THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

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European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

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Webinar on the Management of Extraneous Agents in IVMPs – Part 1

01 April 2020

THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

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Extraneous agents testing in the European Pharmacopoeia (Ph. Eur.) for IVMPs

Introduction

EDQM Webinar on the Management of Extraneous Agents in IVMPs

01 April 2020, Strasbourg

Catherine LANG, EDQM & Group 15V Secretary

Where are we now and next steps

EDQM training for all interested parties on 1st April 2020

10/2016-05/2017 **06/2019** **10/2019** **04/2020** **07/2020**

Training of assessors

Public conference

2 Hearings and consultation in Phpa 30.2 deadline for comments 30/06/2018

Ph. Eur. COM adopted

Ph. Eur. Supplement 10.2
Publication: January 2020
Implementation: 1 July 2020

EMA Q&A document

EDQM Explanatory document

EDQM Technical guide

EDQM Concrete examples

Training by Webinars 1st April 2020

WEBINAR ON THE MANAGEMENT OF EXTRANEOUS AGENTS IN IVMPs 01 APRIL 2020

WEBINARS ON THE NEW EUROPEAN PHARMACOPOEIA APPROACH TO THE 'MANAGEMENT OF EXTRANEOUS AGENTS IN IVMPs'

01 April 2020

Morning Session - Setting the scene
(Webinar 1 for remote participation)

- Documents will be provided beforehand to help participants prepare
- The content of the webinars has been condensed to only focus on core items.
- Any question must be sent in writing, either before or during the webinars.

09:00-09:15	Setting the scene to the changes to the Ph. Eur. requirements for the management of extraneous agents in IVMPs Member of Ph. Eur. Expert Group 15V
09:15-09:30	"*Management of extraneous agents in IVMPs*" - the new General chapter 5.2.5, Member of Ph. Eur. Experts Group 15V
09:30-09:45	New approach for extraneous agents testing - Concrete examples Member of Ph. Eur. Expert Group 15V
09:45-10:00	New approach for extraneous agents testing - Concrete examples Member of Ph. Eur. Expert Group 15V
10:00-10:15	Answers to questions
10:15-10:30	The voice of industry Animal Health Europe
10:30-10:45	The voice of industry Focus on risk assessment
10:45-11:00	Answers to questions

Close of webinar 1

THE MANAGEMENT OF EXTRANEOUS AGENTS IN IVMPs 01 APRIL 2020

Afternoon Session - Regulatory landscape
(Webinar 2 for remote participation)

14:00-14:15	EMA Guidelines (including needs for revision or elaboration of new guidelines) and Q&A document as a tool for harmonised assessment Member of the EMA Immunological Working Party (IWP)
14:15-14:30	The particular case of old master seeds used for the production of new vaccines: re-testing of well-established cell banks and master seeds? What can be used to justify no retesting? Member of Ph. Eur. Expert Group 15V
14:30-14:45	Historical value of the previous requirements and detailed testing methods as mentioned in the Ph. Eur.: can the "old" detailed protocols now available in the Ph. Eur. archives still be used? Member of the EMA Immunological Working Party (IWP)
14:45-15:00	Validation of new test techniques - expectation with regard to validation and documentation in the dossier Member of the EMA Immunological Working Party (IWP)
15:00-15:45	Answers to questions

Close of webinar 2

Huge thanks to everyone involved

- Experts of Group 15V and its Chairs, Céline Lorteau, Lukas Bruckner, Prof. Person
- EDQM team in charge of the secretary to Group 15V

Thank you for your attention

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Setting the Scene: Ph.Eur. changes in management of extraneous agents in IVMPs ….risks, challenges, why and how……..

Anna-Maria Brady Uk 15V expert

OVERVIEW

- Drivers for change
- Existing situation
- Change: why, challenges, how
- Risk Management Approach
- Opportunities and Benefits
- Conclusions

Drivers for Change

- Regulatory acknowledgement & **capitalisation** of new science/ technology and modern molecular methods
- Noting the changes in the wider regulatory landscape….Continuous Improvement and regulatory harmonisation
- Consistency Approach to manufacturing quality control: moving quality control upstream and removing reliance on batch testing: building quality into the process rather than at the end
- Need for a flexible dynamic framework and tools for industry and regulators to respond quickly to emerging infectious agents…….
- Reduction, refinement and replacement of in vivo tests –3Rs agenda

Limitations of the established approach to handling extraneous agents

- No harmonized approach, requirements scattered over several texts
- Focus on laboratory testing only
- Consequences of good manufacturing not taken in account
- Testing requirements different from species to species
- Newer methodology such as molecular methods neglected

PRESCRIPTIVE

LIMITATIONS = RISKS

- Some existing methods are known to be insufficiently sensitive or of variable detection: e.g. general test: it is known that detection may in fact vary depending on the strain of virus and cell line used to perform the test
- **Methodology not generally reflective of modern methods and no longer fit for purpose to underpin a risk management approach** *e.g. limited validation requirements ….* Internal validation: how to compare test results from different sources
- Existing methods may not be suitable for state of the art products …..limit market availability
- Tick box approach not flexible and does not allow mechanism for dealing with new infectious agents…….limit market availability

EMERGING INFECTIOUS AGENTS

- Lists of agents represent known occurring disease agents across regions
- Infectious Disease is dynamic e.g. bluetongue/avian flu outbreaks 2000s ---agents largely already known
- New diseases and agents: Schmallenberg, RD 114, Torque Teno virus, BSE prion

Generic lists cannot cover all possibilities and there must be a dynamic mechanism and tools available for industry and regulators to respond to emerging infectious agents……. Risk management and risk assessment…. flexibility

What is risk management?

A step wise process to identify, evaluate and assess the risk allowing it to be controlled and mitigated against resulting in elimination or reduction of the risk to a negligible or acceptable level.

- **Identify**: biologicals starting materials and biological materials used during the process
- **Mitigate and control**: Sourcing and treatment/ process mitigations
- **Assess and evaluate risk**: May lead to removal of tests for risk agents in end product if absent or negligible

New Ph.Eur. Texts …….

NEW CHAPTERS 5.2.5 and 2.6.37 provide

- a framework and step wise approach to allow risks to be managed
- general principles and examples of parameters to be taken into account to use fit-for-purpose methods and widens use of state of the art methods
- a comprehensive list of agents to be considered
- a decision tree to enable identification of mitigations and control steps during sourcing and manufacture of vaccines

How to implement change: rationale of Ph.Eur. revisions

- Build on existing chapters with risk management approach especially chapter 5.2.5 which covers impact of manufacturing process on risk management.
- New Chapter 5.2.5 introduces new methods and allows a mix and match approach and individual product risk evaluation and justification to authorities rather than tick box approach
- New chapter 2.6.37 keeps existing methods although in less detail (can be used in liaison with CVMP reflection paper re historic data plus CVMP/IWP Q+A document)
- Deletion of unnecessary tests such as final product extraneous agents testing in specific inactivated vaccines
- Consistency of manufacture and risk assessment approach introduces the potential for an overall reduction of testing

Challenges of change

- Would revalidation of existing methods be required? Would this lead to termination of older master seeds/ old products?
- Would introduction of new methods mean existing master seeds terminated due to cost, lack of MS for testing, discovery of extraneous agents
- Would introduction of new approach cause misinterpretation leading to delay/prevent development of new products and re testing of old products?
- Molecular techniques…No indication of current infectivity of agent, expensive, only detect one virus (**newer methods can overcome this with bioinformatics**), Primer specificity: how to standardise/validate methods; what do the results mean?

Coordinated Ph. Eur./EU approach allows all information to sit in one place and updating of species extraneous agents lists

Ph.Eur. 15V has worked with IWP to develop training for assessors and Q+A documents for industry and developers

Risk Management Approach

- Exploits and builds on consistency of manufacture approach
- May lead to removal of end product tests for specific products
- May reduce in -process testing upstream
- Provides a mechanism to handle new extraneous agents which may not have a practical risk of infection e.g. torque tenovirus
- Provides mechanism to deal with results from increased sensitivity of tests
- Reflects May 2017 revision to **EMA/CVMP/IWP/206555/2010**

OPPORTUNITIES

- New approach based on risk assessment allows reduction in testing during manufacture and deletion of unnecessary tests for EAs on final product
- Comprehensive requirements for EA testing are centralised, Ph. Eur. texts now cover all species, this brings more clarity (no duplication, no discrepancies)
- Flexibility to choose methods for specific EA testing – fit-for-purpose sensitive techniques reflecting progress in science
- Methods no longer described in detail, building in flexibility of approach and allowing tailoring to individual product needs
- Use of state-of-the-art methods results in reduction of *in vivo* testing (decreased reliance on less robust methods)
- Coordinated Ph. Eur./EU approach, important also in a global context
- Reduction in costs per batch

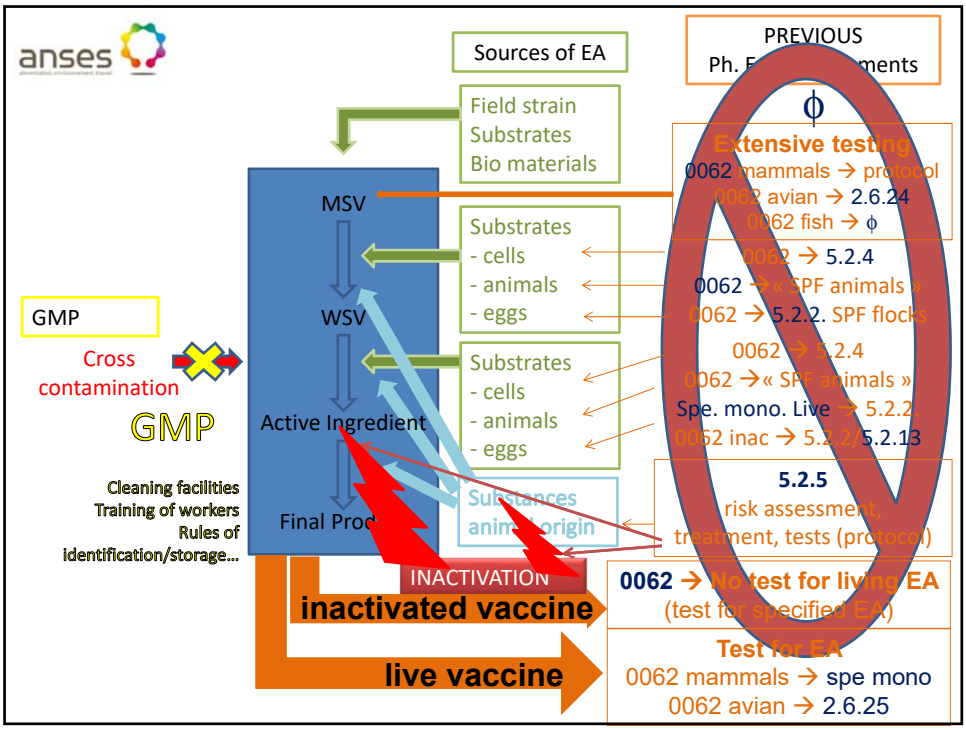
And Finally……..

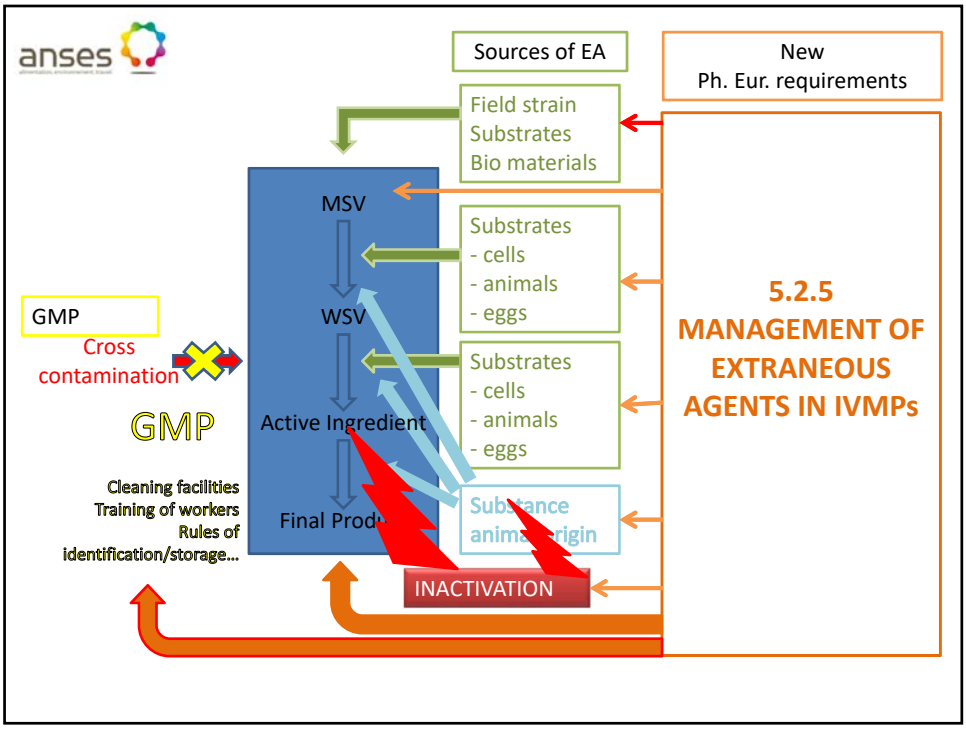
- It is not all new: mix and match risk assessment approach has been used for EMA; DCP products have used “old “ data sets without the advantage of the consistency approach
- There will be challenges because of emerging new technology irrespective of legislative change It may be better to have an up to date framework
- Industry and regulators must work together to provide robustly safe and efficacious IVMPs using fit for purpose methodology which reflects modern science in a cost effective manner

Management of extraneous agents in IVMPs
The new chapter Ph. Eur. 5.2.5

EDQM Training - Strasbourg
01/04/2020

Céline Lorteau
ANSES - French Agency for Food, Environmental and Occupational Health & Safety

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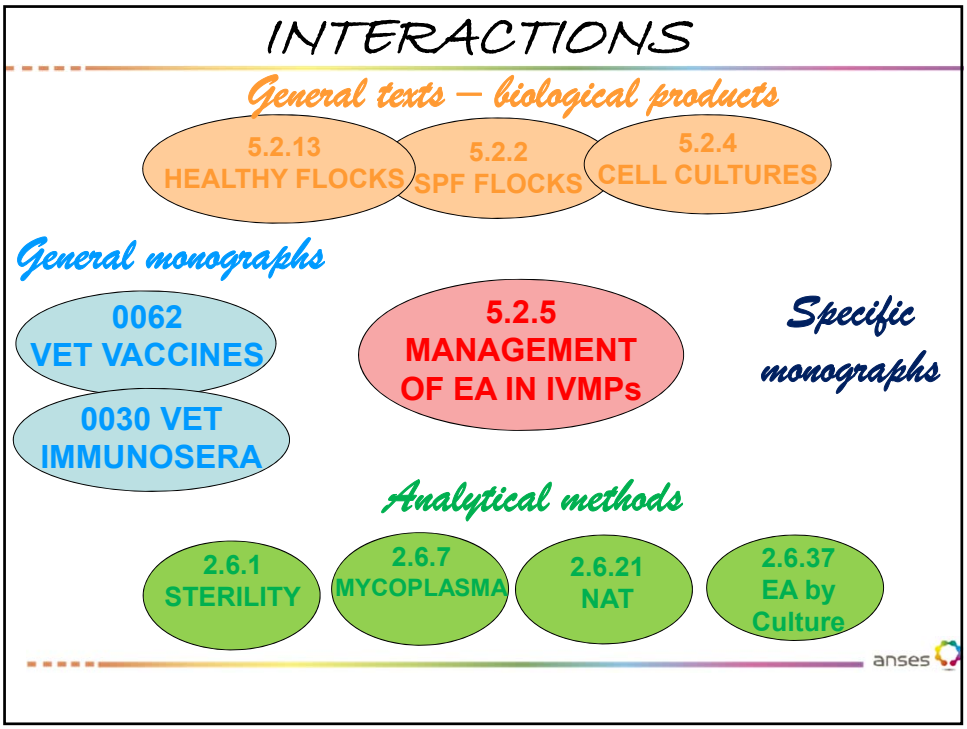
Sources of EA
New
Ph. Eur. requirements
Field strain
Substrates
Bio materials
MSV
WSV
Active Ingredient
Final Prod
Substrates
- cells
- animals
- eggs
Substrates
- cells
- animals
- eggs
Substance
anim rigin
INACTIVATION
GMP
Cross
contamination
GMP
Cleaning facilities
Training of workers
Rules of
identification/storage...
5.2.5
MANAGEMENT OF
EXTRANEOUS
AGENTS IN IVMPs


INTERACTIONS
General texts – biological products
5.2.13
HEALTHY FLOCKS
5.2.2
SPF FLOCKS
5.2.4
CELL CULTURES
General monographs
0062
VET VACCINES
0030 VET
IMMUNOSERA
5.2.5
MANAGEMENT
OF EA IN IVMPs
Specific
monographs
Analytical methods
2.6.1
STERILITY
2.6.7
MYCOPLASMA
2.6.21
NAT
2.6.37
EA by
Culture
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TEMPLATE - 5.2.5

I - SCOPE

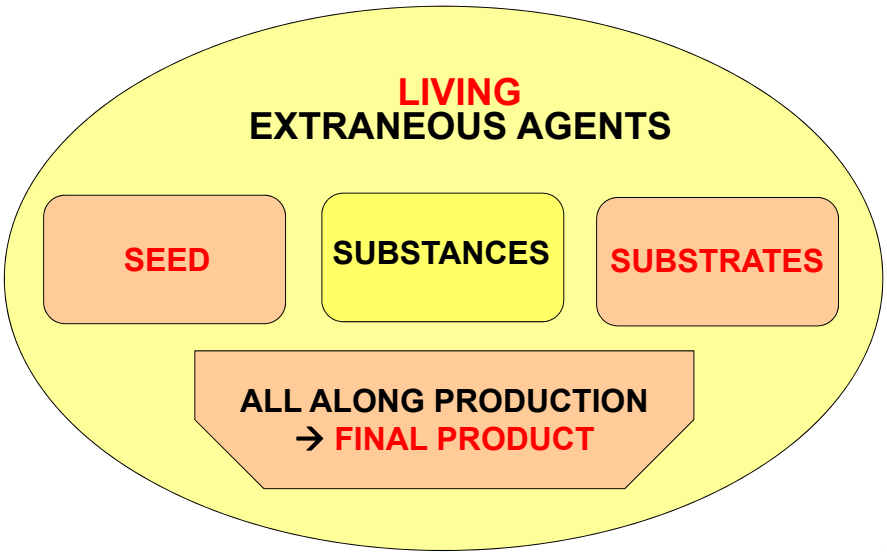
II – GENERAL PRINCIPLES AND REQUIREMENTS

III – RISK MANAGEMENT
- risk assessment
- risk control

IV – CONTROL MEASURES

ANNEXES I and II

SCOPE



GENERAL PRINCIPLES

According to the principles of risk management, […] the list of extraneous agents to be TESTED in the final product is LIMITED to those that cannot be excluded by other means.

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ANNEX I

ANNEX I: LIST OF EXTRANEOUS AGENTS TO BE CONSIDERED FOR THE RISK ASSESSMENT

AVIAN (Poultry) - main list	
Viral agents	**Bacterial agents**
Aviadenoviruses	*Salmonella pullorum*
Avian encephalomyelitis virus	*Avibacterium (Haemophilus) paragallinarum*
Avian leucosis virus (excluding endogenous type)	*Mycobacterium avium*
Avian nephritis virus (ANV)	*Chlamydia* spp.
Avian orthoreoviruses	
Avian paramyxovirus type I	
Avian poxvirus	
Avian reticuloendotheliosis virus	
Avian rotavirus	
Avian metapneumovirus	
Atadenovirus (group III avian adenoviruses)	
Infectious bursal disease virus type I and II	
Marek's disease virus and meleagrid herpesvirus type 1 (HVT)	
Type A influenza virus	

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Annex I

AVIAN (additional list for Chicken)	
Viral agents	**Bacterial agents**
Avian infectious bronchitis virus Chicken anemia virus (CAV) Gallid herpesvirus type I	
AVIAN (additional list for Duck)	
Viral agents	**Bacterial agents**
Duck hepatitis B virus (DHBV) Duck and goose parvoviruses Duck enteritis virus Duck hepatitis virus type 1	
AVIAN (additional list for Goose)	
Viral agents	**Bacterial agents**
Duck and goose parvoviruses Duck enteritis virus Goose haemorrhagic polyomavirus (GHPV)	
AVIAN (additional list for Turkey)	
Viral agents	**Bacterial agents**
Avian paramyxoviruses serotype 3 (APMV-3) Siadenovirus (group II avian adenovirus) Turkey coronavirus Turkey viral hepatitis virus Turkey lymphoprofilferative disease virus	
AVIAN (additional list for Pigeon)	
Viral agents	**Bacterial agents**
Columbid herpesvirus 1	

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REQUIREMENTS

– any **MASTER SEED LOT** (after processing, if relevant) found to contain extraneous agents of any kind, other than the species and strain stated, is unsuitable for vaccine production

– any **SUBSTRATE** (after processing, if relevant) found to contain any extraneous agent shall be discarded or used only in exceptional and justified circumstances

– any batch of **SUBSTANCE** (after inactivation or processing, if relevant) found to contain any extraneous agents shall be discarded or used only in exceptional and justified circumstances; to be accepted for use, further processing must be carried out that will ensure elimination or inactivation of the extraneous agent in the final product, […]

– unless otherwise prescribed, any **FINAL PRODUCT** found to contain any extraneous agent shall be discarded.

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RISK ASSESSMENT

Country ?

Target species ?

Source species ?

Inactivation ?

Tissue ?

Amplification removal?

Change incidence?

Change process?

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RISK CONTROL

RESTRICTION

VALIDATION

Country ?

Target species ?

Source species ?

Inactivation ?

Tissue ?

In process removal?

IMPLEMENTATION

TESTING

for EA that cannot be excluded

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GMP
SEED LOT Σ

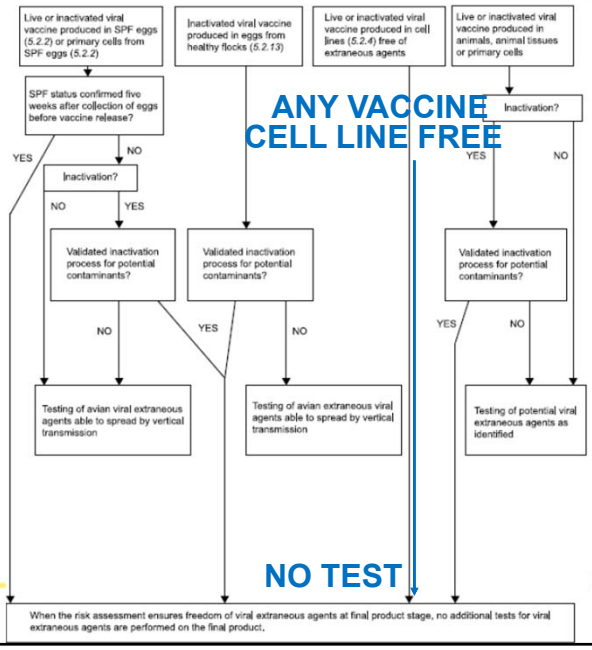
+

MSV
FREE OF EA

+

SUBSTANCES
FREE OF EA

ANNEX II: TESTING STRATEGY - EXAMPLE OF A DECISION TREE



ANY VACCINE
CELL LINE FREE

NO TEST

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CONTROL MEASURES - STARTING MATERIALS

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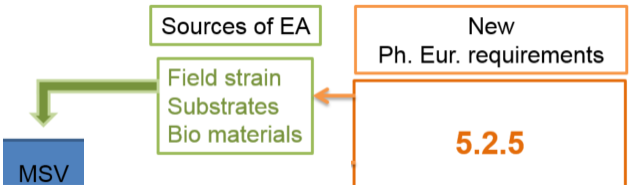
CONTROL MEASURES FOR STARTING MATERIALS (1)

Preventive measures during sourcing and preparation



Seed lots **A NEW CONSIDERATION**

Whenever possible, restrictions are placed on substrates and substances used for the propagation of the virus or bacteria between the initial isolate and the established master seed (i.e. the use of embryonated eggs free from specified pathogens (SPF) for isolation) to prevent the introduction of extraneous agents into the seed material. Such measures are documented and taken into account in the risk assessment.

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CONTROL MEASURES FOR STARTING MATERIALS (3)

Embryonated hens' eggs **A CLARIFICATION**

Where vaccine organisms are grown in chicken embryos for the production of a master seed lot and for all passages of a microorganism up to and including the working seed lot, eggs from SPF flocks (*5.2.2*) are used.

For production of inactivated vaccines, where vaccine organisms are grown in chicken embryos from the working seed lot onwards, such embryos are derived either from SPF flocks (*5.2.2*) or from healthy non-SPF flocks (*5.2.13*).

For production of live vaccines, where vaccine organisms are grown in chicken embryos from the working seed lot onwards, such embryos are derived from SPF flocks (*5.2.2*).

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CONTROL MEASURES FOR STARTING MATERIALS (4)

Animals **NEW INFORMATION**

When animals are used for the production of immunosera, they comply with the requirements of the monograph *Immunosera for veterinary use (0030)*.

Where the use of animals or animal tissues in the production of the vaccines is unavoidable, the following requirements apply.

Chicken used for the production of vaccines are obtained from an SPF flock (*5.2.2*).

Other animals used for the production of vaccines are free from specified pathogens.

The animals used are exclusively reserved for production of vaccines. They are maintained under conditions protecting them from exposure to disease… (detailed requirements)

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CONTROL MEASURES - PRODUCTION

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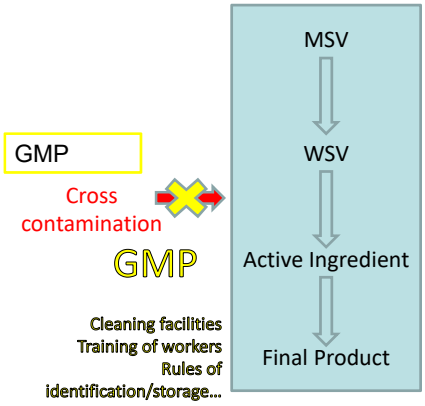
CONTROL MEASURES DURING PRODUCTION (1)

RECALL BASICS FOR THE PRODUCTION SYSTEM

Preventive measures

Unless otherwise justified and authorised, cells and viruses/bacteria/parasites for vaccine production are handled according to a seed lot system. Cross contamination is avoided during production by the application of well-established quality systems (e.g. by production under conditions of good manufacturing practice).



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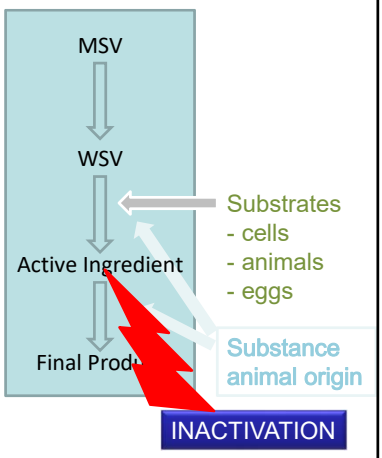
CONTROL MEASURES DURING PRODUCTION (2)

Removal or inactivation of extraneous agents during production

During production, some processing steps can lead to removal or inactivation of possible contaminants.

For instance, in the case of inactivated IVMPs, the method used for inactivation of the active ingredient may be considered as a means of inactivating possible contaminants from materials of animal origin used in the manufacture of this active ingredient.

Likewise, for inactivated vaccines produced on embryonated eggs from healthy flocks, the inactivation process applied to the active ingredient may be considered as a means of inactivating potential contaminants.



AN ILLUSTRATION OF IN PROCESS REMOVAL/INACTIVATION

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METHODS OF DETECTION

A NEW APPROACH

Any method that fulfils the requirements described in this general chapter may be used.
The results of the tests are acceptable if the method has been demonstrated to provide adequate sensitivity and specificity for the detection of the targeted extraneous agent.
Quality control samples, such as appropriate positive run controls with a specified content of a representative agent and negative run controls, are included in each test run to validate the results and evaluate test performance.

METHODS OF DETECTION – GENERAL PREREQUISITES

Molecular methods […] may be used either as an alternative to *in vivo* tests or as a supplement/ alternative to *in vitro* culture tests based on the risk assessment.

The results of molecular methods require appropriate interpretation and further investigation may be necessary. For example, if a positive signal from NAT detection methods is obtained, other *in vitro* methods are used to verify and document the absence of viability of possible contaminants.

In the case of divergent results produced by several different methods, a risk assessment must be performed. […]

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METHODS OF DETECTION – SPECIFIC INFORMATION

Sterility : → chapter *2.6.1*.

For bacteria and fungi that are not detectable by the sterility test other suitable methods are used, e.g. NAT (*2.6.21*).

Mycoplasmas: → chapter *2.6.7*.

Extraneous viruses:

→molecular techniques, e.g. NAT (*2.6.21*),

→or *2.6.37. Principles for the detection of extraneous viruses in immunological veterinary medicinal products using culture methods*.

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CONCLUSION

A CHAPER DEDICATED TO

GLOBAL APPROACH FOR THE MANAGEMENT OF EA

AGENTS TO BE CONSIDERED

RISK MANAGEMENT APPROACH

RISK CONTROL MEASURES – Materials / production system

INFORMATION FOR TESTING

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CL1

Thank you for your attention

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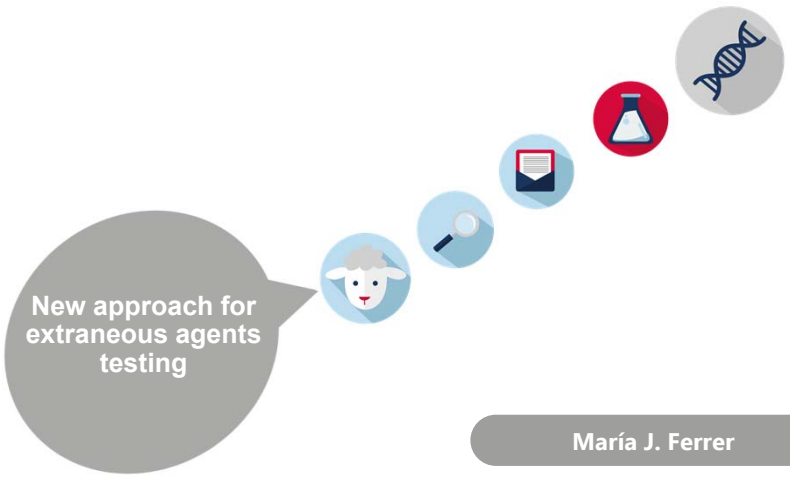


María J. Ferrer

AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS

AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS

Context

Live bovine vaccine

Recently authorised

Directive 2001/82/CE as amended
Ph. Eur. monographs

VACCINE characteristics

- Freeze-dried fraction containing a live attenuated virus (A)
- Conventional method of production – **GMP**
- Seeds produced according to a **Seed Lot System**

FOCUS of this presentation

- Starting material **not listed** in a pharmacopoeia : **Virus (A) MSV (1)**
- Starting materials **listed** in a pharmacopoeia: **peptone (2)**
- **Final product (3)**

Why (1), (2) and (3)?

Because the same approach was taken by the applicant for other starting materials of animal origin

(Seeds, starting materials of animal origin and Final product are mainly affected by changes in Ph. Eur.)

Applicant's approach: summary of the strategy

✓**(1)Virus A**

✓**(2)Peptone**

→ **Absence of EAs**

✓**(3)Final product** → **No EAs test performed**

Since no changes in normative, the TSE risk is not addressed

(1) Virus A (MSV): **Information** provided by the **applicant**

- **Virus isolated more than 50 years ago in the US**
- **Long history of cell passages resulting in MSV – A**
- **MSV-A produced in the last 5 years**

Tests performed (validated) on the MSV -A:
▶Identity ▶ Sterility ▶ Absence of Mycoplasma

For ▶ Extraneous agents, the applicant takes into account the list for "bovine" from Guideline on requirements for the production and control of immunological veterinary medicinal products

BOVINE	
Viral agents	Bacterial agents

(1) Virus A (MSV): **Information** provided by the **applicant**

Bacterial agents

Validation provided

Specific ***testing*** of:

- *Brucella* spp. – ***PCR***
- *Chlamydia* spp. – ***Incubation in SPF embryonated eggs***
- *Coxiella* spp. - ***Incubation in SPF embryonated eggs***
- *Leptospira* spp. – ***PCR***
- *Mycobacterium* spp. – ***Culture method***

EXTERNAL VALIDATION

AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS

(1) Virus A (MSV): **Information** provided by the **applicant**

Viral agents

The absence was shown by one of the following options:

- ✓ Option 1: a **risk assessment** is given to justify assurance of absence of EAs.

Not tested

- ✓ Option 2: by **testing** (general tests like CPE, haemadsorption, immunostaining or specific tests like PCR)

Freedom from EAs shown by testing

(1) Virus A (MSV): **Information** provided by the **applicant**

Extraneous agents listed in Annex 2 EMA (CVMP/IWP/206555/2010)	Not tested	Freedom from EAs shown by testing
Akabane virus	x[1]	
Alcelaphine herpesvirus	x[2]	
Bluetongue virus		x
Borna disease virus		x
Bovine adenovirus		x
Bovine coronavirus		x
Bovine enterovirus		x
Bovine ephemeral fever virus	x[3]	
Bovine herpesvirus (BoHV-1)		X
Bovine papilloma virus	X[4]	
…….		

(1) Virus A (MSV): **Information** provided by the **applicant**

Risk assessment for ***not testing***:

X[1] and **X[2]**: Akabane virus and Alcelaphine herpesvirus

- Virus did not occur in the country of origin of virus seed (**OIE**)
- No CPE was observed in cell culture when virus A was neutralised (according to EMA/CVMP/IWP/251741/2015)

X[3]: Bovine ephemeral fever virus

- Virus did not occur in the country of origin of virus seed (**Chen *et al*. 2010**)
- No CPE was observed in cell culture when virus A was neutralised (according to EMA/CVMP/IWP/251741/2015)

X[4]: Bovine papilloma virus

- Virus does not grow in cell culture according to EMA/CVMP/IWP/251741/2015

(1) Virus A (MSV): **Information** provided by the **applicant**

When tested, **validation** reports provided

Vich GL1: "The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose."

For EAs testing, qualitative tests are needed and the following key parameters were considered:

- Specificity
- Detection limit
- Robustness

(1) Virus A (MSV)

Conclusion:

The risk assessment provided ensures freedom from some extraneous agents.
Specific and general tests cover the rest.

(2) Peptone: **Information** provided by the **applicant**

✓ **Prepared from milk fit for human comsumption. Known and documented origin (certificated by the supplier)**

✓**USP monograph compliance. Total aerobic microbial count, *enterobacteriaceae* and *salmonella* are within specifications (supplier certificate).**

✓**Heat treatments**:

- ✓**Before use , it is autoclaving at ≥121ºC for at least 15 minutes**
- ✓**During down-stream processing of the peptone another heat treatment is applied (validation provided)**

(2) Peptone: **Information** provided by the **applicant**

***Risk assesment*: The suitability of the heat treatment in AEs inactivation is based on the following report:**

IFAH-Europe-Viral inactivation related to **steam sterilisation** of biological products

Lumpy skin disease virus	5 min at 80°C	van den Ende M et al., 1950: J Gen Microbiol. 2: 225-34
Bovine Pseudocowpoxvirus	30 min at 65°C	OIE Disease Card, 2013: Sheep pox and goat pox
Borna disease virus	60 min at 60°C	Extrapolated
Akabane virus	5 min at 56 °C	Takahashi E. et al. 1978: Veterinary Microbiology 3: 45-54
Cache Valley virus	60 min at 60°C	Extrapolated
Rift valley fever virus	60 min at 60°C	Saluzzo et al. 1988; Journal of Virological Methods 22: 165-172
Bovine Coronavirus	1 h at 50°C	Dinter Z. and Morein B., 1990: Virus Infections of Ruminants, page 297
Bovine viral diarrhoea virus	5 min at 50°C 16 min, 60°C	Haas et al. 1995; Rev. sci. Off. int. Epiz 14: 435-445 Borovec S et al, 1998: Biologicals, 26, 237-244
Tick-borne encephalitis virus	5 min at 50°C 16 min, 60°C	Extrapolated
Wesselsbron virus	5 min at 50°C 16 min, 60°C	Extrapolated
Bovine Respiratory syncytial virus	30 min at 56°C	Dinter Z. and Morein B., 1990 Virus Infections of Ruminants, page 363

(2) Peptone: **Information** provided by the **applicant**

For those viruses *not listed* in previous report:

the applicant takes *similar approach* to IFAH, to provide a risk assessment analysis to demonstrate that the applied sterilisation methods are adequate for inactivating all relevant EAs.

Bovine parvovirus	5 min at 80°C 10 hours at 60°C	Groner at al, 2018: Transfusion, 58: 41-51
Bluetongue virus	15 min at 60°C	Svehag SE 1963: Archiv für die gesamte Virusforschung 13: 499-510
Rotavirus	10 min at 60°C	Jim O' Mahony et al. Int J Food Microbiol. 2000 Nov 1;61(2-3):177-85.
Epizootic haemorrhagic disease virus	15 min at 60°C	Extrapolated
Reovirus	15 min at 60°C	Extrapolated
Jena virus (Norwalk-like)	30 min at 64°C	Denholm L. et al, 1996: Disease strategy vesicular exanthema, Australian veterinary emergency plan, Ausvetplan (Edition 2.0)
Bovine enterovirus	30 min 70°C	Extrapolated

(2) Peptone: **Information** provided by the **applicant**

Conclusion:

As heat treatments are considered suitable to inactivate: testing on EAs is not needed

(3)Final product

Ph. Eur. m 5.2.5. *Risk control*

The need to test the final product for the presence of viral extraneous agents and the testing strategy must be evaluated on the basis of a risk assessment as described in section 3-1.

For viral vaccines, testing for viral extraneous agents in the final product may not be necessary, provided all of the following general conditions are met:

- the vaccines are produced according to well-established quality systems (e.g. under conditions of good manufacturing practice);
- the master seed is free from extraneous agents (based either on risk assessment or testing);
- the other materials used in the production process are free from extraneous agents (based on risk assessment, testing or treatment); amongst these materials, the quality of the substrates can be considered according to a decision tree of the type proposed in Annex II to possibly alleviate testing of extraneous agents in final products.

(3)Final product

By testing :

▶ Sterility ▶ Absence of Mycoplasma

By risk assessment:

▶ Extraneous agents:

A. All relevant EAs listed in Annex 2 to EMA/CVMP/IWP/206555/2010-Rev.1 have been accounted for.
B. Virus A, Virus B and all biological starting materials are free of all relevant EAs and none of them poses a risk with respect to the relevant EAs.
C. During the production process, it is warranted that contamination does not occur and sterilisation methods are validated.
D. Absence of all relevant EAs in final product is either substantiated:
   - •by risks assessments,
   - •by test data proving absence

When the risk assessment ensures freedom of viral extraneous agents at final product stage, no additional tests for viral extraneous agents are performed on the final product.

(3) Final product

Conclusion

The test for absence of EAs on the finished product is considered to be redundant

Applicant's approach summary of the strategy:

✓**(1)Virus A**

✓**(2)Peptone**

→ **Absence of EAs**

✓**(3)Final product** → **Supression of the EAs test**

amb14

AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS

New approach for extraneous agents testing

Risk assessment

Thank you very much

www.aemps.gob.es

AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS

New approach for extraneous agents testing
Concrete examples

Renáta Kováčová
Institute for State Control of Veterinary Biologicals and Medicaments (ISCVBM), Slovak Republic & Member of Ph. Eur. Expert Group 15V

Approach to EA testing

- Different approaches to EAs management
- Different procedures (national, MRP/DCP, CAP)

Combined approach – testing and RA already used in past

⬇

Exclusion of testing of potential EAs based on e.g.:

- solvent treatment of MSVs during isolation and preparation, testing of viruses that may survive the treatment by cell culture testing, PCRs
- MC bank - exclusion of testing for viruses by RA due to geographical origin, target and source species

Overview of the presentation

Example 1	Risk Management **Vaccine component B produced from eggs from healthy chicken flocks**
Example 2	Risk assessment **Test for Avian reticuloendotheliosis virus – sensitivity issue**
Example 3	Risk assessment **Schmallenberg virus in WCB**

Example 1

Risk Management

Vaccine component B produced from eggs from healthy chicken flocks

Context of the example

Avian live vaccine

Live attenuated virus A

Vaccine component B (inactivated)

material of animal origin

Eggs from healthy chicken flocks

- one supplier, country of origin – XY
- certificate of analysis + veterinarian inspection certification

Regulatory framework relevant for the example

„Old“ approach

Ph.Eur. chapters and monographs

- **0062** Vaccines for veterinary use
- **2.6.25** Avian live virus vaccines: tests for extraneous agents in batches of finished products
- **5.2.13** Healthy chicken flocks for the production of inactivated vaccines for veterinary use
- **5.2.2** Chicken flocks free from specified pathogens for the production and quality control of vaccines
- **5.2.5** Substances of animal origin for the production of immunological veterinary medicinal products

„New“ approach

New Ph.Eur. chapter:

- **2.6.37** Principles for the detection of extraneous viruses in IVMPs using culture method

Revised Ph.Eur. chapters and monographs:

- **5.2.5** Management of extraneous agents in immunological veterinary medicinal products
- **0062** Vaccines for veterinary use

Others:

- **5.2.2** Chicken flocks free from specified pathogens for the production and quality control of vaccines
- **5.2.13** Healthy chicken flocks for the production of inactivated vaccines for veterinary use

Risk assessment
Presence of EAs at healthy flocks level

Available results/information provided by applicant:

- geographical origin ⟶ no elimination, global prevalence
- source and target species ⟶ chicken
- Tests results:

  ⟶ Compliance with Ph.Eur. 5.2.13: ***M. gallisepticum, M. synoviae, S. enteritidis, S. typhimurium, S. pullorum***

  Negative serology for **ILTV, TRTV, AIV, FAV**

  Compliant serology (vaccination) for **NDV, IBV, EDS, ReoV, AEV, CAV, IBDV**

Risk assessment focuses on:

- Remaining EAs listed in table 5.2.2.-1. vertically transmitted (egg extraction)
- Processing of eggs (production steps)
- Inactivation procedure

Agents considered for RA

Agent	Vertical transmission	Consideration for further RA (potential contaminants)
Avian adenoviruses, group 1	Yes	YES
Avian encephalomyelitis Virus	Yes	YES
Avian Infectious bronchitis Virus	No	No vertical transmission
Avian infectious laryngotracheitis virus	No	No vertical transmission , negative serology
Avian leucosis viruses	Yes	YES
Avian nephritis virus	No	No vertical transmission
Avian orthoreoviruses	Yes	YES
Avian reticuloendotheliosis virus	Yes	YES
Chicken anaemia virus	Yes	YES
Egg drop syndrome virus	Yes	YES
Infectious bursal disease virus	No	No vertical transmission
Influenza A virus	No	No vertical transmission , negative serology
Marek´s disease virus	No	No vertical transmission
Newcastle disease virus	No	No vertical transmission
Turkey rhinotracheitis virus	No	No vertical transmission, negative serology
Fowl pox virus	No	No vertical transmission
Mycoplasma gallisepticum	Yes	NO, absence required by 5.2.13
Mycoplasma synoviae	Yes	NO, absence required by 5.2.13
Salmonella pullorum	Yes	NO, absence required by 5.2.13

Risk control: Production process

Vaccine component B:

- extracted from eggs from healthy flocks

Extraction steps include:

- Dilution
- pH adjustment
- Filtration

These steps could minimise the risk of contamination, however not all extraction steps are validated

→ Additional data still required

Risk control – Inactivation procedure

- Inactivating treatment using BEI
- Validation of the BEI inactivation treatment based on bibliographic data
- Bibliographical data available for avian and non-avian agents
- Virus models (physic-chemical resistance based on genetic material and structural properties), minimum 6 logs reduction in titre

Bibliographic data*/experience**

Structural properties			List of potential viruses at risk	Physico-chemical resistance	Virus models
Enveloped	RNA	ss	**Avian leucosis virus** **Avian reticuloendotheliosis virus**	Low	AIV and NDV*
Non-enveloped	DNA	ss	**Chicken anemia virus**	Very high	Porcine parvovirus*
		ds	**Avian adenovirus** **Egg drop syndrome virus**	Medium	EDSV**
	RNA	ss	**Avian encephalo-myelitis virus**	High	FMD*
		ds	**Avian orthoreovirus**	Medium	Avian reovirus*

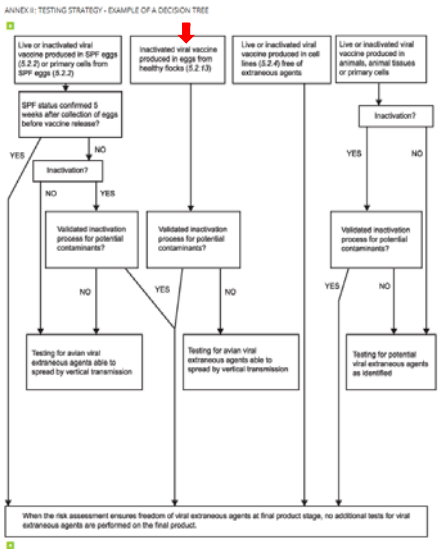
Risk management – new approach

Ph.Eur. 5.2.5.:

...the list of extraneous agents to be tested in the final product is limited to those that cannot be excluded by other means..

The evidence for the efficacy of the procedure may take the form of references to published literature and/or experimental data generated by the manufacturer, but must be relevant to the conditions that will be present during the production and inactivation/processing of the material.

....the other materials used in the production process are free from extraneous agents (based on risk assessment, testing or treatment); amongst these materials, the quality of the substrates can be considered according to a decision tree of the type proposed in Annex II to possibly alleviate testing of extraneous agents in final products.



RA evaluation

- Agents routinely monitored in healthy chicken flocks excluded
- Agents excluded by certificate confirming their absence
- Agents not vertically transmitted excluded
- Agents inactivated by BEI excluded

Risk concluded as negligible by the applicant and no additional tests on the final product are considered

✓**Accepted**

Example 2

Risk assessment

Test for Avian Reticuloendotheliosis virus (REV) – sensitivity issue

Context of the example

Starting material of biological origin:

⬇

Master seed virus - Avian live virus

⬇

Titer
Identity
Bacterial and fungal sterility
Detection of Mycoplasma
Test for Eas using embryonated hens´eggs
Test for Eas in chicken kidney cells
Test fo Eas using chicks

Test for ALV (RT-PCR)

Test for REV – RT PCR ⬅

Test for CAV (PCR)

Regulatory framework relevant for the example:

„Old“ approach

Ph.Eur. 0062 Vaccines for veterinary use
Ph.Eur. 2.6.24 Avian viral vaccines: tests for extraneous agents in seed lots

4.Test for avian reticuloendotheliosis virus (cell culture method)

General provisions
h) NAT can be used after validation for sensitivity and specificity

Sensitivity of the RT PCR

Fit for purpose according to „New approach“?

RT-PCR for REV

- Validation report provided by the applicant
- Validation parameters: LOD, accuracy and precision, specificity, robustness (VICH 1 and 2)
- Results:

Sensitivity of the NAT method

LOD 10^3 $CCID_{50}$ (ALV: 10 $CCID_{50}$; CAV:10 $CCID_{50}$) considered high in comparison to ALV, CAV

RT-PCR for REV

Solution:

- **Pre-amplification step – 2 passages in chicken kidney cell culture to improve the sensitivity**

growth in CK cells supported by bibliographic data, but scientific evidence to support detection of potential contaminant using this NAT not available

- **Re-testing of the MSV for REV by RT-PCR after pre-amplification step**

Absence of REV in MSV confirmed

REV diluted to final concentration of 10 CCID50 detected in MSV/WSV after pre-amplification step using NAT method

REV diluted to final concentration of 10 CCID50 without pre-amplification step – REV not detected

✓ Accepted

New approach
Requirements for „Fit for purpose“ method

Result of RA : EA (REV) cannot be excluded – need for testing ⟶ RT PCR for REV

Requirements for the method	Reference to Ph.Eur. chapter
Adequate sensitivity	Ph.Eur.5.2.5., 4-3-1
Adequate specificity	
Quality control samples - positive and negative run controls	
Alternative *in vitro* method preferred	
Positive signal – confirmation of absence of viability	Ph.Eur.5.2.5., 4-3-1 Other in vitro methods available, e.g. cell culture method ⟶ Ph.Eur. 2.6.37 (in connection with requirements stated in Ph.Eur. 5.2.5.)
Further requirements for molecular methods	Ph.Eur.5.2.5., 4-3-2 with reference to Ph.Eur. 2.6.21 (NATs)

Example 3

Risk assessment
Schmallenberg virus in WCB

Context of the example

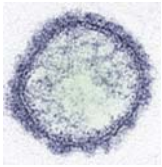
Starting material of biological origin

↓

Master cell bank (VERO)

↓

Working cell bank



Testing:

Bacterial and fungal sterility

Brucella spp., Salmonella spp., Mycobacterium spp., Coxiella burnetti, Chlamydia

Mycoplasma

Eas – cytopathogenic, haemadsorbing or haemagglutinating agents

Specific viruses

Retroviruses

Regulatory framework relevant for the example:

Ph.Eur. 0062 Vaccines for veterinary use

5.2.4. Cell cultures for the production of vaccines for veterinary use

EMA guideline:
Guideline on requirements for the production and control of immunological veterinary medicinal products

Risk assessment for Schmallenberg virus

Applicant justification for not testing (1):

- Can be isolated in cell culture (KC, BHK, Vero; O.I.E.)
- CPE on VERO – 4 to 5 days (biographical data)
- CPE on VERO performed – absence of the virus
- Geographical origin

→ not accepted

- Adaptation to cell culture is necessary for in vitro growth, isolation in cells can be difficult (O.I.E.)
- Bibliographic data available for adapted strain not for wild strain
- General test not sufficient to detect potential contamination
- Geographical origin – accepted for VERO cells but not for serum
- Bovine serum for cultivation of cells - not sufficient data (irradiation) to eliminate the risk

Risk assessment for Schmallenberg virus

Applicant justification for not testing (2):

- Internal data supporting of in vitro growth of SBV on VERO
- MSV origin – wild strain successfully passaged in VERO cells
- Serum – geographical origin excludes contamination by SBV at the time of establishment of WCB batch
- Irradiation – validation report provided – „Bunyaviridae“ not included

Bibliographic data available for similar ssRNA enveloped Akabane virus – NO risk of contamination (reduction of at least 14 log)

✓**Accepted**

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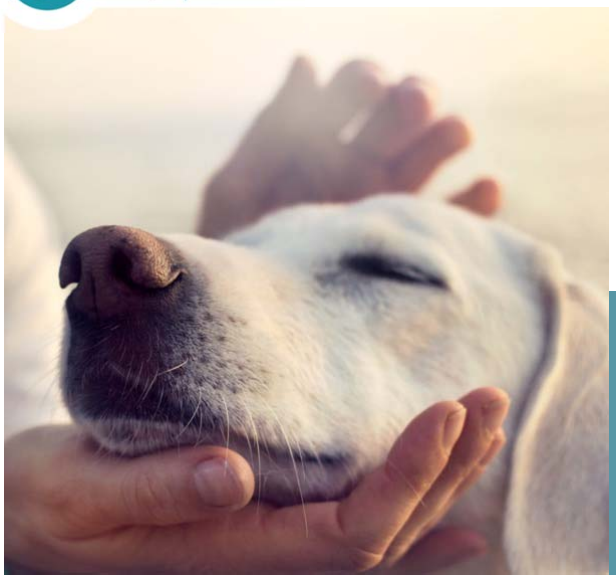

MANAGEMENT OF EXTRANEOUS AGENTS IN IVMPs

Manufacturers' point of view

Dr Frédéric Descamps

Training EDQM 1st April 2020

@animalhealthEU
/animalhealthEU
AnimalhealthEurope

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Agenda

Introduction

Consequences of the Ph. Eur. changes

General recommendations

Specific recommendations

Introduction

Changes to viral safety-related Ph. Eur. have a big impact on IVMPs Industry

Key to remember that the previous (current) system is/was working well (no major concern for the last 20 years)

AHE appreciates the Authorities' efforts and welcomes this online training

Impossible to go through all concerns/questions in 15'

A face-to-face meeting with EDQM, Assessors and Industry is (still) highly desirable

Consequences of the Ph. Eur. changes

Decreased predictability

Removal of all EA technical requirements (Ph. Eur. 5.2.4, 0062, 2.6.24, 2.6.25) – Previously accepted as validated (rare questions)

The risk assessment may be perceived differently by different assessors

List of EA is open, and subject to change over time

Explicit preference for NAT – Despite presumed high sensitivity, also limitations (such as, detection of non-living agents)

Extent of expected validation (primer coverage, positive controls…) ?

More focus on non-seed materials (rare questions till now)

Consequences of the Ph. Eur. changes

Existing seeds

Typically tested using cell- and/or egg-based assays (not NAT)

Typically not tested for all (relevant) current EA's

Historic documentation not always compelling

Risk assessment may not be sufficient for the new EA's

Additional testing may jeopardize existing products (notification/batch recalls/etc)

Even if risk to detect an EA is negligible, may just stop the project

Impact is "real" a.o. on availability of (improved) products:

Shift from new multivalent vaccine development to associated use claim; New fall-out of an existing multivalent vaccine will not be registered;…

Consequences of the Ph. Eur. changes

New seeds

Very likely, a maximum of precautions :

- -Test for EAs, even where risk assessment concludes on negligible risk
- -Probably extensive use of NAT (where available)
- -Consider all international requirements, where seeds intended to be used globally

New approach possibly linked with more testing than previously

Particular case of avian seeds

- -New seeds expected to heavily rely on Ph. Eur. 2.6.24

Consequences of the Ph. Eur. changes

Existing products

In principle, retrospective compliance to Ph.Eur. 5.2.5 not expected.

Consistent with 3Rs - Expectation to be pushed towards removal of finished product testing (where *in vivo* testing involved)

To remove finished product testing, compliance to Ph.Eur. 5.2.5 will be needed. However…available documentation/testing may not be enough. Plus, reluctance to put at risk existing product (in case additional testing is required). And, testing may still be required for other regions. Net effect may be to not proceed further with removal.

Potential GMP compliance issues (MA dossiers referencing compliance to Ph. Eur. 2.6.25, for example)

NAT for all EAs may not be developed/available yet

Consequences of the Ph. Eur. changes

Virus seed positive by NAT for one EA

If replicative assay exists (BVD, for example) – Potential way forward

If replicative assay does not exist, how to handle ?

…Possible to use the seed if the EA is not on the EA list ?

…Possible to use the seed if the EA is from non-target animal species, and no related disease reported in the target species ?

…Possible to use the seed if no EA detection (by NAT) at a next production step (or final product) ?

…Other suggestions ?

Risk: different interpretation by non-EU countries. A decision tree is needed

General recommendations

Increase predictability

- **Consistent (and regulatory-based) risk assessment**
- **Benefit of common Assessor and Industry trainings**
- **Additional (published) guidance required (Q&A or other)**
- **Continue to work on EA-cell pairs/detection methods for additional animal species (incl. NAT)**
- **Harmonized guidance in case of positive "finding" (for existing product/existing seed/existing material of animal origin)**
- **Allow for transition period (especially for avian)**

Specific recommendations

In the spirit of risk assessment, …

- **Continue to allow cell- and egg-based assays, and do not request "highest sensitivity"**
- **Expect and allow reduced testing for WS versus MS (also for cell seeds)**
- **Recognize the use of historic safe use in the field**
- **Develop official guidelines on accepted treatment (pH, T°,…) for the exclusion/inactivation of the listed EA for the most commonly used materials of animal origin (bovine/foetal sera, peptones, trypsin). This could be done in a similar fashion like the EMA reflection paper.**
- **Accept as "supportive" (no question) any testing done to satisfy non-EU regions (and concluded as testing not required from risk assessment)**

Specific recommendations

"Officialize" the link between Ph. Eur. 5.2.5 and CVMP reflection paper (CVMP/IWP/251741/2015)

No questions if the EA-cell pairs/detection methods are used

No questions if (previous versions of) Ph. Eur. 2.6.24, 2.6.25, 5.2.4 are used

Bank of primers to be developed and maintained by EDQM / Alternatively, include acceptable primers in the CVMP reflection paper

NGS (when further developed) will also need guidance

In absence of a health issue, consider a positive finding (on existing product/seed/other material) as a quality issue (not a safety issue), and allow for a transition period to solve this when needed

Risk analysis for extraneous agents – example of methodology on poultry live viral vaccine

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Extraneous agent test for live poultry vaccines produced in SPF eggs or primary cells from SPF eggs -now

a) General virus tests:

- 3 tests on SPF eggs
- Test on CEF

b) Specific virus tests:

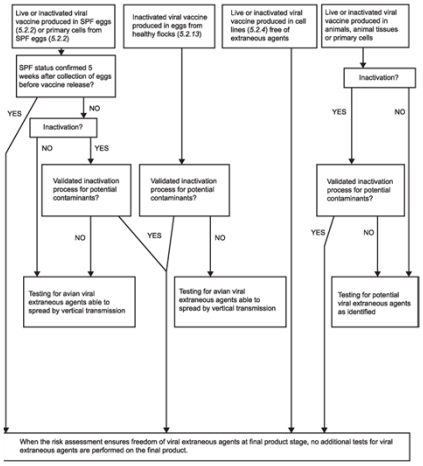
Chicken anemia virus

Marek's disease virus

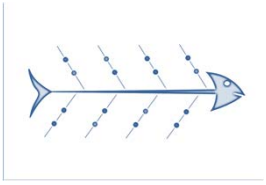
Egg drop syndrome

Turkey rhinotracheitis virus

Extraneous agent test for live poultry vaccines produced in SPF eggs or primary cells from SPF eggs – July 2020



Risk analysis



- Ishikawa diagram – cause-effect diagram
- All potential risks for extraneous agents listed and analysed
- Concern: not exact as testing to present to regulatory agencies and GMP inspectors

Step 1. Virus seed

MSV	
Origin Date of isolation	Viruses from list in Annex I not present in geographical region in the time of isolation
Passage history	SPF eggs or cells free from extraneous agents from list in Annex I
Documented production process	Same approach as batch of vaccine at the time point of production

- In case of doubt - test on the remaining agents listed in Annex 1

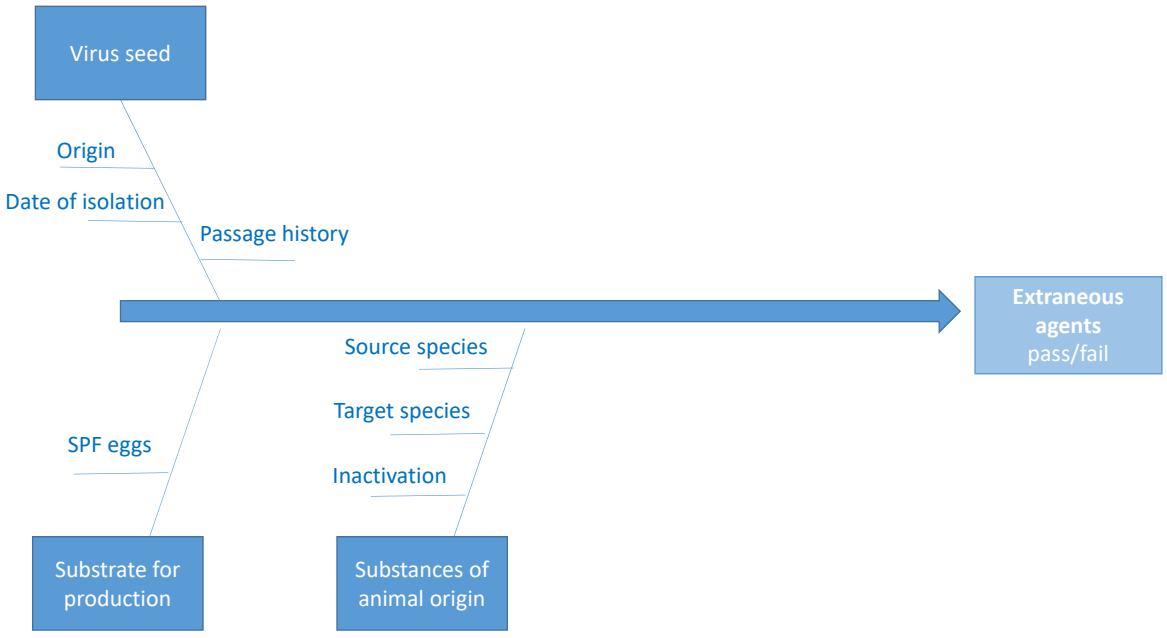
WSV	
Same approach as batch of vaccine at the time point of production od WSV	Documented risk assessment

Step 2. Substrate for production

- SPF eggs
  - check CoA for SPF status 5 weeks after collection of eggs
  - What about Avian poxvirus and Avian rotavirus -not on SPF list (5.2.2.)?

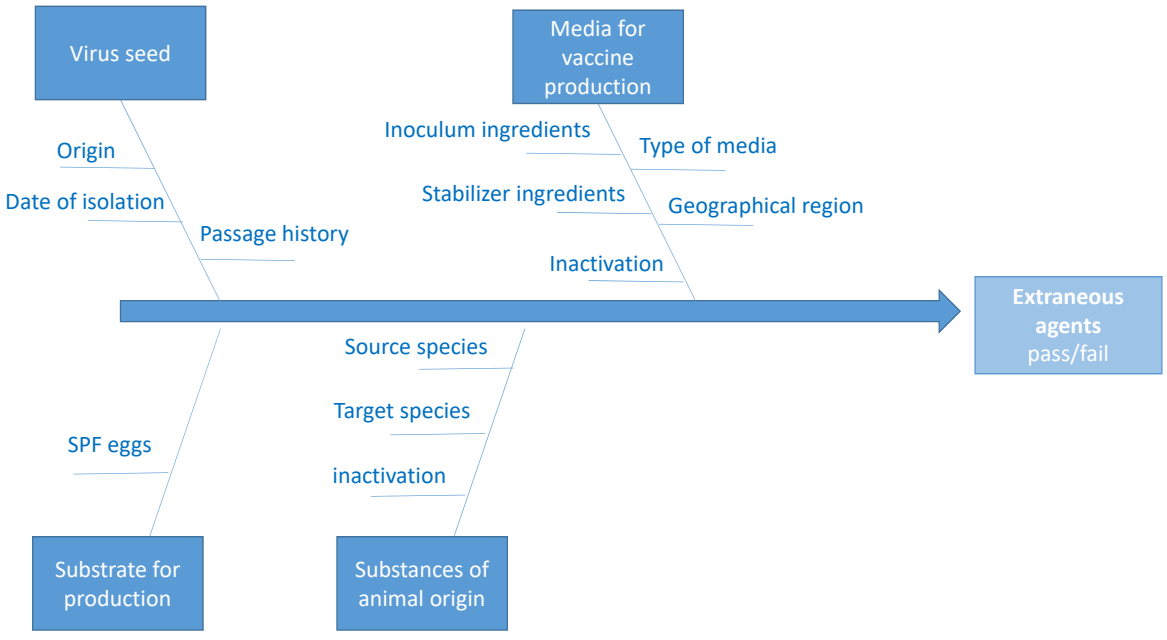
Step 3. Substances of animal origin

- Avoid or keep on a minimum
- List all
- Expected or demonstrated to be free from extraneous agents
- Potential infectious diseases that may occur in the source species
- Potential infectious diseases that may occur in the target species
- Inactivation procedure



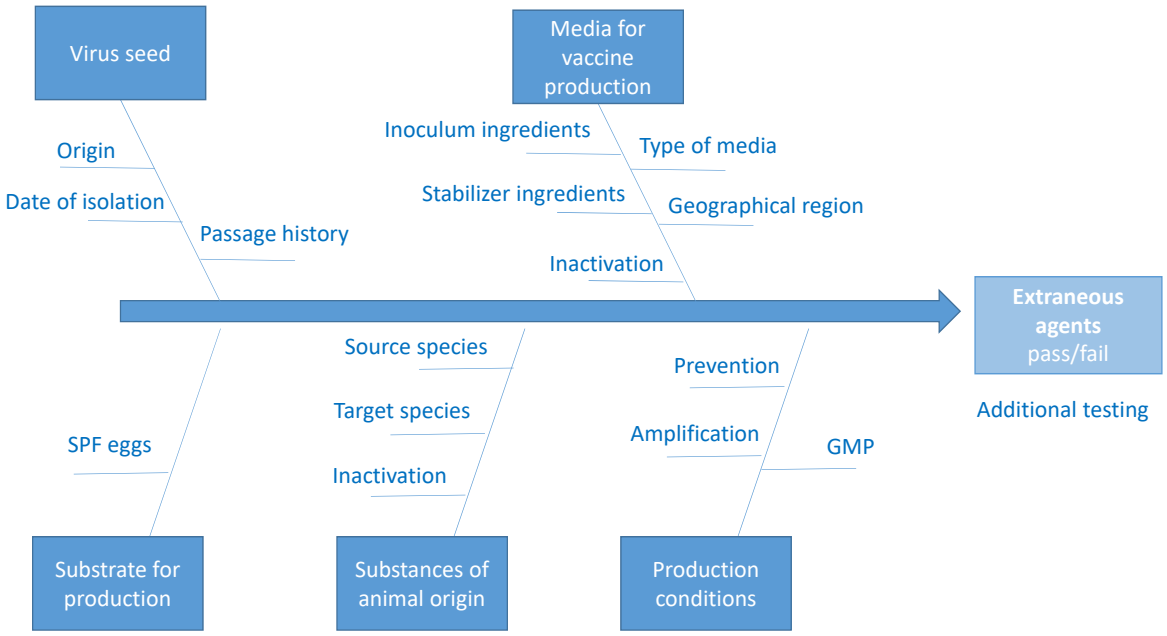
Step 4. Media for vaccine production

- All ingredients for inoculum in SPF eggs
- All compounds of stabilizer
- Type of media (is it likely to have viruses)
- Geographical region of production
- Inactivation process

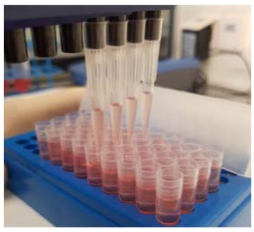


Step 5. Production conditions

- Prevention the introduction of extraneous agents during production
- Capacity of the production process to amplify an extraneous agent or to remove it
- GMP
- Standardized production
- Trained personnel
- Well-controlled process
- Cleaning validation
- Virus cross contamination assurance



Additional testing



- List of viruses in Annex I
- Validated methods

- Concerns:
  - Should we develop and validate methods for all viruses listed in Annex I before registration of the product/variation in existing file (July/2020)?
  - QC test should be under GMP-how to outsource this specific testing?

Risk control

- Placing restriction on the source of the material and auditing these restrictions
- Using validated inactivation procedures
- Testing the extraneous agents in cases where their presence cannot be excluded during the risk assessment

Risk analysis -how often?

- SPF status for every batch
- MSV and WSV at time of production – documented
- Changes in the incidence of disease occurring in the region or country of origin of substances for production or production itself
- Positive results of any available tests for extraneous agents

Conclusion