# The Marketing Authorisation process for animal medicines in Europe

animalhealth europe
THE VOICE OF THE ANIMAL MEDICINES INDUSTRY

This brochure outlines the Marketing Authorisation procedures to which animal medicines companies must adhere to obtain a licence for placing products on the European market.

The rules governing medicinal products for veterinary use in the European Union (EU) sets standards and procedures so that these important products are correctly regulated, both before and after entering the marketplace.

Before any new veterinary medicinal product can be placed on the market, an in–depth review must be carried out by the regulatory authorities, which then decide whether or not the product meets the required standards.

For this “Marketing Authorisation process”, any new medicine needs to be supported by a detailed data dossier that establishes the safety, quality and efficacy of a product.

The data dossier is reviewed by independent experts working on behalf of European and national regulators. They conduct a comprehensive scientific assessment of the data, in–cluding a benefit–risk analysis, to decide whether or not to recommend that the medicine be granted a Marketing Authorisation, with defined conditions of use.

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# A regulated industry
# The pathway to licensing animal medicines

## Objectives of registration

The objectives of registration are to ensure the medicinal product will not cause harm and can deliver the claimed therapeutic benefits before it is allowed on to the market. Registration also allows the regulatory authorities to keep track of which products are in the marketplace, and to ensure their on-going safety is continually monitored.

## How registration has evolved

The legislation governing the registration of veterinary medicines has evolved to reflect scientific progress and the increasing levels of cooperation within EU Members States to facilitate the single market.

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| **1960s**<br>First European Medicines Directive | The registration process for licensing animal medicines has its origins in the 1965 EC Medicines Directive which laid down the three criteria of safety, quality and efficacy. |
| **1980s**<br>Improving the way Member States worked together | In 1981 two European Directives were published with the intention of improving and harmonising the registration process for medicinal products within the European Union (EU). These were later extended to include vaccines and homeo-pathic medicines. |
| **1990s**<br>New centralised EU procedures | In the 1990s controls were further harmonised and tightened with the introduction of legislation covering residues in food, a centralised registration procedure and the rules for Good Manufacturing Practice. |
| **2004**<br>Improved efficiency for an enlarged EU | In 2004 the legislation was amended to increase the efficiency of the procedures which coincided with the arrival of the 10 new Member States that joined the EU on 1 May 2004. |
| **2019**<br>Updating to scientific and technical progress | In 2019 the legislation was further strengthened particularly to enhance the controls on the use of antimicrobials in veterinary medicine, stimulate investment and support innovation, take into account "novel therapies", modernise the system of post-marketing surveillance and improve the functioning of the single market. |

## The authorisation process

Registration results in the granting of an offical “Marketing Authorisation”. The basis of the authorisation process is a scientific review of a data–file, or “dossier”, which is sub–mitted by the applicant company to the regulatory authorities for a scientific review. This is an ex–haustive investigation involving all aspects of the new product. It is based on trial results that must fulfil a set of requirements laid out in the legislation, covering the following three criteria:

- **Safety:** the product is safe for the animal itself, the consumer of food derived from treated animals, those handling the product, and the environment;
- **Quality:** the product is of consistent high quality, and has the stability to last at least until the expiry date;
- **Efficacy:** the product’s efficacy brings sufficient benefits and conforms with the claims made on its information leaflet and label.

The government experts examine the data and make a risk assessment, balancing the benefits of the medicine against any risks that it might pose. If this benefit–risk assess–ment is deemed positive, then the product will be granted a Marketing Authorisation with defined conditions of use.

***Objective scientific evaluation***

*This thorough evaluation process is important because it ensures that only safe and effective products of consistent and defined quality are approved for sale in Europe.*

**AnimalhealthEurope’s members comply with all relevant independent regulatory processes for licensing medicines.**

## The leaflet is an integral part of the product

An animal health product does not consist of the medicine alone. The product label and leaflet are also essential parts of the product and its registration process. The leaflet provides more detailed information on how to correctly and safely use the product, such as more information on the medical condition it is designed to treat, the route or method of administration of the medicine, contra–indications, warnings and withdrawal periods[1]. The regulatory authorities must also approve these and any subsequent changes to them.

*1 **Withdrawal period**: when medicines are used for food–producing animals, residue depletion studies assess the time needed for any residues of a sub–stance or its metabolites (see footnote 3), which may still be present in an animal’s tissues, to fall below the level shown to be safe. These include several built–in safety factors. Once this time has been determined, the withdrawal period can be established. This **withdrawal period** is defined as the minimum time lapse required between the last treatment and the collection of animal produce for human consumption.*

# One Health approach: safety, quality and efficacy

## Criteria 1: Safety

The safety criteria that are examined during the registration process cover four areas: the animal, the consumer, the user and the environment.

### 1. The animal

**Safety to the animal is a top priority.** Products are rigorously screened at the development stage for any potential adverse side effects, from acute or long–term exposure to the medicine, and clinical symptoms of over–dosage are carefully evaluated. The product information leaflet will contain information on how the medicine may be used, and if necessary, how it should not be used, to protect the well–being of the animal.

### 2. The consumer

**For food–producing animals, safety to the consumer is essential.** Studies are carried out to guarantee that no harmful residues remain in the food through the setting of maximum residue limits[2]. After treatment with a medicine, it may be necessary to withhold a food–producing animal or its produce from the food chain for a specified period (known as the withdrawal period[1]), until traces of the medicine have dropped to levels that pose no risk to consumers.

### 3. The user

**The safety of the user is very important.** Those who administer the product must not be put at risk whether they are using it in a veterinary surgery, on the farm or at home. The toxic properties of the product are carefully studied and precautionary advice on safe use is included in the product information leaflet.

### 4. The environment

**The environment must be protected.** The product must also be tested to ensure that under the intended conditions of use, it is safe for the environment. For example, the excreta of treated animals, whether pets or farm animals, must be carefully evaluated for any potential impact on other organisms in the environment.

**From development to use, animal medicines have a built–in One Health approach when it comes to safety, quality and efficacy**

*2 **MRL**: Maximum Residue Limit is the maximum concentration of a residue of a pharmacologically active substance which may be permitted in food of animal origin.*

***Science for Safety***

*To comply with these safety requirements, an integrated set of studies – including metabolism[3], toxicity testing and residue depletion rates – must be carried out. The outcome of these studies indicates at what dosage and under what conditions the product is safe for the animal, the consumer, the user and the environment.*

# Criteria 2: Quality

## High standards of purity and consistency

Pharmaceutical quality is an essential ingredient of product safety and requires the product to be manufactured according to specific standards of purity and consistency. These standards apply throughout the formulation and production process.

The pharmaceutical manufacturer is required to guarantee that a medicine contains only those ingredients that are specified in the data file – nothing more, nothing less – and in the quantities indicated. This often requires the use of sophisticated analytical test methods and keeping up to date with advances in analytical chemistry.

Stability studies are used to determine the product's shelf-life and the storage conditions that ensure the product retains its potency, efficacy and safety.

# Criteria 3: Efficacy

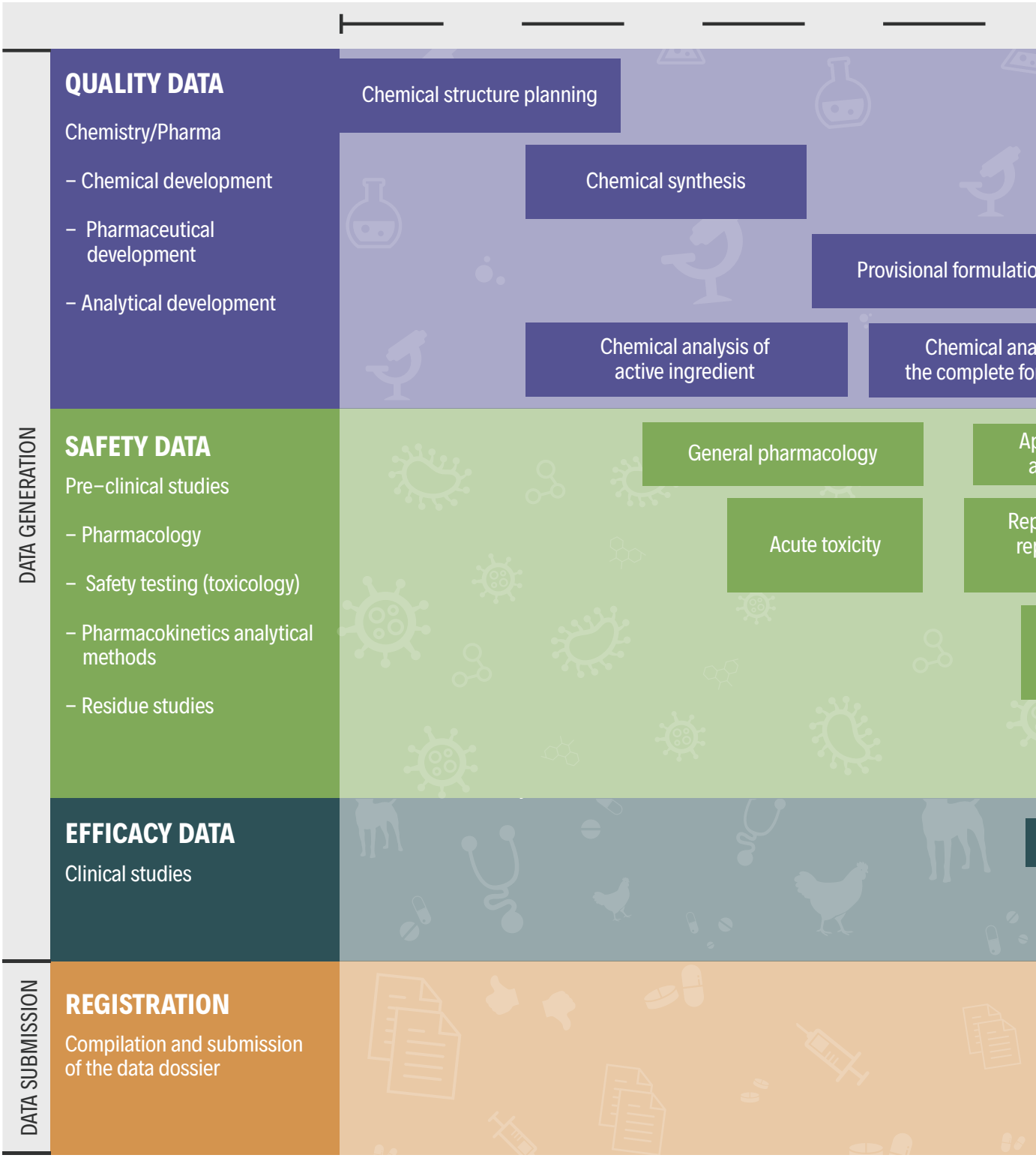
## The product will live up to its claims

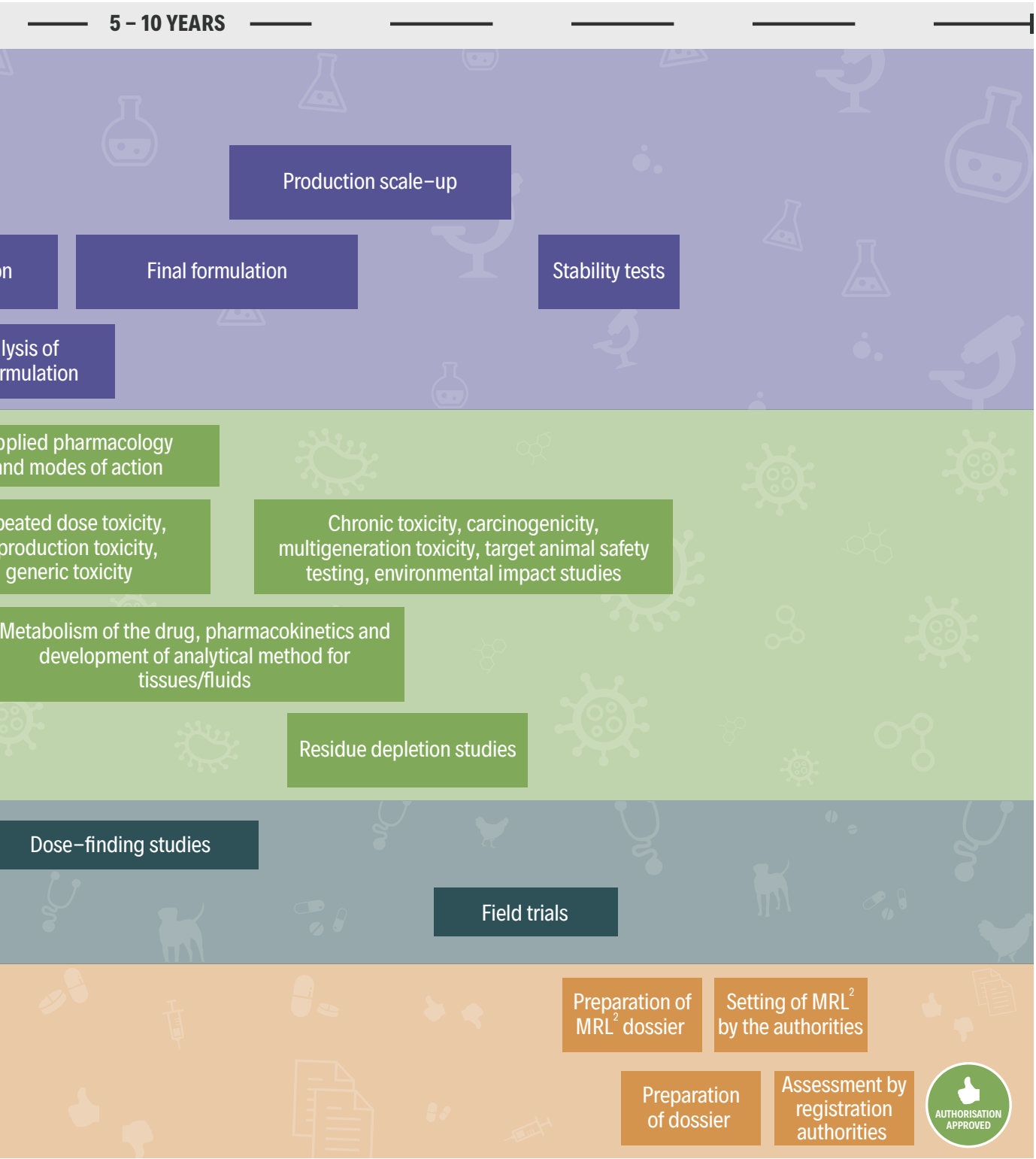
Data must also be provided to prove that the product meets a specified level of efficacy in treating or preventing a particular medical condition. Thus the user can be assured that, when administered as directed (correct dose-rate, frequency and duration of treatment), a product will meet its label claims. To support this claim, a product is tested extensively in the laboratory, in disease challenge studies and finally in field trials, which must demonstrate that it works under conditions of practical use.

*3* ***Metabolism****: set of chemical reactions that occur within the body, which result in the transformation or breaking down of substances into smaller molecules so that they can either be used by the body or excreted. This takes place in specialised organs, mainly the liver. The transformed molecules that are the result of this metabolism are called "metabolites." The toxic potential of the substance or its metabolites is assessed and, after application of an appropriate safety factor, a level shown to be safe either for the consumer or, in animal excreta, for the environment, can be established.*

# Development of a new veterinary medicine

## The research and development project timeline




5 – 10 YEARS
Production scale–up
Final formulation
Stability tests
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nd modes of action
eated dose toxicity,
production toxicity,
generic toxicity
Chronic toxicity, carcinogenicity,
multigeneration toxicity, target animal safety
testing, environmental impact studies
Metabolism of the drug, pharmacokinetics and
development of analytical method for
tissues/fluids
Residue depletion studies
Dose–finding studies
Field trials
Preparation of
MRL2 dossier
Setting of MRL2
by the authorities
Preparation
of dossier
Assessment by
registration
authorities
AUTHORISATION
APPROVED

# Research and Development

## Investing in innovation

Ongoing research and innovation is helping to address existing unmet animal health needs through the use of new technologies, including digital, to deliver solutions to future challenges. There is no room for complacency in the battle against disease. Many disease challenges still remain in veterinary medicine and many new challenges continually appear, so continued research is essential. The vast range of specific requirements inherent to the animal health sector (large number of different species, different diseases, difficult to administer treatments...) drives the need for innovative approaches and requires a highly significant research effort.

Research and development are time and cost intensive. The requirements of safety, quality and efficacy demand complex scientific programmes to provide all the necessary data for regulatory approval. Research and development programmes needed to take a new product from inception to the market can cost up to € 150 million and can take between 5 and 10 years to complete. Much of the time needed for researching and developing the new animal health product is spent on pharmacokinetic[4], toxicity and metabolism studies.

Indeed, successful discovery and development in the laboratory is only the start of the process of bringing a new veterinary medicine to the market (see diagram on page 8). The registration process itself can take up to two years.

## Study results: the dossier

All the study results are assembled in a series of files called the Marketing Authorisation "dossier". This is set out in a standard structure and contains all the information needed to assess a product's safety, quality and efficacy.

Quite often more data, requiring additional studies, may be requested by the regulatory authorities during the registration process. The manufacturer can elect to appear before the regulatory authority's scientifc committee for veterinary medicinal products to present new information and provide additional explanations in support of its application.

*4* ***Pharmacokinetics*** *is the study of the rate of absorption and subsequent excretion of a medicine. Medicines may be administered on the skin, via injec–tion, or orally. The active ingredient of the medicine may be absorbed by the skin or the gut. Excretion may be via the urine or faeces.*

# A transparent registration process encourages investment

The process of research, development and registration of a medicinal product requires significant investment in both time and money. Companies, whether large or small, will only risk this substantial commitment to their resources if the registration process is predictable.

To achieve this the registration requirements must be transparent and based on science. Transparency is provided via a comprehensive set of procedural and scientific guidelines. This must be supported by a clear legal framework and mechanisms for dialogue and exchange of information between the regulator and the applicant company.

Equally important is respect for that system. Its independence, objectivity and credibility must not be undermined by non-scientific considerations.

## A balanced benefit-risk assessment

For any medicine, the potential benefits must be weighed up against the potential risks. There is no such thing as zero risk in any field. Therefore it is imperative that the benefits and risks of a medicine are correctly evaluated and effectively communicated, for example via the medicine's information leaflet.

The outcome of the benefit-risk assessment is made transparent to the general public through the publication of the "Public Assessment report" on the websites of the regulatory authorities responsible for the registration of veterinary medicines.

## Scientific assessment by the regulatory authority

It is the responsibility of the regulatory authority to assess the data dossier, and to approve, ask questions, or recommend rejection if the data provided is inadequate, or does not adequately demonstrate the required levels of safety, quality and efficacy.

Committees composed of independent experts carry out the official assessment of all data submitted in the Marketing Authorisation "dossiers". Their knowledge and experience allow them to make objective judgements based on the data submitted by manufacturers in support of new products.

A pool of other scientists, who give advice on matters of particular scientific specialisms, can be asked to assist these independent experts.

*The registration process must be based on an evaluation of scientific evidence. This ensures it remains predictable and objective. Product development is a long-term commitment. Sudden changes to the regulatory requirements can undermine investment in product research as the investment risk becomes too high. This would have a detrimental effect on innovative research and the development of new veterinary medicines.*

## Procedural and scientific guidelines

An extensive library of guidelines has been developed to provide more detailed information on specific aspects of the data requirements, and fulfil two important functions. Firstly, they assist in the harmonisation of the process in the EU Member States, by providing a common understanding of the data requirements. Secondly, they provide transparency to the applicant company on what data is required.

The scientific committees of the European Medicines Agency (EMA) draw up draft guidelines, and the industry, through its European trade bodies such as AnimalhealthEurope, provides practical comments and suggestions for how the draft guideline can be improved from the perspective of a "user" of the guideline.

This cooperation recognises that availability of clear, workable guidelines facilitates a good understanding between the regulatory authorities and the animal health industry regarding what information is required, how it should be generated and presented, and how it will be evaluated.

*Because of the complexity of the regulatory system there are procedures to allow the good exchange of information between the regulatory authorities – at EU and Member State level – and with the animal health industry. This may take the form of formal scientific advice on individual product applications, or workshops on general or specific scientific or procedural topics. This helps to build transparency into the registration system.*

## Responsibility to society

A key objective of the regulatory process is to protect the public without over–regulation stalling innovation. Regulatory authorities and the animal health industry are conscious of their responsibilities to society and their roles in the task of bringing products to the market, which are of high quality, safe and effective to use.

The rules governing veterinary medicinal products have an important role to play in ensuring that the availability of medicines and vaccines can be maintained to the benefit of our animals. This will help to ensure healthy companion animals and safe affordable food from healthy farm animals.

## Continual safety surveillance in the marketplace

Companies marketing medicinal products must establish and maintain a system for the collection, collation and analysis of reports from veterinarians and animal owners of adverse reactions (or events) connected to the use of a veterinary medicinal product.

This process of continual safety surveillance in the marketplace is known as "pharmacovigilance". The pharmacovigilance data must be entered into a single EU database by the companies, and it is the responsibility of companies to continually monitor the safety of their products through analysis of this data.

The veterinarians and animal owners may also report adverse events directly to the authorities, who must also enter the data into the EU database and inform the company. The authorities can review the safety and benefits profile of medicinal products at any time, both of individual products or groups of similar products, for example those containing the same active ingredient.

# Procedures for registering animal health products in Europe

## Registration in Europe today

Since 1981 there has been a legal framework to harmonise procedures and requirements across the Member States of the EU. The legislation has continued to slowly evolve to remove the remaining barriers to the free movement of veterinary products within the EU, by gradually harmonising the different registration systems that existed in each Member State. From 1993 Member States have been required to recognise the decision of the competent authorities of other Member States, through a regulatory procedure called "Mutual Recognition".

In 1995 a new "Centralised Procedure" for authorisation of medicinal products in the EU came into effect through the establishment of the European Medicines Agency (EMA).

Finally, in 2004, the Mutual Recognition Procedure was complimented with a new "Decentralised Procedure". So now there are several ways by which a product can obtain a Marketing Authorisation in the EU, but all require the same standards of quality, safety and efficacy.

The four routes to a Marketing Authorisation (MA) are:

- National Procedure, to obtain a single MA in just one Member State
- Mutual Recognition Procedure, to extend a single national MA to other Member States
- Decentralised Procedure, to obtain MAs in several Member States
- Centralised Procedure, to obtain a single pan–European MA.

These four procedures are described in more detail on the following pages.

Companies may register a product in just one Member State or a selected group of Member States, to deal with localised diseases or species, or in all EU Member States. The choice of registration procedure (see page 19) is partly restricted because products involving new and innovative aspects must use the Centralised Procedure (see page 18).

## EU legislative framework for registration of animal health products

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| **Regulation 2019/06 on veterinary medicinal products** | Harmonised procedures for<br>• registration for veterinary medicinal products including vaccines<br>• variations to a Marketing Authorisation<br>• manufacturing controls<br>• pharmacovigilance<br>• use, distribution and retail<br>• penalties and controls |
| **Annex to EC Regulation 2019/06** | "Norms and protocols" Outlines the curriculum of tests to be carried out to meet safety, quality and efficacy requirements |
| **Regulation (EC) N° 470/2009** | Procedure for establishing EU maximum residue limits (MRLs) for substances used in food–producing animals |
| **EC Directive 91/412 (1991)** | The principles and guidelines of Good Manufacturing Practice for veterinary medicinal products |
| **Council Regulation (EC) N° 297/95 (1995) as amended by Commission Regulation (EC) N° 494/2003 (2003)** | The fees payable to the European Agency for the evaluation of medicinal products |

*(For more information: http://pharmacos.eudra.org)*

## The National Procedure

Each Member State has its own competent regulatory authority, in the form of an inde–pendent government agency or a department within the Ministry of Health and/or Agri–culture.

If a company wishes to license a product in just one Member State (e.g., for a local disease or species) it can submit an application for Marketing Authorisation to that one national authority.

The dossier is reviewed and evaluated by national experts on quality, safety and efficacy. The outcome of the review is an assessment report and either a recommendation for a Marketing Authorisation to be granted, a request for further information, or a refusal of approval.

## The Mutual Recognition Procedure

A company is obliged to use the Mutual Recognition Procedure (MRP), if it wishes to extend an existing national licence to additional Member States of the European Union. The applicant company can select as many or as few additional Member States as it wants, depending upon where it wishes to market the product.

If the product has already been granted a Marketing Authorisation in one or more Member States, then the company can use the MRP to have the existing licence "mutually recognised" in other Member States.

Under this procedure the dossier has already been examined by the national authority that granted the initial Marketing Authorisation. This Member State then becomes the "Reference Member State" (RMS) for the procedure, and produces an updated assessment report.

The Authorities in the other Member States selected by the company receive a copy of the original dossier and a copy of the assessment report. They should then "mutually recognise" the decision of the RMS. If a member state has concerns then it can trigger and additional review procedure and arbitration (see page 19).

## The Decentralised Procedure

A company can use the Decentralised Procedure for a new product that has no existing national Marketing Authorisation, to obtain Marketing Authorisations in several or all Member States. (N.B. The company may also consider the Centralised Procedure if it wants a pan–EU Marketing Authorisation covering all Member States).

Under this Decentralised Procedure the dossier is sent to one selected national authority. This "Reference Member State" (RMS) then carries out a scientific assessment and produces a draft assessment report (no decision is taken yet).

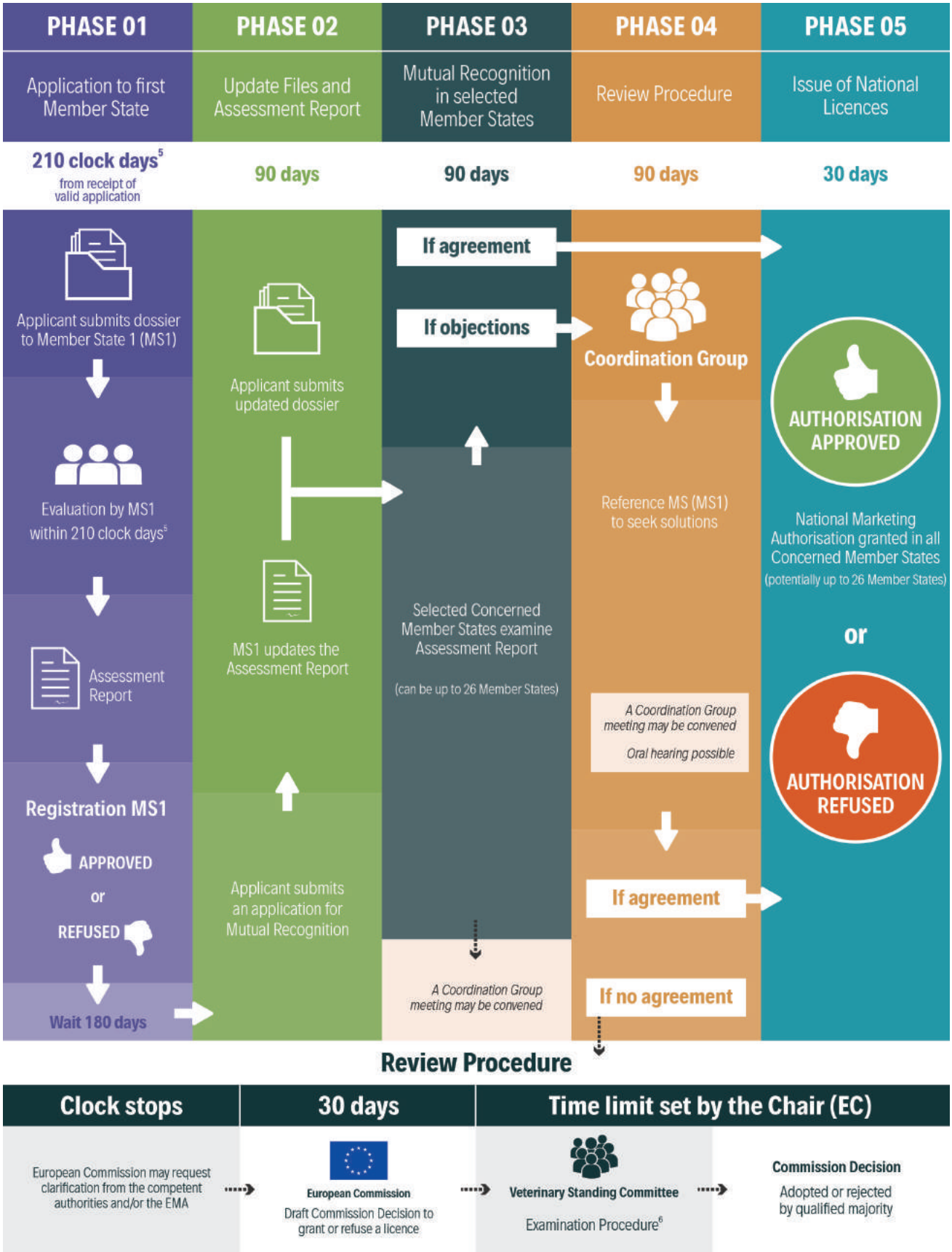
The Authorities in the other Member States selected by the company receive a copy of the original dossier and a copy of the draft assessment report. They should then discuss and agree to a final assessment report, leading to the granting of a Marketing Authorisation in all the selected Member States.

## The Centralised Procedure

The fourth route to obtaining a Marketing Authorisation is the Centralised Procedure, leading to a single Marketing Authorisation valid throughout the EU. This Centralised Procedure is compulsory for medicinal products derived from biotechnology, for products containing a new active substance and for "novel" therapies.

Under this procedure the dossier is submitted directly to the EMA for a scientific evaluation by the Committee for Veterinary Medicinal Products (CVMP). The CVMP opinion is trans–mitted to the European Commission, which prepares a Commission Decision to grant or refuse a Marketing Authorisation that is binding in all Member States of the EU.

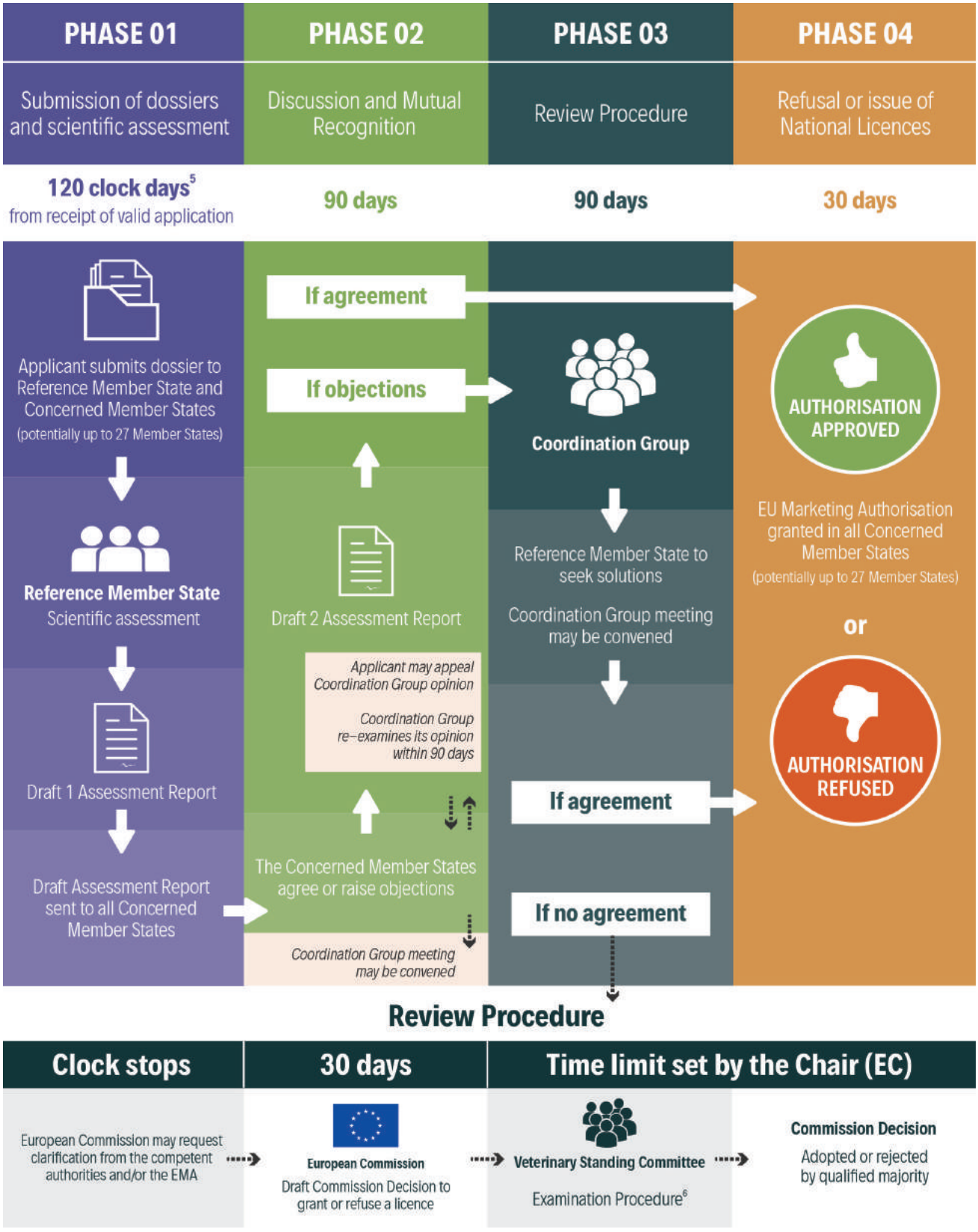
# The Mutual Recognition Procedure



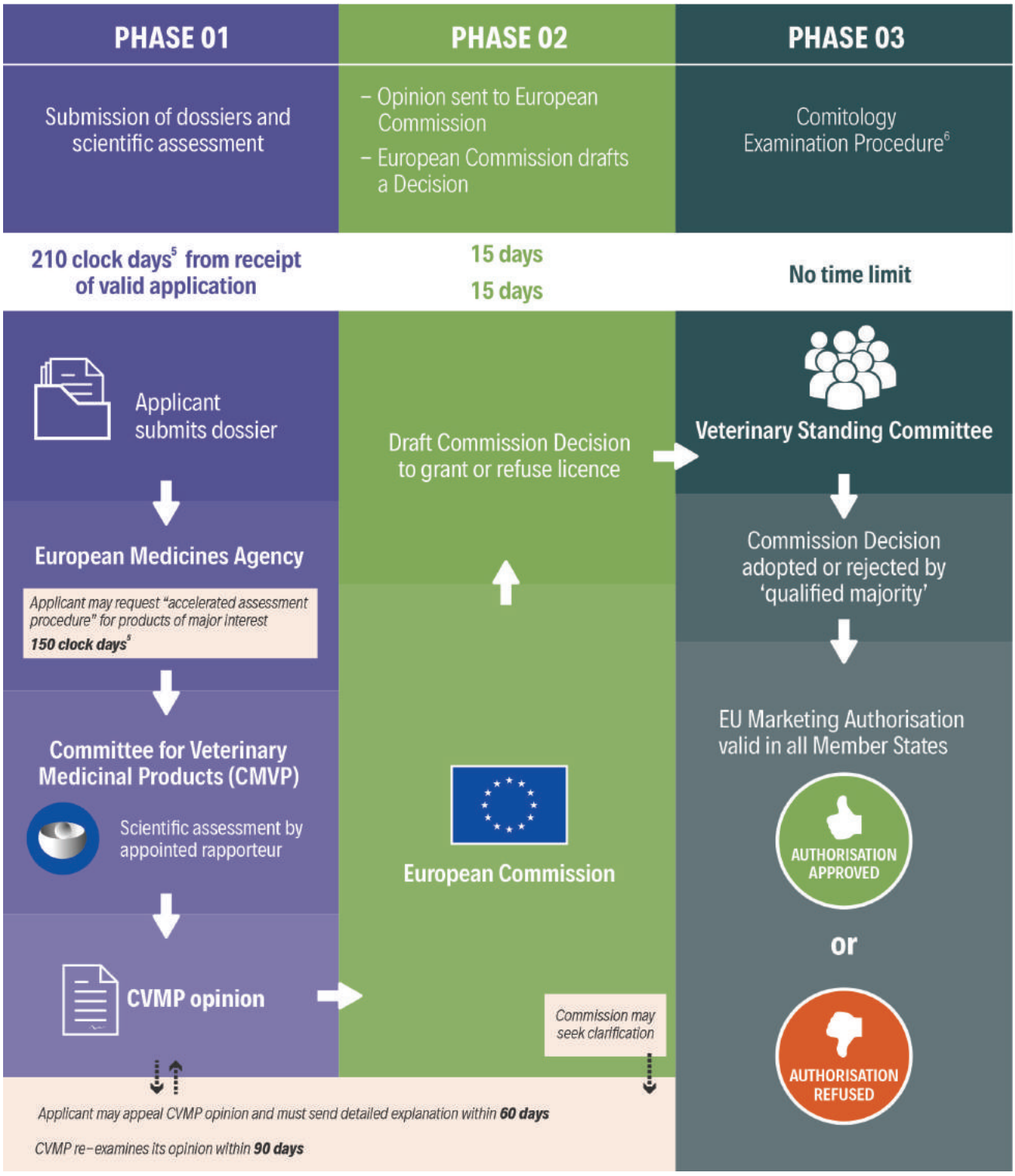

***5 Clock days:*** *if questions are sent to the applicant the "clock" is stopped, and it is only started again when answers have been received from the applicant.*

***6 Examination Procedure:*** *Article 145 of Regulation 2019/06 refers to Comitology Regulation 182/2011, article 5.*

# The Decentralised Procedure



# The Centralised Procedure




***Since 2022 the Centralised Procedure is open to all types of veterinary medicinal products***

## European Medicines Agency

To implement the Centralised Procedure the European Medicines Agency (EMA) was created in 1995. Originally headquartered in London, and now relocated in Amsterdam, the EMA's task is to provide the best possible scientific advice on the evaluation of the safety, quality and efficacy of medicinal products. This is achieved through the services of its Committee for Veterinary Medicinal Products (CVMP), which is made up of scientific experts sent from all of the Member States.

The EMA also provides independent arbitration in the event of disputes in the Mutual Recognition or Decentralised Procedures through the Review Procedure.

## Arbitration

During the Mutual Recognition Procedure or the Decentralised Procedure, Member States often ask further questions and a Member State may raise an objection. If they cannot reach agreement, the disputed point is passed to the Coordination Committee for further discussion (see pages 16 and 17). If the objection cannot be resolved then it is passed to the European Commission to make a decision via the Review Procedure. The European Commission will consult the Committee for Veterinary Medicinal Products (CVMP) of the European Medicines Agency (EMA).

If the objection is valid, the application is rejected (and, for the Mutual Recognition Procedure, the company loses the original national Marketing Authorisation). If the objection is not considered valid by the CVMP then all the Member States must approve and license the product.

## The choice of registration procedure

Companies may choose whether to obtain their registration from the national authorities in one or more individual Member States or centrally, via the EMA. Such a decision clearly depends on whether the company intends to sell the new product throughout the EU or only in certain countries. This might be influenced by which countries the company operates in, and in which countries the animal species and/or disease is present.

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THE VOICE OF THE ANIMAL MEDICINES INDUSTRY

AnimalhealthEurope represents companies that research, develop and manufacture veterinary medicines in Europe.

It represents innovators and generics alike, as well as large, medium–sized and small companies.

AnimalhealthEurope's membership covers 90% of the European market for veterinary products.

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