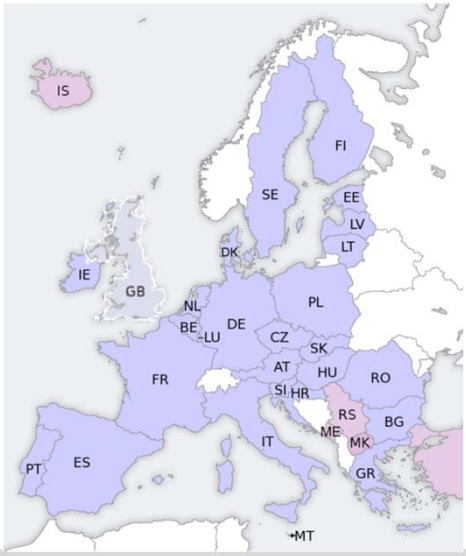
EDQM TRAINING SESSION: VETERINARY BATCH RELEASE NETWORK

Current marketing authorisation procedures for IVMPs in the EU

REGISTRATION IN EUROPEAN UNION



European Union:

One unified region

REGISTRATION IN EUROPEAN UNION

But still:

28 (27) different countries

It is evolving, …slowly.

This has consequences on registration systems

Will NVR (New Veterinary Regulation) improve this?

SOME KEY DATES FOR MA & IVMP

Art 1. 7. Immunological veterinary medicinal product:
A veterinary medicinal product administered to animals in order to produce active or passive immunity or to diagnose the state of immunity (2001/82 EC as amended).

65/65/EEC: definition of medicinal product

87/22/EEC: biotechnology-product

90/677/EEC (81/851/EEC) IVMP are EU-regulated (technical Annex: Dir 92/18/EEC)

(EEC) 2309/93 ((EC) 726/2004): EMA and CP

93/40/EEC & 2001/82/EC (& 2004/28/EC): MRP (& DCP)

→(EU) 2019/6: NVR (28 January 2022)

REGISTRATION / MA

Registration is the precondition for placing a product on the market

– Key parameters considered are: Quality, Safety and Efficacy
– Defined by 2009/9/EU (81/852/EEC) describing norms & protocols
– Based primarily on positive benefit/risk assessment

Registration is part of a system

- Close monitoring after MA:
  – 'Pharmacovigilance'
  – Good Manufacturing Practice inspections
  – sampling and testing programs
- Living environment:
  – Renewal (unique)/Variations to improve/adapt MA to science/knowledge
  – suspension / withdrawal

MA is the contract between industry and authorities

KEY PRINCIPLES/FACTS

Any contract is based on trust (MSs, companies, experts)

Part of a system: PhV, GxP, registration, variation, inspection, …

To remain efficient and realistic:
it is moving from final checks on product to build-in quality

Changes … so 'Difficult to let it go'
(TAST, TABST, consistency approach, continuous re-assessment, …)

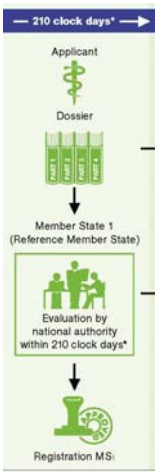
Harmonised assessment/same regulatory basis/similar conclusions?

REGISTRATION PRINCIPLE

A registration process is very simple:

- Applicant sends information
- Authorities assess
- Authorities ask questions
- Applicant receives questions
- Applicant answers questions
- Authorities assess
- Authorities ask for clarification
- Applicant clarifies
- Decision is made.
- MA is granted/updated

NATIONAL PROCEDURE



First available tools (before EU and new directive for harmonisation start)

Basis for a lot of existing products

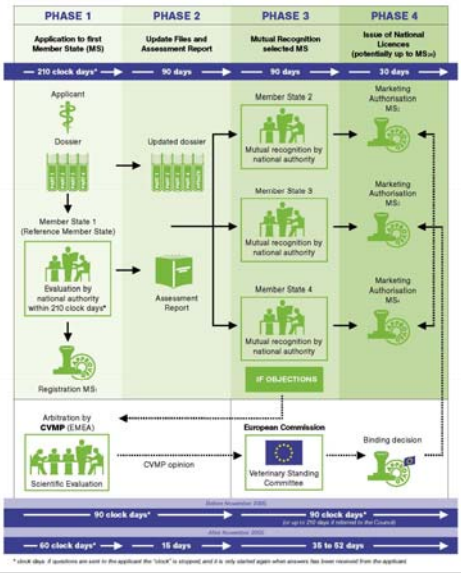
Harmonised in content by « 92/18 review process »

Timelines (210 days) variable, often prioritised with European procedures

Usually split in 120+clock stop+90 days

Multiple MAs (one by country)

MUTUAL RECOGNITION PROCEDURE



First available tools to harmonise

"Recognise" first assessment based on same basic requirements (Reference MS)

Reduce resources need (Concerned MS)

Timeline (90d) strictly applied, the 30d to MA are very variable

X identical MAs

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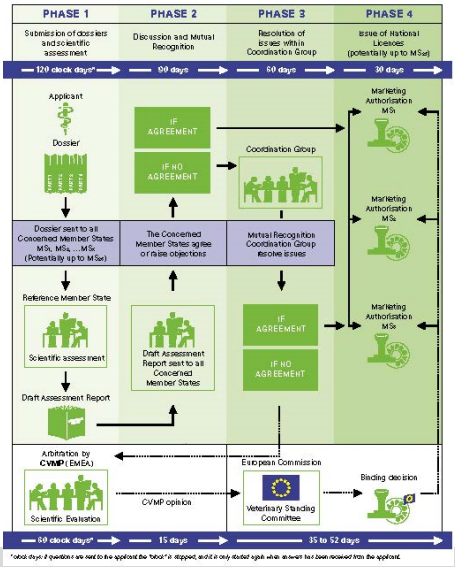
DECENTRALISED PROCEDURE



Improved MRP, having all steps in one procedure

"Recognise/delegate" first assessment based on same basic requirements

Reduce resources need (CMS, if trust)

Timeline (120+90d) strictly applied, the 30d to MA are very variable

X identical MAs

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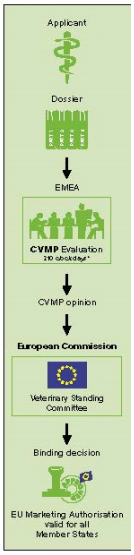
CENTRALISED PROCEDURE



The tool for European single market

Scope reduced/restricted to some products

Timelines (210 days) strictly applied

Time span to MA quite stable

ONE MA for all Member States

HOW TO CHOSE?

CP compulsory: Art 3.1 (EC)2004/726

- recombinant DNA technology,
- controlled expression of genes
- hybridoma and monoclonal antibody methods
- performance enhancers

CP possible: Art 3.2

- new active substance (not authorised)
- significant therapeutic, scientific or technical innovation or is in the interests of animal health at Community level.
- IVMP for diseases subject to Community prophylactic measure

DCP/MRP vs CP

If some MS are opposed/not facilitating a type of product

If product is regionalised (epidemiology, absence of disease, target animals)

To get specific distribution status (CP=compulsory POM under art 67d)

Simplicity of CP (one discussion/one body)

DCP vs MRP

To consolidate certain approaches or if already some existing national actions/MA.

ADAPTATION OF MA = VARIATION SYSTEM

Need to update documentation and assessment for the product to keep it current

Same kind of regulatory evolution as MA over years.

Now: Harmonised system ((EC)1234/2008, (EC)712/2012),

Improvement as you can:

- Group variations
- Have a worksharing (one authority drives the system for all)

Still few discussions possible as:

classification guidelines (Annex II of the regulation) is subject to interpretation, not frequently updated

VARIATION PROCEDURES

Type IA "Do and Tell": No prior approval

- IA_{IN}: to be notified immediately after the changes have been implemented
- IA: to be notified within 12 months following implementation (annual report with all IA changes)

Type IB = Tell, Wait and Do

- To be notified before implementation but do not require a formal approval (MAH must wait 30 days before implementing the change)

Type II*

- Require prior approval before implementation
- For most type II variations, a 60-day assessment time table will apply (sometimes 90 days)

*almost all variations are type II for IVMPs

OTHER TYPES OF ACCESS TO MARKET

726/2004 art 39 (7) and 2001/82/CE Art 26 (3) Exceptional Circumstances MA (e.g. BTV)

art 7 (product with MA in other MS)

art 8 (bio product without MA)

Cascade (other species/indication/human N/A)=> art7 or autogenous vaccine

(Extension, repeat use)

CONCLUSIONS

System based on trust (whatever the people/country/company/authority)
Still complex system, with no full harmonization

Some adaptations took place in the **NVR**

- More opening to CP
- Some constraints to MRP/DCP/NP
- Variation w/o approval
- No sunset
- Signal detection for PhV
- Consideration of novel therapies,

- And the entire annex to write/update very soon (part of several delegated/implementing acts)

NEW VETERINARY REGULATION

L 4/24 EN Official Journal of the European Union 7.1.2019

REGULATION (EU) 2019/5 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 11 December 2018

amending Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, Regulation (EC) No 1901/2006 on medicinal products for paediatric use and Directive 2001/83/EC on the Community code relating to medicinal products for human use

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Article 114 and Article 168(4)(c) thereof,

Having regard to the proposal from the European Commission,

After transmission of the draft legislative act to the national parliaments,

Having regard to the opinion of the European Economic and Social Committee (1),

Article 5

Entry into force and application

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

Points (2) to (5), (10), (12) to (16), (18), (26), (28), (29), (31), (37), (38), (40), (42) to (44) and (46) of Article 1, and Articles 2, 3 and 4 shall apply from 28 January 2019.

Points (1), (6) to (9), (11), (17), (19) to (25), (27), (30), (32) to (36), (39), (41) and (45) of Article 1 shall apply from 28 January 2022.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Strasbourg, 11 December 2018.

For the European Parliament — *The President* — A. TAJANI

For the Council — *The President* — J. BOGNER-STRAUSS

NEW REGULATION (EU) 2019/6

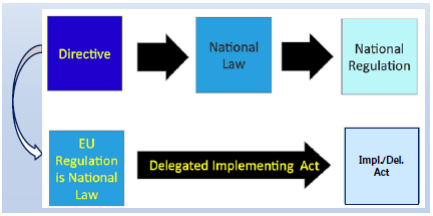
The new Regulation (EU) 2019/6 on veterinary medicinal products, published on 7 January 2019, repeals Directive 2001/82/EC and brings the following main achievements:

- harmonises the internal market for veterinary medicinal products
- reduces the administrative burden
- enhances the internal market
- stimulates innovation
- provides for incentives to increase the availability of veterinary medicinal products
- strengthens the EU action to fight antimicrobial resistance.

- IVMP: veterinary medicinal product intended to be administered to an animal in order to produce active or passive immunity or to diagnose its state of immunity;

NEW REGULATION (EU) 2019/6

Advertising for vaccination
Signal detection, no PSUR



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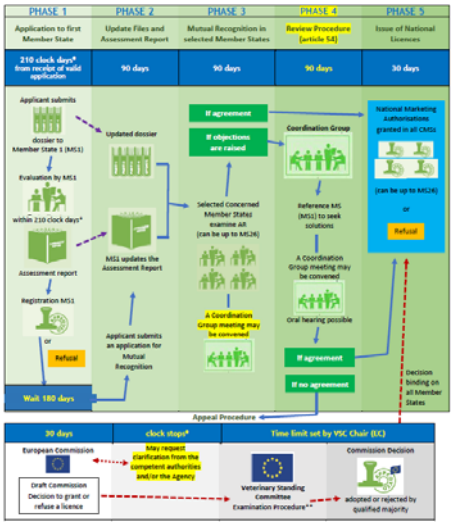
NEW MUTUAL RECOGNITION PROCEDURE



Six months must elapse between the date of MA in RMS and submitting an application for MR

- A Coordination Group meeting may be convened during the 90-day MR period (already in practice)
- The CVMP referral if no agreement has been replaced with a Coordination Group 'Review Procedure' and an 'Appeal

procedure, during which the EC "May request clarification from the competent authorities and/or the Agency"

- The EC Decision Making Procedure timelines have been changed, and will be longer and less predictable

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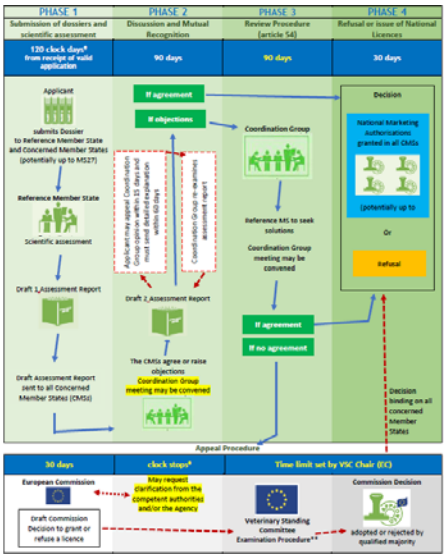
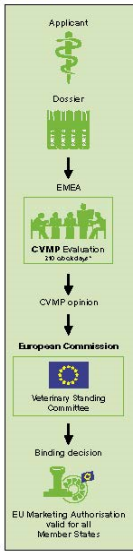
NEW DECENTRALISED PROCEDURE



A Coordination Group meeting may be convened during the 90-day MR period (already in practice);

- Phase 3 has increased from 60 to 90 days;
- The 'CVMP referral if no agreement' has been replaced with "May request clarification from the competent authorities and/or the Agency";
- The EC Decision Making Procedure timelines have been changed, and will be longer and less predictable

NEW CENTRALISED PROCEDURE

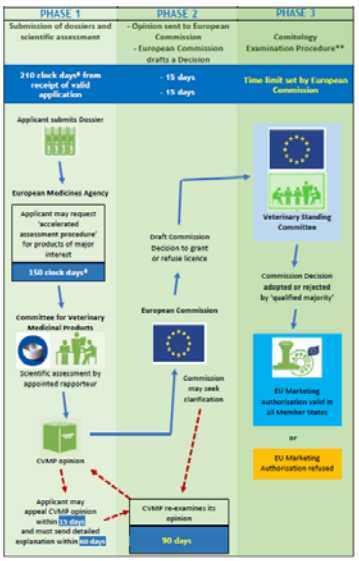


No big difference (timelines)

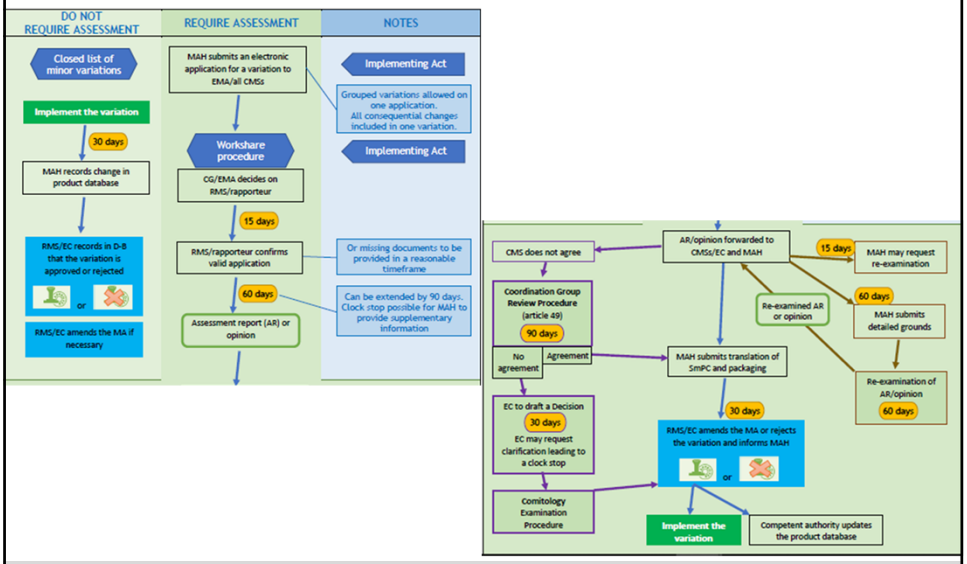
Scope is now for all.

Time for CVMP to re-examine its opinion has been increased from 60 days to 90 days

- There is no set time limit for phase 3 (comitology); currently the Veterinary Standing Committee has 22 days to comment, and the EC must issue the final Decision within 15 days after the end of the comitology procedure.



NEW VARIATION SYSTEM



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THANK YOU
ANY QUESTIONS?

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Boehringer Ingelheim

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

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

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

An overview of European OCABR/OBPR for IVMPs;

Legal context, key principles, outline of the procedure and tools

EDQM Workshop:

OMCL Batch Release of IVMPs

October 29-30, 2019 EDQM, Strasbourg

Catherine Milne, EDQM, DBO

Presentation Outline

Context and Key Principles

- EDQM, COE and the EU
- The European Medicines Regulatory Network
- EU Legislation: Integrated Framework for Control of IVMPs
- OBPR
- OCABR
- Eligibility for OCABR
- OCABR-OBPR Choice
- OCABR recognition
- Key Players
- VBRN
- Main Goal

Procedure for OCABR/OBPR

- Achieving the Goal
- Main Procedures and Guidelines
- Outline of the Procedures
- Arranging for OCABR with and OMCL
- Time Lines
- Certificates
- OCABR:How it works
- Protocol Templates
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- Marketing Information Form
- Good Practice: 1 batch- 1 certificate

Communication, Other Procedures, 3Rs and Benefits

- Communication
- Electronic Tools for Information Exchange for VBRN
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- Elaboration
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- 3Rs for animal use
- Benefits of the Network
- More than just batch release
- VBRN Actors

EDQM, Council of Europe and the EU/EEA

Council of Europe

47 Member States of the Council of Europe

COE Member states
Albania, Andorra, Armenia, Austria, Azerbaijan, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxemburg, Malta, Moldova, Monaco, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Russian Federation, San Marino, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, "the former Yugoslav Republic of Macedonia", Turkey, Ukraine, United Kingdom

Observers
Canada, Holy See, Japan, Mexico, USA

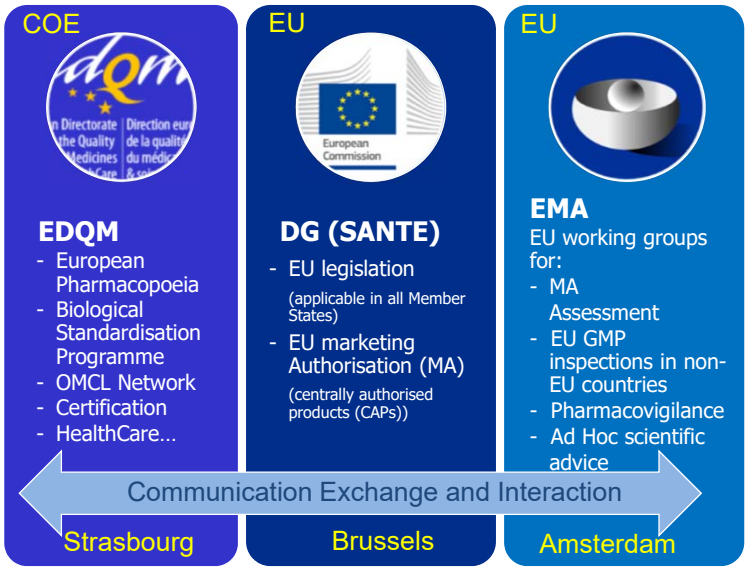
European Pharmacopoeia Members and Observers

European Union

European Union/EEA Countries – 28 + 3

Overlapping but not identical scope

EU Medicines Regulatory Network



Regulatory Network Supported by National Competent Authorities

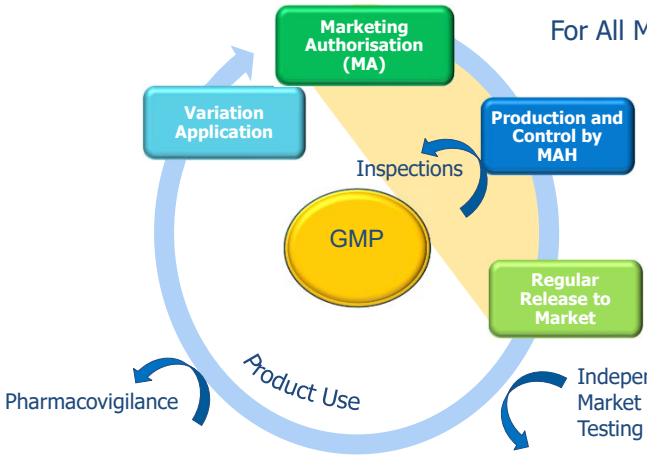
- National Legislation (including transposed EU Directives)
- National MA (for non-CAP)
- GMP inspections (on behalf of the community)
- Physical Control of Medicines (batch release, market surveillance)

EU: European Union, COE: Council of Europe, EMA: European Medicines Agency EDQM: European Directorate for the Quality of Medicines and HealthCare, OMCL :Official Medicines Control Laboratories, Certification : Certification of Suitability of Monographs of the European Pharmacopoeia, HealthCare: Transplantation, transfusion, counterfeits, cosmetics, packaging etc.

EU Legislation: Integrated Framework for Control of IVMPs

EU legislation in place to define rules for establishing and monitoring quality, safety and efficacy for all vet medicinal products *EU Directive 2001/82/EC (2004/28/EC as amended) - replaced by Regulation (EU) 2019/6**

Rules regarding:
- Licensing (MA defining controls by the manufacturer),
- GMP standards,
- Possibilities for
  - inspections,
  - market surveillance by independent authorities
- Pharmacovigilance



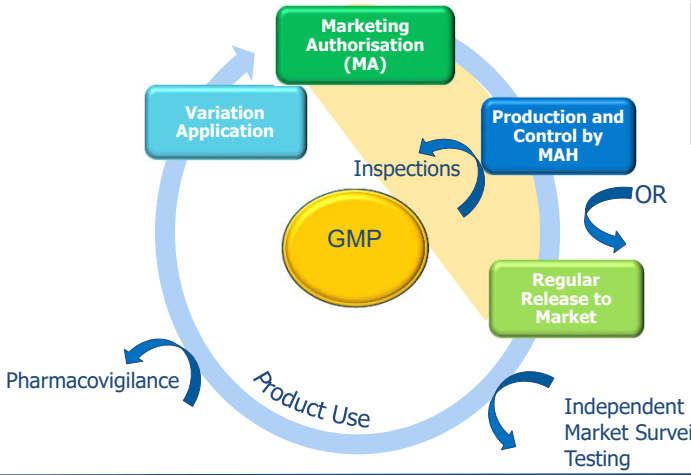
For All Medicinal Products

*Applicable from 28/01/22

EU Legislation: Integrated Framework for Control of IVMPs

IVMPs – additional batch to batch control is possible.

Treated differently because of special characteristics eg. inherent variability in product, in manufacture and in test methods and nature of use (eg preventive mass vaccination)



Article 81*
Offical Batch Protocol Review
- **Mutually Agreed Recognition** of Results in all Member States

Independent protocol review

Article 82*
Independent Official Control Authority Batch Release
- **May clause**
- **Mandatory Mutual Recognition** of Results in all Member States

Independent protocol review and testing

*Article 128 of Reg. 2019/6

OBPR

OBPR: Based on Article 81
All licensed IVMPs are eligible
Review of manufacturer's batch protocol in comparison to the approved Marketing Authorisation.
Common agreement among Member States (MS) to recognise OBPR performed by another MS (EU OBPR Certificate) **provided the codified procedure is followed**. **Batch should only be sent to 1 MS for OBPR**
Relevant Procedures, Guidelines and Templates
• EU Administrative Procedure for a Harmonised Application of Article 81 for OBPR of IVMPs • Protocol Templates for manufacturers

Article 81 (*paraphrased*)

1. *Member States shall take appropriate measures to ensure the Marketing Authorisation Holder (MAH)/manufacturer furnish proof of control tests carried out on final IVMP and/or consituents and intermediates of the manufacturing process in accordance with the methods laid down in the Marketing Authorisation.*
2. *For the purpose of paragraph 1 a MS may require the MAH to submit to the competent authorities copies of all the control reports signed by the qualified person.*
   - *The MAH shall ensure that an adequate number of representative samples are held in stock at least up to the expiry date and provide samples promptly to the CA on request.*

OCABR

OCABR: Based on Article 82

Licensed IVMPs on pre-defined short-list are eligible

Review of manufacturer's batch protocol in comparison to the approved Marketing Authorisation

Plus

Testing of samples using agreed tests

Mandatory mutual recognition of OCABR performed by another Member State (EU OCABR Certificate): **codified procedure must be followed**.

Batch must only be sent to 1 MS for OCABR

Relevant Procedures, Guidelines and Templates

- EU Administrative Procedure for Application of Article 82 for OCABR of IVMPs
- Protocol Templates for manufacturers
- Product Specific Guidelines for OMCLs tests

Article 82 (*paraphrased*)

1. *Where it considers it necessary a MS may require the MAH of an IVMP to submit samples of the bulk and/or IVMP for control by an OMCL before the product is put into circulation.*
2. *On request of the CA the MAH shall promptly supply the samples.*
   The CA shall inform the other MS of its intention to control batches.
   If a batch is controlled by one MS it shall not be re-controled by another MS.
3. *After studying the control reports the OMCL shall repeat the tests carried out by the manufacturer on the finisihed product as defiend in the MA*
   The list of tests repeated may be restricted to justified tests provided that all concerned MS and if appropriate EDQM agree.
   For IVMPs authorised in the centralised procedure (Reg 726/2004) the list should also be agreed by the Agency
4. *All MS shall recognise the results of the tests*
5. *Unless the Commission is informed the control is compeletd within 60 days.*
   The CA shall make the notification within this time
   If the batch is not in conformity the CA shall take all necessary measures with teh MAH/manufacturer ad shall inform the other MS

Eligibility for OCABR

Products groups eligible for systematic OCABR using a reduced testing scheme are defined in a short-list based on risk assessment and agreed by the concerned Member States in the Network – List re-confirmed yearly

List in annex 1 of OCABR (Art. 82) Administrative Procedure

Current list :

- **IVMPs against Aujeszky's Disease**
- **IVMPS against Brucellosis**
- **Equine Influenza**
- **IVMPs against Infectious Bovine Rhinotracheitis**
- **IVMPs against Newcastle Disease Vaccine**
- **IVMPs against Rabies**
- **IVMPs against Swine Erysipelas** (excluding inactivated vaccines)
- **Tuberculin Purified Protein Derivative (PPD) (Avian and Bovine)**
- **Brucellin Preparations**

OCABR-OBPR Choice

Choice of application of article 81/82 up to individual Member States

May clause (article 82) means.....
Same product can have different batch release requirements in different MS

e.g. Vaccines short-listed for Article 82 (eg. rabies vaccine, inactivated)

- Some MS require OCABR – only OCABR certificate accepted
- Some MS require OBPR – OBPR or OCABR certificate accepted
- Some have no pre-market batch requirement – batch goes directly to market

Up to the MS to duly inform the MAH of the procedure in force for the product

OCABR recognition

If OCABR is required by a Member State and an OCABR certificate has been issued by another Member State the OCABR certificate MUST be accepted without further control of the batch before release.

Additional post market controls remain possible.

Key Players

- Individual Competent Authorities (CA)/Official Medicines Control Laboratories (OMCLs)
  - Responsible for the release of individual batches according to the defined rules
- Veterinary Batch Release Network (VBRN)
  - Work together to define and apply codified rules based on the Directive and to communicate information on issues and batches to the network members – Network activity co-sponsored by the EU Commission and the Council of Europe
- Manufacturers
  - Important partners in the process. Produce and submit batches according to the defined rules and communicate with CA/OMCLs and the network on relevant issues.

VBRN

OCABR Network is a specific activity network within the General European OMCL Network (GEON)

EDQM is the secretariat to the network

FULL VBRN

All EU/EEA MS represented

Advisory Group

4 elected + members EU Commission and EMA observer

- **Full VBRN**
  - EU/EEA and MRA partner Switzerland
  - decision making body, share all information including annual activity reports
  - CA/OMCLs carry out day-to-day control of IVMPs
  - Plenary meets once per year
- **Advisory Group**
  - reviews issues and proposes strategies
  - represents the network with external partners
  - Meet twice per year
  - Ad hoc drafting groups as needed

Advantages of a Network

Cooperation **Technical Competence**

Communication

Work sharing **Support** Trust

All essential to support and sustain mutual recognition

EU OCABR Certificate: based on OMCL's results for a subset of tests approved for the product in the marketing authorisation, chosen by risk assessment and agreed by the full network, plus protocol review

1 Certificate for 32 Countries!!

Certificates also recognised outside the EU

All MS receive information on batches, in particular when a batch is rejected

Main Goal

The main goal of the EU legislation and the supporting structure of the CA/OMCLs and VBRN is to ensure good, high standard and consistent quality IVMPs throughout the EU and to facilitate the movement of these goods throughout the territory.

Break

Questions?

Still to come

Procedure for OCABR/OBPR

- Achieving the Goal
- Main Procedures and Guidelines
- Outline of the Procedures
- Arranging for OCABR with an OMCL
- Time Lines
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Achieving the Goal

EU Directives state what should be done - but not how to do it

Effective mutual recognition requires:

- Mutual confidence
- Common transparent procedures
- Open communication

Network provides a framework using commonly agreed procedures and methods, guidelines for testing, platforms for confidential information exchange on batches and methods and work sharing

An effective VBRN results in optimisation of resources while assuring safe, good quality products

A common EU OCABR release certificate is valid throughout the EU - and beyond – this reduces testing – benefits MAH, and Member States.

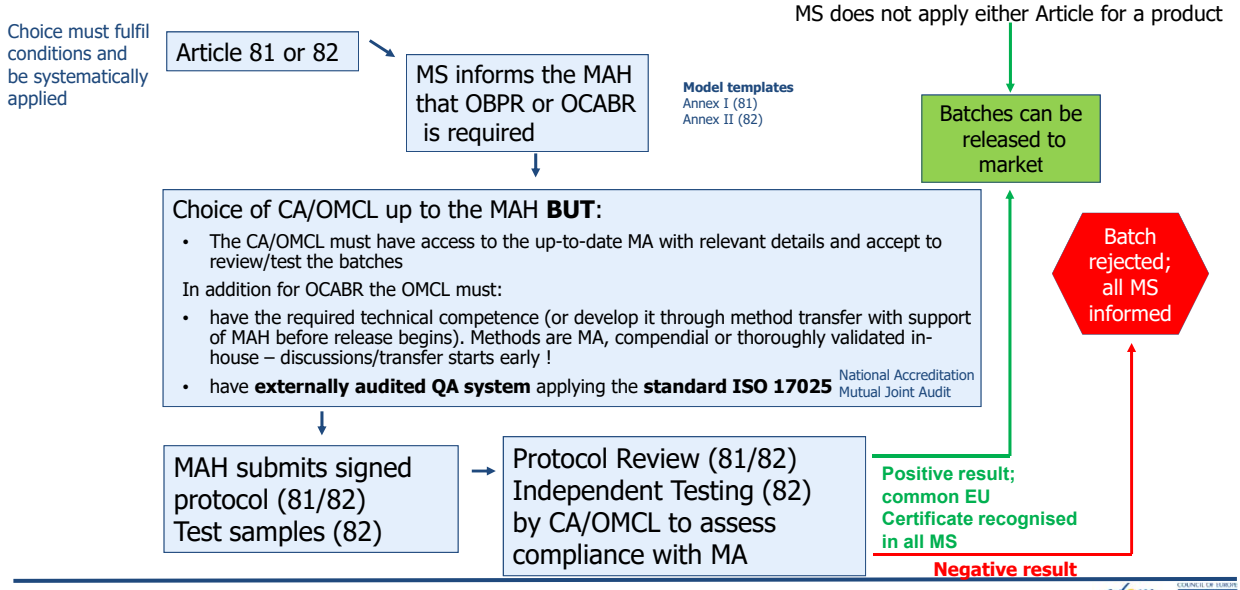
A common EU OBPR certificate also contributes to streamline the system.

Main Procedures and Guidelines

Administrative Procedures	Function
EU Administrative Procedure for the harmonised application of Article 81 for Official Batch Protocol Review of IVMPs (OBPR)	The Administrative Procedures describe the steps to be followed by individual Member States and MAHs when applying OCABR/OBPR OCABR Procedure contains list of eligible products for restricted testing Both provide a series of templates for important documents • Certificates of Compliance • Notice of non-compliance • Model letters for communication with the manufacturer
EU Administrative Procedure for the application of Article 82 for Official Control Authority Batch Release of IVMPs (OCABR)	
Product Specific Guidelines (for OCABR) - Presently 15	Defines the samples to be submitted by the manufacturer and the test(s) to be carried out by the OMCL performing OCABR
Protocol Templates (for OBPR and OCABR) - Presently 5	Provides a framework template for the protocol to be submitted by the manufacturer/MAH – covers critical information and key points in production

These procedures and guidelines are available for download from the EDQM website https://www.edqm.eu/en/Veterinary-OCABR-Guidelines-1531.html

Outline of the Procedures



Arranging for OCABR with an OMCL

How to identify OMCLs

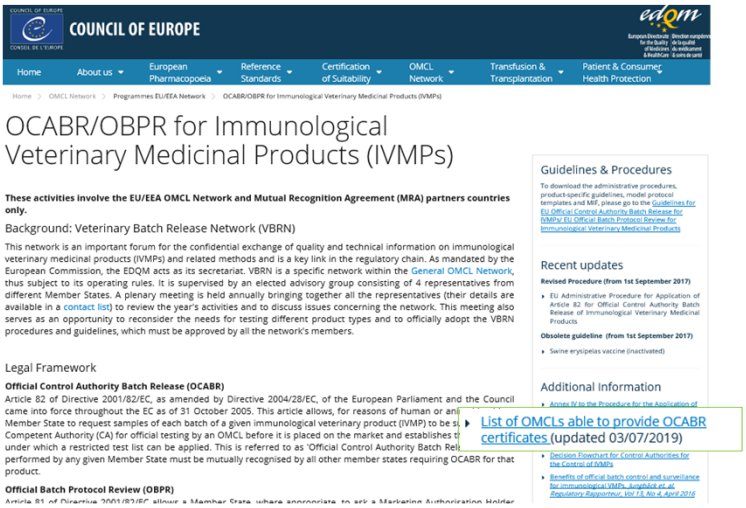


Table identifies the different product categories eligible for OCABR and lists OMCLs that have indicated they are, or would be in a position to test lots

Updated based on information from OMCLs

Manufacturers are encouraged to contact potential OMCLs early in order to ensure the method transfer is complete in time for the testing needs

Time Lines

OBPR Review

A CA/OMCL has **15* days** to complete the procedure.

- The count starts after receipt of all the necessary elements from the manufacturer (signed protocol, fees) – the real time is usually shorter

OCABR Testing

An OMCL has **60* days** to complete the procedure.

- The count starts after receipt of all the necessary elements from the manufacturer (samples, signed protocol, fees)
- To gain time it is encouraged to make arrangements for testing at the OMCL to be done in parallel with the manufacturer ie. samples are sent to the OMCL before the manufacturer has completed their own testing

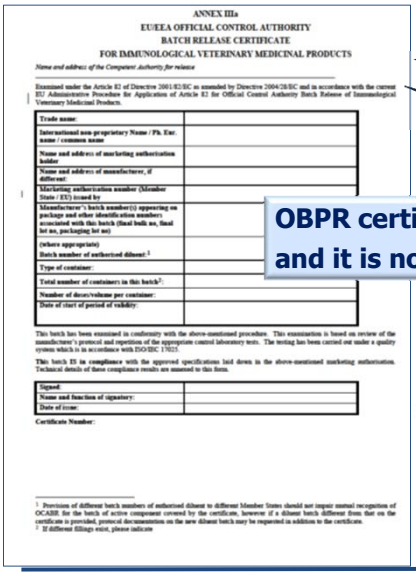
Administrative Release

(accepting an OCABR/OBPR certificate from another CA/OMCL)

CA/OMCL has a maximum of **7*** working days after receipt of the the required documents from the MAH – the real time is usually shorter

*If clarifications are required from the MAH and more information is requested the time for response from the MAH is not included in the count

OCABR/OBPR Certificate



ANNEX IIIa

EU/EEA OFFICIAL CONTROL AUTHORITY BATCH RELEASE CERTIFICATE

FOR IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

Name and address of the Competent Authority for release

Examined under the Article 82 of Directive 2001/82/EC as amended by Directive 2004/28/EC and in accordance with the current EU Administrative Procedure for Application of Article 82 for Official Control Authority Batch Release of Immunological Veterinary Medicinal Products.

Trade name:	
International non-proprietary Name / Ph. Eur. name / common name	
Name and address of marketing authorisation holder	
Name and address of manufacturer, if different:	
Marketing authorisation number (Member State / EU) issued by	
Manufacturer's batch number(s) appearing on package and other identification numbers associated with this batch (final bulk no, final lot no, packaging lot no)	
(where appropriate) Batch number of authorised diluent [1]	
Type of container:	
Total number of containers in this batch[2]:	
Number of doses/volume per container:	
Date of start of period of validity:	

This batch has been examined in conformity with the above-mentioned procedure. This examination is based on review of the manufacturer's protocol and repetition of the appropriate control laboratory tests. The testing has been carried out under a quality system which is in accordance with ISO/IEC 17025.

This batch IS in compliance with the approved specifications laid down in the above-mentioned marketing authorisation. Technical details of these compliance results are annexed to this form.

Signed:	
Name and function of signatory:	
Date of issue:	

Certificate Number:

[1] Provision of different batch numbers of authorised diluent to different Member States should not impair mutual recognition of OCABR for the batch of active component covered by the certificate, however if a diluent batch different from that on the certificate is provided, protocol documentation on the new diluent batch may be requested in addition to the certificate.
[2] If different fillings exist, please indicate

All batches must have a valid certificate when OCABR is required in the MS
An OCABR certificate can also be used when an OBPR certificate is requested

Identification of the certificate

Identification of the releasing Authority and legal context

OBPR certificate is similar but there is no testing and it is not accepted in place of OCABR certificate

ch in question and sation Holder

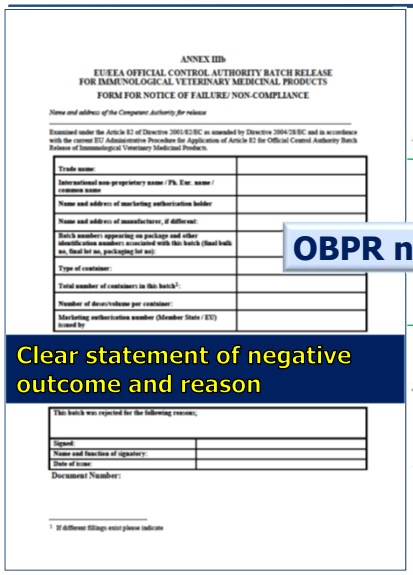
Statement of Compliance with relevant EP monographs and the MA

Signature of responsible person at OMCL/CA

Technical details are annexed

EU OCABR certificates are recognised in all EU/EEA Member States and CH

Notice of non-compliance



ANNEX IIIb

EU/EEA OFFICIAL CONTROL AUTHORITY BATCH RELEASE FOR IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

FORM FOR NOTICE OF FAILURE/ NON-COMPLIANCE

Name and address of the Competent Authority for release

Examined under the Article 82 of Directive 2001/82/EC as amended by Directive 2004/28/EC and in accordance with the current EU Administrative Procedure for Application of Article 82 for Official Control Authority Batch Release of Immunological Veterinary Medicinal Products.

Trade name:	
International non-proprietary name / Ph. Eur. name / common name	
Name and address of marketing authorisation holder	
Name and address of manufacturer, if different:	
Batch numbers appearing on package and other identification numbers associated with this batch (final bulk no, final lot no, packaging lot no):	
Type of container:	
Total number of containers in this batch[1]:	
Number of doses/volume per container:	
Marketing authorisation number (Member State / EU) issued by	

This batch was rejected for the following reasons:

Signed:	
Name and function of signatory:	
Date of issue:	

Document Number:

[1] If different fillings exist please indicate

Batches that do not comply with the MA receive a notice of failure/non-compliance. Notice sent to MAH and all VBRN network contacts.

Identification of the certificate

Identification of the Authority and legal context

OBPR notice is similar but there is no testing

question and n Holder

Clear statement of negative outcome and reason

This batch has been examined in conformity with the above-mentioned procedure. This examination is based on review of the manufacturer's protocol and the repetition of the appropriate control laboratory tests. The testing has been carried out under a quality system which is in accordance with ISO/IEC 17025.

This batch is **NOT in compliance** with the specifications laid down in the above-mentioned marketing authorisation.

Technical details of these non-compliance results are annexed to this form.

This batch was rejected for the following reasons:

Signature of responsible person at OMCL/CA

For OCABR additional technical details are annexed

OCABR: How it works

Vaccine for Rabies vaccine (live)
Licensed in EU meets Ph. Eur. requirements, produced under GMP, has undergone QC testing at the manufacturer
Product is on the annex I restricted list

MAH wants to place a batch on the market but OCABR is required

Batch sent to 1 qualified EU OMCL for testing and protocol review

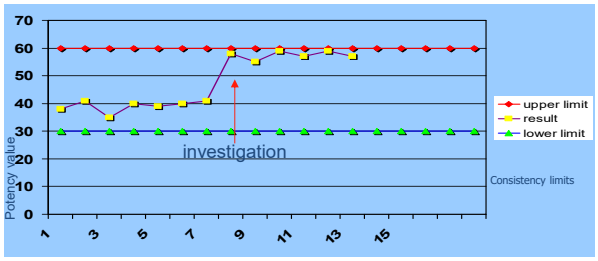
OMCL reviews protocol to ensure compliance with the MA, performs tests according to the Product Specific Guideline
- Appearance
- Virus titre

Batch non-compliant

All elements **COMPLIANT**

MAH and all network members notified of non-compliant batch. Batch release forbidden

EU OCABR certificate issued to MAH recognised in all other Member States



In all cased regular independent monitoring of batches before market release allows effective trend analysis for pro-active action - interaction with MAH/inspectorate/MA authority

Protocol Templates

Detailed protocols submitted for both OBPR and OCABR.

Models provided to help harmonise content and presentation.

5 different models:

- Inactivated bacterial vaccines
- Live bacterial vaccines
- Inactivated viral vaccines
- Live viral vaccines
- Tuberculin PPD/Brucellin preparations

Based on main production steps for the different product types and following Ph. Eur.

Protocol Templates

Section 1 MEMBER STATE SPECIFIC INFORMATION

Section 2 SUMMARY INFORMATION ON THE FINAL BATCH OF FINISHED PRODUCT

- Provides key information for batch identification in the different Member States.

Section 3 and 4 PRODUCTION INFORMATION and FINAL BATCH TESTING

- These sections are models that may vary from product to product.
- A protocol may differ in detail from the model provided. The essential point is that all relevant details demonstrating compliance with the Marketing Authorisation for a particular product should be given in the protocol submitted.
- Results of tests should be provided with sufficient details to allow recalculation of potency or quantiity of active substance. Results of qualification tests for refrence material should also be included.

Section 5 CERTIFICATION BY THE MANUFACTURER

- This is the attestation by the manufacturer that the batch is compliant with the MA and must be signed by the Qualified Person.

Product Specific Guidelines

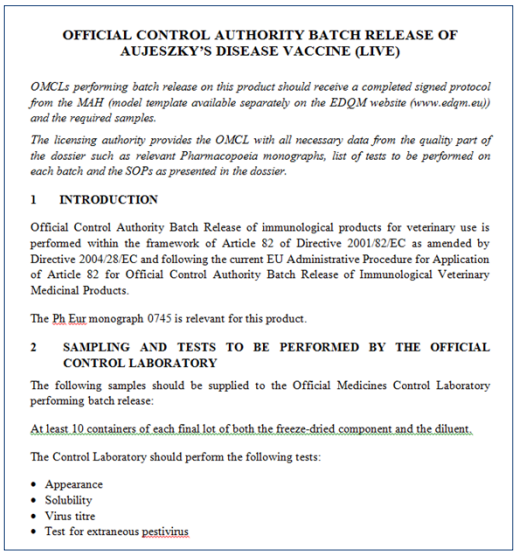
Used when performing OCABR.

Each eligible product group has a guideline.

The guideline:

- Indicates the number and type of samples to be provided by the MAH
- Defines the reduced list of tests to be performed by the OMCL for OCABR

Product Specific Guidelines



OFFICIAL CONTROL AUTHORITY BATCH RELEASE OF AUJESZKY'S DISEASE VACCINE (LIVE)

OMCLs performing batch release on this product should receive a completed signed protocol from the MAH (model template available separately on the EDQM website (www.edqm.eu)) and the required samples.

The licensing authority provides the OMCL with all necessary data from the quality part of the dossier such as relevant Pharmacopoeia monographs, list of tests to be performed on each batch and the SOPs as presented in the dossier.

1 INTRODUCTION

Official Control Authority Batch Release of immunological products for veterinary use is performed within the framework of Article 82 of Directive 2001/82/EC as amended by Directive 2004/28/EC and following the current EU Administrative Procedure for Application of Article 82 for Official Control Authority Batch Release of Immunological Veterinary Medicinal Products.

The Ph Eur monograph 0745 is relevant for this product.

2 SAMPLING AND TESTS TO BE PERFORMED BY THE OFFICIAL CONTROL LABORATORY

The following samples should be supplied to the Official Medicines Control Laboratory performing batch release:

At least 10 containers of each final lot of both the freeze-dried component and the diluent.

The Control Laboratory should perform the following tests:

- Appearance
- Solubility
- Virus titre
- Test for extraneous pestivirus

OMCLs test only a few critical parameters (as decided and approved by the concerned Member States in line with paragraph 3 of Article 82)

The main focus is potency and safety

Specifications for pass/fail are outlined in the Ph. Eur. and the approved Marketing Authorisation . They are not part of Product Specific Guideline.

OCABR Test Methods

METHODS FOR OCABR TESTING

- Use of compendial, MA or fully validated in-house methods
- Have appropriate validation for use of the method for the product in the OMCL
- Use of official standards Biological Reference Preparations (BRPs) (or validated in-house standard) established in International Units (where possible)
- QA systems in place: ISO 17025 is the agreed reference
- Strive to use the fewest animals possible and in the most humane way (application of 3Rs)

Recognition of Certificates

When the MAH receives an OCABR or OBPR certificate from 1 CA/OMCL they should use that certificate to apply for release in other Member States where the certificate is requested. **The goal is to reduce workload for all.**

BATCH with valid EU OCABR certificate → Valid for OCABR or OBPR

BATCH with valid EU OBPR certificate → Valid for OBPR only

→ MAH sends certificate plus any documentary information necessary to demonstrate batch traceability* to CA/OMCL

* Marketing Information Form created for this purpose

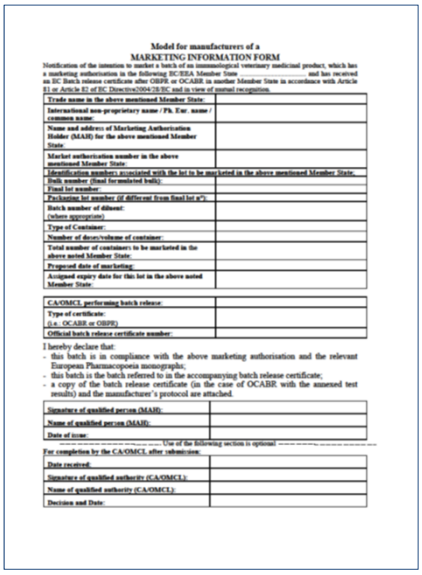
CA/OMCL reviews certificate information and confirms batch identity for their market
No additional testing or protocol review performed

→ 7 working day limit → MAH allowed to release the batch

Each CA/OMCL must inform the MAH of their own process
Eg. Simple notification by email, National certificate, no news is good news after 7 days, etc.

Use of this process does not preclude the right of the CA/OMCL to request batch protocol documentation for their records but this should not block release

Marketing Information Form



Model for manufacturers of a
MARKETING INFORMATION FORM

Notification of the intention to market a batch of an immunological veterinary medicinal product, which has a marketing authorisation in the following EC/EEA Member State ..... and has received an EC Batch release certificate after OBPR or OCABR in another Member State in accordance with Article 81 or Article 82 of EC Directive2004/28/EC and in view of mutual recognition.

Trade name in the above mentioned Member State:	
International non-proprietary name / Ph. Eur. name / common name:	
Name and address of Marketing Authorisation Holder (MAH) for the above mentioned Member State:	
Market authorization number in the above mentioned Member State:	
Identification numbers associated with the lot to be marketed in the above mentioned Member State:	
Bulk number (final formulated bulk):	
Final lot number:	
Packaging lot number (if different from final lot n°):	
Batch number of diluent: (where appropriate)	
Type of Container:	
Number of doses/volume of container:	
Total number of container: to be marketed in the above noted Member State:	
Proposed date of marketing:	
Assigned expiry date for this lot in the above noted Member State:	

CA/OMCL performing batch release:	
Type of certificate: (i.e. OCABR or OBPR)	
Official batch release certificate number:	

I hereby declare that:
- this batch is in compliance with the above marketing authorisation and the relevant European Pharmacopoeia monographs;
- this batch is the batch referred to in the accompanying batch release certificate;
- a copy of the batch release certificate (in the case of OCABR with the annexed test results) and the manufacturer's protocol are attached.

Signature of qualified person (MAH):	
Name of qualified person (MAH):	
Date of issue:	

Use of the following section is optional

For completion by the CA/OMCL after submission:

Date received:	
Signature of qualified authority (CA/OMCL):	
Name of qualified authority (CA/OMCL):	
Decision and Date:	

The MIF is intended to facilitate mutual recognition of certificates and improve the traceability of batches circulating in the EU/EEA and MRA partner states by:

- Identifies the batch and links it to the relevant batch release certificate (OCABR/OBPR).
- Provides any additional market-specific packaging numbers and making the link to final batch numbers/bulk numbers that may appear on the certificate.
- Provides a statement concerning the number of containers for which marketing is requested in the Member State.
- Allows the MAH to confirm that all the specifications in the marketing authorisation where the batch is to be placed on the market have been met even if they differ from those in force in the OMCL/CA where the batch release certificate was granted.

The MIF is available on the EDQM web site

Good Practice: 1 batch - 1 certificate

For OBPR and OCABR **protocol review should be performed for each final lot (batch)**

A certificate is valid for the final lot (batch) named on the certificate **and** for different packaging lots stemming from that final lot.

➢ **The MIF** should be used to clearly indicate all lot/batch identification numbers on the certificates (including the final bulk number) **to facilitate traceability**.

In other situations e.g.

- related final lots (batches) that originate from the **same final bulk, but differ in filling volume and recipient size (antigen content/dose) and thus have different batch documentation** are considered as different final lots (batches) according to the Ph. Eur definition. (e.g. may apply for inactivated vaccines)
- Related lots that originate from the same final lot (batch) and so contain the same amount of material, **but differ in assigned number of doses and consequently in titre/dose so** according to the Ph. Eur. definition they **should have different batch documentation/protocols.** (e.g. may apply for live vaccines)

A new certificate is required since the protocol evaluation is different

Break

Questions?

Still to come

Communication, Other Procedures, 3Rs and Benefits

- Communication
- Electronic Tools for Information Exchange for VBRN
- CA/OMCL exchange with manufacturers
- OCABR: Exchange in the Broader Regulatory Environment
- Other VBRN Procedures/Guidelines
- Elaboration
- Procedures
- 3Rs for animal use
- Benefits of the Network
- More than just batch release
- VBRN Actors

Information Exchange

Key to mutual confidence = Communication

Contact lists

Confidential Exchange on batch status

Guidelines, Procedures, Certificate Templates, Forms

Annual activity reports

Meetings

Electronic Tools for Information Exchange: Website

EDQM website: public access

www.edqm.eu

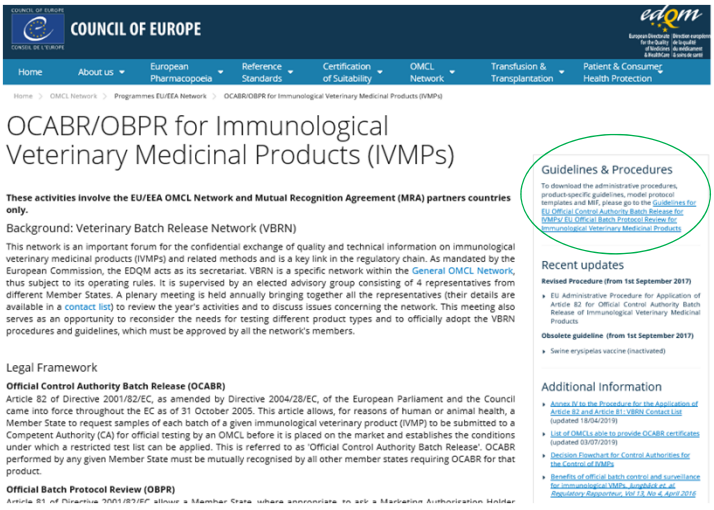
All current published OCABR, OBPR and Administrative Procedures, model protocol templates, MIF and OCABR product specific guidelines are available for download in word format from the website.

Annex IV list of contacts kept up to date on the web site

GEON public documents (e.g. Quality management) also available

Information and documentation on other EDQM activities (European Pharmacopoeia, Certification of suitability program, Reference Standards etc.) also accessed via the EDQM website

Electronic Tools for Information Exchange: Website



GUIDELINES/TEMPLATES FOR VBRN

Document Title	Last Web Update	In force from
Preface and Notes for use (Back to top)	01/03/17	-
Administrative Procedures (Back to top)		
EU Administrative Procedure for a Harmonised Application of Article 81 for Official Batch Protocol Review of Immunological Veterinary Medicinal Products	01/03/14	01/01/13
EU Administrative Procedure for Application of Article 82 for Official Control Authority Batch Release of Immunological Veterinary Medicinal Products	01/03/17	01/01/17
Marketing Information Form (Back to top)	01/03/14	01/01/11
Product Specific Guidelines for IVMPs eligible for OCABR (Back to top)		
Aujeszky's Disease Vaccine (inactivated)	01/03/14	01/01/13
Aujeszky's Disease Vaccine (live)	01/03/14	01/01/13
Brucellosis Vaccine (brucella melitensis rev.1 strain and brucella abortus S19 strain)(Live)	01/03/14	01/01/13
Brucella Preparations	01/03/14	01/01/13
Equine Influenza Vaccine (live)	05/05/15	01/06/15
Equine Influenza Vaccine (inactivated)	01/03/14	01/01/13
Infectious Bovine Rhinotracheitis Vaccine (inactivated)	01/03/14	01/01/13
Infectious Bovine Rhinotracheitis Vaccine (live)	01/03/14	01/01/13
Newcastle Disease Vaccine (inactivated) (EU Emulsion	01/03/14	01/01/13
Newcastle Disease Vaccine (live)	05/05/15	01/06/15
Rabies Vaccine (inactivated)	01/03/14	01/01/13
Rabies Vaccine (live)	01/03/14	01/01/14
Swine Erysipelas Vaccine (live)	01/03/17	01/01/15
Tuberculin Purified Protein Derivative (PPD), Avian	01/03/17	01/01/15
Tuberculin Purified Protein Derivative (PPD), Bovine	01/03/17	01/01/15
Model Protocol Templates for OBPR and OCABR (Back to top)		
Inactivated Bacterial Vaccines	01/03/14	01/04/07
Live Bacterial Vaccines	01/03/14	01/04/07

https://www.edqm.eu/en/ocabrobpr-immunological-veterinary-medicinal-products-ivmps

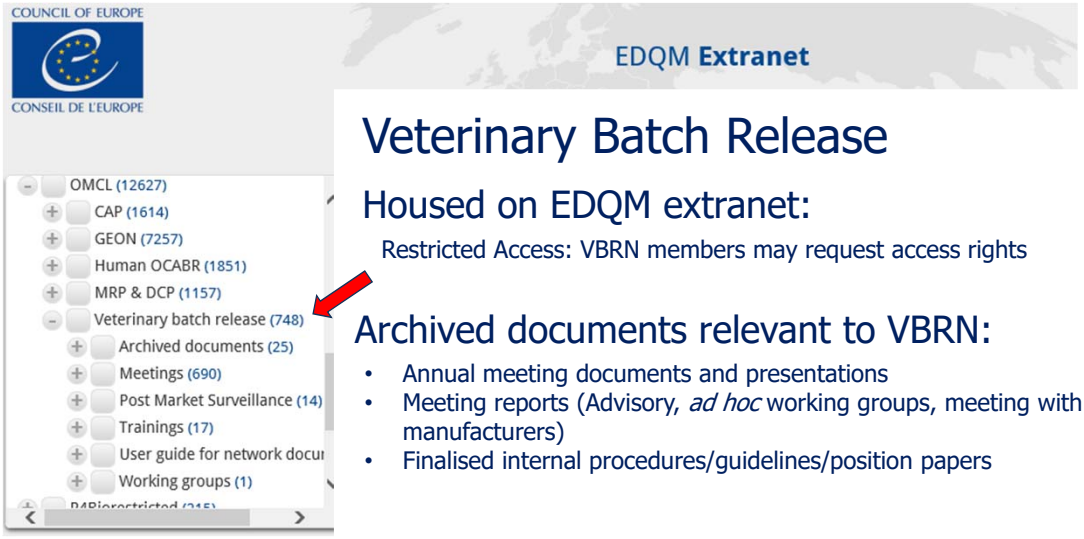
Electronic Tools for Information Exchange: Extranet

EDQM EXTRANET

Restricted Access for identified group members

- Access by login and password
- Sections concerning online meeting agendas, Ph Eur groups' documents, OMCL network documents etc.
- Specific access granted according to group affiliations

Electronic Tools for Information Exchange: Extranet



Veterinary Batch Release

Housed on EDQM extranet:

Restricted Access: VBRN members may request access rights

Archived documents relevant to VBRN:

- Annual meeting documents and presentations
- Meeting reports (Advisory, *ad hoc* working groups, meeting with manufacturers)
- Finalised internal procedures/guidelines/position papers

Electronic Tools for Information Exchange: GEON

As members of the GEON CA/OMCLs who participate in VBRN may also have access to:

- The OMCL section of the extranet
  - Network documents established through the General European OMCL Network (GEON) activity (Quality management, meeting reports, procedures and guidelines etc.)
  - Counterfeit related documents and reports
  - etc.
- The OMCL inventory database (for OMCLs only)
  - Upkeep of data mandatory for GEON members

For further information please contact the secretariat

CA/OMCL Exchange with Manufacturers

OCABR/OBPR is an evaluation of batches by CA/OMCLs carried out independently of the manufacturers

Interaction between CA/OMCLs and manufacturers is however part of the process and clear and open lines of communication are essential e.g.

- Logistical
  - sending protocols, test samples, necessary reagents
- Technical
  - method transfer/validation
- Investigational
  - Response to additional questions/provision of missing information from protocols
  - Experimental investigation and exchange of data to resolve issues identified

OCABR: Exchange in the Broader Regulatory Environment

OCABR- OBBR is not just about batch release

OCABR-OBPR play an important role in the integrated regulatory system for medicines in the EU

Communication with the other branches of the regulatory network are key to making the system work effectively

OCABR: Exchange in the Broader Regulatory Environment

Confidential exchange between Network Members

Network exchange with external partners

Manufacturers' Associations

EU GMP Inspectors

European Pharmacopoeia

EDQM Biological Standardisation

EU Commission

EU Licensing Authorities

3R Groups

Non-EU Authorities

GEON

Other VBRN Procedures/Guidelines

VBRN needs to remain reactive to the ongoing situation for IVMPs in the EU and to respond to surveillance needs in a balanced and timely manner.

A number of procedures have been developed to help the network react appropriately

VBRN also develops guidelines and explanatory notes for internal use to help foster a harmonised approach to common issues (available on extranet)

- Explanatory note on expressing expiry dates
- Explanatory note on twin batches

VBRN Procedures/Guideline: Elaboration

Proposals – can come from anyone (form available in VBRN web page)
Evaluated by Advisory Group (or at AM) and drafter assigned if appropriate

Internal Track

Internal network documents, revisions related to adopted Ph Eur monographs, strictly editorial updates

Draft

⇩

Network Consultation*
(*includes EU Commission and EMA)

⇩

Adoption

External Track

Revisions/new docs with direct impact on external partners

Draft

⇩

Network Consultation* for approval

⇩

External Consultation
(also to Network)

⇩

Adoption

In all cases the final adoption is by consensus in the full VBRN

Other VBRN Procedures

3 important procedures aimed to address the OCABR needs

Procedure to:

- Modify the list of products eligible for OCABR (annex I) – add or remove products
  - Risk assessment tool
- Apply short term testing to products not on the restricted list – to address specific product concerns
- Suspend OCABR testing for specific products - based on product consistency

Procedures to modify OCABR Testing

	General skeleton of Procedures
	Proposal • Dossier Submitted by CA/OMCL • Explains reasons and gives evidence
↓	Preliminary evaluation by Advisory Group for completeness and sutability for the procedure in question
↓	MAH notified, Additional information collected (from other CA/OMCLs, from MAH)
↓	Full package sent to official VBRN contacts for a decision
↓	Application of the decision with, if appropriate, the new situation in place
↓	Monitoring of the situation and need to modify

- Each procedure has its specific requirements for the type of data required, the timelines and the type of final outcome
- All contain interaction with the involved manufacturers and consultation in the network
- A consensus of involved network members is required for final approval

3Rs for animal use

VBRN committed to 3R principles (reduce, replace, refine animal use) and application of Directive 2010/63/EU

- Recognition of common certificates (1 test for all MS)
- Only 1st batch received from final bulk is tested
- Batch potency test used in preference where possible
- Key innovators in alternative assay development
  - Newcastle Disease Vaccine *in vitro* assay
  - Erysipelas vaccine antigen quantification *in vitro* assay
  - Rabies vaccine (inactivated) serology assay
- Contribute to position papers and guidelines
  - 3R concerns in validation and maintenance of competence (public)
  - Validation of analytical methods (public)

Benefits of the Network

Networking Provides Numerous Benefits Batch Release of IVMPs

Single approval for all MSs, transparent and coherent information exchange, work-sharing and coordinated problem solving, a unified voice for external exchanges MEANS:

- Reduction in administrative work for MAH
- Reduction in laboratory workload
- Improved harmonisation of technology and results
- Reduced costs
- Fewer delays in reaching the market

On-going evaluation ensures that the needs of the present and future for OCABR/OBPR and control of IVMPs in general are addressed adequately and in a timely manner

System will adapt to meet the present and future needs

More Than Just Batch Release

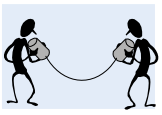
Real-time monitoring of trends in consistency; a global picture, not possible through spot-checks

Proactive action before the product reaches the animal

Compliments GMP inspections, MA evaluation and monograph development (both during the process and as feedback for action)

Helps ensure an independent technical expertise for all branches of the regulatory scheme

Is an open channel for exchange and cooperation with manufacturers



VBRN Network Actors

- **CA/OMCLs**

  See annex IV - Administrative Procedure – contact list available on EDQM website

- **EDQM team**

  Secretariat; BSP/ISA/OCABR section, DBO

  Email: batchreleasevet@edqm.eu
  Helpdesk www.edqm.eu/hd
  Website www.edqm.eu

- **NETWORK PARTNERS**

  European Commission (Co-sponsor)

  European Medicines Agency (EMA

  Heads of Medicines Agencies (HMA),

  Manufacturers

Thank you for your attention

Stay connected with the EDQM

EDQM Newsletter: **https://go.edqm.eu/Newsletter**
LinkedIn: **https://www.linkedin.com/company/edqm/**
Twitter: **@edqm_news**
Facebook: **@EDQMCouncilofEurope**

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

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

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

The OMCL Network: Quality Assurance and Mutual Joint Audit/Visit Schemes: Importance of QA for OMCLs performing batch release

29 October 2019, EDQM, Strasbourg, FRANCE

Maria Silvana Bellini, Department of Biological Standardisation, OMCL Network and Healthcare Department, QA Section, EDQM

What is an OMCL?

- Definition, Objectives & Missions, Composition
- Scope of analysed products
- Roles of OMCLs in Europe
- Joint Programmes
- Veterinary OMCLs in GEON
- Pillars of the GEON

Definition, Objectives & Missions

Official **M**edicines **C**ontrol **L**aboratories are:

- Independent public laboratories
- Established and nominated by National Authorities

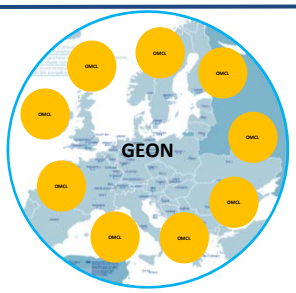
OMCL Objectives:

- Support national regulatory authorities in quality control of medicinal products for human and veterinary use
- Ensure quality of medicines to enhance patient and animal welfare

OMCL Missions:

- Perform independent quality control of medicinal products
- React quickly in times of crisis to test and investigate quality issues

GEON Composition



- 27 out of the 28 EU countries (except Malta)
- 7 European non-EU countries: Belarus, Bosnia & Herzegovina, Republic of Moldova, Russian Federation, Serbia, Republic of North Macedonia, Ukraine
- Norway (EEA) & Switzerland (MRA)
- 7 non-European partners (Australia, Canada, Israel, Kazakhstan, Morocco, Singapore and Taiwan FDA): associate members as observers to Ph. Eur. Convention

More than 70 **OMCLs** from **40+ countries**

Members and Observers of the European Pharmacopoeia Convention

- **Full, associate or limited membership**

Status: March 2019

5

Scope of analysed products

Medicines for human and veterinary use:

- Chemical products
- Biological products: vaccines, blood and plasma derivatives, immunological products
- Herbal medicines
- Homeopathics

Including:

- Stockpiled medicines

Ingredients, products, preparations:

- Active Pharmaceutical Ingredients (APIs)
- Excipients
- Radiopharmaceutical products
- Allergens and gene therapy products
- Falsified and other illegal medicines including "Medicines in disguise"
- Other pharmaceutical preparations
- Non-medicinal products

Roles of OMCLs in Europe

OMCLs' main activities:

Pre- and Post-marketing test programmes:

- (Sampling) and analysis

Laboratory testing of medicines & active ingredients:

- Innovator medicines
- Generic medicines and biosimilars
- Extemporaneous and stock preparations
- Suspected falsified/illegal medicines

Packaging and labelling controls

OMCLs adopt a risk-based approach in all their activities

Joint Programmes

The GEON operates several different **surveillance programmes** and engages in a wide range of support activities… these are all coordinated by the EDQM

- CAP Sampling & Testing Programme (only EU/EEA Members)
- MRP/DCP Post-Marketing Surveillance Scheme (only EU/EEA Members)
- MSS Programme (all Members and Observers)
- OCABR for Human Biological Medicinal Products and **OCABR/OBPR Immunological Veterinary Medicinal Products** (EU/EEA OMCL Network and partner countries with formal agreements with the EU)

Veterinary OMCLs in GEON

13 OMCLs test/control Immunological Veterinary Medicinal Products

How are VET activities organised in the Network? (acc. OMCL db)

Several cases e.g. in a Country:

- An OMCL controls all VET and Human products (i.e. chemical and immunologicals - e.g. Serbia).
- An OMCL (Biological) controls VET and Human immunologicals (e.g. Belgium, Germany).
- A VET OMCL tests all VET products (e.g. Slovak & Czech Republic).
- Separate VET OMCLs VET chemicals/VET immunologicals (e.g. France).

Pillars of the GEON

General European OMCL Network

Policies and Rules:

- Terms of Reference
- Procedures
- Guidelines
- Other General Docs
- Risk-based Approaches

Human Resources:

- Plenum Groups (discussions & decision-making)
- Advisory Groups (advice & planning)
- Expert Groups (elaboration of guidelines, procedures, etc.)
- EDQM Secretariat (coordination)

Harmonised Quality Management Systems (QMS):

- According to the ISO/IEC 17025 standard
- Supported by OMCL Quality Guidelines
- In compliance with Ph. Eur. requirements

The GEON's Quality Management System

- GEON QM System: Standards
- Proficiency Testing Scheme
- Trainings
- Audits/Visits
- Management of MJA/MJV scheme
- Conclusion: Importance of QMS in OMCLs

GEON QM System

The OMCLs work to **one common** QM system.

This QM system is based on **internationally recognised standards**:

- **ISO/IEC 17025** " General requirements for the competence of testing and calibration laboratories"
- **OMCL Guidelines / Documents:** to complement / interpret ISO/IEC 17025 and respond to specific needs of OMCLs (GEON's interpretation of standards), officially adopted by the OMCL Network, published in the **EDQM website**
- **the legal standards** laid down in the **European Pharmacopoeia (Ph. Eur.)**

The QM system is supported by:

- **Proficiency Testing Schemes (PTS)**
- **Training and educational activities**
- **Audit/Visit Programme(MJA/MJV)**

Proficiency Testing Scheme

- Aimed to assess the analytical performance of the OMCLs.
- PTS are a further means to ensure harmonisation, confidence and mutual recognition within the OMCL Network.
- ISO/IEC 17025, clause 7.7.2. a) requires that laboratory monitor its performance by comparison with results of other lab, including participation in PT.
- PTS organised by EDQM are done according to ISO 17043.
- Separate physico-chemical and biological programmes are offered to OMCLs and external labs.
- Currently in IVMP field only PTS studies for physico-chemical methods offered by EDQM.

Training and educational activities

Training Visits

The EDQM organises the visit of staff members of an OMCL to the facilities of another OMCL to receive practical training on QM or technical topics.

Training Courses and Webinars (examples)

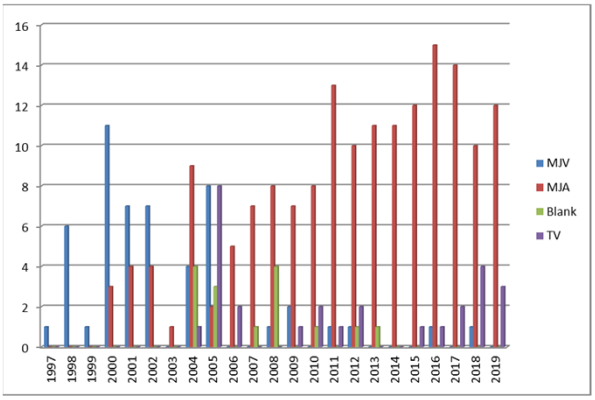
- QM training courses, e.g. ISO 17025:2017, QM Guidelines..
- Technical training on Chemical/Biological topics, e.g. falsified/illegal medicines testing, metrological practices..
- Training courses and workshops for experienced auditors or candidate auditors.
- Database training.

Audit/Visit Programme

Mutual Joint Visits (MJV): aimed to help OMCLs implementing a QMS if not yet in place, or giving recommendations for improvement if QMS is under development.

Mutual Joint Audit (MJA): once the QMS is established, its compliance is periodically verified with respect to the requirements stated in ISO/IEC 17025, the OMCL Guidelines and Ph. Eur. Non compliance leads to non-conformities.

Statistics 1997 - 2019



Management of MJA/MJV scheme

Audit Team:

- Audit Co-ordinator: usually from EDQM, acts as organiser/co-ordinator and in addition as quality or technical auditor.
- Auditors: members from the OMCL Network, competent in the field of audits and qualified for this purpose.
- Qualification of Auditors last for unlimited time, based on regular participation in MJAs/MJVs. Participation in other ISO 17025 internal/external audits is further proof of maintenance of qualification.

Administrative support by EDQM Assistants.

Management of MJA/MJV scheme

- **Phases**:
  - Preparation: preliminary activities (organisational, provision of documents) before the actual Audit.
  - On-site: includes pre-meeting, opening meeting, assessments, reporting and closing meeting.
  - Follow-up: includes finalisation of the Audit report, follow-up of the non–conformities, provision of evidences of implementation of corrective actions, follow-up report and closure of the Audit (MJA Attestation, valid 4 years)
- **Feedback** (administrative & team competences)
- Records and documents shared by **electronic platforms** with controlled access rights, managed by EDQM.

Conclusion: Importance of QMS

The established and harmonised Quality Management System across all OMCLs has several advantages:

- High confidence in test results => **mutual recognition of results**
- Testing processes under control => **reduces the risk of errors**
- High **traceability** of all testing and other activities
- Facilitates **co-operation / exchanges / harmonisation** between OMCLs
- Makes good use of resources => **reduces costs**
- Helps to **protect public and animal health**

Thank you for your attention

Stay connected with the EDQM

EDQM Newsletter: **https://go.edqm.eu/Newsletter**
LinkedIn: **https://www.linkedin.com/company/edqm/**
Twitter: **@edqm_news**
Facebook: **@EDQMCouncilofEurope**

Role and functions of OMCL/CA in performing OBPR

OMCL Batch Release of IVMPs

EDQM Training Session in Strasbourg, France
Veterinary Batch Release Network
29 – 30 October 2019

Renáta Kováčova

Institute for State Control of Veterinary Biologicals and Medicaments (ISCVBM), Nitra, Slovakia

Overview of the presentation

- OBPR legal basis
- Tool to apply Article 81
- EU administrative procedure steps
- Practical implementation and experiences of OBPR procedure in Slovakia (ISCVBM)

OBPR legal basis (1)

Directive 2001/82/EC of the European Parliament and of the Council as amended by Directive 2004/28/EC

Article 81

1. Member States shall take all appropriate measures to ensure that the MAH and, where appropriate, the holder of the manufacturing authorization **furnish proof of the control tests carried out on the VMP and/or on the constituents and intermediate products of the manufacturing process**, in accordance with the methods laid down for the purposes of marketing authorization.

OBPR legal basis (2)

- 2. For the purposes of implementing paragraph 1, **MSs may require the MAH for immunological veterinary medicinal products to submit to the competent authorities copies of all the control reports signed by the qualified person** in accordance with Article 55.
- The marketing authorization holder for immunological veterinary medicinal products **shall ensure that an adequate number of representative samples of each batch of veterinary medical products** is held in stock at least up to the expiry date, and provide samples promptly to the competent authorities on request.

Tool to apply Article 81

EU ADMINISTRATIVE PROCEDURE FOR A HARMONISED APPLICATION OF ARTICLE 81 FOR OFFICIAL BATCH PROTOCOL REVIEW OF IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

https://www.edqm.eu/en/ocabrobpr-immunological-veterinary-medicinal-products-ivmps

Common tool allows MSs to:

- apply harmonised approach to OBPR > from communication with MAH to rapid information exchange among MSs
- mutual recognition of certificates > eliminates duplication of work & time saving
- promote the free movement of IVMPs throughout the EU/EEA and CH

EU administrative procedure steps

Step 1: **Notification of the MAH by the Member State's Competent Authority**

Step 2: **MAH's Responsibilities**

Step 3: **OBPR by an CA/OMCL**

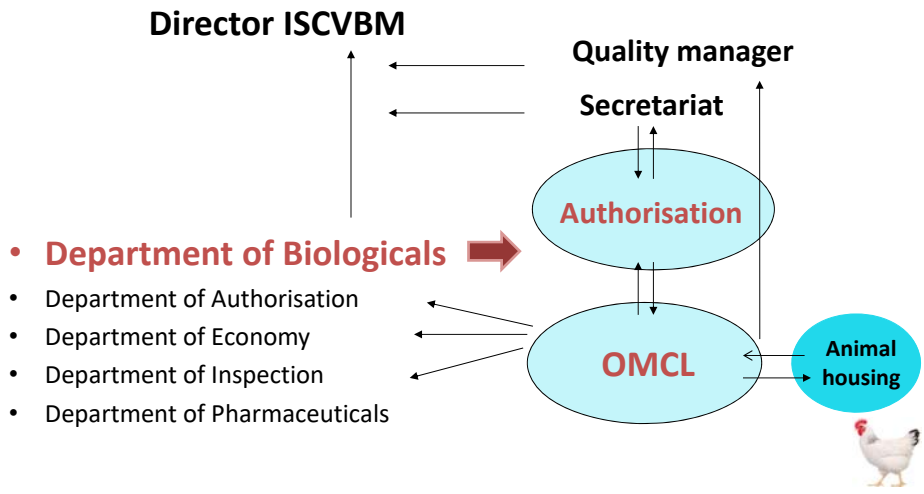
Step 4: **Notification of the OBPR results by the chosen CA**

Step 5: **Use of the OBPR certificate by the MAH for a given batch**

Step 6: **Annual Reports**

Practical implementation/ experiences of OBPR procedure at ISCVBM in Slovakia

OBPR/OCABR activities



- **Department of Biologicals**
- Department of Authorisation
- Department of Economy
- Department of Inspection
- Department of Pharmaceuticals

QA - System

- **ISO 9001 certification** since 2007
  (Last audited in December 2018)
- **ISO 17 025** applied by MJA in 2017;
  (Attestation number: EDQM/MJA-124, valid until March 2021)
- The internal audits are performed according to ISO 19011.

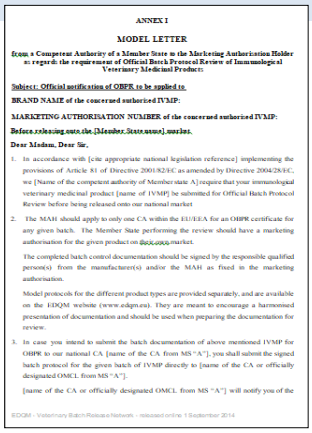
=> Mutual recognition of results

STEP 1: Notification of the MAH by the Member State's Competent Authority

„Where the Competent Authority in a Member State "A" requires Official Batch Protocol Review for a given IVMP, it informs the Marketing Authorisation Holder that its particular authorised IVMP is subject to Official Batch Protocol Review before being placed onto their national market."

Principles:

- Official notification of OBPR to be applied to given authorised IVMP (CA to MAH)
- Application to be send only to one CA for an OBPR certificate for any given batch (MAH to CA)
- Batch protocol to be signed by the QP
- Contact information (CA, OMCL)
- 15 working days for the review (CA, OMCL)
- 7 working days for the recognition of the OBPR certificate



ANNEX I

MODEL LETTER

from a Competent Authority of a Member State to the Marketing Authorisation Holder as regards the requirement of Official Batch Protocol Review of Immunological Veterinary Medicinal Products

Subject: Official notification of OBPR to be applied to

BRAND NAME of the concerned authorised IVMP:

MARKETING AUTHORISATION NUMBER of the concerned authorised IVMP:

Before releasing onto the [Member State name] market.

Dear Madam, Dear Sir,

1. In accordance with [cite appropriate national legislation reference] implementing the provisions of Article 81 of Directive 2001/82/EC as amended by Directive 2004/28/EC, we [Name of the competent authority of Member state A] require that your immunological veterinary medicinal product [name of IVMP] be submitted for Official Batch Protocol Review before being released onto our national market
2. The MAH should apply to only one CA within the EU/EEA for an OBPR certificate for any given batch. The Member State performing the review should have a marketing authorisation for the given product on their own market.

   The completed batch control documentation should be signed by the responsible qualified person(s) from the manufacturer(s) and/or the MAH as fixed in the marketing authorisation.

   Model protocols for the different product types are provided separately, and are available on the EDQM website (www.edqm.eu). They are meant to encourage a harmonised presentation of documentation and should be used when preparing the documentation for review.
3. In case you intend to submit the batch documentation of above mentioned IVMP for OBPR to our national CA [name of the CA from MS "A"], you shall submit the signed batch protocol for the given batch of IVMP directly to [name of the CA or officially designated OMCL from MS "A"].

   [name of the CA or officially designated OMCL from MS "A"] will notify you of the

EDQM - Veterinary Batch Release Network - released online 1 September 2014

A template for a model letter (Annex1)

STEP 1: ISCVBM

- ISCVBM does not require OBPR for any product or product groups of IVMPs – products are directly released on to the SK market
- No specific procedure included in QMS

STEP 2: MAH's Responsibilities

- MAH to provide the complete documentation of the batch to CA, OMCL (product licenced on their own market) for batch protocol review
- Application to be send only to one CA
  - **<u>One</u> OBPR certificate per batch-**
- **Model protocols** for different product types:
  - *Inactivated and live bacterial vaccines*
  - *Inactivated and live viral vaccines*
  - *Tuberculin PD/Brucellin preparations*

  Harmonised documentation
- Batch documentation (CoA) to be signed by QP

STEP 2: ISCVBM

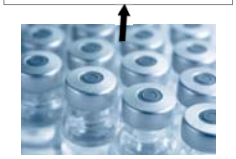
OBPR performed upon request of domestic manufacturer/MAH for the following type of products:

- Rabbit haemorrhagic disease vaccine inactivated
- Myxomatosis vaccine live
- Fowl-pox vaccine live
- Porcine actinobacillosis vaccine inactivated
- Newcastle disease vaccines inactivated (OCABR)
- Newcastle disease vaccines live (OCABR)

STEP 2: ISCVBM internal procedures

MAH

OBPR request
Manufacturer's batch protocol
Analytical certificate
Samples



Batch of IVMP released by MAH

ISCVBM

Fees

Secretariat
Documentation registration procedure

Samples – Form F 163b

Centrálny príjem (sekretariát riaditeľa ÚŠKVBL)

Záznam o príjme vzorky

Názov								
Výrobca, resp. dodávateľ								
Dátum a čas prijatia (centrálny príjem)								
Číslo záznamu								
Súlad prijímaného predmetu skúšania s popisom skúšania alebo špecifikáciou								
Kontrola celistvosti balenia zásielky								
Iné nezvyčajnosti alebo odchýlky od zvyčajných alebo špecifikovaných podmienok								
Kontrola dokumentov	Žiadanka		Dodací list		Kontrola záznamu teploty		Iné	
	Áno	Nie	Áno	Nie	Áno	Nie	Áno	Nie

Podpis osoby, ktorá prijala zásielku (centrálny príjem) :

Dátum a podpis osoby, ktorá prevzala zásielku z centrálneho príjmu __/__/201_ ,_____hod.

Department of Biologicals

- Documentation registration procedure (ÚŠKVBL-OB/01) including management of samples
- Distribution of documentation to responsible person –
  * **assessor** familiar with the given product (OBPR)
  * **OMCL/technical manager (OCABR)**

STEP 3: OBPR by an CA/OMCL

- **Official Batch Protocol Review (OBPR) :**

  It is a procedure to control individual batches of any IMVP by review of the results and data in the manufacturer`s batch release protocol as provided by the MAH before the product is release on the market.

- **It is a document control of the concerned batch performed by CA/OMCL in terms of specifications laid down in the marketing authorisation for the given IVMP valid in this MS**

STEP 3: ISCVBM OBPR examination

- **OPBR/OCABR – considered as one of the primary tasks in QM of the Institute**
- **Examination of the MAH documentation by responsible person on the basis of SOP related to the specific product (e.g. ŠPP-OB-UŠ-01/obpr);**
- **SOPs are regularly checked/updated and in case of variations in MA immediately adapted**
- **Collaboration with manufacturer is very important when SOP is/has been elaborated and the first OBPR request is submitted**
- **In case of OBPR, samples of a given batch are not tested**
- **In case of OCABR, OBPR is usually performed after testing when OMCL results are available**

STEP 3: ISCVBM SOPs for OBPR

General product information
Summary of batch information
Production information

Steps information
Site of manufacture for each antigen:
STARTING MATERIALS
Virus seed lots
Substrate
INTERMEDIATE STAGES OF PRODUCTION
Production of antigen:
Inactivation:
FORMULATION OF THE FINISHED PRODUCT
Antigen:
Adjuvant:
Excipients:
FILLING
ANTIGEN STORAGE DURING PRODUCTION
AF before inactivation
AF after inactivation

Manufacturer's batch number(s) appearing on package and other identification numbers associated with this batch (final bulk no, final lot no, packaging lot no)
Batch number of diluent (where appropriate)
Type of container
Total number of containers in this batch
Number of doses/volume per container
Date of start of period of validity/Exp.
MAH contact
QP:

Name and address of MAH
Name and address of manufacturer, if different
Trade name of IVMP:
International non-proprietary Name / Ph. Eur. name / common name
Target species
Pharmaceutical form
Storage temperature
Marketing authorisation number for vaccine/diluent (Member State / EC) issued by

In-process control tests (specifications, notes)
Control test on the final batch (bulk, batch - specifications, notes)

STEP 3: ISCVBM frequent findings

- **MS specific information** - Trade name, MA number
- **Summary information on the final batch of finished product** - Expiry date
- **Product information** - MSV, WSV batch number; different dates (e.g. infection – harvest); inactivation data; formulation of the vaccine and quantity of the final bulk;
- **In-process controls and final batch/bulk tests**– all tests covering all antigens, specifications, dates!, …
- **Others** – e.g. numbering, QP signature...

Findings were usually not product-related!

STEP 4: Notification of the OBPR results by the chosen CA

- 15 working days after the completed signed protocol is received

CA prepares

- In compliance:

EU/EEA Official Batch Protocol Review Certificate of Approval for IVMP(Annex IIa)

- if in the national language of CA it must be accompanied by an EU certificate in English

- Non-compliance:

Form for notice of failure/ non-compliance

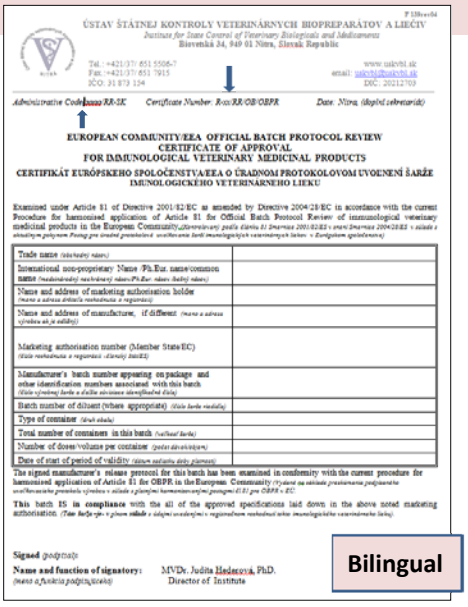
(Annex IIb)

- reasons for the non-compliance;

- rapid information exchange – Annex IV

- in English

STEP 4: ISCVBM results reporting



ÚSTAV ŠTÁTNEJ KONTROLY VETERINÁRNYCH BIOPREPARÁTOV A LIEČIV
Institute for State Control of Veterinary Biologicals and Medicaments
Slovenská 34, 949 01 Nitra, Slovak Republic

EUROPEAN COMMUNITY/EEA OFFICIAL BATCH PROTOCOL REVIEW
CERTIFICATE OF APPROVAL
FOR IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS
CERTIFIKÁT EURÓPSKEHO SPOLOČENSTVA/EEA O ÚRADNOM PROTOKOLOVOM UVOĽNENÍ ŠARŽE IMUNOLOGICKÉHO VETERINÁRNEHO LIEKU

Examined under Article 81 of Directive 2001/82/EC as amended by Directive 2004/28/EC in accordance with the current Procedure for harmonised application of Article 81 for Official Batch Protocol Review of immunological veterinary medicinal products in the European Community

Trade name	
International non-proprietary Name /Ph.Eur. name/common name	
Name and address of marketing authorisation holder	
Name and address of manufacturer, if different	
Marketing authorisation number (Member State/EC)	
Manufacturer's batch number appearing on package and other identification numbers associated with this batch	
Batch number of diluent (where appropriate)	
Type of container	
Total number of containers in this batch	
Number of doses/volume per container	
Date of start of period of validity	

The signed manufacturer's release protocol for this batch has been examined in conformity with the current procedure for harmonised application of Article 81 for OBPR in the European Community

This batch IS in compliance with the all of the approved specifications laid down in the above noted marketing authorisation.

Signed
Name and function of signatory: MVDr. Judita Hedarová, PhD.
Director of Institute

Bilingual

ÚSTAV ŠTÁTNEJ KONTROLY VETERINÁRNYCH BIOPREPARÁTOV A LIEČIV
Institute for State Control of Veterinary Biologicals and Medicaments
Slovenská 34, 949 01 Nitra, Slovak Republic

EUROPEAN COMMUNITY/EEA OFFICIAL BATCH PROTOCOL REVIEW
FOR IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS
FORM FOR NOTICE OF FAILURE/ NON-COMPLIANCE
ÚRADNÉ PROTOKOLOVÉ UVOĽŇOVANIE ŠARŽE IMUNOLOGICKÉHO VETERINÁRNEHO LIEKU
V EURÓPSKOM SPOLOČENSTVE/EEA
OZNÁMENIE O NEZHODE

Examined under Article 81 of Directive 2001/82/EC as amended by Directive 2004/28/EC in accordance with the current Procedure for harmonised application of Article 81 for Official Batch Protocol Review of immunological veterinary medicinal products in the European Community

Trade name	
International non-proprietary Name /Ph.Eur. name/common name	
Name and address of marketing authorisation holder	
Name and address of manufacturer, if different	
Batch number appearing on package and other identification numbers associated with this batch	
Type of container	
Total number of containers in this batch	
Number of doses/volume per container	
Marketing authorisation number (Member State/EU)	

The signed manufacturer's release protocol for this batch has been examined in conformity with the current procedure for harmonised application of Article 81 for OBPR in the European Community

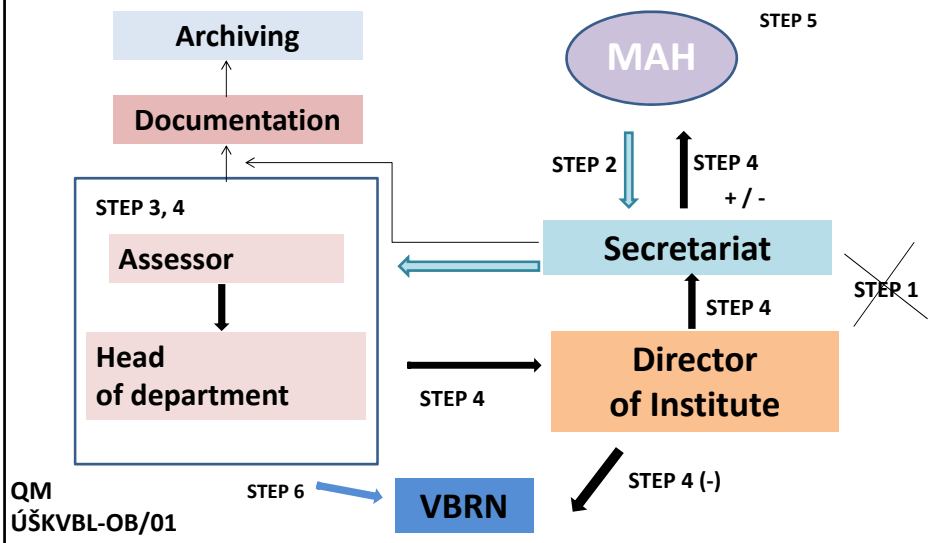
This batch is **NOT** in **compliance** with the all of the approved specifications laid down in the above noted marketing authorisation.

Technical details of these non-compliance results are noted below:

This batch is not compliant for the following reasons:

Signed
Name and function of signatory: MVDr. Judita Hedarová, PhD.
Director of Institute

STEP 4: ISCVBM results reporting



STEP 5: Use of the OBPR certificate by the MAH for a given batch

- Permission to place the given batch on the market in MS performing OBPR
- MS requiring OBPR for this product – MAH provides a copy of the given OBPR certificate and necessary additional information or OCABR certificate shall be accepted
- 7 working days procedure for recognition of certificates

STEP 5: ISCVBM

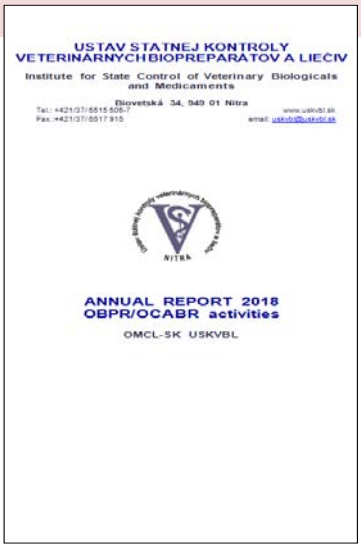
- Not applicable
- In case of MSS – request to MAH to provide OCABR certificates (e.g. for rabies vaccines) – OCABR certificate is accepted and recognised

STEP 6: Annual Reports (VBRN)

- Information regarding intention for application of Article 81, 82 for the coming year and questionnaire
- Number of batches review under Article 81, 82 during the reported period including evaluation status (EXCEL-Template)
- Batches received through mutual recognition of a certificate from another Member State
- Trend analysis...

STEP 6: ISCVBM annual OBPR/OCABR report

- **A list of products for which Article 81 was required – NOT REQUIRED in SK**
- **A list of products for which Article 81, 82 was applied in the previous year**
  (Excel data sheet – detailed information created by VBRN to harmonise reporting)
- **No changes in Application of Article 81, 82 proposed for the following year - OBPR will be performed on request of domestic manufacturer**
- **Trend analysis done for products for which Article 82 is applied**


USTAV STATNEJ KONTROLY VETERINARNYCH BIOPREPARATOV A LIECIV
Institute for State Control of Veterinary Biologicals and Medicaments
Biovetská 34, 949 01 Nitra

ANNUAL REPORT 2018
OBPR/OCABR activities
OMCL-SK USKVBL