

# Regulations governing veterinary medicinal products containing genetically modified organisms in the European Community

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## Summary

This paper describes particular aspects of the marketing of veterinary medicinal products (VMPs) that contain or consist of genetically modified micro-organisms (GMMs) or genetically modified organisms (GMOs). The regulatory requirements and the procedures applied in the European Union for each phase (pre-marketing, authorisation process, and post-authorisation labelling and monitoring) are explained.

In most cases VMPs are subject to both pharmaceutical and GMO regulations. In the early stages of the process, before applications for marketing authorisation are submitted, the assessment of clinical trials and experiments in contained areas is principally the responsibility of national authorities. However, the marketing of all VMPs containing or consisting of GMOs must be authorised at European level, although the national authorities are informed and involved in the assessment process.

## Keywords

Biotechnology – European Community – Genetically modified micro-organisms – Genetically modified organisms – Marketing authorisation – Procedure – Regulatory aspect – Veterinary medicinal product.

## Introduction

A veterinary medicinal product (VMP) may only be placed on the market in the European Union (EU) if authorised by the relevant competent authority (a national or EU authority, according to the intended market of the product). In order to obtain this authorisation, a marketing authorisation dossier must be submitted to the competent authority. This dossier should demonstrate the quality of the VMP, that it is safe for the consumer, the animal, the environment and that it has acceptable efficacy.

The marketing authorisation dossier can be based on experimental trials, field trials or a bibliography of previous tests. If the dossier is judged satisfactory by the competent authorities, a marketing authorisation can be granted.

The product can then be marketed under specific rules for labelling and subject to post-marketing monitoring through a so-called 'pharmacovigilance' system. An inspection system, which is the responsibility of Member States, is also in place. Inspections (performed by pharmacists or veterinary inspectors) cover the manufacture, control, importation and distribution of the VMP.

This paper will consider the particular regulatory regimes for the marketing of VMPs that contain genetically modified micro-organisms (GMMs) or genetically modified organisms (GMOs). For each phase in the process (pre-marketing, authorisation process, and post-authorisation labelling and surveillance), the regulatory requirements and the procedures applied in the EU will be described.

## Experimentation on veterinary medicinal products

In order to obtain a marketing authorisation for a veterinary medicinal product, the applicant must provide a review of the relevant literature, including the published scientific literature, pre-marketing studies of the quality, safety and efficacy of the product, and post-marketing studies on similar products (or the same product if it has already been marketed outside the EU). Studies performed by pharmaceutical companies may be conducted in the laboratory, in experimental conditions or in the field.

### Experimentation on veterinary medicinal products in contained areas

#### Provisions applying to all veterinary medicinal products

Directive 2001/82/EC, recently modified by Directive 2004/28/EC, is the basic directive governing veterinary medicinal products (7, 12). In the annex to this directive, which defines what information the marketing authorisation dossier must contain, it is stated that Member States shall ensure that tests are performed in accordance with the provisions for good laboratory practice (GLP) prescribed by Council Directive 2004/9/EC and Council Directive 2004/10/EC on the inspection and verification of GLP (10, 11). This obligation applies to all VMPs.

#### Additional provisions for veterinary medicinal products containing or consisting of genetically modified micro-organisms

Directive 90/219/EC on the contained use of genetically modified micro-organisms, modified by Directive 94/51/EC and Directive 98/81/EC, applies to VMPs containing GMMs (1, 3, 4), and forms the basis of the regulation to be applied in all EU Member States.

The directive states that anybody conducting experiments using genetically modified micro-organisms must notify the relevant authority in their country, and the authority is responsible for ensuring that the notification supplies all the necessary information, e.g. the source(s) and the intended function(s) of the genetic material(s); the purpose of the contained use including the expected results; and a summary of the risk assessment. In France, for example, this procedure is regulated by the Environmental Code (Article L. 532-533) (17), and a commission of genetic engineering is in charge of risk assessment. A specific authorisation must be given for each new use of a GMO.

At the European level, Article 16 of Directive 90/219/EC discusses some of the responsibilities of Member States in relation to the accidental release of a GMO into the environment. The directive states that Member States must consult other Member States that are likely to be affected in the event of an accident in order to draw up emergency plans. It also states that information must be submitted to the EU Commission as soon as possible if an accident occurs.

### Experimentation on veterinary medicinal products in the field

#### Provisions for all veterinary medicinal products

In Directive 2001/82/EC, recently modified by Directive 2004/28/EC, Article 9 indicates in particular that clinical trials are regulated by national legislation (7, 12).

In France, this directive has been transcribed in the Public Health Code (Article R 5141-8) (18). The French Food Safety Agency (AFSSA) is responsible for the assessment of clinical trials, and the General Director of AFSSA can reject any clinical trial if there is justification.

Where VMPs contain GMOs, additional regulations are applied in all EU Member States, as discussed below.

#### Additional provisions for veterinary medicinal products containing or consisting of genetically modified organisms

Directive 2001/18/EC established a step-by-step approval process for a case-by-case assessment of risks to human health and the environment that must be undertaken before any GMO, or product containing GMOs, can be released into the environment or placed on the market (6).

For experimental releases, any person must, before undertaking a deliberate release of a GMO, submit a notification to the competent authorities of the Member State where the release is to take place. The notification must include a technical dossier (8) that supplies the information necessary to perform an assessment of the environmental risk posed by the deliberate release of the GMO. This risk assessment will cover animal health (in both target and non-target species) as well as human health.

The competent authority shall assess the notification, taking into account any observations made by other Member States, within 90 days of receipt of the notification. There will be public consultation, except in specific circumstances where a different procedure has been proposed on the grounds that sufficient experience has been obtained from previous releases of certain GMOs.

Following this assessment, during which questions can be asked of the notifier, the competent national authority shall either accept or reject the release of the GMOs.

The notifier may proceed with the release only after receiving the written consent of the competent authority, which may be subject to meeting certain conditions.

In France, for example, this procedure is regulated by the Environmental Code and a commission for the study of the dissemination of GMOs is responsible for risk assessments. For trials with veterinary medicines, a specific scheme is in place involving both the national authority responsible for experiments with veterinary medicines and the GMO commission mentioned above (16). In France, AFSSA is responsible for assessments and for consultation with other Member States. Advice is taken from the GMO commission during the assessment procedure.

In brief, experimentation on VMPs containing GMOs or GMMs is regulated in the EU by both pharmaceutical and GMO legislation. On the basis of Directive 2001/18/EC, the national competent authorities have the principal responsibility for assessments. Information is shared at European level and procedures exist for accidental events.

## Authorisation of veterinary medicinal products

### Provisions for all veterinary medicinal products

In order to gain permission to market a VMP, the applicant must submit a marketing authorisation dossier, which can be assessed by means of three different procedures, as follows:

- the national procedure that is used for VMPs that are intended for use within one country only or that will be subject to a mutual recognition procedure
- the mutual recognition procedure that enables a marketing authorisation holder (MAH) that has already obtained marketing authorisation in one Member State to ask for the recognition of this authorisation in other States
- the centralised procedure that is valid for the whole EU. This means that companies submit one single marketing authorisation application to the European Medicines Agency (EMA) and a single evaluation is carried out through the Committee for Medicinal Products for Veterinary Use (CVMP) (an EMA committee consisting of national scientific experts). The opinion of the CVMP is subject to the EU decision-making process, but if the opinion is positive, the authorisation obtained is valid for all EU Member States and is considered as an *acquis communautaire*, i.e. when a new country enters the EU, the

marketing authorisation automatically becomes valid in this new Member State.

### Additional provisions for veterinary medicinal products that contain or consist of genetically modified organisms

In Europe, Regulation 2309/93/EC states that medicinal products developed by means of one of the following biotechnological processes shall be authorised through the centralised procedure (2):

- recombinant deoxyribonucleic acid technology
- controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes, including transformed mammalian cells
- hybridoma and monoclonal antibody methods.

Regulation 2309/93/EC also states that medicinal products developed by other biotechnological processes which, in the opinion of the European Medicines Agency (EMA), constitute a significant innovation may be authorised through the centralised procedure.

The biotechnological processes quoted in this regulation correspond to the techniques referred to in the definition of GMOs in Directive 2001/18/EC (Article 2, paragraph 2 and Annex 1, see Appendix), even if the exact wording is not identical (6). Consequently, in Europe, VMPs containing or consisting of GMOs are assessed through the centralised procedure, i.e. there is only one assessment (performed by the CVMP), and one marketing authorisation is granted for all EU Member States.

Article 28 of Regulation 2309/93/EC indicates that the opinions expressed by the CVMP should respect the criteria laid down by Directive 2001/18/EC to ensure that all appropriate measures are taken to avoid adverse effects on human health and the environment. The same article prescribes formal consultation among the 2001/18/EC competent authorities (2, 6).

A Notice to Applicants document published by the EMA ('Guideline on GMOs: updated notice to applicants guidance') (14) describes the dossier to be provided for the environmental risk assessment (Part II.H of the marketing authorisation dossier).

The procedures followed by the EMA and the CVMP when evaluating marketing authorisation applications are described in a standard operating procedure 'SOP-V-4012' published by the EMA (15). In brief, the 2001/18/EC competent authorities are informed of the timetable for the procedure (which lasts 210 days) and receive Part II.H of the marketing authorisation dossier. They are asked to

provide comments and ask questions by Day 90 of the procedure. These comments and questions will be considered and discussed by the CVMP and the rapporteur of the dossier (a CVMP member appointed to lead the evaluation). Any answer from the company on questions related to Part II.H will be transmitted to the competent authorities (6).

A recent proposal is to appoint a lead 2001/18/EC competent authority in order to facilitate communication between marketing authorisation authorities and 2001/18/EC authorities. Other proposals to streamline the procedure have been implemented (6).

A new regulation, 726/2004/EC, will replace the current 2309/93/EC in November 2005, but will not alter the requirements concerning VMPs that contain GMOs (13, 2).

The VMPs containing or consisting of GMOs authorised in the EU are listed in Table I.

## Labelling of veterinary medicinal products

Labelling of VMPs is regulated under Directive 2001/82/EC (Title V) (7), but there is no specific regulations for the labelling of GMO content. Moreover, VMPs are explicitly excluded from the scope of Regulation 1830/2003, which concerns the traceability and labelling of GMOs (9). Directive 2001/18/EC (Article 26), however, is applicable to VMPs that are used for experimental purposes (6).

**Table I**  
**Authorised veterinary medicinal products containing or consisting of genetically modified organisms**

Regime	Vaccine name (producer)	Target species	Authorised	Component	
Authorised under the centralised procedure	Bayovac CSF marker (Bayer)	Pig	2001	Classical swine fever virus – inactivated	
	Equilis strep E (Intervet)	Horses	2004	Live <i>Streptococcus equi</i> strain – deleted	
	Eurifel FELV (Merial)	Cat	2000	Feline leukaemia virus – recombinant	
	Eurifel RCP FELV (Merial)	Cat	2002	Panleucopenia virus – attenuated Canarypox-FELV virus Feline calicivirus – inactivated Viral rhinotracheitis (feline herpesvirus type 1) antigen	
	Fevaxyn pentofel (Merial)	Cat	1996	Pentavalent feline vaccine (four viral antigen + 1 chlamydial antigen) – inactivated	
	Gallivac HVT IBD (Merial)	One-day-old chicken/chicken embryo	2002	Live herpes recombinant virus vHVT013-69	
	Ibraxion (Merial)	Pig	2000	Inactivated gene deleted (gE-) marker IBR vaccine virus	
	Neocolipor (Merial)	Pig	1998	<i>Escherichia coli</i> – inactivated	
	Porcilis ART-DF (Intervet)	Pig	2000	<i>Bordetella bronchiseptica</i> cells – inactivated <i>Pasteurella multocida</i> – inactivated	
	Porcilis pesti (Intervet)	Pig	2000	Classical swine fever virus – inactivated	
	Porcilis porcoli (Intervet)	Pig	1996	<i>E. coli</i> – inactivated	
	Proteq flu (Merial)	Horse	2003	Equine influenza virus VCP1529 VCP1533 virus	
	Proteq flu T (Merial)	Horse	2003	Equine influenza virus VCP1529 VCP1533 virus <i>Clostridium tetani</i> toxoid	
	Suvaxyn Aujeszky 783 (Fort Dodge)	Pig	1998	Live attenuated Aujeszky's disease virus – live	
	Virbagen omega (Virbac)	Dog/cat	2001	Recombinant omega interferon of feline origin	
	Authorised before the implementation of Regulation 2309/93	Begonia Aujeszky IDAL (Intervet)	Pig	1992	Swine herpes virus – live deleted
		Begonia Aujeszky (Intervet)	Pig	2002	Swine herpes virus – live deleted
		Eurican herpes 205 (Merial)	Dog	2001	Canine herpes virus – inactivated
		Leucogen (Virbac)	Cat	1988	Leukaemia feline virus – inactivated
Nobilis <i>E. coli</i> (Intervet)		Chicken	1998	<i>E. coli</i> – inactivated	
Porcilis injeszky (Intervet)		Pig	2000	Swine herpes virus – inactivated	
Raboral V-RG (Merial)		Fox	1994	Rabies virus – recombinant	

## Post-authorisation surveillance of veterinary medicinal products

A pharmacovigilance system is compulsory for VMPs (Directive 2001/28/EC, Title VII [5]). This system requires veterinary practitioners and other healthcare professionals to report adverse reactions related to any VMP. The MAH is responsible for recording all suspected serious reactions and reporting within 15 days to the Member State authority. The MAH is also required to submit regular safety update reports (every six months for the first two years, annually in the two following years, and then every three years) to the competent authorities for all adverse reactions recorded on approved products.

The pharmacovigilance system monitors adverse reactions in particular, but also addresses the validity of the withdrawal period, the efficacy of the product and potential environmental problems (7).

No specific additional requirements apply to VMPs containing or consisting of GMOs.

## Conclusion

During the early stage of experimentation before a marketing authorisation application is submitted, GMO regulations govern experiments in contained areas and both pharmaceutical and GMO regulations apply to clinical trials. Veterinary medicinal products that contain GMOs are authorised at European level, although national GMO authorities are informed and involved in the assessment process.

## Appendix

### Directive 2001/18/EC (Article 2, paragraph 2)

‘Genetically modified organism (GMO)’ means an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.

Within the terms of this definition:

- a) genetic modification occurs at least through the use of the techniques listed in Annex I A, part 1
- b) the techniques listed in Annex I A, part 2, are not considered to result in genetic modification.

### Annex I A-Techniques referred to in article 2 (2)

#### Part 1

Techniques of genetic modification referred to in Article 2 (2)(a) are *inter alia*:

- 1) recombinant nucleic acid techniques involving the formation of new combinations of genetic material by the insertion of nucleic acid molecules produced by whatever means outside an organism, into any virus, bacterial plasmid or other vector system and their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation
- 2) techniques involving the direct introduction into an organism of heritable material prepared outside the organism including micro-injection, macro-injection and micro-encapsulation
- 3) cell fusion (including protoplast fusion) or hybridisation techniques where live cells with new combinations of heritable genetic material are formed through the fusion of two or more cells by means of methods that do not occur naturally.

#### Part 2

Techniques referred to in Article 2 (2)(b) which are not considered to result in genetic modification, on condition that they do not involve the use of recombinant nucleic acid molecules or genetically modified organisms made by techniques/methods other than those excluded by Annex I B:

- 1) *in vitro* fertilisation
- 2) natural processes such as: conjugation, transduction, transformation
- 3) polyploidy induction.



## Réglementation européenne des médicaments vétérinaires à base d'organismes génétiquement modifiés

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### Résumé

Cet article aborde les aspects particuliers de la commercialisation des médicaments vétérinaires contenant des micro-organismes génétiquement modifiés (MGM) ou des organismes génétiquement modifiés (OGM). L'auteur décrit les exigences réglementaires et les procédures appliquées dans l'Union européenne pour les différentes phases (études précédant la commercialisation, procédure d'autorisation, étiquetage et contrôle des produits commercialisés). Dans la plupart des cas, les médicaments vétérinaires sont soumis à la fois à la législation pharmaceutique et aux réglementations sur les OGM.

Les autorités nationales sont généralement chargées d'évaluer les expérimentations se déroulant en milieu confiné ainsi que les premiers essais cliniques réalisés préalablement à la demande d'autorisation de mise sur le marché. Tous les médicaments vétérinaires qui contiennent des OGM doivent cependant être autorisés au niveau européen, bien que les autorités nationales soient informées de la procédure d'évaluation et y participent.

### Mots-clés

Aspect réglementaire – Autorisation de mise sur le marché – Biotechnologie – Communauté européenne – Médicament vétérinaire – Micro-organisme génétiquement modifié – Organisme génétiquement modifié – Procédure.



## Reglamentación europea de los medicamentos veterinarios que contienen organismos modificados genéticamente

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### Resumen

El autor describe una serie de aspectos particulares de la comercialización de los medicamentos veterinarios que contienen o están compuestos por microorganismos u organismos modificados genéticamente. También expone los requisitos reglamentarios y los procedimientos que se aplican en la Unión Europea en cada etapa (antes de la comercialización, durante el proceso de autorización y, una vez obtenida la licencia, en las fases de etiquetado y control). En la mayoría de los casos, a los medicamentos veterinarios se les aplican tanto el reglamento sobre productos farmacéuticos como el relativo a los organismos modificados genéticamente.

Las autoridades nacionales suelen ser las encargadas de evaluar los experimentos en zonas de confinamiento y los ensayos clínicos que se llevan a cabo en las primeras fases de experimentación, antes de presentar una solicitud de comercialización. Sin embargo, en el caso de los medicamentos veterinarios que contienen o constan de organismos modificados genéticamente, la autorización se otorga desde instancias europeas, aunque las autoridades nacionales reciben información del proceso de evaluación y participan en él.

### Palabras clave

Aspecto reglamentario – Biología – Comunidad Europea – Licencia de comercialización – Medicamento veterinario – Microorganismo modificado genéticamente – Organismo modificado genéticamente – Procedimiento.



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