



The Director General

Maisons-Alfort, 21 October 2013

OPINION
**of the French Agency for Food, Environmental
and Occupational Health & Safety**
on autogenous vaccines for veterinary use

ANSES undertakes independent and pluralistic scientific expert assessments.

ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.

It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its opinions are made public.

1. BACKGROUND AND PURPOSE OF THE REQUEST

On 17 June 2011, ANSES received a formal request from the French Union for the Veterinary Medicinal Product & Reagent Industry (SIMV) relating to the general issue of autogenous vaccines.

The request was expressed as four questions:

- *Question 1:* Considering the history of the use of autogenous vaccines in France and the available data, what conclusions can be drawn in terms of efficacy?
- *Question 2:* Apart from a problem with inactivation during preparation (since in principle this risk is controlled), what potential risks can be identified with regard to the use of autogenous vaccines in animal husbandry?
- *Question 3:* Is it desirable to conduct further tests (bacteriological or epidemiological for instance) to decide whether or not the use of an autogenous vaccine is appropriate? If so, which ones?
- *Question 4:* Is the use of an autogenous vaccine – rather than a vaccine with marketing authorisation (MA) containing the same bacteria – justified on the basis of specific bacterial characteristics? If so, which bacterial characteristics should be considered to justify the benefits of the autogenous vaccine?

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French Standard NF X 50-110 “Quality in Expert Appraisals – General requirements of Competence for Expert Appraisals (May 2003)”.

ANSES entrusted the collective expert appraisal of this request to a multidisciplinary working group (WG) consisting of field experts, virologists, bacteriologists, immunologists and regulatory experts, selected following a call for applications. This Working Group on Autogenous vaccines for veterinary use reported to the French Commission for Veterinary Medicinal Products (CNMV) and the ANSES Expert Committee on Animal Health (CES SANT).

The methodological and scientific aspects of the work were regularly submitted by the WG to the CES SANT and the CNMV. The report produced by the WG takes account of the observations and additional information supplied by the members of the CES and the CNMV.

This work was therefore produced by a group of experts with complementary skills.

The publications analysed by the WG were extracted from the PubMed database (<http://www.ncbi.nlm.nih.gov/pubmed/>).

The CNMV and the CES SANT endorsed the collective expert appraisal work and its conclusions and recommendations, as described in the WG's report, at their respective meetings on 17 and 18 September 2013 and informed ANSES's General Directorate accordingly.

3. ANALYSIS AND CONCLUSIONS OF THE CES SANT AND THE CNMV

Following an examination of the questions asked, two types of questions were identified. Firstly those requiring a legal analysis of the legislative and regulatory measures in force in France (verification of the safety of autogenous vaccines, pharmacovigilance system, use of an autogenous vaccine in farms different from the one where the pathogen was isolated, for example) and secondly, those of a technical and scientific nature.

In order to respond to the questions asked, therefore, it was initially necessary to devote a chapter of the report to the regulatory and technical aspects of autogenous vaccines and their specific characteristics compared with conventional vaccines, then to review the use of autogenous vaccines in France, for each of the different animal production sectors.

Finally, answers were provided to the four questions in the request.

3.1. Review of the regulations and technical specifications for autogenous vaccines

The review of the regulations focused on the definition of autogenous vaccine and the good preparation practices (GPP) applying to autogenous vaccines for veterinary use, as well as the implementation of the "cascade" approach and its limits in the field of vaccinology.

Autogenous vaccines are not presently authorised for use in ruminants in France, due to the risk of prion transmission. The WG did not therefore address these species in its report.

The WG's report reiterated the fundamental principles currently governing the granting of authorisation for the preparation of autogenous vaccines:

- enable the prescriber to benefit from the widest possible vaccine arsenal;
- give priority to vaccines with MA, as autogenous vaccines can only be defined as being complementary to vaccines with MA (since an autogenous vaccine is by definition an extemporaneous preparation);
- do not make autogenous vaccines a subcategory of vaccines with MA by easing the scientific requirements that vaccines with MA must meet.

Authorisation for the preparation of autogenous vaccines is based on a positive list of pairs of pathogens/target species for which there is no available vaccine with MA in

France for the indication and species considered. This list may be revised at any time in response to changes in demand and in vaccines with MA. Derogations may be considered in relation to vaccines with MA, especially in the event of suspected lack of efficacy, technical infeasibilities concerning administration, or stock shortages of vaccines with MA.

Authorisation also establishes a positive list of usable adjuvants, which may be revised at any time. Only adjuvants without a maximum residue limit (MRL) can be included on this list.

In addition, establishments preparing autogenous vaccines are inspected regularly, in accordance with standards of good preparation practice (GPP). The preparation of autogenous vaccines relies on a quality assurance system relating to personnel, premises, preparations and verifications, which aims to ensure the quality of the autogenous vaccines prepared, but also and more importantly, to qualify the scientific and technical environment (best effort undertaking) of the laboratory preparing the autogenous vaccines.

At present in France, autogenous vaccines for veterinary use are overwhelmingly used in the prevention of bacterial diseases. An inventory of the use of autogenous vaccines shows that over 50 million doses are produced each year. Demand relates mainly to the poultry (69% of doses produced in 2011) and fish sectors (29.7%), followed by the swine sector (1.2%).

The report gives several examples illustrating the use of autogenous vaccines in production sectors. It appears that veterinary practitioners have sole responsibility for their prescription, which is indicated:

- for a minor indication and/or a minor species, or in the event of multiple serotypes, given the difficulty of developing a “universal” vaccine to cover all serotypes (lack of available vaccine with MA);
- for a different animal category or production stage and indication to those targeted by a vaccine with MA;
- in the event of antigenic drift, which is not covered by vaccines with MA;
- to alleviate any potential breakdown in the manufacturing process of a vaccine with MA, in the absence of possible imports;
- to obtain a quick response in the event of emergence of a new disease, pending availability of a vaccine with MA, a situation that rarely occurs.

Prescription of autogenous vaccines is therefore intended to act as a complement to vaccines with MA, and is the last resort for controlling certain epidemiological situations. It is then up to the prescribing veterinarian to advocate the rational use of autogenous vaccines depending on the specific conditions. In the event of unsatisfactory results in terms of efficacy and/or adverse effects, the veterinarian will then cease prescribing them.

The use of autogenous vaccines is defined at farm level. This is interpreted in its strict sense as the facility in which the animals are raised (geographical concept) and by their belonging to the same breeder (concept of ownership); the regulations do not include the concept of epidemiological link between production units that are geographically distinct (and sometimes far away from each other), especially for animals intended for trade and having different owners, each specialising in a production segment (production of hatching eggs, production of eggs for consumption, farrowing operator, growing/finishing farm, etc.).

3.2. Answers to the four questions in the request

Question 1: Considering the history of the use of autogenous vaccines in France and the available data, what conclusions can be drawn in terms of efficacy?

The scientific literature includes a number of publications on autogenous vaccines, whose scope is limited, given the very definition of autogenous vaccine. The results are only valid with respect to the batch(es) used and cannot be extrapolated to future batches or other similar autogenous vaccines. The few data available on the efficacy of autogenous vaccines, along with studies showing the induction of a specific immune response following the injection of inactivated bacteria and an adjuvant, provide proof of concept for the efficacy of autogenous vaccines.

The studies emphasise the importance of the choice of vaccine strain and adjuvant in the efficacy of vaccine preparations. Regularly updating knowledge about the bacterium or bacteria present on a farm is an important part of maintaining the efficacy of the autogenous vaccine.

Feedback from prescribing veterinarians and results of experimental tests on the target species show that preparations can claim a certain level of efficacy, despite the recognised failures. It is impossible to be more precise, as each autogenous vaccine preparation requires a case-by-case assessment.

The use of autogenous vaccines to combat bacterial diseases, on condition that they provide adequate protection that complements the available vaccines with MA, can therefore be part of the arsenal contributing to a reduction in the prescription of antibiotics to livestock.

Question 2: Apart from a problem with inactivation during preparation (since in principle this risk is controlled), what potential risks can be identified with regard to the use of autogenous vaccines in animal husbandry?

For livestock animals, the greatest risks relating to vaccination are the risk inherent in the use of adjuvants according to the target species and the risk of infection.

The risk associated with the use of adjuvants is manifested by local and/or general reactions that can lead to economic losses (livestock losses, seizure of meat at the slaughterhouse, etc.). Choosing adjuvants suitable for the target species can partially control this risk.

The risk of infection can result from the contamination of raw materials, specifically samples taken at the farm, or of the autogenous vaccine when it is being prepared. This type of infection risk is reduced by obliging the preparer to meet the requirements of good preparation practices.

Veterinary prescribers are aware of these risks and weigh them against the expected benefit in a given clinical context.

For the user, the risk is negligible and limited to accidental injection (importance of the adjuvant).

For the consumer, there is no risk, since only adjuvants without an MRL are authorised for use.

Question 3: Is it desirable to conduct further tests (bacteriological or epidemiological for instance) to decide whether or not the use of an autogenous vaccine is appropriate? If so, which ones?

The prescribing veterinarian has sole responsibility for deciding whether or not the use of an autogenous vaccine is appropriate, in accordance with the law and as part of the diagnostic approach described in the report. Once the etiologic diagnosis (which includes the isolation and identification of the bacterial strain) has been established on the farm, no further examination is needed to justify the veterinarian's choice.

Question 4: Is the use of an autogenous vaccine – rather than a vaccine with marketing authorisation (MA) containing the same bacteria – justified on the basis of specific bacterial characteristics? If so, which bacterial characteristics should be considered to justify the benefits of the autogenous vaccine?

Preparing an autogenous vaccine, when a vaccine with MA containing the same bacteria is already available on the market, requires obtaining a derogation, in a situation involving either lack of efficacy of the vaccine with MA or a difference between the vaccine strain and the strain isolated on the farm (bacterial characterisation). The report examines different situations in which preparers of autogenous vaccines requested such a derogation in order to use autogenous vaccines on some farms.

The report first underlines the difficulty, most of the time, of demonstrating the lack of efficacy of a vaccine with MA, especially for practitioners who can only note a treatment failure in field conditions and are unable to confirm whether this corresponds to an actual lack of efficacy. Nevertheless, it is important that the industry and the Agency are made aware of these treatment failures under the pharmacovigilance scheme. A simplified system for reporting or exchanging experiences in this area should be considered.

Secondly, the report analyses bacterial characterisation through examples, some of which may show its limitations. It appears that bacterial classifications are useful for qualifying the bacteria, but are not the key point in vaccinology. Serological typing, which is most frequently used, is only of interest if the characterised antigens play a part in protective immunity. Determining bacterial characteristics should therefore be done on a case-by-case basis and depends on the practical availability of the tools needed for their detection, which could lead to real problems in objective assessment.

Therefore, it is not always possible to consider bacterial characterisation alone when deciding whether or not a request for a derogation for the preparation of an autogenous vaccine is appropriate. Other information can be provided, in particular by the prescribing veterinarian, to support this request.

3.3. Recommendations

The CNMV and the CES SANT validated the findings and recommendations of the WG's work:

- to continue encouraging the reporting of adverse effects observed and suspected lack of efficacy of vaccines;
- to encourage the production of a good practice guide for the prescription of autogenous vaccines by practitioners;
- to raise the issue of a possible revision of the regulations on autogenous vaccines in ruminants, given the change in the epidemiological situation regarding TSE since 2003;
- to change the French regulations on autogenous vaccines for veterinary use to ensure coherent support and supervision of health management of farming methods in integrated, highly segmented and specialised production sectors, by including the concept of epidemiological link between farms (prior administration of autogenous vaccines to animals destined to be moved to another farm or to their parental lines, in order to confer immunity to the animals before they encounter the pathogen in the farm they are transferred to);
- to organise, at the initiative of practitioner organisations, the voluntary exchange of information on the use of autogenous vaccines.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

ANSES reiterates that under French regulations, autogenous vaccines for veterinary use are immunological medicinal products prescribed and used as extemporaneous preparations, on a small number of animals from which the pathogen has been isolated. Their use is confined to the individual farms.

They are currently used primarily in the prevention of bacterial diseases. They are prohibited in cattle, sheep and goats as part of animal health measures to combat TSEs.

The French Agency for Food, Environmental and Occupational Health & Safety endorses the conclusions and recommendations of the working group, the CNMV and the CES SANT.

ANSES advocates the following:

- a revision of the regulations for autogenous vaccines for veterinary use in France, to avoid the persistent use of an autogenous vaccine without periodic reassessment of its efficacy with regard to the strains present on the farm;
- consideration by the legislature of a possible revision of the regulations on autogenous vaccines in ruminants.

The Director General

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KEY WORDS

Autogenous vaccine, veterinarian, poultry, fish, swine