a live pathogen, develops the disease, and becomes immune as a result of the primary immune response. The active immunity can also be induced by a vaccine that stimulates an immune response without causing symptoms of the disease. This principle of vaccines is explained in more detail on page 10.

4. Passive immunity: a gift from the mother

Newly born offsprings have not had time to build up their own active immunity and are at high risk from infection. However, they can become naturally protected through the mother, if she is already herself actively immune from previous exposure to the disease, or if she has been vaccinated.

Depending on species, maternal antibodies are transferred from mother to offspring either across the placenta (e.g. humans and primates), or in the first milk, called colostrum (e.g. cattle) or through the placenta and the first milk (e.g. companion animals). The antibodies present in the first milk are absorbed through the intestinal wall into the blood stream during the first 24 hours after birth, but soon thereafter the intestinal cells change into digesting cells, and subsequently the ingested milk antibodies get destroyed. Thus, it is critical for the new born calf to receive colostrum right after birth in order to provide the young animal with initial protection while it builds up its own active immunity in the early weeks of life.

Since, in this case, the young animal itself has not produced the antibodies, the protection is called **passive immunity**.

5. Passive immunity: administered by the veterinarian

Sometimes an infectious organism or a poisonous substance can have such a rapid deleterious effect that the victim does not have time to develop an immune response promptly enough.

At such times immunisation of the patient with antiserum containing pre-formed antibodies can provide life-saving assistance in combating the pathogen or poison. This protection is termed **induced passive immunity**, as it resembles natural passive immunity passed on from mother to offspring. As in the natural case the protection, while immediate, is **short-lived**. It is not boosted by further exposure to the disease. The animal has to develop any active immunity separately, by disease exposure or vaccination.

An example is tetanus antiserum or antitoxin.

PRINCIPLE AND ADVANTAGES OF VACCINATION

Principle

The basic principle of vaccination is one of biological bluff. If a small amount of a weakened or inactivated (killed) pathogen is introduced into the body, it stimulates the body's immune system to fight back (see "immune response" on page 8). The immune system then **remembers** the pathogen and can defend the body against any natural exposure to that pathogen in the future. That memory allows the body to respond rapidly and strongly to a re-infection with the same pathogen.

Advantages

Animals do not have to get sick to become protected

The vaccine (containing antigen) when administered **stimulates the animal to produce its own protective antibodies**, as if it had been exposed to the natural infection, but **without the danger of contracting serious clinical disease**. The immunity is therefore active but, in this case, it is artificially induced and the animals do not have to get sick in order to be resistant to future exposure to the disease.

Tailor made protection

There are other advantages in using vaccines or antisera, rather than relying on natural immunity that only reflects the organisms in the locality. During vaccine or serum manufacture, **the strains of micro-organism can be chosen** to meet the expected patterns of disease over a wider field and varied as these patterns change.

For example, influenza viruses continuously change over time. As newer virus strains appear, the antibodies against the older strains may not recognise the "newer" virus, and infection with a new strain can occur. To combat this, the virus strains in the influenza vaccine are repeatedly updated to keep up with the changes in the circulating flu viruses and thus keep people and animals, such as pigs and horses, properly immunised.

One injection - multiple protection

Another advantage of vaccination is that more than one disease strain, or even more than one disease, can be incorporated in one single injection to provide **combined protection** against several strains of micro-organisms or several diseases.

VACCINE PRODUCTION

Conventional vaccines are derived from the pathogen causing the disease and hence are specific for that disease. Only in very limited cases can a vaccine be produced from other related disease organisms, (although the original vaccination against smallpox, using cowpox, was just such an example).

Sometimes only part of the micro-organism is used or a secretion from it. In some cases, following culture, toxins responsible for the disease are separated from the whole culture and treated to render them harmless, while retaining their immunising properties. They are purified and formulated to form the final vaccines or "toxoids". Tetanus and diphtheria vaccines are prepared in this way.

Bacterial vaccines generally consist of suspensions of "antigenic material", such as attenuated or inactivated whole organisms or their products.

The manufacture of viral vaccines follows similar general principles to those for bacterial vaccines.

Live and killed vaccines

Vaccines can be produced using live micro-organisms that have been "attenuated" in some way (see box with example for viral vaccines on this page) to make them harmless. These are known as "live", or "attenuated" vaccines. Alternatively, vaccines can be produced using killed micro-organisms. In either case the ability of the micro-organism to cause an immune response is preserved. The micro-organisms are then harvested, purified and formulated to preserve them and give the vaccine a reasonable shelf-life. For more information, see the boxes on this page.

Attenuated (live) viral and bacterial vaccines *are made from organisms cultured for many generations in laboratory conditions, which encourage viral / bacterial growth while inhibiting or totally removing the ability to cause disease. The immunity induced by such "live" vaccines is strong, and long lasting.*

The cell lines used to culture viral vaccines are extensively tested to ensure they do not harbour any pathogenic agents, which could be inadvertently transmitted at the time of vaccination.

There are several ways to reduce a micro-organism's virulence. It is the basis of many vaccine production methods.

- **Use of a related virus from another animal** – for example the use of cowpox to prevent smallpox.
- **Administration of the virus by an unnatural route** – the virulence of the virus is thus reduced as the virus has to "adapt" to that different route.
- **Passage of the virus in an "unnatural host" or host cell cultures** – as Pasteur did with his first rabies vaccine.

  The major vaccines used in man and animals are derived this way. After repeated passages, the "weakened" virus is administered to its natural host. The initial passages are now performed in cell cultures, which are well characterised and proven safe.
- **Development of temperature sensitive mutants** – these viruses are virulent at a certain temperature, but lose their pathogenic properties while still able to multiply at the host natural body temperature.

Inactivated (killed) vaccines *consist of suspensions of killed virus or bacteria. For inactivated vaccines the chosen strain of virus or bacteria is multiplied and then killed by heat or chemical treatment. The immunity induced by such vaccines is not as strong as live, attenuated vaccines. Therefore, in inactivated vaccines, substances may be added which, not being themselves antigenic, strengthen the immune response to the vaccine. These are termed* ***adjuvants.***

Safe and stable

Compared with most chemicals, vaccines are generally less stable, with shorter shelf-lives and stricter storage requirements, such as refrigeration.

In addition to the preparation of the antigenic material, the formulation of vaccines is vital. They must be free of any other infective agents and stable. Assurance is needed that the antigen content of the vaccine remains sufficient to induce a protective immune response throughout storage or the shelf life.

Some vaccines are presented as liquid suspensions or solutions, others originate from living organisms are thus fragile and must be prepared as freeze-dried doses, for reconstituting at the time of use.

Producing vaccines against other organisms

Infections with parasites, for example ringworm, which is a contagious fungal disease, or larger organisms such as intestinal or lungworms, can stimulate an immune reaction.

A fairly basic and relatively easy made oral vaccine, consisting of irradiated lungworm larvae was made as long ago as 1957. It has not yet been significantly changed or followed by successors. A problem has been to make enough antigenic raw material by conventional methods to prepare an effective and economically acceptable product. Biotechnology may offer promise in this area.

Recently, a vaccine has been developed and commercialised for ringworm in cattle, cats, dogs and horses that is used to both reduce the risk of a clinical infection, and also as a treatment for accelerating the healing of patchy hair loss in animals infected with ringworm.

Serum production for passive immunity

Serum containing a high level of antibodies to a specific disease (see page 9) confers immediate passive immunity. Because of its protective role against disease in being anti-bacterial, anti-toxic or anti-viral it is often called “antiserum” (plural = antisera).

To produce an antiserum, increasing doses of the appropriate antigen are given to the donor animal, often a horse. Initially these stimulate a normal active immunity. With further doses the antibodies are boosted to a very high level – a hyper-immunity. Then, blood is drawn off, the liquid antiserum is separated and the blood cells and other valuable constituents are **returned to the donor animal**. The antiserum is further processed and standardised to produce a stable, sterile antiserum. Once manufactured, the antiserum requires careful storage and refrigeration to preserve potency and shelf life.

ADMINISTERING VACCINES

The ease of administration of vaccines is a very important practical factor in their usefulness. Vaccines were originally given via a scratch or by injection. Newer forms of inactivated vaccines can now be given orally, in food or water, by inoculation spray or through the skin (without needle).

Where large numbers have to be treated, for example broiler chickens, some form of mass medication is necessary. Routinely, drinking water application or nebulisation of live viral vaccines have been used for many years now. Recently it has even become possible to vaccinate fertile poultry eggs, to protect the chicks as they hatch.

Under heavy infective challenge, vaccination cannot be guaranteed to provide complete immunity to disease. However, with modern vaccines, properly administered, a very high level of protection is achieved under both intensive and extensive husbandry systems. It is important to ensure that all the flock or herd is vaccinated simultaneously, as otherwise those which are missed can act as carriers and incubate the disease, remaining a latent threat, as immunity in the vaccinated animals declines. This is very significant among range cattle or hill sheep.

Vaccinating the young

Any successful vaccination programme must follow the full routine for initial immunisation – and booster doses at specified intervals. The routines vary with the vaccine. It is particularly important to have breeding females properly vaccinated so that they can transfer passive protection to their offspring, which can then be actively immunised by vaccination later.

Chick vaccination

However, as natural passive immunity is passed to the young animal from the mother, vaccinating too early in life may be less effective. The maternal antibodies inhibit the reaction to the vaccine by destroying the vaccine antigens before they have time to induce the young's active immunity. The "Directions for Use" have to strike a balance between the risk of early exposure, as passive immunity declines, from vaccinating too late and a poor immune response from vaccinating too early.

Hence, when young animals such as puppies are vaccinated for the first time, a booster injection is needed. As a precaution, the puppies should be kept away from animals with unknown vaccination status, while immunity is developing.

TRANSPORTING VACCINES

An important restriction with some vaccines is the need to store and transport them under refrigerated conditions. The need to maintain a refrigeration “cold chain” increases transport costs and is inconvenient even in developed countries.

In many developing tropical countries agriculture is already marginal and malnutrition is rife. Often these countries are also almost totally reliant on animals as a source of food, draught power for cultivation and transport. Here the cold-chain requirement remains an obstacle to establishing much needed vaccination programmes and improved methods of disease control and animal husbandry.

Some newer vaccine technologies hold promise of more heat-stable products, with more latitude in storage and transport conditions. This will be a significant contribution to tropical agriculture and to human nutrition and prosperity.

NEW GENERATION VACCINES

There is a constant quest for new preventive measures to meet the changing challenges to animal health. Indeed there is an evolution in the diseases threatening animals. Vaccines, when available, provide an effective and safe answer and represent an important field of ongoing research.

Modern techniques have greatly improved the available range of vaccines and the methods of administering them. Vaccines are now designed to avoid side-effects and residual virulence. They can actively protect against a variety of diseases in a single product. They can be administered via a wide variety of routes: through water, baits, air-spray, eye inoculation, intranasally, through the skin (without needles) or using the more classical injection.

New techniques – based on old principles…

Biotechnology is as old as brewing, cheese making, flax processing, baking or even selective breeding.

…provide new goals

This technology is revolutionising research goals and industrial production techniques and will ultimately result in vaccines:

- Against diseases for which it is currently impossible to vaccinate;
- With additional safety and efficacy characteristics;
- Which enables the identification of vaccinated animals (using a diagnostic test) from non-vaccinated or naturally infected animals (these are called **“marker vaccines”**).

Identifying genetic information and its application

Each cell stores all the necessary information in its nucleus. Genetic instructions are carried by genes on strands of DNA (Deoxyribonucleic Acid) within the chromosomes.

The technology to identify the role of individual genes, to map their relative positions and to isolate them has been developed over the past two decades. The genes can then be selectively removed, augmented or reassembled on the DNA strands (a process called “Recombination”). The desirable characteristics are retained or enhanced and the adverse or superfluous ones discarded.

For vaccines, this recombinant approach is used to improve immunity, introduce new, useful properties and exclude unwanted side effects.

New generation vaccines

The different types of vaccines derived from biotechnology are presented on the following pages. Some are fully developed while others are still at the research phase.

DNA double helix

Subunit vaccines

Subunit vaccines contain purified antigens. In order to develop subunit vaccines, it is critical to identify the genes that are important for inducing protection and eliminate the genes responsible for virulence.

Over the last few years, research has been conducted into producing vaccine antigens in plants: the genes from the micro-organism that code for the production of the relevant protein (the antigen) are inserted into plants, which start producing antigens. The antigen can be purified from the harvested plants. Alternatively, these plants are then included in the diets of animals that are fed and vaccinated at the same time. The great advantage of this type of vaccination is that no refrigeration is required.

Other advantages of using subunits as vaccines are:

- An **increased safety;**
- Less antigenic competition, since only a few components are included in the vaccine;
- The ability to **differentiate vaccinated animals from unvaccinated animals** that are or have been infected (see example on next page of marker vaccines in action).

Live recombinant vaccines

Live vaccines are generally believed to give **excellent immune responses** because they simulate a natural infection as they are still able to multiply in the host cells. Novel approaches to attenuation are being developed. It is now possible to **identify specific virulence genes** and to induce mutations or deletions (changes in the virulent genes). This can result in a safer vaccine than using conventional attenuation technologies, because the chances of reversion to virulence are dramatically reduced. "**Marker vaccines**" can also be engineered as based on the same principle as above. By deleting an essential gene, one can also develop replication incompetent micro-organisms in the live vaccines, which are extremely safe since **they cannot be spread into the environment**.

Live-vectored vaccines

It is also possible to introduce genes coding for protective antigens from one pathogen into another pathogen, and thereby immunise animals against both pathogens. **These live-vectored vaccines** are being used to not only control infectious diseases of domestic animals, but of wildlife as well (see example on next page of live vectored vaccines in action).

Polynucleotide vaccination (DNA vaccination)

The most recent development is vaccination with just the genetic material contained in certain pathogens. This technology has been referred to as **genetic immunisation or DNA immunisation**. The basis for this approach to immunisation is that cells can take-up DNA genes and produce the viral antigens themselves. Thus, the animal acts as a bioreactor to produce the vaccine within its own body. This makes the vaccine relatively inexpensive to produce and extremely safe.

Although this is one of the most attractive developments in vaccine technology, there is a great need to develop better delivery systems to improve its efficiency.

NEW GENERATION VACCINES IN ACTION

A practical example: the marker vaccines and Aujeszky's disease

One long-standing problem was to discriminate between an animal carrying antibodies following exposure to infection and one that may have been vaccinated. For example, Aujeszky's disease is a serious, frequently fatal, infection in pigs. Animals that recover can continue to harbour latent infection and are a risk to others. Early vaccines contributed to a reduction in disease. However, they left the vaccinated pig with antibodies indistinguishable from those in an animal that had recovered from the disease but remained a "carrier".

It was thus impossible to distinguish the vaccinated animal from the unvaccinated carrier.

Disease control…

Disease eradication programmes involve the detection and elimination of any clinical cases and carrier animals from the herd. Thus the only safe course was to remove all pigs tested positive for Aujeszky's disease antibodies, whether from infection or vaccination. Clearly this was wasteful and extremely expensive.

…using marker vaccines

The solution lay in redesigning the vaccine with the help first of a naturally deleted product and then by means of a virus from which genes were deleted so that the antibodies generated by the immune response of the vaccinated animals were slightly different from those generated by the immune response to a natural infection. In this way, it was possible with an accompanying diagnostic tool (e.g. blood test) to differentiate vaccinated animals from those naturally infected, so that the vaccinated animals could be saved.

This may be done also by a viral deleted vaccine where genes inducing virulence and a non-essential glycoprotein (part of the virus cell-wall) were eliminated. By using a blood test for the presence of antibodies to the glycoprotein, it became possible to differentiate between naturally recovered and vaccinated pigs, since the latter lacked antibodies against the glycoprotein. Today maker systems (deleted vaccine and its corresponding diagnostic tool) are also available for highly infectious diseases such as foot-and-mouth disease and classical swine fever and can thus prevent the killing of thousands of animals in the emergency situation of an outbreak.

Another example on how live-vectored vaccines save foxes and… people

The reduction of rabies in wild foxes is a practical application of the use of the live-vectored vaccine technology. In various parts of Western Europe foxes act as a reservoir of rabies infection for animals and humans. The programme involves scattering baits over wide areas. Each piece of bait, which is eaten by the fox, carries an oral form of rabies vaccine in a capsule. So far, this scheme has considerably reduced the incidence of rabies and death in the fox population and hence the hazard to humans and other species.

A similar vaccination programme using baits and conventional vaccine has started to control hog cholera in wild boar.

THE MARKETING AUTHORISATION PROCESS

The manufacture of veterinary medicines, including vaccines, is strictly regulated in Europe, providing the **best possible guarantees** of safety, quality and efficacy.

The industry and the regulatory authorities share responsibility for the maintenance of these standards of excellence.

In 2001 the European Commission made proposals for improvements to the legislation governing the procedures for the assessment and authorisation of medicinal products and new amended legislation was adopted in 2004.

The animal health industry supports the amended legislation as it builds on the success achieved to date. It will encourage harmonised decision-making across Europe and will put increased focus on monitoring the safety of products in the marketplace to protect the health of consumers, animals, operators and the environment.

What is registration?

Before any new vaccine can be placed on the market, it must obtain a marketing authorisation. This involves a stringent, scientific and independent review by the regulatory authorities of data submitted by the manufacturer to ensure it is:

a) safe towards the consumer, the user, the animal and the environment;

b) of high quality;

c) efficacious.

This detailed in-depth registration process is called “marketing authorisation”[1].

The basis of the review is the **Dossier**, which contains the necessary information needed to carry out the **assessment** and is often voluminous, from **5,000 to 50,000 pages**. This Dossier is submitted by the Applicant Company to the authorities. The latter may ask the Applicant to provide more data or to perform additional studies.

Pharmacovigilance:

This is the systematic collection and analysis of reports from veterinarians and animal owners regarding adverse reactions connected to the use of the vaccine. The company must immediately inform the authorities if any serious adverse reaction is reported. The company must also submit regular summary reports of all recorded incidents.

The registration process may last for several years and generally results in a marketing authorisation (MA). This MA is initially valid for a 5-year period, after which the company can apply for a **renewal**. The decision to authorise renewal is mainly based on the **pharmacovigilance** records (see box). Thereafter, a MA does not have to be renewed again, although the authorities can review its safety and benefits profile at any time.

A marketing authorisation can be obtained at the national level, via national authorities, or as a Community marketing authorisation from a “Centralised Procedure” via the European Medicine Agency (EMEA) in London. The European legislation also provides registration procedures that permit some or all the national authorities to collaborate in a single registration procedure, called Mutual Recognition and Decentralised Procedures. This is intended to avoid duplication of efforts by having to separately repeat the registration process in each Member State of the European Union.

1 A more detailed description is provided in the IFAH-Europe brochure “The Marketing Authorisation Process for Veterinary Medicinal Products in Europe ”.

The EMEA, London

Choice of the registration procedure

All biotechnology-derived vaccines must be registered centrally via the EMEA in order to ensure a harmonised approach using the best scientific expertise across Europe. For other vaccines, the choice of registration procedure depends on whether the company intends to sell the vaccine throughout Europe or just in a few selected countries.

International harmonisation of standards

Trade and testing of imported vaccines

International trade in vaccines is complicated by legislation in the USA, Japan and Australia. The import into the USA of European vaccines is impossible because of the perceived risk from "exotic diseases". Export to Japan and Australia is difficult because of additional testing requirements. A similar situation occurs regarding the import into the European Union of vaccines licensed in accordance with European requirements but manufactured elsewhere. These must be retested upon importation in the receiving Member State.

The health risk in batches from well-regulated sources is infinitesimal but the laws impose trade barriers and more must be done to obtain the mutual recognition of standards between different regions of the world.

European Medicine Agency: Headquartered in London, the EMEA's essential task is to provide scientific advice on the evaluation of safety, efficacy and quality of medicinal products, including vaccines. This is achieved through the service of its CVMP, i.e. Committee for Veterinary Medicinal Products, a committee made of scientific experts from all European member states.

Harmonisation of guidelines for product development

A trilateral (EU-Japan-USA) programme aimed at harmonising technical requirements for veterinary medicinal product registration began in 1983, culminating in the formation of the VICH (the Veterinary International Cooperation on Harmonisation) in April 1996.

Harmonising such an enormous amount of technical requirements and obtaining an agreement between all the involved parties make it a long-term project. A nine-step procedure is followed in developing, implementing and revising each guidance text. So far, only two guidelines specific to vaccines have been finalised. The others are still under discussion.

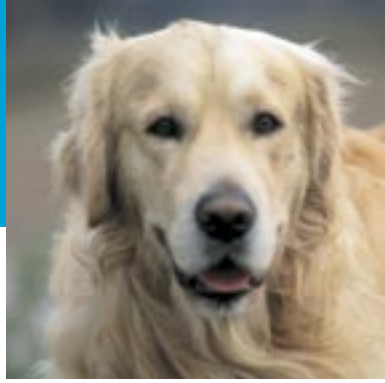
Once adopted, the VICH recommendations should replace corresponding regional requirements. These recommendations should focus on the essential scientific requirements and eliminate unnecessary or redundant requirements.

CONSUMER SAFETY

As explained above, the licensing system evaluates all safety aspects of a new vaccine to ensure the product is safe to the animal, the consumer and the environment. Data must be provided from several studies designed to examine the various safety aspects of a new vaccine. One important aspect of consumer safety is how long after treatment is it safe for the animal produce to enter the food chain. Produce coming from vaccinated animals can enter the food chain immediately as there is no consumer health risk. For example, The Food Standards Agency (UK) has stated that eating meat, milk or other produce from animals that have been treated with authorised foot and mouth disease vaccines does not have any implications for food safety.

Meat from vaccinated animals is potentially healthier as it means that the animal has not become sick, and so is less likely to carry a significant number of disease organisms. Particularly for zoonotic disease organisms, vaccination can reduce the zoonotic risk for the consumer.

THE VACCINE MARKET



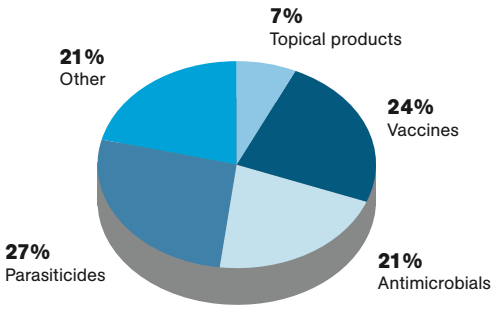
Western Europe[1] is one of the world's most important markets for veterinary medicines and vaccines due to the large number of animals and the high standards of healthcare given to them (see table).

Total European animal health product sales amounted to **$ 4,800 million in 2004**, representing **35%** of the worldwide sales. Western Europe represented 31% and Eastern Europe[3] 4% of worldwide sales. (Source: Wood Mackenzie, 2005).

In comparison, the Western European human pharmaceutical sales were worth approximately **$ 145,590 million** (€ 117,000 million) in 2004. (Source: EFPIA, 2005).

In Western Europe the animal health market represented approximately **3.3%** of the human medicines market in 2004. Vaccines accounted for **24%** of the European market in 2004, parasiticides 27%, antimicrobials 21%, topical products 7% and other 21%. (Source: CEESA, 2005[4]).

Market share of veterinary medicinal product groups in Europe (2004)



The development and registration costs to bring a new product to market are very high, particularly from high-tech sources. Typically, the research and development programmes needed to take a new product from its discovery to the market cost up to **€ 50 million** and takes between 5 and 11 years to complete.

The veterinary vaccines market is relatively small and highly fragmented frequently with quite small production runs. It calls for individual vaccines for a wide variety of species, each with a multiplicity of diseases. This contrasts with human vaccines, which, by definition, are only concerned with one species and a limited number of diseases. This imposes demands and hence costs on the veterinary vaccines sector, which are absent from many other product ranges.

Animal population (in million) in the European Union[2]	
Cattle	**76**
Horses	**5**
Pigs	**120**
Sheep	**87**
Goats	**11.5**
Laying hens	**360**
Dogs	**41**
Cats	**45**
Rabbits	**190**

[1] *Western Europe includes EU-15, Norway, Switzerland, Iceland and Greenland.*

[2] *Eurostat, 2003 for EU-15*

[3] *Eastern Europe includes Central and Eastern European countries and Former Soviet Union.*

[4] *Data coming from 14 IFAH-Europe/CEESA members, representing 95% of the European animal health market over 15 countries (UK, F, D, I, E, PT, NI, B, A, CH, DK, Ir, Pl, Hu)*

FUTURE PROMISE AND OPPORTUNITY

One of the most important natural defence mechanisms of the body is the complex system of immunity to infection. By using vaccines, the veterinarian can even improve natural immunity by stimulating the response before disease strikes or, with antisera, in the very early stages of infection. In addition, with vaccines, whole flock or herd protection can be achieved, as well as protection of the individual.

Vaccines may be seen as an insurance policy, taken out to protect a susceptible animal or population. However, they must always be accompanied with both good husbandry practices and good biosecurity measures, and they must be administered before the anticipated disease threat, to allow active immunity to develop. Antisera are used to treat clinical disease but also give immediate short-term protection to animals in contact or at risk of infection. Vaccination programmes can be classified into four groups:

- Immunisation of individuals: dogs, cats, horses, zoo animals;
- Immunisation of flocks or herds: cattle, pigs, sheep, goats, poultry, fish;
- Immunisation of wild fauna: feral foxes against rabies, wild boars against hog cholera;
- Strategic vaccination of animals to provide a disease barrier, as a “cordon sanitaire” or immunological fire-break to limit the spread of disease.

Vaccines are valuable and specialised products, of great diversity. From Jenner’s first steps, which ultimately removed the threat of smallpox from the world and with all the other advantages they bring, these products occupy an important position in the fight against disease.

They have already achieved great success in controlling many diseases of vital importance in farm and companion animals or which threaten human health. While at present they do not cover all infections, access to modern research holds great promise for the future, as new techniques are mastered. These relate not only to new disease applications and prolongation of immunity, but also to better practical aspects, such as product stability and less dependence on cold-storage. Present and future immunological products increase the ability to keep animals healthy, rather than awaiting the onset of disease with all the consequent losses.

This contributes to the economics of farming, to livestock welfare and to companion animal health. With improvements in vaccines and reduction in “cold-chain” requirements, it should become possible to include more animals in vaccination programmes in developing countries, where food shortages and human malnutrition are common; this will contribute to better standards of animal health and farming prosperity, which in turn benefit human health and the cost of producing safe food.

GLOSSARY

Adjuvant:	Substance that strengthens the immune response.
Antibody/antibodies:	A blood protein that is produced in response to and counteracts an antigen. Antibodies are produced in disease states and help the body fight against the particular disease.
Antigen:	Something, such as a component of an invading micro-organism, that is recognised by the body's immune system as being "foreign" and induces an immune reaction. Vaccines are made using antigenic material.
Antiserum/Antisera:	Liquid extracted from the blood and containing antibodies against specific antigens.
Attenuated (vaccine):	Weakened or treated in such a way as to decrease the ability of a micro-organism to cause infection or disease.
Bacterium/bacteria	Microscopic organism composed of a single cell. Many but not all bacteria cause disease.
Bio-security	Any of a broad range of practices enforced at a farm to prevent transmission of pathogens from other sources (feed, cattle, people, or other animals)
Colostrum:	Milk produced by the mother's mammary glands during the first hours after birth. It provides life-supporting antibodies that insure the health and vitality of the newborn.
Deoxyribonucleic Acid (DNA):	DNA molecules carry the genetic information necessary for the organisation and functioning of cells and control the inheritance of characteristics. The DNA is in the form of two complementary strands.
Freeze-dried (Lyophilised):	Dried by freezing in a high vacuum without destroying their physical structure.
Genetic engineering:	The technique of removing, modifying or adding genes to a DNA molecule in order to change the information it contains.
Genes:	Genes contain the instructions that make up the structure of cells and direct their activities.
Latent infection:	Present but not seen; a latent viral infection is one in which the virus persists hidden in the cells. Under certain circumstances, the virus can be reactivated and the disease reoccurs (as in herpes cold-sore infections).
Immune response/ reaction:	The immune response is the general reaction of the body to substances that are foreign.
Immunity:	Ability to resist disease by identifying and destroying foreign substances or micro-organisms.
Immunisation:	Process of inducing immunity to an infectious agent by administering a vaccine.
Immunology:	Science that studies immunity.
Inactivated (vaccine):	Killed by heat or chemical treatment.
Micro-organism:	An organism that can be seen only with the aid of a microscope; also called a microbe.
Pathogen:	A disease-causing micro-organism.
Strain:	A group of organisms within a species.
Toxin:	A poisonous substance produced by a living organism (e.g., a bacterium, a plant, or an animal).
Toxoid:	Inactivated or killed toxin (such as tetanus) used in vaccine production. A toxoid vaccine is made from a toxin (poison) which has been made harmless.
Virus:	Ultramicroscopic infectious agent that replicates itself only within cells of living hosts.
Zoonosis:	A disease that may be transmitted to people from animals.

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