Federal Institute for Vaccines and Biomedicines

Paul-Ehrlich-Institut

Stakeholder focus group meeting on availability of Lumpy Skin Disease (LSD) vaccines authorised to EU standards

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Lessons learnt from authorisations under exceptional circumstances at NCA and EMA level

Lessons learnt by EU regulators from the authorisations of Foot-and-Mouth Disease, Avian Influenza, Bluetongue and Schmallenberg vaccines in the EU

LSD Focus group meeting,

London, 31.01.2017

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Agenda

- Legal requirements - Directive 2001/82/EC
- Emergency Animal Disease – a challenge for animal and human health
- Foot and Mouth Disease (FMD)
- Avian Influenza (AI)
- Bluetongue (BT)
- Regulatory methods in place to address animal health needs
- Experiences and examples
- Regulatory expectation for the future

Legal requirements - Directive 2001/82/EC

- **Art. 5 of Dir. 2001/82/EC**
  Requires that, with only minor exceptions, all veterinary medicinal products (VMPs) that are placed on the market in the EU must hold an marketing authorisation (MA)

- **Art. 7 and 8 of Dir. 2001/82/EC**
  Exceptional deviations are laid down here.

- **Art. 12 to 13d of Dir. 2001/82/EC**
  Define the particulars and documents accompanying an application for MA

- **Annex I of Dir. 2001/82/EC**
  Requirements that VMPs must meet for granting a MA.

Legal requirements - Directive 2001/82/EC

- **Art. 7 of Dir. 2001/82/EC**

  Where the health situation so requires, a Member State (MS) may authorise the marketing or administration to animals of VMPs which have been authorised by another MS in accordance with this Directive.

- **Art. 8 of Dir. 2001/82/EC**

  In the case of a lack of suitably authorised products national competent authorities (NCAs) can respond to an outbreak of an serious epizootic disease with emergency vaccination by implementing Art. 8 of Dir. 2001/82/EC to provisionally allow the use of vaccines without an authorisation.

Emergency Animal Disease – a challenge for animal and human health

- **Emergency Animal Disease or animals disease emergencies**
  (also called: transboundary animal diseases)
  - Affect large numbers of livestock
  - Most highly contagious / spread easily & rapidly
  - Animal health impact (high morbidity & mortality, cause pain & suffering)
  - Severe economic consequences (affect food and nutrition security, production losses, trade implications,
  - Human health impact (zoonosis, mental health impact)
  - Environmental consequences (die-offs in wildlife populations)

Emergency Animal Disease – a challenge for animal and human health

- **Animal disease emergencies**
  may occur when there are unexpected outbreaks of epizootic diseases or other animal health-related events which have the potential to cause serious socio-economic consequences for a country.

- **Continuous risk of outbreaks of new diseases in EU Countries**
  due to epizootiological situation of major infectious diseases in neighbouring European countries as well as worldwide (not necessarily only exotic or foreign animal diseases).

- **Occurrence of one of these diseases**
  may have disastrous consequences for a country/region, pose a serious risk to world animal agriculture & food security & compromise international trade.

Emergency Animal Disease – a challenge for animal and human health

- **International Office of Epizootics (OIE)**
  list of epizootic animal diseases of major economic importance – (2016: list includes 118 animal diseases, infections and infestations)
- **Serious animal epidemics** have affected or threatened EU countries in recent years
  (e.g. African & Classical Swine Fever, FMD, Bluetongue, Lumpy Skin Disease, Avian Influenza)
- Extensive experience with eradicating animal diseases has been gained over recent years in EU.

Emergency Animal Disease – a challenge for animal and human health

Situation

- Lack of authorised products for serious epizootic diseases.
  + their repeated use in emergency situations.
  + risks associated with the use of unauthorised products during emergency circumstances.
- Unequivocal preference by all stakeholders, notably NCAs, farmers and consumers, to have access to vaccines with a MA that is valid for the territory concerned for MSs to use.

→ Need for regulatory measures to promote their authorisation.

Advantages of vaccines being submitted via CP in the interests of achieving a harmonised pan-European approach to such vaccines.

Emergency Animal Disease – a challenge for animal and human health

- Depending on the level of emergency, the **use of vaccines as one of the most effective methods to prevent and manage infectious diseases** can be of crucial relevance for the control of outbreaks or the eradication of diseases in livestock animals.
- **Vaccination programmes** are pivotal in the control of many emergency animal diseases, but should be carefully planned and targeted to meet a well-defined objective.
- Fight against through the use of vaccines is a priority and the measures to stimulate the development of vaccines should be encouraged

Emergency Animal Disease – a challenge for animal and human health

- Recommendation to implement incentives for industry, such as
  - Fee waivers.
  - Development of a veterinary GL on an accelerated assessment procedure for veterinary medicinal products.
- Concept of a core-dossier (multi-strain dossier) containing a large pool of authorised master seeds from which the manufacturer can then select a number of antigens, up to a specified limit, to formulate each batch of product.

Foot and Mouth Disease (FMD)

- **2001**: CVMP agreed to set up an ad hoc group on FMD vaccines to harmonise existing GLs from CVMP, FAO & EDQM.
- **FMD vaccines** (like human influenza vaccines) represent a special case in terms of need for rapid and constant change in the strains included and therefor do not fit well within the general regulatory model for vaccines.
- **Concept paper** on vaccines used for vaccination against FMD describing the current problems with the evaluation of FMD vaccines in the EU (June 2001).
- **Position paper** considering scientific issues raised by FMD vaccines and proposing methods that can be used to demonstrate that vaccines meet the necessary technical standards (Oct 2002).

Avian Influenza (AI)

- **Autumn 2005**: CVMP began to consider initiatives in relation to AI at request of the EC.
- Main factors for these discussions: growing threat of outbreaks of AI within EU and lack of authorised vaccines.
- CVMP agreed **short, medium & long-term actions** with the objective of achieving MAs for AI vaccines, which permit timely adaptations to pandemic situations.
- **Reflection paper** on minimum data requirements for authorisation under exceptional circumstances for vaccines for emergency use in birds against H5 and/or H7 highly pathogenic AI virus.

Avian Influenza (AI)

- **Short-term**: Development of GL on minimum data requirements for an authorisation under exceptional circumstances for vaccines for emergency use against H5 and/or H7 highly pathogenic AI viruses.
- **Medium-term**: legislative amendments in place, which would allow the authorisation of vaccines against AI , and possibly even other diseases such as FMD, in order to permit authorised vaccines that can be adapted quickly to a pandemic situation.
- **Long-term**: recommendation to revise the current regulatory approach to tests that allow differentiation of vaccination from infection.

Avian Influenza (AI)

Autum 2005	**CVMP discussion**
Jan/Feb 2006	**Reflection paper:** *Minimum data requirements for an authorisation under exceptional circumstances for vaccines for emergency use in birds against H5 and/or H7 highly pathogenic avian influenza virus.*
Mar/Apr 2006	**Concept paper** *on requirements for vaccines for use in birds against Avian influenza virus.*
Jun/Jul 2006	**Guideline** *on requirements for an authorisation under exceptional circumstances for vaccines for use in birds against avian influenza.* (release for consultation)
Mar/Apr 2007	**Guideline** (final adoption)
Nov 2007	**Guideline** (date for coming into effect)

Bluetongue (BT)

- **2006/2007:** Increased number of BT outbreaks - disease is spreading fast through Europe and became endemic in many EU countries.
- Urgent need to make authorised products available.
- Similar approach should be followed as the one that was applied for AI vaccines.
- Recommendation to draft a **guideline** on minimum data requirements for an authorisation under exceptional circumstances for vaccines for emergency use against bluetongue to facilitate a rapid authorisation of vaccines.

Bluetongue (BT)

Jan 2007	**CVMP discussion**
Mar/Apr 2007	**Reflection paper:** *Minimum data requirements for an authorisation under exceptional circumstances for vaccines for emergency use against bluetongue.*
Feb/Mar 2008	**Concept paper** *on minimum requirements for an authorisation under exceptional circumstances for vaccines for emergency use against bluetongue.*
Jun 2008	**Guideline** *on requirements for an authorisation under exceptional circumstances for vaccines against bluetongue.* (release for consultation)
Oct/Nov 2008	**Guideline** (final adoption)
May 2009	**Guideline** (date for coming into effect)

Regulatory methods in place to address animal health needs

- **“Exceptional circumstances” clauses**

  (Art 26(3) of Dir. 2001/82/EC & Art 39(7) of Reg. (EC) No 726/2004)

Provisions have been applied in order to facilitate rapid authorisation of vaccines in advance of generation of data to meet the full requirements of Annex I to Dir. 2001/82/EC.

- Specific procedures imposed as part of the marketing authorisation.
- Such authorisations may be granted only for objective, verifiable reasons.
- Post-authorisation obligations to complete the product’s incomplete data package.
- Continuation of the authorisation link to annual re-assessment.
- Update of the MA, product is no longer under exceptional circumstances (all specific obligations have been fulfilled).

Regulatory methods in place to address animal health needs

- **Guidelines on requirements for an authorisation under exceptional circumstances**
  for vaccines for emergency use against Bluetongue & avian influenza to facilitate a rapid authorisation of vaccines.

  Guidance on minimum requirements on quality, safety & efficacy data for authorisation of these vaccines.

- **Position paper on requirements for vaccines against Foot-and-Mouth disease**

Regulatory methods in place to address animal health needs

- **Accelerated assessment (Art. 39 (8) of Reg. 726/2004)**
  - Request for an accelerated assessment procedure: application for a VMP of major interest.
  - Eligible products: Response to unmet medical needs or constitute a significant improvement over available methods of prevention, diagnosis or treatment of a condition.
  - Accelerated procedures: intended to speed up access to new medicines.
- **Guideline on the procedure for accelerated assessment**
  - Guidance on the submission of a request for accelerated assessment (justification of major health interest / of therapeutic innovation).
  - Timetable: opinion day 150.

Regulatory methods in place to address animal health needs

- **'Conditional marketing authorisation'**
  (Art. 14 (7) of Reg. 726/2004)
  Certain categories of **medicinal products**, in order to meet unmet medical needs of patients & in the interest of public health, it may be necessary to grant a MA on the basis of less complete data than is normally required.

  In such cases, it is possible for **CHMP** to recommend the granting of a MA subject to certain specific obligations to be reviewed annually.

Regulatory methods in place to address animal health needs

- **Use of autogenous vaccines**
  (Art. 3 (b) & 4 of Dir. 2001/82/EC)
  covered by national legislation in Member States
  useful addition to authorised vaccines in animal disease control and in maintaining animal health.

- **Use of cascade**
  (Art. 11 & 10 of Dir. 2001/82/EC)
  No suitable veterinary medicine authorised to treat a condition in a particular species.
  Risk based decision tree that allows the vets to use their clinical judgement to treat an animal under their care by deciding which product to use when there is no authorised VMP available.

Regulatory methods in place to address animal health needs

Possibilities according to national laws

- **UK:** 2 types of exceptional MA: provisional (no fully authorised product available in the UK to prevent or treat a particular condition) and limited (help to fill an existing therapeutic gap and where the product is not expected to be sold in vast quantities).
  Special Import Certificate (SIC) for EU authorised VMPs & Special Treatment Certificate (STC) for all other products.

- **DE:** MA for IVMPs with a significant therapeutic or prophylactic value and public interest
  Special approvals/certificates of exception

- **FR:** Provisional MAs, special import certificates (SICs)
  …….

Experiences and examples

AI vaccines authorised under exceptional cases

Product name	*Active substance*	*MA date*	*Duration*	*Target species*
Nobilis Influenza H5N2*	avian influenza virus type A, H5N2 subtype	01/09/2006	4 mo	chicken
Nobilis Influenza H5N6**	avian influenza virus type A, H5 subtype	31/01/2008	11 mo	chicken
Nobilis Influenza H7N1**	avian influenza virus type A, H7N1 subtype	14/05/2007	6 mo	chicken ducks
Poulvac Flufend H5N3 RG**	recombinant inactivated avian influenza virus	01/09/2006	4 mo	chicken, ducks

*Accelerated procedure

** Accelerated procedure / withdrawn after MA

BTV vaccines authorised under exceptional cases

Product name	*Active substance*	*MA date*	*Duration*	*Target species*
Bluevac BTV8*	BTV serotype 8	14/04/2011	15 mo	cattle, sheep
Bovilis BTV8	BTV serotype 8	06/09/2010	29 mo	cattle, sheep
BTVPUR	BTV serotype 1 & 8	17/12/2010	12 mo	cattle, sheep
BTVPUR AlSap 1	BTV serotype 1	17/12/2010	12 mo	cattle, sheep
BTVPUR AlSap 2-4	BTV serotype 2 & 4	05/11/2010	35 mo	sheep
BTVPUR Alsap 8	BTV serotype 8	17/03/2009	12 mo	cattle, sheep
Zulvac 1 Bovis*	BTV serotype 1	05/08/2011	12 mo	cattle
Zulvac 1 Ovis*	BTV serotype 1	05/08/2011	13 mo	sheep
Zulvac 1+8 Bovis*	BTV serotype 1 & 8	08/03/2012	13 mo	cattle
Zulvac 1+8 Ovis	BTV serotype 1	14/03/2011	12 mo	sheep
Zulvac 8 Bovis	BTV serotype 8	15/01/2010	12 mo	cattle
Zulvac 8 Ovis	BTV serotype 8	15/01/2010	21mo	sheep

*Accelerated procedure

AI/BT vaccines authorised under exceptional cases

- MA: subject to compliance with the specific obligations set out, which shall be reviewed annually.
- Completion of a programme of studies within a specified time frame/submission of an action plan together with timelines for all points that require resolution (in order to revert the MA to normal status) - results will form basis of the annual reassessment of the benefit/risk profile.
- Updated risk assessment on the continuous use of vaccines taking into account the continued need, its history of use and progress made in addressing the items that require resolution.
- Regular submission of PSURs

Schmallenberg virus vaccines

- **UK**

  Provisional MA for inactivated vaccines for sheep and cattle

- **FR**

  MA under exceptional circumstances for an inactivated vaccine for sheep and cattle

- **Centralised**

  Zulvac SBV – MUMS product

  Data requirements in the appropriate CVMP guideline on "minor use minor species (MUMS)" have been applied when assessing the application

Foot and Mouth disease virus vaccines

- **Centralised**

  Aftovaxpur DOE
  - submitted in accordance with the **multi-strain dossier** approach which was introduced in the revised Annex I to Directive 2001/82/EC.
  - maximum of three inactivated, purified FMD virus strains of the seven strains.
  - for cattle, sheep and pig.
- Further MAs after **national and MR procedures**

Regulatory expectation for the future

- **Need for effective preparedness for & response to emergencies**
- **Early warning of diseases**
- **Early reaction to disease outbreaks**
- **Ensured access to quality-assured vaccines**

  Useful to identify potential vaccine candidates (i.e. “in peace times”, before problems emerge)

  - to facilitate the availability in time before an emergency occurs,
  - to avoid the potential risks associated with the use of unauthorised vaccines in emergency situations,
  - to investigate the possibility to set specific requirements for their authorisation.

Regulatory expectation for the future

- **Identification of a list of infectious diseases** which are considered to have a major impact on animal health but also on trade or human health (epizootic disease, zoonotic diseases).
- **Identification of infectious diseases** for which vaccines (or antigens) should be available **or** should be recommended.
- **Identification of the most appropriate type of dossier** to be submitted (i.e. reduced data requirements, post authorisation commitments, etc.)**.**
- **Identification of the most appropriate procedure** to be followed "in peace times" for granting a MA to vaccines to be used for emergency animal disease.

Thank you for listening!