



EUROPEAN COMMISSION
HEALTH & CONSUMERS DIRECTORATE-GENERAL

Directorate D — Animal Health and Welfare
D1-Animal Health and Standing Committees

Brussels, May/2010

SANCO/7070/2010/summary

Summary of

**EXPERT OPINION ON VACCINE AND/OR DIAGNOSTIC
BANKS FOR MAJOR ANIMAL DISEASES**

**STRATEGIC PLANNING OPTIONS FOR EMERGENCY
SITUATIONS OR MAJOR CRISES**

This document does not necessarily represent the views of the Commission Services

Please note that this document is the outcome of an expert group and has been prepared for information and consultation purposes only. It has not been adopted or in any way approved by the European Commission and should not be regarded as representative of the views of the Commission Services either. The European Commission does not guarantee the accuracy of the information provided, nor does it accept responsibility for any use made thereof.

ACRONYMS AND ABBREVIATIONS

AHS	African Horse Sickness
AHSV	African Horse Sickness virus
AI	Avian Influenza
ASF	African Swine Fever
ASFV	African Swine Fever virus
BT	Bluetongue
BTV	Bluetongue virus
CRL	Community Reference Laboratory
CSF	Classical Swine Fever
CSFV	Classical Swine Fever virus
CVMP	Committee for Medicinal Products for Veterinary Use
DG SANCO	Directorate General Health and Consumers
DIVA	Differentiating infected from vaccinated animals
EC	European Commission
EFSA	European Food Safety Authority
ELISA	Enzyme-linked Immunosorbent Assay
EMA	European Medicines Agency
EU	European Union
EUFMD	The European Commission for the Control of foot-and-mouth disease
FMD	Foot-and-mouth disease
FMDV	Foot-and-mouth disease virus
GMP	Good Manufacturing Practice
HPAI	Highly Pathogenic Avian Influenza
LPAI	Low Pathogenic Avian Influenza
MS	Member State
NRL	National Reference Laboratory
OIE	World Organisation for Animal Health
PCR	Polymerase chain reaction
Ph. Eur.	Pharmacopoeia Europaea
rRT-PCR	Real Time Polymerase Chain Reaction:

KEY MESSAGES

1. Vaccination is a fundamental tool in a strategy to control and eradicate major emerging diseases.
2. Emergency vaccination has to be considered as one tool in a whole range of measures as a part of a complex strategy to control and eradicate major animal diseases.
3. Emergency vaccination for most of the relevant infectious diseases should in general be seen in a new light, directly linked to the availability of effective diagnostic tools substantiating that vaccinated animals, or meat and other products obtained from vaccinated animals, are free from pathogens and can be traded safely.
4. Emergency vaccination has to be understood as *vaccinate-to-live*, meaning that vaccinated animals are kept to the end of a normal production cycle, and that their meat and other products can be marketed.
5. Diagnostic banks for particular infectious diseases are necessary to supplement vaccine banks to enable a holistic strategy of disease control and eradication.
6. The establishment and maintenance of vaccine and diagnostic banks must be part of a strategic plan prepared during 'peace time' ready for an emergency.
7. The issue of vaccine and diagnostic banks can only be treated in the context of a control and eradication strategy specific to each major animal disease (e.g. FMD, CSF, AI) and various outbreak scenarios.
8. For most of the relevant infectious diseases, existing legislation regarding emergency vaccination should be amended in such a way that vaccination becomes a realistic option in the event of a crisis.
9. Trade issues regarding vaccinated animals or fresh meat and meat products obtained from vaccinated animals should be resolved.
10. Relevant legislation regarding veterinary medicinal products is not well suited to approve the use of vaccines in emergency situations.
11. The current review of legislation dealing with veterinary medicinal products is an ideal opportunity to introduce a mechanism for the approval of vaccines for emergency use at European level.
12. Proposals to be considered could include alternatives to vaccine banks, such as vaccine master seed stocks and 'mock up' authorisations for particular vaccines.
13. Vaccination and testing should replace unnecessary culling.

SUMMARY

Background

Vaccination is a fundamental tool in a strategy to control and eradicate major emerging diseases. Vaccine and diagnostic banks improve the feasibility of emergency vaccination by guaranteeing supplies if there is no immediate alternative and/or by bridging the period until a Member State can purchase its own vaccines and diagnostic tests.

The European Commission launched an external evaluation to review its animal health policy in 2005. Based on the results of this evaluation, strategic aims and objectives for animal health were set out in the Commission Communication on the new EU Animal Health Strategy¹ where '*Prevention is better than cure*' and its Action Plan² respectively, which cover the period 2007–2013. The action plan is structured around four main pillars or areas of activity:

1. Prioritisation of EU intervention;
2. The EU Animal Health framework;
3. Prevention surveillance and preparedness;
4. Science, Innovation and Research.

Identifying problems before they emerge while being ready to manage major animal disease outbreaks and crises is one of the expected outcomes of the Animal Health Strategy. This is an essential component of Pillar 3 of the new strategy.

Under Pillar 3 in particular, as point 24 of the programming document³ for the Action Plan, a task force was created to assist the Commission in the development of a policy paper on EU vaccine/antigen banks for major animal diseases such as foot-and-mouth disease (FMD), classical swine fever (CSF), avian influenza (AI) and others. Such banks should be available in emergency situations or major crises.

It is widely agreed that in many cases, the best means of combating animal diseases once they occur is in accordance with the principle that 'vaccination is better than unnecessary culling'. This has also been confirmed by opinions from the other European institutions and stakeholders during the drafting of the Strategy and its Action Plan.

Emergency vaccination has to be seen in a new light, directly linked to the availability of effective diagnostic tools substantiating that vaccinated animals or the meat and meat products obtained from vaccinated animals are free from pathogens and can be traded safely.

That is why it is necessary to discuss the availability and quality of diagnostic tests when discussing vaccines. Furthermore, the issue of EU vaccine banks can only be treated in the context of a specific vaccination strategy for each major disease (e.g. FMD, CSF, AI). The establishment and maintenance of vaccine and diagnostic banks must be part of a strategic plan prepared during 'peace time', ready for an emergency.

¹ COM (2007)539 final, 19.09.2007.

² COM (2008)545 final, 10.09.2008.

³ http://ec.europa.eu/food/animal/diseases/strategy/pillars/action_en.htm.

The document focuses mainly on diseases which have historically had a major impact in the European Union or which are considered to be major risks in future; and on vaccines and/or diagnostic tests which can or should be applied in an emergency situation. The exercise of categorising animal diseases, as provided for in the Animal Health Strategy, is of capital importance for setting priorities for intervention in the field of animal health. In addition, DISCONTTOOLS⁴ may be a good support tool for identifying further relevant issues (e.g. diseases for which veterinary medicines need to be developed or other means of control for certain diseases).

However, all elements concerning vaccination need further reflection in a number of fora in the coming years. Hence the present paper does not go into the area of measures that should be taken, nor does it suggest policy options to ensure the free circulation of products derived from vaccinated animals. Although this puts a brake on the use of vaccination as a tool in combating the spread of contagious animal diseases, other tools and policy options will be addressed in a broader context. Such options might include, *inter alia*, a ban on consumer labelling of products derived from vaccinated animals, effective public communication strategies regarding the harmlessness of products derived from vaccinated animals, and the conclusion of conventions on the free circulation of products derived from vaccinated animals between governments, farmers' organisations, consumer organisations and retail and trade operators. These issues remain outside the scope of this paper.

Scope of this paper

The scope of this paper is:

- Identification of the infectious diseases for which vaccine or antigen banks should be available in the EU in the near future;
- Conditions under which vaccination against certain infectious diseases is recommended;
- Recommendations for vaccination strategies under emergency situations;
- The use of vaccines as part of DIVA-strategies⁵;
- Estimates of size and costs of envisaged vaccine stocks;
- Identifying the need for diagnostic banks (e.g. for particular ELISA or PCR tests);
- Recommendations for improving EU legislation on use of vaccines in emergency or endemic situations.

Criteria for vaccine banks

Council Directive 82/894/EEC of 21 December 1982 on the notification of animal diseases in the Community lists in Part A of Annex I the diseases of terrestrial animals which are subject to notification. In total, 22 infectious diseases are listed, all of which are traditionally considered to have a major impact on animal health, but also on trade or human health (zoonotic character). They are therefore used as an initial pool of diseases for this exercise.

⁴ Disease Control Tools, www.discontools.eu.

⁵ DIVA: Differentiating infected from vaccinated animals.

However, not all of these diseases have been judged as justifying emergency vaccine and diagnostic banks. The diseases identified so far for this strategy are: FMD, AI, CSF, AHS, BT, ASF.

The criteria identified for having a vaccine and/or diagnostic bank are:

- That vaccination against the particular disease is a possible and effective control tool to protect animals from infections and prevent the spread of the disease;
- That vaccination can be part of a holistic strategy, including other methods to control and eradicate the disease;
- That vaccination is a realistic and cost-effective strategy compared to others based on non-vaccination;
- That trade issues are resolved regarding the vaccinated animals or the fresh meat and meat products obtained from vaccinated animals;
- That adequate vaccines or antigens and the means to vaccinate large numbers of animals are available, or could be made available for a programme to control the infection at short notice.
- That adequate diagnostic tools and/or surveillance systems are in place to substantiate that vaccinated animals are free from the infectious agent against which the vaccine has been used;
- That there is a legal basis for emergency vaccination;
- That there is a legal basis for the vaccines/antigens bank, including testing procedures for antigens/vaccine and the emergency release of vaccines;
- That there are surveillance systems in place to ensure the closest possible vaccine match where pathogens tend to antigenically diversify (early warning); and administrative and legal procedures to allow rapid adaptation of vaccine variants to the specific epidemiological situation.

Conditions for emergency vaccination

Emergency vaccination, supported where necessary by a vaccine and diagnostic bank, is needed in an emergency situation when an infectious agent is introduced under circumstances with potential for rapid spread and significant damage, such that a policy of non-vaccination risks failure or would require massive resources and/or culling of animals. Conditions under which emergency vaccination is recommended include, for example:

- Where infection has occurred in or threatens an area with a relatively high-density population of vulnerable animals;
- Following multifocal introduction of infection, or where infection has not been rapidly detected and controlled, leading to multifocal spread;
- Where there is a high risk of uncontrollable spread of infection, for example by the airborne route;

- Where there is inadequate capacity or resources for control by non-vaccination, or where such measures are considered economically, socially or ethically unacceptable; or not practically feasible for any other reason;
- Where there is a significant risk of a (potential) zoonotic agent spreading from animals to humans or vice versa.

Alternatives to vaccine banks

The probability and impact of certain exotic diseases affecting the EU's livestock populations and spreading may be too low to justify setting up a ready or near-ready stock of vaccines or antigens, though this would be technically feasible. A less costly, but still beneficial alternative might be to provide funds to establish specific vaccine master seed-stocks, from which vaccines could be produced and deployed more quickly than if starting from scratch.

However, a number of regulatory and legal issues would have to be addressed to ensure that vaccine master seed-stocks could become a useful additional tool to combat such incursions. Without substantial amendment of existing legislation on veterinary medicinal products, it is difficult to envisage a system of common master seed-stocks which could be used as a source for the rapid manufacture of authorised veterinary vaccines for emergency use. For example, master seed-stocks would have to be tested according to the *Pharmacopoeia Europaea* (Ph. Eur.) requirements to ensure they were free of potential contaminants.

An interesting regulatory concept that has been introduced for human influenza vaccines is that of a 'mock up' authorisation. The applicant company chooses a strain that is a good candidate for a future outbreak, provides the formulation data, the selected dose and very limited clinical data. Once this has been reviewed by regulators, the company receives a 'mock up' licence authorising use of the product only in case of an epidemic of that specific strain. If an epidemic occurs with a different strain, the licence can be activated following the rolling review concept, where regulators assess data with the new strain as they become available.

Recommendations for particular vaccine and diagnostic banks

Foot-and-mouth disease (FMD)

- There is a continuing need for an EU FMD vaccine bank, containing stored antigens in sufficient quantity to provide up to 5 million doses per strain, depending upon the level of risk.
- The selection of vaccine strains to be represented should be based on risk assessment informed by up-to-date knowledge of the global distribution of FMDV serotypes and strains and of the likelihood of their spreading to the EU.
- Industry could be contracted to prepare vaccine seed-stocks to cover strains of lower perceived risk, but regulatory procedures add considerably to the time needed before such seed-stocks could be turned into final product.
- Efforts should be made to harmonise procedures and reach agreement on sharing of vaccine antigens or formulated vaccines between vaccine banks of Member States,

including the EU Bank. This could give access to greater quantities of vaccine, for more diverse strains.

- The Commission should continue to support research efforts intended to produce more potent and more thermostable FMD vaccines with more rapid onset of protection, improved DIVA properties and broader strain coverage.
- A bank of pen-side FMDV-detection systems should be established, providing rapid access to 500 lateral flow devices and 5 portable nucleic acid detection systems.
- A commercial supply of DIVA serological test kits should be established, to enable at least 2.5 million animals to be tested at short notice.
- There is a need to review the supply of serotype-specific serological test kits to see if diagnostic reagent banks are also warranted for these assays. This could be undertaken by Commission services with technical assistance from the European Union Reference Laboratory for FMD and the EU FMD Research Group.

Avian Influenza (AI)

- The only scenario where emergency vaccination might be applied is in an area at risk of HPAI because of a neighbouring infection. It is difficult to foresee the possible application of metaphilactic vaccination in an area where a HPAI virus is already actively circulating, due to the rapid spread of infection and the time needed to induce an adequate level of immunological protection in a large poultry population at high risk of AI.
- Recommendations on which AI vaccines are most likely to be required for emergency vaccination may be provided by the OIE/FAO Network of AI Reference Laboratories. National and Regional AI vaccine banks, including those of individual EU Member States and of the EU, should be advised on vaccine strain selection by the National and the European Union Reference Laboratory respectively.
- It is recommended to have stocks of vaccine available for two H5 viruses and two H7 viruses from the Eurasian ‘lineage’, possessing different neuraminidases (N) subtypes. The establishment of a stock that includes a bivalent (H5 and H7) inactivated vaccine should be considered to improve efficiency. The option of stocking H9 vaccine should also be evaluated, as it is considered a potential candidate for a human pandemic.
- A minimum number of doses should be established, based on the number needed to sustain an emergency vaccination programme for at least three months in areas with the highest poultry population densities. Therefore a minimum of 7-8 million doses are needed.
- Taking into account the need to store vaccine strains of at least four virus subtypes to perform heterologous vaccination, the size of the AI vaccine bank should be around 30–40 million doses. This could be reduced if a bivalent (H5 and H7) inactivated vaccine were available.
- Under certain epidemiological circumstances, the vaccine bank should also be available to control LPAI outbreaks.

- The relatively short shelf life of inactivated AI vaccines (12-24 months) needs to be taken into account in planning for an AI vaccine bank. This problem may be overcome by applying the principle of an antigen bank, or by applying the rolling stock principle.
- AI viruses appear to be evolving antigenically. Constant monitoring of antigenic characteristics of circulating AI viruses by testing new virus isolates is recommended.
- The availability of a diagnostic bank with a suitable discriminatory test is not an essential pre-requisite to implement rapid emergency vaccination, if sentinel birds are part of the strategic programme. However, the European Union Reference Laboratory for AI should provide recommendations on how a suitable antibody ELISA could be made available in due time should emergency vaccination be necessary.

Classical swine fever (CSF)

- Emergency vaccination should be accepted as an important and valuable tool for the control of CSF in wild boar and domestic pigs. Strategic programmes for emergency vaccination should become part of the contingency plans of Member States with a high pig density.
- To allow efficient and timely emergency vaccination, an EU vaccine bank with a live attenuated vaccine (e.g. C-strain) is needed, enabling vaccination of at least 2 million pigs.
- Alternatively, the storage of the E2-subunit vaccine as an antigen should be tested and evaluated by the European Union Reference Laboratory for CSF or by other appropriate mechanisms. Providing the evaluation is positive an antigen bank should be implemented.
- A diagnostic bank for an E^{RNS}-marker ELISA is needed, together with the marker vaccine bank. Test kits for not less than 50 000 pigs should be available within seven days of a request. The availability of a diagnostic bank with a suitable PCR test is not an essential pre-requisite.
- Practically oriented screening schemes are needed to identify infected animals in a post-vaccination area.
- A properly designed and implemented emergency vaccination strategy together with a targeted search for chronically-infected animals in vaccinated herds during final screening would mean a lower risk for fresh meat than a conventional non-vaccination strategy.
- If one of the new prototype modified live marker vaccines is licensed, it should be included in the vaccine bank together with the appropriate diagnostic tests.

African horse sickness (AHS)

- A vaccine bank with live attenuated vaccines against serotypes 2, 4 and 9 of AHSV should be established. However, other serotypes, e.g. serotype 5, should be considered for future planning of vaccine banks.

- If one of the new prototypes of recombinant vaccines is licensed, it should be included in the vaccine bank as a priority.
- The vaccine bank should contain a minimum of 150.000 doses for each of the proposed serotypes.
- In addition, developing a working seed bank for all nine serotypes of the virus is recommended, to cover the first steps for developing an inactivated vaccine.
- The availability of a diagnostic bank with a suitable test is not an essential prerequisite.
- After establishing the initial stock, continuous monitoring of the epidemiological situation of AHS in the countries geographically close to the EU is recommended, to identify serotypes which might become risks for EU livestock, and so adjust the development and procurement of vaccines against those serotypes.

Blue tongue (BT)

- Establishing vaccine seed-stocks for BTV serotypes not currently present in the EU is recommended.
- The vaccine seed-stocks should enable the production of enough inactivated vaccine to provide up to 5 million doses for each of the proposed serotypes.
- Establishing continuous monitoring of the epidemiological situation of BT in countries geographically close to the EU is recommended to identify serotypes which might become risks for EU livestock, so as to adjust the development and procurement of vaccines against those serotypes.
- The availability of the BT diagnostic tests is not a problem; therefore a diagnostic bank is not needed.

African swine fever (ASF)

- No vaccines exist against ASF.
- A diagnostic bank should be established with antibody ELISA test kits for testing not less than 100 000 pigs.

General issues related to the vaccines industry

To establish a vaccine or antigen bank, industry needs to respond to a relevant tender. To market authorised vaccines in the EU, the size of the vaccine/antigen bank, the price per dose, the shelf life of the vaccine or antigen and renewal plans are important issues. For vaccines that are not yet authorised in the EU, the existence of a vaccine elsewhere in the world, the need to start a development programme, and standards relating to safety, quality and efficacy need to be considered.

A cost-efficient method to make available a vaccine bank rapidly is to deploy 'rolling stock' where a company has ongoing production and increases its reserve stock by the quantity of the tender. The advantage of this is that emergency vaccine is manufactured, tested and released in accordance with European legislation and can be distributed quickly.

Consideration needs to be given to the merits of creating an antigen bank rather than a vaccine bank. An antigen bank has many advantages over vaccine banks, and is especially suitable if the vaccine has a short shelf life, or in case of diseases with antigenic variance, such as FMD, AI, etc where the formulation of the vaccine can be decided once the field virus has been typed.

The only disease for which there is a regulatory framework within the EU for rapid release of vaccine from pre-tested antigen is FMD (Ph. Eur. Monograph 0063). To apply the principle of a vaccine or antigen bank for diseases other than FMD, appropriate regulatory aspects need to be addressed in EU legislation.

The vaccine industry needs a financial incentive to develop a vaccine against a new disease or new serotype. If there is no vaccine against an emerging disease and there is no existing market for such a vaccine, there is no such incentive. For such emerging diseases, public funding is recommended for vaccine development, along with a commitment for an antigen/vaccine bank linked to this funding.

Relevant legislation regarding veterinary medicinal products is not well suited to approving the use of vaccines in emergency situations. The current review regarding legislation dealing with veterinary medicinal products is an ideal opportunity to introduce a mechanism for approving vaccines for emergency use at European level.

Overview of proposals for vaccine and diagnostic banks

DISEASE	Vaccine Bank		Diagnostic Bank	
	Type	Size	Type	Size
FMD	Selection of vaccine strains based on up-to-date risk assessments	2.5 – 5 mil doses per strain	<ul style="list-style-type: none"> • Serological tests kits • Lateral flow devises • Portable PCR systems 	<ul style="list-style-type: none"> • for 2.5 mil animals • 500 • 5
AI	H5 and H7 strains (selection of vaccine strains based on recommendation of OIE/FAO Network of AI)	7 – 8 mil doses per strain	Not needed	
CSF	<ul style="list-style-type: none"> • Live attenuated vaccine • E2 subunit vaccine 	2 mil doses	<ul style="list-style-type: none"> • Not needed • E^{rns} ELISA 	<ul style="list-style-type: none"> • for 50.000 animals
AHS	Against serotypes 2, 4 and 9	150.000 doses per serotype	Not needed	
BT	Vaccine seed-stocks for the BTV serotypes not currently present in the EU.	5 mil doses of final vaccine per serotype	Not needed	
ASF	No vaccine available		Antibody ELISA	for 100.000 animals

ACKNOWLEDGEMENTS

DG SANCO, Unit D1 wishes to thank the experts of the task force for the preparation of this policy paper, which will help the Commission in the development of future actions, particularly as regards managing major animal disease outbreaks and crises situations and reinforcement of EU vaccine and diagnostic banks:

- Martin Beer
- David Paton
- Armin Elbers
- Stefano Maragon
- Luis Jose Romero
- Nikolaus G. Križ
- Declan O'Brien
- Johanna Koolen
- Menke Steenbergen

Scientific and technical coordination: Unit D1, DG SANCO: Klaus Depner and Isabelle Omer.