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Swiss Confederation

Federal Department of Economic Affairs FDEA Institute of Virology and Immunoprophylaxis IVI

Vaccine control

## European Regulatory Framework and Practices for Veterinary Leptospira Vaccine Potency Testing

Lukas Bruckner

International Workshop on Alternative Methods for Leptospira Vaccine Potency Testing, Ames, IA, U.S.A., September 19- 21, 2012

## Synopsis

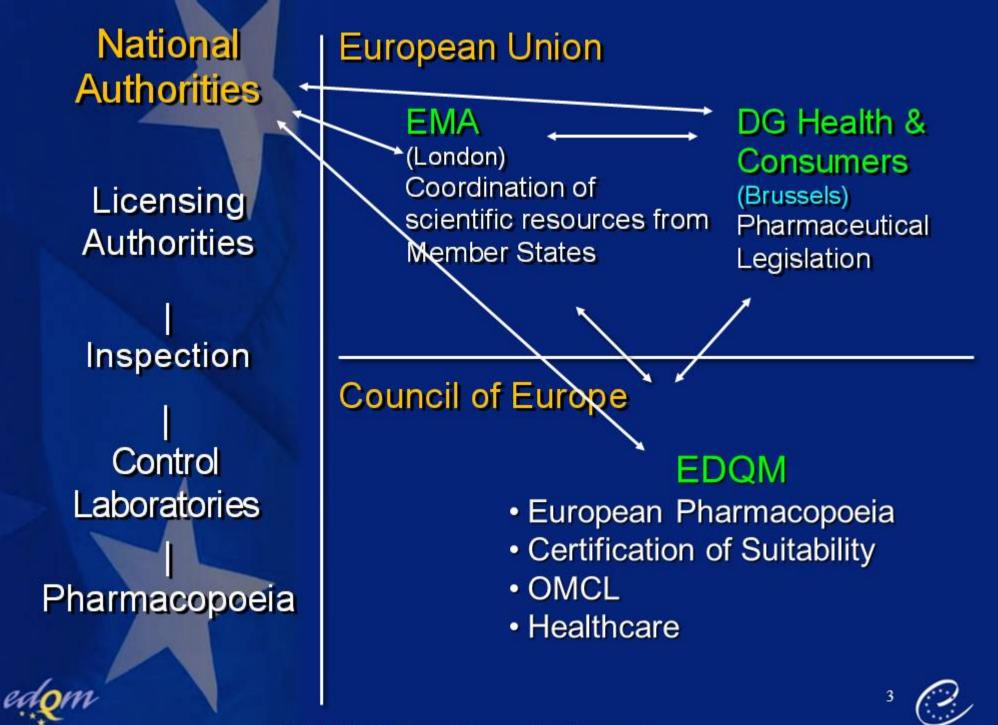
#### Role of

- → National Authorities
- $\rightarrow$  the EU
- $\rightarrow$  the Ph.Eur.

#### • Organization & Products of the Ph.Eur.

#### • The Pharmacopoeia

- Elaboration
- Content
- Leptospira vaccine monographs
- Recent developments in Leptospira vaccine testing



## **The European Pharmacopoeia**

 1964: Convention on the elaboration of a European Pharmacopoeia

## • Today:

- 36 member states + the European Union
- 24 observer countries and international organisations including World Health Organization (WHO)





#### **Member States and Observers**

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# **European Union (EU)**



# Its legal status

- Lays down common, compulsory quality standards for all medicinal products in Europe, i.e. raw materials, preparations, dosage forms, containers
- Mandatory at the same date in 36 states (CoE) and the EU
- National pharmacopoeias to cover subjects of solely national interest
- 1975: Mandatory status reinforced in the EU pharmaceutical legislation for the EU/EEA member states (Directives 2003/63/EC, 2001/83/EC, 2001/82/EC)



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### Organization of the Ph. Eur.

- Commission
  - "Ph. Eur. Parliament"

# **Ph. Eur. Commission**



- One delegation per member state or observer
- 36 Member States plus a delegation from the EU (a representative from DG Health & Consumer and the EMA);
  24 Observer countries and World Health Organization (WHO).
- Persons come from health ministries, health authorities, pharmacopoeias, universities, or industry and are appointed by the national authorities on the basis of their expertise.

 Three sessions a year; texts are adopted by unanimous vote.







### Organization of the Ph. Eur.

- Commission
  - "Ph. Eur. Parliament"

#### Expert groups

- Biologicals methods and statistical analysis
- Organic chemistry Synthetic products
- Veterinary sera and vaccines
- Technical Secretariat (EPD)



### "Products"

#### • European Pharmacopoeia

- $\rightarrow$  Book
- $\rightarrow$  On-line (http://online.edqm.eu)
- $\rightarrow$  USB-stick





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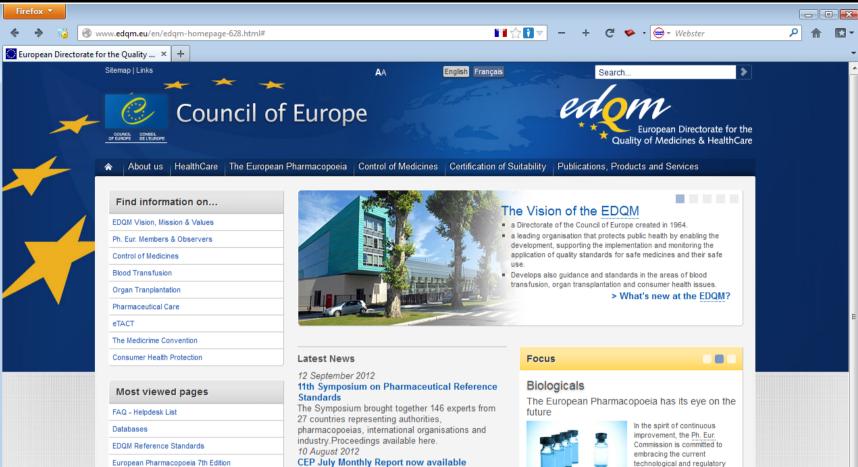
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CEP July Monthly Report now available

The DCEP publishes on a monthly basis a report containing some relevant figures relating to its main activities.

#### 09 August 2012

Upcoming Events

27-29 September

Mumbai, India

3-8 October 2012

13 October 2012

**FIP Centennial Congress** 

Amsterdam, The Netherlands

Furnham Day for Organ Donation &

EDQM Publishes Annual Report for the year 2011 The report outlines its different activities and provides overview of achievements and results from 2011.

IPA/ EDQM/ WHO Technical Conference "Current

Challenges in Global Regulatory Compliance"

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Read more on the European Pharmacopoeia

trends, but also appropriately

paves the way for the future. In response to this, the EDQM

has undertaken an extensive

consultation among regulatory authorities and Expert Groups.

#### <sup>7th</sup> Edition Book

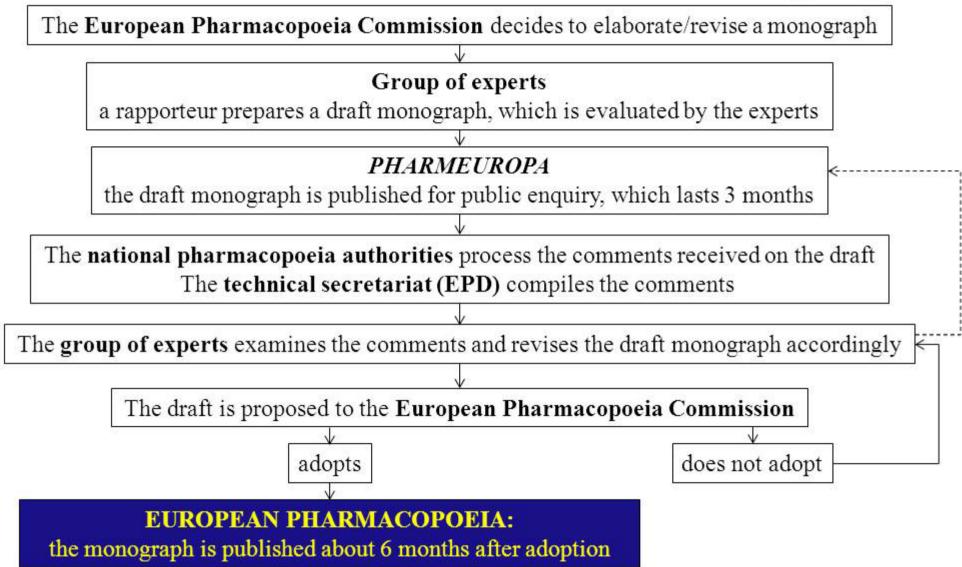
**USB Stick & Online** 



The electronic versions contain all the European Pharmacopoeia texts and provide additional and unique features: fully searchable, hyperlinks in the text of a monograph give access to information on general methods ...

The electronic versions are bilingual

# Elaboration of a Ph.Eur monograph





- → legal requirements
- General Notices
- Monographs

- Vaccines for Veterinary Use (0062)
- Vaccine specific monographs
- Supplementary texts
  - 2.6.1. Sterility
  - 5.2.4. Cell cultures for the production of veterinary vaccines
  - 5.2.6. Evaluation of safety of veterinary vaccines and immunosera
  - 5.2.7. Evaluation of efficacy of veterinary vaccines and immunosera

for use or may be used in pregnant bitches, use not fever than for use or may be used in program otenies, use out terms that 10 bitches at the stage of programs in accordance with the to microst at one atage or pregnancy in accordance what use tehedule to be recommended or at different stages of pregnancy. scheduus to be recommended or at universit stages or pregnant, Administer to each bitch a double dose of the vaccine. If the Accounters vo caen unen a oruene doce or une vaceme, et une recommended schedule requires a second dose, administer one recommentaria serverane requires a second poor, auminitier on doise after the recommended interval. Observe the bitches at The vaccine complies with the test if no bitch shows abnormal least daily until one day after whelping. The vaccine compose with the text is not when anores amoremation local or systemic relations, tiggs of disease or dist from chuzes near or systemic reactions, signs or ossesse or one from cas attributable to the vaccine and if no adverse effects on the 222. Immunogenicity. For each type of the servicers against pregnancy or the offspring are noted. which protective immunity is elaimed on the label, carry out which protective immunity is causica on the label, carry out a separate test with a challenge strain representative of that

Canine leptospirosis vaccine (inactivated)

CANINE LEPTOSPIROSIS VACCINE

(INACTIVATED)

Vaccinum leptospirosis caninae inactivatum

Canine leptophrotis vaccine (inactivated) is a preparation

Canine reprosperous vaceme (inacurated) is a preparation of inactivated whole organisms and/or antigenic estract(s)

or inactivated whole organisms and/ or anogene extracts) of one or more builtable strains of one or more of Leptospire

or one un more sumane strains or one or more or seprenpria interrogent serovar canicola, serovar interchaemorrhagiae or

interrogens serovar canicola, serovar interronaemormagiae or any other epidemiologically appropriate serovar, inactivated

any other epidemiologically appropriate server, matterated while maintaining adequate immunogenic properties. This

The seed material is cultured in a suitable medium; each strain

to contribute acquaratory, sourcing production, vanious parameter such as growth rate are monitored by suitable methods; the

orparatery and macrosated by a suitable memory, the a may be concentrated. The vaceine may be adjuvanted.

2.2. CHOICE OF VACCINE COMPOSITION

The seed material is cultured in a sustance memory, each estan-is entrivided separately. During production, various parameters

such as growth rate are menitored by autaced methods: the values are within the limits approved for the particular product.

runny and soennity are vermen on the narvest using surgave methods. After cultivation, the bacterial harvests are collected

memode. After cumulation, the pacterial narvers are concered toparately and inactivated by a suitable method. The antigen

The vaccine is shown to be satisfactory with respect to safety

the vacuue is known to be causactory with respect to carey (5.2.6) and efficacy (5.2.7) for the dogs for which it is intended.

The following texts for safety (section 2.2.1) and immunogenicity

The reasoning sets for safety (section 2023) and immunogenicity (section 2.923) may be used during the demonstration of safety

23-1. Safety. Carry out the test for each route and method of

Sol 2 basety. Carry out the sets for each route and method or administration to be recommended for vaccination and in dogs

of each category for which the vaceine is to be intended. Use a

or each caugory for which the vacone is to be mended. Use a batch of vacone containing not less than the maximum antigen

varion or vacuum countaining not icea man the maximum and content and/or potency that may be expected in a batch of

22-11. General safety. For each test, use not fewer than

10 dogs that do not have antibodies against the principal

av oogs mat oo not nave antwoones against the principal L interrogans servirat (iderobaemorthagiae, canicola,

vaccination, 4 h later and daily for 4 days

L interropana serovara licteronaemorrhagiae, eanicola, grippotyphosa, serioe, hardio, hebdomonadia, pomona, australia

supporyproca, server, narojo, neosumenaona, pomona, autoana and autumnalis). Administer to each dog a double dose of the

and autumnants). Administer to each one a source over or the vaccine. If the recommended schedule requires a second doze, vaceine, it the recommended schedule requires a second doze, administer one doze after the recommended interval. Observe

the dogs at least daily until 14 days after the last administration.

ton organs react using union are dairs after the task administration Record body temperatures the day before each vaccination, at

The vaccine complies with the test if no dog shows abnormal

une vaceme compress wan une vess a no une arme accortant local or systemic reactions, signs of disease or dies from causes

2012. Safety in pregnant bitches. If the vaccine is intended

values are within the smith approved for the particular product Purity and identity are verified on the harvest using suitable

monograph applies to vaccines intended for the active

immunication of dogs against leptospirosis.

2.1. PREPARATION OF THE VACCINE

2. PRODUCTION

Each test is carried out for each route and method of saon user is carriero oue for each runte ano mession or administration to be recommended for vaccination, using in

covara, non executes aren or sections equipments, exeptoquia from more than one seriorar (for example L, interrogens seriorar reen more man une uccever (un example al onerrogens serve canicola and serverar interchaemornhagiae) has been used to prepare the vaccine, carry out a batch potency text for each prepare the vacone, carry out a baten potency test for each serovar against which protective immunity is claimed on the label. Use for the test 10 healthy hamiters not more than See the information section on general monographs (cover pages)

nas ocen carrieo out using a caren or various while a minim potency. Where the text is not carried out, an alternative potency, where the test is not carried out, an alternative validated method is used, the criteria for acceptance being set vancance memory is used, the errors for acceptance being set with reference to a batch of vaccine that has given assistationy vents reference to a batch of vaccine that has given satisfactory results in the test described under Potency. The following tests 2-3-1-1. For paceines with or without adjugants. If leptospira

rotency tree tacenon and for each oaten of the vacuum in the high state of the second se

Potency test (arction 3-5.) for each batch of the vacane if it

toe number or soarney samples in wesen the organisms are detected is statistically lower for the vateinates than for the 2.3.1. Batch potency test. It is not necessary to carry out the 23. MANUFACTURER'S TESTS

where the vaccine is intended to have a beneficial effect where the vaccine is intensed to have a beneficial criter, against urinary tract infection and exerction, the number than for the controls, against unnary tract intertion and eseretoin, the number of days that the organisms are detected in the urine and or ease that the organized are detected in the unite and the number of kidney samples in which the organized are

where the vacone is memory to have a cenericial effect against infection, the number of days that the organisms are against innection, the number of days that use organisms are detected in the blood is statistically lower for the vaccinates

for the vaccinates than for the controls, where the vaccine is intended to have a beneficial effect

where the vaccine is intended to have a beneficial the following it also shown: where the vacenne is intended to have a concritical effect against cights of disease, the clinical second and eners against eigne or ossease, the currical scores and harmatological and biochemical scores are statistically lower

or the variables show no more than this upper to excesse (for example, transient hypertherma) and, depending on the rer example, transfere systemerina) and, oepending on one interrogent serovar used for the challenge, one or more of

L'interrogent serovar challenge strain is reigolated from or is interrogens service ensuring extrain is resource from o demonstrated by another suitable method to be present in ormonserates by another sumance method to be present in fewer than 2 samples on fewer than 2 different days, to show sewer than a samples on sewer than a difference days, to show infection has been established in fewer than 80 per cent of the The vacance complies with the test if: at least 60 per cent one vacume compose with the sets n. is least or per cent of the vacunates show no more than mild right of disease

examination on any use that one outring the order ration p and on the remainder when exhanised at the end of the and on the remainder when cuthamized at the end of the observation period. In particular, examine the liver and kidneys osservation perios, in particular, examine the user and signed for macrocoopic and microcoopic signs of leptospira infection. for macroscopic and microscopic signs or representa microson. Take a sample of each kidney and test each blood, urine and vanc a sample of each somey and test each blood, urine an bidney tample for the presence of challenge organisms by kienky sample for the presence or enailenge organisms by reisolation or by another suitable method. Analyse blood reisoiation or by another custance metrico. Analyse toood samples to detect biochemical and haematological changes The test is invalid if: samples give positive results on day 0; indicative of infection and score these.

Unaisenge each dog after 20-20 days by the executive and of intraperitoneal route with a sufficient quantity of a suspension intrapernoneai route with a summerie quantity or a supprision of the relevant pathogenie L interrogant serovar. Observe the dogs at least daily for 28 days after challenge. Examine the dogs daily and record and score clinical signs estamine the dogs dany and record and core context upna observed postchallenge and any deaths that occur. If a dog observes prevenancings and any deaths that occur. If a dog shows marked signs of disease, it is euthanised. Monitor body some marses signs or encase,  $\pi$  is cumanised, aronnor body temperatures each day for the first week after challenge. Collect temperatures each day for the tirts week after enauenge, concer blood samples from each dog on days 0, 2, 3, 4, 5, 5 and 11 port evolos samples from each dos on days V, =, a, a, a, a, o, o and 11 pole challenge. Collect urine samples from each dos on days 0, 3, 5, chailenge. Contect unne tampies from each oog on says 0, 9, 9, 8, 11, 14, 21 and 26 poet challenge. Eurhanise turviving dogs 0, 14, 24, 24 and 20 point charrenge. Evaluation e serviring ongs at the end of the observation period. Carry out postenoriem at the end of the observation period. Carry out postmortem examination on any dog that dies during the observation period

Use for the test not fewer than 12 dogs that do not have use for the year not never than as cogs that on not nave antibodies against the principal seroyars of L interrogens antibogies againat une principal seriovars de Li interropons (interobaemorrhagiae, canicola, grippotyphosa, teiroe, hardio, ueteronaemorrnagiae, cantonia, gripporyprota, sejron, narojo, hebdomonadia, pomona, australis and autumnalia). Vareinate neocomonadia, pomona, autrant and autumnant), vare not fewer than 6 dogs, according to the schedule to be not rewer than 0 0054, according to the seneruse to be recommended. Maintain not fewer than 6 dogs as controls. recommenses, maintain not rever than 6 dogs as control. Challenge each dog after 25-28 days by the conjunctival and/or

01/2008:0447 each case dogs of the minimum age to be recommended. The each case dogs of the minimum age to be recommension, the vaccine administered to each dog is of minimum antigen content

EUROPEAN PHARMACOPULA

with the test if no growth occurs in either medium. At the same time, carry out a control test by inoculating a further quantity of the medium with the vaccine together with a quantity of a culture containing approximately 100 leptoepirae and incubating at 30 °C: the test is invalid if growth of leptoepirae administered by a recommended route and method. General Notices (1) apply to all monographs and other texts

3.5. Potency. The vaccine complies with the requirements of the test mentioned under Immunogenieity (section 2.3.2.) when

34. Residual live bacteria. Carry out a test for live leptoepirae

by inoculation of a specific medium. Inoculate 1 mL of the

vaccine into 100 mL of the medium. Incubate at 30 °C for

14 days, subculture into a further quantity of the medium and

incubate both media at 30 °C for 14 days: the vaccine complies

23 ade vir bel 24 of 3-1. Identification. When injected into healthy animals that do not have specific antibodies against leptospira serovar(s) present in the vaccine, the vaccine etimulates the production of present in the vectore, the vactore communes the production is such antibodies. If test 2:3-1:3 is used for batch potency test, it also serves to identify the vaccine. 3.2. Bacteria and fungi. The vaccine and, where applicable, the liquid supplied with it comply with the test for sterility prescribed in the monograph Vaccines for selectionary use 3-3. Safety. Lise 2 dogs of the minimum age recommended for vaccination and that do not have antibodies against the leptoepira serovar(s) present in the vaceine. Administer to each dog by a recommended route a double doce of the vaccine. Observe the dogs at least daily for 14 days. The vaccine complies with the text if no dog shows notable signs of disease or dise from causes attributable to the vaccine.

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3. RATCH TESTS

23-13. For vaccines without adjuvants. For each of the cerovars present in the vaccine, a suitable validated in silvo test may be carried out to determine the content of one or more may be carried out to occur none one vention of one or more antigenic components which are indicators of protection and which are specific for that serouar. The criteria for acceptance are set with reference to a batch of vaccine that hat given are set with reservice to a parent or vaccine share the gri-satisfactory results in the test described under Potency.

14 days of receiving the challenge suspension and if not fewer than 4 of the 5 vaccinated hamsters remain in good health for 14 days after the death of 4 control hameters. 23-1-2. For vaccines with or without edjuvents. A suitable validated sero-response test may be carried out. Vaccinate 2. each animal in a group of experimental animale with a suitable 2.13 dose. Collect blood samples after a suitable, fixed time after vaccination. For each of the servire present in the vaccine, The an in sitro test is carried out on individual blood samples to 2.2 determine the antibody response to one or more antigenie 2.2.1 components which are indicators of protection and which are components makes are innerators to protection and attended of that perovae. The criteria for acceptance are set requi with reference to a batch of vaccine that has given satisfactory Vàcei 23.0 The . safer! inte

3 months old, that do not have antibodies against the principal e monare oral, and an oral service and an oral and a service and a servi grippotyphoca, sejroe, hardjo, hebdomonadis, pomona, australie and autumnalic) and which have been obtained from a regularly tested and certified leptospira-free source. Administer 1/40 of the dose for dogs by the subcutaneous route to 5 hamsters. the once my ongo by the autoentaneous rouse to a naminers. Maintain 5 hamsters as controls. Challenge each hamster after 15-20 days by the intraperitoneal route with a sufficient quantity of a virulent culture of leptocpirae of the service against which protective immunity is claimed on the label. The vaccine protective minimum is claimed on the second incovacing complies with the test if not fewer than 4 of the 5 control hamstere die showing typical signs of leptospira infection within Can ofal This immi paral

EUROPEAN PHARMACOPOEIA 7.0

Vaccinum 1. DEFINITION Bavioe Teptosp inactivated wh one or more s borgpetersen scrovar hards while mainta monograph immunisativ 2. PRODU 2-1. PREF The seed is cultiva such 25 values 2 scal Purity method by a st vaccin 22 The 15.2 The (100

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#### BOVINE

#### if 1 dose contains not les on the label. 37. Potency. The vacci the test prescribed une administered by a reco necessary to carry out vaccine if it has been a vaccinating dose co titre stated on the la -0

10.0

ous agents. The va agents in batches of s. Use not fewer that ind of the youngest ag riter by a recommender en 10 doses of the vacu the chickens show abnorr Not attributable to the vacci test if no chicken shows no from causes attributable to 36. Virus titre. Titrate th suitable cell cultures (5.2

e leptospirosis vaccine (inactivated)

ropriate days, determined by the ie model. In the case of serovars vidence that the serovar has a tract, a lower rate of infection a their tissue tropism, for some im other tissues/body fluids can e cattle are infected or not by

2

THE REAL PROPERTY.

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ot necessary to carry out the 3 batch of vaccine if it has vaccine with a minimum ried out, an alternative ria for acceptance being set e that has given satisfactory Potency. The following test

rotection is claimed, the nimals is measured. Use ng 250-350 g that do not enii serovar hardjo and az ticterohaemorrhagiae, hebdomonadis, pomona, been obtained from a free source. The dose that fraction of a cattle ation studies to provide of 10 guincapigs with in 2 guinea pigs as inge of 19-23 days h guincapig and idated method such e antibodies in each

dy levels are equal ch that has given er Potency and tre in the controls.

> r animals that do pira serovar(s) he production

applicable. or sterility nary use

cattle older minimum age n 6 months less than 6 amended for against the ter to each vaccine,

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notable vaccine. tospirae the for m and mplies e same intity

rae

## **Canine leptospirosis vaccine (inactivated)**

### **Batch potency test** (Hamster Test)

It is not necessary to carry out the Potency test (test in dogs) for each batch of the vaccine if it has been carried out using a batch of vaccine with a minimum potency. Where the test is not carried out, an alternative validated method is used, the criteria for acceptance being set with reference to a batch of vaccine that has given satisfactory results in the test described under Potency. The following tests may be used.

2-3-1-1. *For vaccines with or without adjuvants*. If leptospira from more than one serovar (for example L. interrogans serovar canicola and serovar icterohaemorrhagiae) has been used to prepare the vaccine, carry out a batch potency test for each serovar against which protective immunity is claimed on the label. Use for the test 10 healthy hamsters not more than 3 months old, that do not have antibodies against the principal serovars of L. interrogans (icterohaemorrhagiae, canicola, grippotyphosa, sejroe, hardjo, hebdomonadis, pomona, australis and autumnalis) and which have been obtained from a regularly tested and certified leptospira-free source. Administer 1/40 of the dose for dogs by the subcutaneous route to 5 hamsters. Maintain 5 hamsters as controls. Challenge each hamster after 15-20 days by the intraperitoneal route with a sufficient quantity of a virulent culture of leptospirae of the serovar against which protective immunity is claimed on the label. The vaccine complies with the test if not fewer than 4 of the 5 control hamsters die showing typical signs of leptospira infection within 14 days of receiving the challenge suspension and if not fewer than 4 of the 5 vaccinated hamsters remain in good health for 14 days after the death of 4 control hamsters.

## **Canine leptospirosis vaccine (inactivated)**

## **Batch potency test (ctd.)**

2-3-1-2. *For vaccines with or without adjuvants*. A suitable validated sero-response test may be carried out. Vaccinate each animal in a group of experimental animals with a suitable dose. Collect blood samples after a suitable, fixed time after vaccination. For each of the serovars present in the vaccine, an in vitro test is carried out on individual blood samples to determine the antibody response to one or more antigenic components which are indicators of protection and which are specific for that serovar. The criteria for acceptance are set with reference to a batch of vaccine that has given satisfactory results in the test described under Potency.

## Serological Test

2-3-1-3. *For vaccines without adjuvants*. For each of the serovars present in the vaccine, a suitable validated in vitro test may be carried out to determine the content of one or more antigenic components which are indicators of protection and which are specific for that serovar. The criteria for acceptance are set with reference to a batch of vaccine that has given satisfactory results in the test described under Potency.

## >Antigen Quantification Test

## **Bovine leptospirosis vaccine (inactivated)**

## Batch potency test (Serological Test)

It is not necessary to carry out the Potency test (test in cattle) for each batch of vaccine if it has been carried out using a batch of vaccine with a minimum potency. Where the test is not carried out, an alternative validated method is used, the criteria for acceptance being set with reference to a batch of vaccine that has given satisfactory results in the test described under Potency. The following test may be used.

For each of the serovars for which protection is claimed, the antibody response from vaccinated animals is measured. Use not fewer than 12 guinea-pigs weighing 250-350 g that do not have antibodies against *L. borgpetersenii* serovar hardjo and the principal serovars of *L. interrogans* (icterohaemorrhagiae, canicola, grippotyphosa, sejroe, hardjo, hebdomonadis, pomona, australis and autumnalis) and that have been obtained from a regularly tested and certified leptospira-free source. The dose to be administered to the guinea-pigs is that fraction of a cattle dose which has been shown in the validation studies to provide a suitably sensitive test. Vaccinate each of 10 guinea-pigs with the suitable dose. Maintain not fewer than 2 guinea-pigs as controls. At a given interval within the range of 19-23 days after the injection, collect blood from each guinea-pig and prepare serum samples. Use a suitable validated method such as a micro-agglutination test to measure the antibodies in each sample.

The vaccine complies with the test if antibody levels are equal to or greater than those obtained with a batch that has given satisfactory results in the test described under Potency and there is no significant increase in antibody titre in the controls.

# **EDQM Workshops**

# on Alternatives to the Leptospira Vaccine potency test with participants from

- Licensing authorities
- Official Medicines Control Laboratories
- Industry
- Academia
- OIE reference laboratory

**1999:** Participants from Europe and U.S.A. **2012:** Participants from Europe

- Ph.Eur. monograph is outdated
- Hamster Potency test has deficiencies
- Alternative methods should be based on efficacy tests in the target species

Monographs revised, Conclusions integrated as "door openers"

- Working group should be created
  - sharing knowledge and
  - to coordinate efforts to replace the hamster test

European Regulatory Framework and Practices for Veterinary Leptospira Vaccine Potency Testing Lukas Bruckner, International Workshop on Alternative Methods for Leptospira Vaccine Potency Testing, Ames, IA, U.S.A., September 19- 21, 2012

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#### LPS immunodominant

- candidate antigen for antigen quantification
- due to antigen variation no common reference material
- mAbs may be obtained from Royal Tropical Institute Amsterdam (NL)
- 2 manufacturers have CA approved vaccine on the market, tested for potency with an *in vitro* test

LipL32 no evidence for protection

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#### • In vitro assay may be used to assess

- Antigen quantification
- Potency
- (Stability)

#### • No single, universal alternative method

- due to the complexity of the vaccines
  - $\rightarrow$  number of serotypes, number of serovars
  - $\rightarrow$  specific antigens as protective agents
  - $\rightarrow$  combinations
  - $\rightarrow$  presence/absence of adjuvants

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- Consistency approach may reduce final product testing
- EDQM might provide standard mAbs for ELISA test

#### • Press release

http://www.edqm.eu/medias/fichiers/edqm\_workshopleptospirosis\_vaccine\_batch\_potency\_t.pdf

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## **Further steps**

#### ✓ Information of Ph. Eur. Commission

- Revision of the monograph for vaccines for dogs
  - On the agenda of expert group 15V
- Develop guidance on implementation of consistency approach
- ✓ Update of EPAA
- ✓ Update of EMA/CVMP/IWP



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Swiss Confederation

Federal Department of Economic Affairs FDEA Institute of Virology and Immunoprophylaxis IVI

Vaccine control

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