Role and functions of OMCL/CA in performing OCABR

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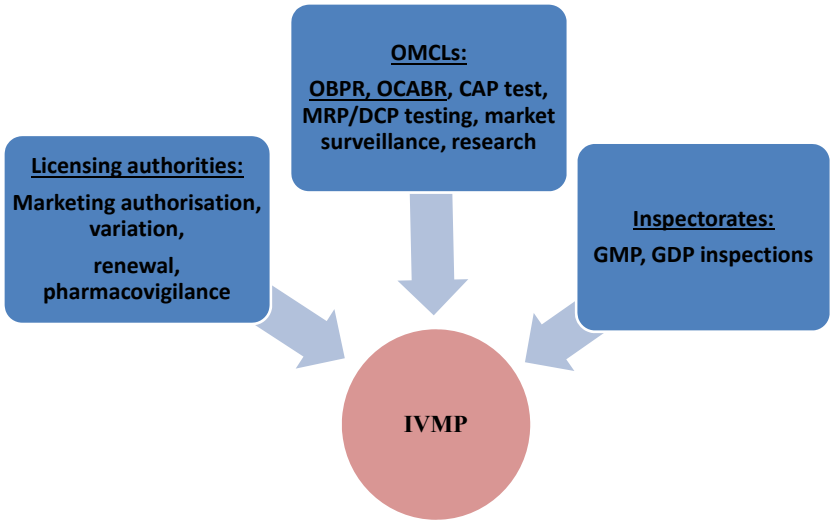
Presentation overview

- **Authority control of IVMPs – general overview**
- **Introduction of the OCABR system**
  - **background: VBRN**
  - **legal framework**
  - **principles of the system**
  - **practical issues**
  - **special procedures**
- **How can OCABR work effectively?**
- **Why do we need to maintain the OCABR? – an authority perspective**

Different branches, different roles, SAME GOAL



Background: Veterinary Batch Release Network

- VBRN is a specific network within the General OMCL Network
- an important forum for the confidential exchange of quality and technical information on IVMPs
- main activity: batch release (OCABR and OBPR) of IVMPs
  - in operation since March 2007
  - These activities involve the EC/EEA OMCL Network and Mutual Recognition Agreement (MRA) partners countries only
- VBRN is supervised by an elected advisory group consisting of 4 representatives
- a plenary meeting is held annually

Legal framework

- **Official Control Authority Batch Release of certain IVMPs may be required by Member States as specified under Article 82 of EU Directive 2001/82/EC as amended by Directive 2004/28/EC:**

"Where it considers it necessary for reasons of human or animal health, a Member State ***may require the marketing authorisation holder*** *for an immunological veterinary medicinal product* ***to submit samples of batches*** *of the bulk product and/or veterinary medicinal product* ***for control by an Official Medicines Control Laboratory before the product is put into circulation."***

- **EU/EEA Member States + Switzerland (Mutual Recognition Agreement)**

Principles

- ***may*** **clause - Art 82 is an option for MSs**
- shortlist of IVMPs for which Art 82 may be applied
- restricted test sheme
- mutual recognition of test results and certificates

Member States performing and requiring OCABR

	OCABR performed	OCABR required
Belgium	yes	yes
Czech Republic	yes	yes
Finland	yes	yes
France	yes	yes
Germany	yes	yes
Hungary	yes	yes
Poland	yes	yes
Romania	yes	yes
Slovak Republic	yes	no
Switzerland	yes	yes
Slovenia	no	yes

Principles

- *may* clause - Art 82 is an option for MSs
- **shortlist of IVMPs for which Art 82 may be applied**
- restricted test sheme
- mutual recognition of test results and certificates

Shortlist

IVMPs against	exempted categories
Aujeszky's Disease	none
Brucellosis	none
Equine Influenza	none
Infectious Bovine Rhinotracheitis	none
Newcastle Disease	none
Rabies	none
Swine Erysipelas	inactivated vaccines
diagnostics	**exempted categories**
Brucellin Preparations	none
Tuberculin PPD, Avian	none
Tuberculin PPD, Bovine	none

- **The list is reviewed regularly and updated as necessary**

Principles

- *may* clause - Art 82 is an option for MSs
- shortlist of IVMPs for which Art 82 may be applied
- **restricted test sheme**
- mutual recognition of test results and certificates

Restricted test scheme

- **inactivated vaccines:**
  - **appearance**
  - **potency**
- **live vaccines:**
  - **appearance**
  - **solubility**
  - **virus titre or live bacteria count**
  - **test for Pestiviruses or for extraneous microorganisms**
  - **purity**
  - **identity**
- ***in vivo* diagnostics:**
  - **appearance**
  - **sensitizing effect**
  - **potency**

Principles

- *may* clause - Art 82 is an option for MSs
- shortlist of IVMPs for which Art 82 may be applied
- restricted test sheme
- **mutual recognition of test results and certificates**

Mutual recognition

- **the results and the OCABR certificate is recognised by all members of the network**
- **a certain batch can not be tested twice**
- **OCABR certificate can not be replaced by an OBPR certificate**

Practical aspects

- **first step: examination of the batch protocol from the manufacturer**
  - **(OBPR certificate can be replaced by an OCABR certificate)**
- **OCABR is a 60 days procedure**
- **batch release certificate**
  - **the results of the re-testing comply with the approved specifications for that given IVMP as laid down in the relevant marketing authorisation dossier**
- **non-compliance certificate**
  - **the batch may not be placed on the market and the network is notified**
- **To facilitate the recognition of certificates throughout the EU a Marketing Information Form should also be provided to the CA/OMCL when submitting an OCABR certificate.**

Time limited OCABR

- **Individual products (manufacturer specific) from categories not on the restricted list may require OCABR due to specific circumstances**
- **testing of additional parameters of products on the short list**
- ***A list of justified tests to be repeated may also be established for products not falling under the restricted list of products but considered to be subject to re-testing for specific reasons of human and animal health and information about an agreement on such tests should be ensured via the OMCL network.*** **(EU Commission Recommendation, 20 March 2007)**
- **Should be exceptional and limited in time**

Time limited OCABR (cont.)

- **Examples of relevant reasons for time restricted OCABR**
  - new licensing application accepted with **reduced pre-approval criteria** for reasons of special need
  - IVMPs used in **new official eradication programs**
  - VMPs from a manufacturer demonstrated **to have difficulties to meet the specifications**
  - IVMPs that have been subject to recent **rapid information** within the EDQM/OMCL-network and/or **rapid alert** within the inspector's or pharmacovigilance network
  - IVMPs where the recent **GMP inspections** on the production site found **deficiencies** with impact on the product quality
  - IVMPs subject to **variations,** which cover major changes in production and performance and/or character of tests used for in process and/or final product control

To suspend OCABR for a specific product

- **OCABR testing may be reduced or removed in some cases for specific products if there was a demonstration of good consistency and quality of the product and reliability of the test methods used by the manufacturer (EU Commission Recommendation, 20 March 2007)**
- **products, which do not fall in a risk category considered unacceptable by the VBRN**
- **evidence from past batches suggests that future batches produced and tested in the same way would be acceptable**
- **in case a positive decision, the product**
  - **will no longer undergo OCABR, but may still be subject to OBPR**
  - **will be monitored continuously**

Fundamental issues

- **Legal background: implementation of Art. 82**
- **Laboratory background**
  - **technical facilities**
  - **staff**
  - **quality management system (Mutual Joint Audit and/or accreditation)**

And some other important points

- permanent discussion with manufacturers
- effective communication and interaction between different authority branches
- marketing authorisation and variation dossiers should be available for OMCLs
- results of GMP inspection should be available to the licensing a authorities and OMCLs
- inspectors should communicate the inspection data to licensing authorities and OMCLs
- OMCLs should inform assessors and inspectors on all quality problems, they detected

Advantages of the system

- a well established system at European level
- predictable, testing the same batch in multiple MSs is avoided
- the technical and scientific capacity of the independent laboratory network are important elements of the regulatory system: complement GMP inspections and marketing authorisations
- independent testing increases confidence in IVMPs
- EU certificates provide a quality label for the EU and beyond
- product defects, trend changes, etc. can be found before the product enters the market, which may prevent post marketing withdrawal
- expertise in experimental testing contributes to preparedness for crisis situations

nébih

Thanks for your attention!

OCABR/OBPR : ROLE AND FUNCTION OF MAH

Official Batch Protocol Review (OBPR « article 81 »)

Official Control Authority Batch Release (OCABR « article 82 » / short list vaccines)

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

29/10/2019 Version 1 Desprels S. - Teichner M. - Lechenet J.

THE STARTING POINT FOR MAHS…

The Competent Authority (CA) of the Member State (MS) « A » informs the Marketing Authorization Holder (MAH) that OBPR (Official Batch Protocol Review / article 81) or OCABR (Official Control Authority Batch Release / article 82) is required for one of its Immunological Veterinary Medicinal Products (IVMP)

THE MODEL LETTER TEMPLATE

Competent Authorities use the template for a model letter to notify MAH of this requirement :

- Annex I of the Administrative Procedure for OBPR / Article 81

https://www.edqm.eu/medias/fichiers/procedure_article_81.zip

- Annex II of the Administrative Procedure for OCABR / Article 82

https://www.edqm.eu/sites/default/files/procedure_article_821.zip

CONTENT OF THE MODEL LETTER TEMPLATE

•The letter specifies :

– the name of the requesting Competent Authority

– the name of the IVMP for which OBPR or OCABR is requested

• The letter requests that :

– for any given batch the MAH should apply for OBPR or OCABR to only one CA within the EU (European Union) / EEA (European Economic Area)

– the batch control documentation included in the application should be signed by the responsible Qualified Person as fixed in the marketing authorisation

CONTENT OF THE MODEL LETTER TEMPLATE

- The letter recommends that model protocols available on the EDQM (European Directory for Quality of Medicines) website are used to present batch information
- The letter communicates standard timelines and mentions fees are due

  OCABR : 60 days

  OBPR : 15 working days
- The letter confirms that releasing the concerned batch of IVMP on the market is subject to satisfactory OBPR or OCABR

OBPR: FOR WHICH PRODUCTS?

OBPR can be requested for any IVMP

OBPR: WHAT DOCUMENTATION?

Model format protocol templates are available to help harmonize protocol submission.

A given protocol may differ in detail from the model : the essential point is that all relevant details demonstrating compliance with the Marketing Authorization and the Ph. Eur. monograph(s) (where existing) be given in the protocol.

OBPR: WHAT DOCUMENTATION?

Model protocol templates exist for :

- Inactivated Bacterial vaccines
- Live Bacterial vaccines
- Inactivated Viral vaccines
- Live Viral vaccines
- Tuberculin PPD / Brucelin preparations

They are available at : https://www.edqm.eu/en/guidelines-eu-ocabr-ivmps

OCABR: FOR WHICH PRODUCTS?

For IVMPs of the short-list (annex I of the administrative procedure for application of article 82)

Boehringer Ingelheim

OCABR: FOR WHICH PRODUCTS?

OCABR can be requested for IVMPs of the short-list (annex I of the administrative procedure for application of article 82)

https://www.edqm.eu/sites/default/files/procedure_article_821.zip

OCABR: FOR WHICH PRODUCTS?

Short list of IVMPs for which a restricted test list for OMCLs has been defined	Exempted Categories	Relevant guideline(s) (PA/PH/OMCL …)
Brucellin Preparations	none	(04) 119 DEF 2CORR
IVMP's against Aujeszky's Disease	none	(03) 7 DEF 2CORR & (03) 8 DEF 2CORR
IVMPs against Brucellosis	none	(03) 23 DEF 2CORR
IVMPs against Equine Influenza	none	(04) 4 DEF 2CORR & (14) 81 R
IVMPs against Infectious Bovine Rhinotracheitis	none	(03) 9 DEF 2CORR & (03) 6 DEF 2CORR
IVMPs against Newcastle Disease	none	(02) 3 DEF 2CORR & (02) 4 DEF 2CORR
IVMPs against Rabies	none	(11) 209 DEF 2CORR & (04) 05 DEF 2CORR
IVMPs against Swine Erysipelas	Inactivated vaccine	(03) 10 DEF 2CORR
Tuberculin PPD, Avian	none	(14) 126 DEF
Tuberculin PPD, Bovine	none	(14) 125 DEF

OCABR: FOR WHICH PRODUCTS?

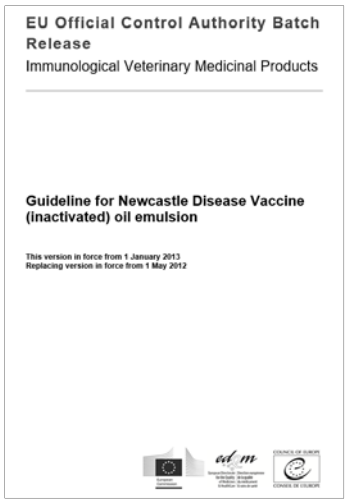
Under special circumstances, a CA can also request short-term OCABR testing for another IVMP, if technically warranted.

OCABR: WHAT TESTS?

Product Specific Technical Guidelines list tests that can be performed by OMCL (Official Medicines Control Laboratories) involved in OCABR on « short listed » products

These Guidelines are also available on EDQM's website : https://www.edqm.eu/en/guidelines-eu-ocabr-ivmps

EXAMPLE OF PRODUCT SPECIFIC TECHNICAL GUIDELINE



EU Official Control Authority Batch Release

Immunological Veterinary Medicinal Products

Guideline for Newcastle Disease Vaccine (inactivated) oil emulsion

This version in force from 1 January 2013
Replacing version in force from 1 May 2012

OFFICIAL CONTROL AUTHORITY BATCH RELEASE OF NEWCASTLE DISEASE VACCINE (INACTIVATED) OIL EMULSION

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 0870 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 5 containers of each final lot.

The Control Laboratory should perform the following tests:

- Appearance
- Potency - Potency testing is done on the first batch from a final bulk and then all other batches derived from that same bulk shall not be re-tested.

IN WHICH COUNTRY?

EU and partners

IN WHICH COUNTRY?

all EU Member States, EEA partners (Iceland and Norway) and MRA partners (e.g. Switzerland) may participate

The final decision on applying article 81 or article 82 remains with the Member States as described under « step 1 » of the administrative procedures (« the letter »)

IN WHICH COUNTRY (CONTINUED)?

A list of OMCL able to deliver OCABR is available :

https://www.edqm.eu/sites/default/files/medias/fichiers/OMCL/veterinary_batch_release_network_list_of_omcls_able_to_provide_ocabr_certificates_august_2019.pdf

As well as a contact list for the network of competent authorities for the IVMP :

https://www.edqm.eu/sites/default/files/webannex_iv_contact_list_18-04-2019.pdf

VBRN OMCLs able to provide OCABR Certificates
List updated 03/07/2019[1]

Products on the Restricted List[2]

Unless indicated (*) OCABR could be set up within 4-8 weeks. * indicates more than 8 weeks required.

Product Group	Member State
Aujeszky's Disease vaccine (live)	Belgium, Germany, Hungary , Romania
Aujeszky's Disease vaccine (inactivated)	Hungary
Equine influenza vaccine (live recombinant)	Germany, Hungary
Equine influenza vaccine (inactivated)	Czech Republic, Germany, Hungary, Switzerland
Infectious Bovine Rhinotracheitis Vaccine (live)	Belgium, Germany, Hungary, Romania
Infectious Bovine Rhinotracheitis Vaccine (inactivated)	Belgium, Germany, Hungary
Newcastle Disease Vaccine (live)	Belgium, Czech Republic, Germany, Hungary, Romania, Slovak Republic
Newcastle Disease Vaccine (inactivated)	Belgium (La Sota strain only), Czech Republic, Germany (* for HI), Hungary, Slovak Republic
Rabies Vaccine (live)	Czech Republic, Finland, France, Germany, Hungary, Switzerland, Romania, Poland
Rabies Vaccine (live recombinant)	France, Germany, Hungary
Rabies vaccine (inactivated)	Belgium, Czech Republic, France, Germany, Hungary, Switzerland
Swine Erysipelas Vaccine (live)	Czech Republic, Germany
Tuberculin PPD avian	Hungary
Tuberculin PPD bovine	Germany, Hungary

IN WHICH COUNTRY (CONTINUED)?

Example of requirements for a vaccine production site :

Country	Requires OBPR for	Requires OCABR for
Portugal	All vaccines	None
UK	All vaccines except 1	1 rabies vaccine
Finland	All vaccines except 1	1 rabies vaccine
Austria	All vaccines except short listed	Short list vaccines
Belgium		
Croatia		
Germany		
Hungary		
Poland		
Slovénie		
Switzerland		
Bulgaria	None	All rabies vaccines
Czeck R.		
France		
Serbia		All rabies & Newcastle disease vaccines
Spain	6 specific vaccines	None
Romania	Vaccines against rabies and blue tongue	Newcastle disease vaccines

MARKETING AUTHORIZATION HOLDERS (MAH)

Role and function concerning OCABR/OBPR

ROLE AND FUNCTION OF MAH

When the MAH receives the letter notifying that OCABR or OBPR is required for a given IVMP, it should consider this a release requirement for this IVMP in the country and reorganize release operations accordingly.

Appropriate communication within the MAH's organization is necessary to make sure that this new requirement is communicated

- from those who receive the letter (Regulatory Affairs of MAH)
- to those who are in charge of releasing IVMP batches (Quality Assurance)
- but also to local RA/QA and to supply chain

The organization of this activity of obtaining OCABR / OBPR certificates should be described in Standard Operating Procedures (SOPs).

ROLE AND FUNCTION OF MAH

- Clearly identify which IVMP require OBPR and/or OCABR for which country
- Decide from which OMCL OCABR will requested (technical knowledge & expertise, delays, established relationship…)
- Specify documents / samples to be included in applications (considering specificities that exist at national level)
- Ensure that batches of IVMP that require OBPR or OCABR cannot be released to a given market before the required certificate is received from the Competent Authority (CA) of this market.
- Ensure that requests for OBPR/OCABR are submitted to a country that holds an MA for the IVMP.
- As far as possible, ensure that only one application is submitted for a given batch

ROLE AND FUNCTION OF MAH

- « Phase 1 »:
  - Apply for European Release to the chosen CA / OMCL that will examine the batch documentation provided by the MAH (OBPR and OCABR) and perform testing (OCABR only) and issue an OBPR or OCABR certificate of approval (if satisfactory)
  - This original certificate allows to market the given batch in the country of the issuing CA / OMCL

ROLE AND FUNCTION OF MAH

- « Phase 2 »:
  - Provide this original certificate and the batch traceability (Marketing Information Form or equivalent) to CA/OMCL of other countries that also require OCABR/OBPR for this IVMP and need to be supplied with « sister » batches
  - The recognition of the original certificate allows to market « sister » batches in countries where the original certificate has been recognized by relevant CA / OMCL

OBPR PROCEDURE

https://www.edqm.eu/medias/fichiers/procedure_article_81.zip

OBPR PROCEDURE (« PHASE 1 »)

MAH provides the complete EBRP for the batch, signed by the responsible QP, to a CA or officially designated OMCL in country "A".

Notification of results should occur within **15 working days** of receipt of the completed signed protocol and any fees where required.

OBPR PROCEDURE (« PHASE 1 », CONTINUED)

If a batch has been shown to comply with all of the specifications of the marketing authorisation and is thus satisfactory for approval, the Competent Authority in country "A" will prepare an Official Batch Protocol Review Certificate of Approval.

Upon the receipt of the EU/EEA OBPR certificate of approval, the MAH may consider that it has permission to place the given batch on the market in country "A".

OBPR PROCEDURE (« PHASE 2 »)

If the MAH wishes to market in country B, where the IVMP is authorised and OBPR is required by CA, a commercial batch issued from the same final lot. MAH shall provide to the designated contact in country "B":

- a copy of the given OBPR Certificate
- documented information necessary to ensure the traceability of the commercial batch to be put on the market in Member State "B" to the to the final lot described in the OBPR already delivered.
- A Marketing Information Form (MIF) or equivalent

OBPR PROCEDURE (« PHASE 2 », CONTINUED)

In this phase 2, the Marketing Information Form (MIF) is used to:

- Identify clearly the commercial batch to be marketed
- Link commercial batch to the relevant OBPR and to the final lot/ bulk numbers that appear on the certificate.
- State the number of containers for which marketing is requested.
- Confirm that all the specifications in the marketing authorisation where the batch is to be marketed are met, even if they differ from those in force in the OMCL/CA where the batch release certificate was granted.

Link to the Marketing Information Form :
https://www.edqm.eu/sites/default/files/marketing_information_form.zip

OBPR PROCEDURE (« PHASE 2 », CONTINUED)

The contact in Member State B informs the MAH of the procedure for recognition of the OBPR certificate in their Member State. The procedure should be completed in a maximum of **7 working days**.

OCABR PROCEDURE

https://www.edqm.eu/sites/default/files/procedure_article_821.zip

OCABR PROCEDURE (« PHASE 1 »)

For any given batch of IVMP, only one request for testing and OCABR certificate should be submitted.

If a batch has been shown to comply with the specifications of the marketing authorisation and is thus satisfactory for release, the Competent Authority or the officially designated OMCL will prepare an OCABR certificate.

The CA or the OMCL communicates the results of the tests within **60 days** of receipt, of the samples together with the signed and complete MAH control protocols.

OCABR PROCEDURE (« PHASE 1 », CONTINUED)

Provided the batch in question is acceptable, the MAH should receive a EU/EEA OCABR certificate from the Competent Authority of the Member State “A” that performed OCABR testing.

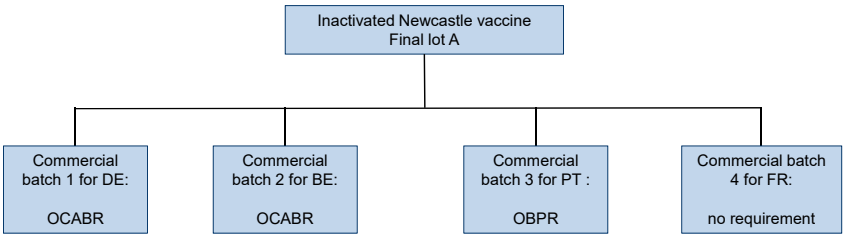
Upon the receipt of this certificate, the MAH may consider that it has permission to place the given batch on the market in Member State “A”.

OCABR PROCEDURE (« PHASE 2 »)

Phase 2 is similar for OCABR and OBPR => see previous part

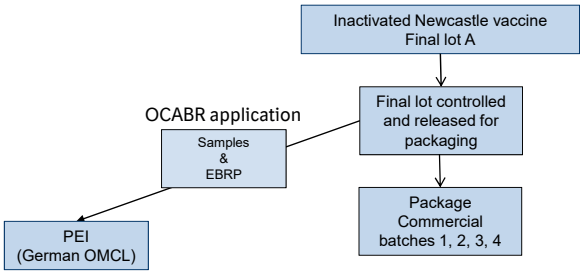
EXAMPLE

EXAMPLE:



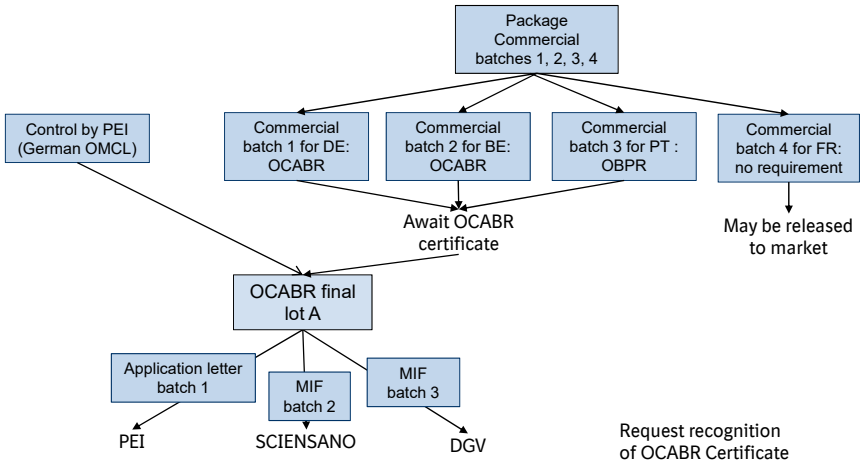
EXAMPLE:

Step 1 : Submit samples to PEI in DE to initiate OCABR testing



EXAMPLE:

final lot packed for all four countries under commercial batches n° 1, 2, 3 & 4



DIFFICULTIES ENCOUNTERED

PRACTICAL DIFFICULTIES

Variability in requirements amongst countries and products => this activity is complex and keeping a description of requirements per country and product is necessary.

Differences also exist in practicalities :

- documents to be submitted,
- Specification about number of units
- samples,
- prefered method of sending requests,
- contacts ….) and such may vary a lot more in time.

Defining how fees are paid.

DIFFICULTIES PROCESS DESIGN

Ensuring that one batch is not submitted to more than one CA/OMCL needs a specific monitoring

… and in some cases is not possible

Manufacturing sites, when they have a global overview of what batch is packed for which market, might in a better position than local affiliates to coordinate the system…. But local affiliates have a better chance of establishing a solid working relationship with the competent autorities, as it avoids cultural or language bias.

DIFFICULTIES (SMALL/SPECIFIC MARKET)

- Some CA require OBPRs but no OMCL in the country can deliver it => OBPR must be requested to an OMCL in another country
- However the IVMP must be licensed in said country market for it to be able to deliver an OBPR

  => May become a problem for IVMP with small/specific markets

DELAYS

Obtaining OCABR / OBPR significantly impacts leadtimes : these additional delays must be built in the planning of production to avoid delays in product availability

Theoritical delays:

- OBPR : « notification of results should occur within 15 working days of receipt of the completed signed protocol and any fees where required »
- OCABR: « the CA shall notify the MAH of the results of the tests within 60 days of receipt of the samples together with the signed and complete control protocols »
- Recognition of an existing OCABR or OBPR certificate « should be completed in a maximum of 7 working days »

COSTS

Costs should be budgeted:

- Fees (highly variable depending on countries and type of certificate/testing)
- Shipping (documents, samples)
- Specific reagents costs
- Increased lead time / storage time
- Loss of sales due to technical problems blocking control
- Resources to coordinate the system, prepare documentation, send samples, submit applications, answer questions …
- Training for these ressources (potentially large number of persons on both marketing and manufacturing sites)
- …

MAKING SENSE IN DAY TO DAY LIFE?

Most MAH personnel still do not know OBPR / OCABR procedures. Even less understand them. Most frequent questions I've encountered concern

Can we reduce delays ?

Redundancy of OMCL control vs MAH control (for OCABR) ?

Contents of article 82 short list ?

Changes in article 82 short list ?

Why do we need a local (MS) approach ? Could we simplify ?

Federal Institute for Vaccines and Biomedicines

Paul-Ehrlich-Institut

www.pei.de

Advantages of OMCL - MAH interaction for batch release

Michael D. Muehlebach
Paul-Ehrlich Institut, Germany

Strasbourg, October 29, 2019

Why official batch release??

- Issue of coordination for MAH
- Time needed by OMCL
- Fees
- Need of establishing testing capacity in OMCLs
- MAH are perfectly capable of performing batch release testing
- On other markets (e.g. US) no need for official batch release

Goal of Batch Release

OBPR/OCABR:

The **ultimate <u>common</u> goal** of interaction between OMCLs/CAs and MAHs is the placement of **safe** and **efficacious batches** of IVMPs on the market.

- **Interaction**

A kind of action that occurs as two or more objects have an effect upon one another.

The two-or-more-way-effect is essential.

Partners involved

- MAH members involved in final product testing (QP, QC)
- OMCL members performing official batch control and release

Important:

Direct communication helps a lot!

Why official Batch Release by Control Authority?

1.) Vaccines are applied to healthy individuals – these can get only worse, on the short run.

2.) Vaccines can be extremely powerfull (or not) to prevent disease or cause adverse events (in healthy)

3.) Murphy´s Law: Sh… happens

4.) Strengthening position of QC

5.) Independent, certified test results

Paul-Ehrlich-Institut

Success story:

Co-operation between Swiss and German OMCL on post-market investigation on suspected quality defect in a poultry vaccine

Problem

Two pharmacovigilance reports from commercial breeders in Sept/Oct ´18:

- Concerning one veterinary vaccine
- Fledglings of vaccinated parental animals with increased frequency of infection and death in two different farms in more than 10 offspring flocks
- Antibody titers seemed to be too low

Suspected lack of potency of two batches of the respective vaccine!

Contact

Von: Hanspeter.Ottiger@ivi.admin.ch [mailto:Hanspeter.Ottiger@ivi.admin.ch]
Gesendet: Mittwoch, 24. Oktober 2018 09:39
An: Mühlebach, Michael
Betreff: Anfrage Vigilance Fall

Hallo Michael,

wir haben Vigilance Meldungen zu [redacted] (2 Lots betroffen, verschiedene Betriebe eines Grossverteilers). Die Herden zeigen einen ungenügenden Schutz (Impfdurchbrüche, hohe Abgangsraten, unbefriedigende Mastleistungen). Geimpft wird seit vielen Jahren mit diesem Produkt. Die Telefone laufen heiss ...

Wir versuchen nun die Ursachen abzuklären.

Anfrage: Könntet Ihr den Titer unserer batches überprüfen? Ev. hat es mit der Stabilität etwas zu tun. Ausserdem prüfen wir die Kühlkette, Impftechniken etc.
Da wir keine Tierversuche machen wären wir um Unterstützung froh. Ev habt Ihr noch andere Hinweise und Erfahrungen.

Vielen Dank für ein rasches Feedback.

Grüsse
Hanspeter

➡ Intense conversation by Email and directly about lots, available assays, potential to test, etc.in a few days

Situation at PEI

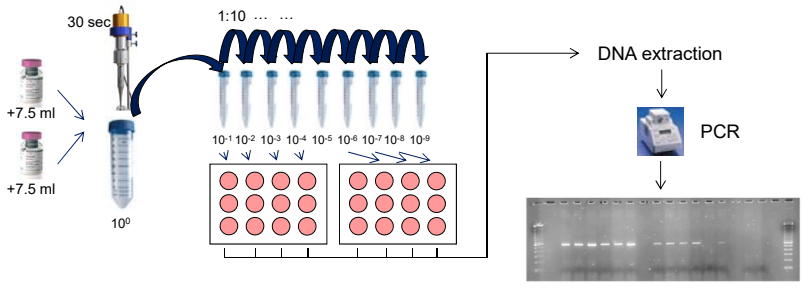
- As it turned out, the respective product:

- is also licensed in Germany
- Tests for vaccine potency (virus titration on target cells with PCR) were established and validated
- The lots in question had also been released to the German market
- For both lots, retention samples had been send by the MAH to PEI and had been stored under QC conditions (general PEI policy)

Preparation & Shipment of Samples

- Documented shipment - especially of field samples - is necessary!
- Shipments of 12 samples (120 g) with 5.4 kg cooling elements in 34 x 31 x 39 cm Box with courier service
- Monitoring of temperature!
- Shipment time: 1 day
- Samples received at PEI: 08.11.18 at +3°C

Potency Test

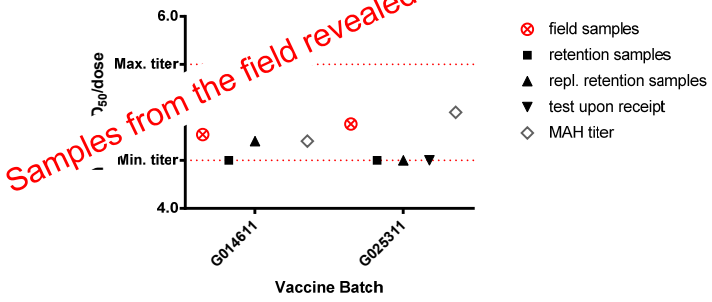


- Titration on MDCC-MSB-1 cells and read out of positive wells by PCR
- Test performed 12.11. - 06.12.18
- according to internal SOPs 4/3-S-084 and 4/3-S-079
- Based on the method described by the manufacturer
- All batches were tested in parallel to a reference preparation
- Uncertainty of measurement: 0,27 $\log_{10}$ per dose (CV: 6,6%)

Results

- Manufacturer specifications: $10^{4,5}$ - $10^{5,5}$ $TCID_{50}$ /dose
- Result reference material: $10^{5,04}$ (valid range: $10^{4,21}$ – $10^{5,30}$ TCID)
- Field sample batch G014611A: $10^{4,77}$ $TCID_{50}$ /dose
- Field sample batch G025311M: $10^{4,88}$ TCID

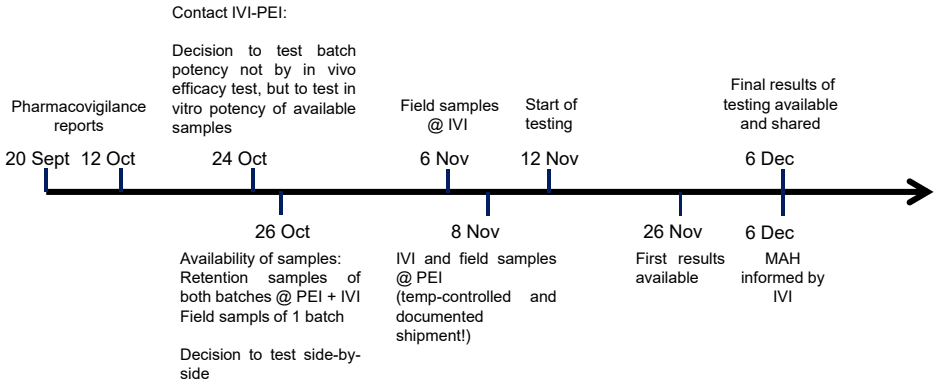
Samples from the field revealed required potency in valid test!



Communication of Results

- First results were available at PEI on Nov 26 and communicated to IVI awaiting confirmation by replication
- Final results were available at PEI on Dec 6 and directly shared with IVI
- IVI communicated results to manufacturer on Dec 6

Timeline



Outcome

- Initial hypothesis that sub-potent batches were responsible in the field for pharmacovigilance signal was falsified
- Other grounds for infection in vaccinated flocks had to be determined (potential: mis-application, dosing, inadequate transport / storage….)
- MAH could be saved from law-suits

Lessons learned

- Cooperation and communication is advantageous
- Need for pre-qualified / validated tests within OMCL!
- Retention samples at OMCL can be extremely valuable
- MAHs can significantly profit from „OCABR“ capacity on non short-listed products

Strengthening Interaction

Means:

- exchange of general information
- information on missing data
- exchange of reference material
- information on test results
- collaborative studies
  - comparison of methods
  - development of methods/protocols/reference material

Last, but not least: Take advantage of possibilities!

- Advantage of parallel testing:

Example: - live virus vaccine
- specification: virus titers by titration on cell substrate

MAH uses parallel testing approach

Release times over 5 years / batch:

Mean of 4.1 days! –> OBPR release times!!

Acknowledgements

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Thank you for your attention

Questions?

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

OMCL Batch Release of IVMPs
EDQM Workshop
Strasbourg, 29-30 Oct 2019

EDQM Biological Standardisation Programme
Contributions to the Quality Control of IVMPs

Dr Michael Wierer,
Head of Medicines Division,
DBO, EDQM, Council of Europe

Biological Standardisation Programme (BSP)

- What is the BSP?
- How does the BSP work?
- Establishment/validation of methods for QC of IVMPs
- Establishment of reference standards for QC of IVMPs

Biological Standardisation Programme

- Exists since 1994
  - First project on IVMPs: 1997
- Sponsors:
  - Council of Europe (EDQM)
  - EU Commission

Goals

For Quality Control of Biologicals

- Establishment of Ph. Eur. reference working standards (BRPs) & reagents (BRRs)
- Standardisation of methods, focus Ph. Eur.
- Application of 3R concept (refine, reduce, replace) to Ph. Eur. methods
- International harmonisation (VICH), collaboration with OIE, USDA etc.

Scope: Biologicals

- Biotech products
- Vaccines, sera, human use (Ph. Eur. Expert Groups 15)
- Vaccines, sera, vet. use (Ph. Eur. Expert Groups 15 V)
- Blood products, contaminants
- Allergens

Organisation (1)

- Steering Committee:
  - 14 Members (incl. chairs biological groups) + 1 observer (WHO)
  - Composition reflects interested parties (incl. BWP-, IWP-, EMA representatives)
  - Decision on start of projects
  - Final approval of reports
- EDQM DBO:
  - Coordination & management of projects

Organisation (2)

Steering Committee members from veterinary field:

- Lukas Bruckner, CH, Chair
- Gabor Kulcsar, HU, Co-opted expert
- Céline Lorteau-Sourgen, FR, Chair Gr 15V
- Esther Werner, DE, Chair IWP

Method of Work (1)

- Proposal for new standard/method (e.g. Expert Group, OMCL)
- Decision by Steering Committee
- Start BSP project including collaborative study
- Approval of report by BSP SC, Group of Experts
- Adoption by Ph. Eur. Commission (for standards)
- Publication in Pharmeuropa-Bio & SN

Method of Work (2)

International collaborative study to evaluate proof of principle, determine precision, transferability

- Project Leader from OMCL
- International participants
- OMCLs, manufacturers, authorities
- Common protocol, reporting sheets & reagents
- Participants: <10 (in vivo study) to 40 (in vitro study)

BSP does not do

- Method validation outside QC field
- Method development from scratch
- Complete validation for individual products
- Method validation for single products or single manufacturers

BSP Achievements – Summary

- 157 projects initiated since 1992
- 39 projects on methods development
- 22 projects on 3R methods
- 144 projects on establishment of BRPs/BRRs

Around 15 % of projects for IVMPs

Methods - IVMPs

Concluded studies

- Erysipelas vaccine (inact.): in vitro ELISA to determine the level of antibodies in the batch potency test (serology assay)
  - Included in Ph. Eur.
- Newcastle Disease vaccine (inact.): replacement in vivo assay by in vitro test
  - Included in Ph. Eur.
- Rabies vaccine (inact.): replacement NIH challenge test by serology test (single dose for batch release)
  - Included in Ph. Eur.

Methods - IVMPs

Ongoing Projects

- Clostridium septicum vaccine: MLD- & TCP test with in vitro readout
  - Study completed; Currently discussed with Gr 15 V
- Tetanus vaccine: BINACLE assay: test for free tetanus toxin

Potential future project (???)

- Rabies vaccine for vet. use, ELISA assay

Reference Standards

- Status & use of standards
- Established IVMP standards
- Monitoring of suitability
- Dissemination of information

Reference Standards

- Biological Reference Reagents (BRRs)
- Biological Reference Preparations (BRPs)
  - In most cases established against IS
  - For relative measurements
- Use in conjunction with Ph. Eur.
- Adopted by Ph. Eur. Commission
- Working standards (most cases)
- Mostly lyophilised preparations
- Available from EDQM

Use of Reference Standards

- Identification tests (e.g. hormones)
- System suitability tests
- Assays (immunogenicity, challenge, …)
  - Reference preparations
  - Challenge strains
  - Antisera
- Limit tests
- Reagents (BRRs)
- Calibration of in-house standards

Examples IVMP Standards

- Vaccines
  - Newcastle Disease, rabies
- Antisera
  - Clostridia (rabbit and GP (tetani), rabbit (multi-component), equine flu (against 5 different subtypes)
- Challenge strains
  - Erysipelas (2)
- Contaminants
  - Mycoplasma (5 strains);
- Reagents
  - Erysipelas ELISA coating antigen

Monitoring BRPs

Goal: Assure suitability for intended purpose

- Reference: material kept at lower temperatures (if possible) or IS
- Case to case decision with project leader
  - frequency (based on stability data)
  - parameter (based on use)
- Water content for freeze-dried BRPs in vials

Dissemination of Results

BSP studies results are:

Reported to:

- Participants - Organising Institutes
- BSP Steering Committee
- Experts of Ph. Eur. groups (6, 6B, 15, 15 V)
- Ph. Eur. Commission

Published in:

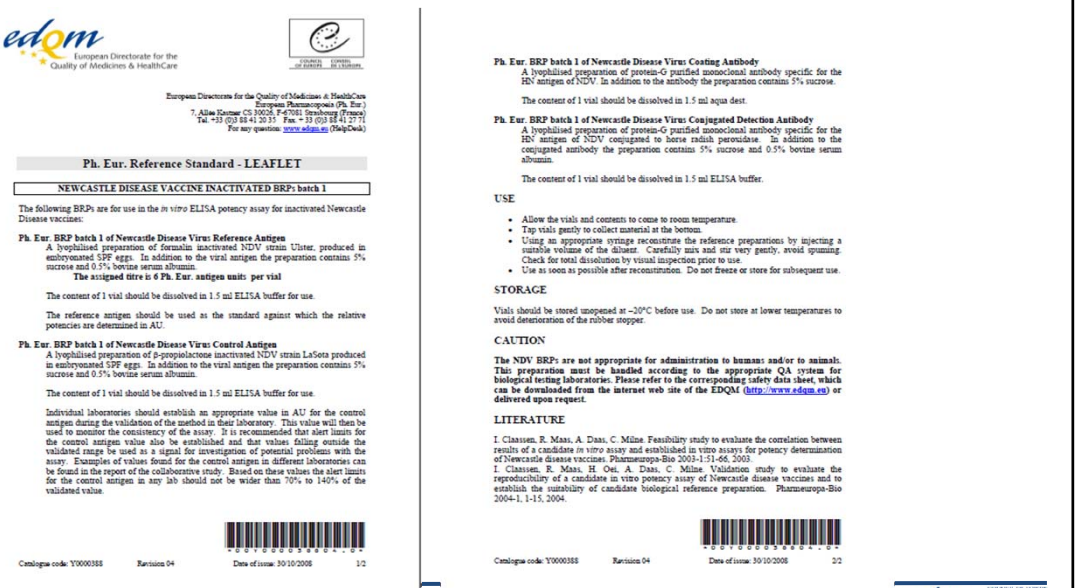
- Pharmeuropa-Bio & Scientific Notes: complete data set (e-journal, free access)
- Peer reviewed scientific journals (some studies)

Information on Reference Standards

Available from EDQM website for free:

- (www.edqm.eu)
- Leaflets
- Material Safety Data Sheets
- Batch Validity Statements: Batch of RS valid at day of printing

BRP Leaflet



European Directorate for the Quality of Medicines & HealthCare

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Ph. Eur. Reference Standard - LEAFLET

NEWCASTLE DISEASE VACCINE INACTIVATED BRPs batch 1

The following BRPs are for use in the *in vitro* ELISA potency assay for inactivated Newcastle Disease vaccines:

Ph. Eur. BRP batch 1 of Newcastle Disease Virus Reference Antigen
A lyophilised preparation of formalin inactivated NDV strain Ulster, produced in embryonated SPF eggs. In addition to the viral antigen the preparation contains 5% sucrose and 0.5% bovine serum albumin.
The assigned titre is 6 Ph. Eur. antigen units per vial

The content of 1 vial should be dissolved in 1.5 ml ELISA buffer for use.

The reference antigen should be used as the standard against which the relative potencies are determined in AU.

Ph. Eur. BRP batch 1 of Newcastle Disease Virus Control Antigen
A lyophilised preparation of β-propiolactone inactivated NDV strain LaSota produced in embryonated SPF eggs. In addition to the viral antigen the preparation contains 5% sucrose and 0.5% bovine serum albumin.

The content of 1 vial should be dissolved in 1.5 ml ELISA buffer for use.

Individual laboratories should establish an appropriate value in AU for the control antigen during the validation of the method in their laboratory. This value will then be used to monitor the consistency of the assay. It is recommended that alert limits for the control antigen value also be established and that values falling outside the validated range be used as a signal for investigation of potential problems with the assay. Examples of values found for the control antigen in different laboratories can be found in the report of the collaborative study. Based on these values the alert limits for the control antigen in any lab should not be wider than 70% to 140% of the validated value.

Catalogue code: Y0000388 Revision 04 Date of issue: 30/10/2008 1/2

Ph. Eur. BRP batch 1 of Newcastle Disease Virus Coating Antibody
A lyophilised preparation of protein-G purified monoclonal antibody specific for the HN antigen of NDV. In addition to the antibody the preparation contains 5% sucrose.

The content of 1 vial should be dissolved in 1.5 ml aqua dest.

Ph. Eur. BRP batch 1 of Newcastle Disease Virus Conjugated Detection Antibody
A lyophilised preparation of protein-G purified monoclonal antibody specific for the HN antigen of NDV conjugated to horse radish peroxidase. In addition to the conjugated antibody the preparation contains 5% sucrose and 0.5% bovine serum albumin.

The content of 1 vial should be dissolved in 1.5 ml ELISA buffer.

USE

- Allow the vials and contents to come to room temperature.
- Tap vials gently to collect material at the bottom.
- Using an appropriate syringe reconstitute the reference preparations by injecting a suitable volume of the diluent. Carefully mix and stir very gently, avoid spurning. Check for total dissolution by visual inspection prior to use.
- Use as soon as possible after reconstitution. Do not freeze or store for subsequent use.

STORAGE

Vials should be stored unopened at –20°C before use. Do not store at lower temperatures to avoid deterioration of the rubber stopper.

CAUTION

The NDV BRPs are not appropriate for administration to humans and/or to animals. This preparation must be handled according to the appropriate QA system for biological testing laboratories. Please refer to the corresponding safety data sheet, which can be downloaded from the internet web site of the EDQM (http://www.edqm.eu) or delivered upon request.

LITERATURE

I. Claassen, R. Maas, A. Daas, C. Milne. Feasibility study to evaluate the correlation between results of a candidate *in vitro* assay and established in vitro assays for potency determination of Newcastle disease vaccines. Pharmeuropa-Bio 2003-1:51-66, 2003.
I. Claassen, R. Maas, H. Oei, A. Daas, C. Milne. Validation study to evaluate the reproducibility of a candidate in vitro potency assay of Newcastle disease vaccines and to establish the suitability of candidate biological reference preparation. Pharmeuropa-Bio 2004-1, 1-15, 2004.

Catalogue code: Y0000388 Revision 04 Date of issue: 30/10/2008 2/2

Batch Validity Statement

BATCH VALIDITY STATEMENT
EUROPEAN PHARMACOPOEIA REFERENCE STANDARDS (CRS) & (BRP)
This Batch Validity Statement has to be used in conjunction with Ph. Eur. general chapter 01/2008:51200 Reference Standards.

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Fax: +33 (0)3 88 41 27 71
Internet : http://www.edqm.eu

Name	Newcastle Disease Vaccine (inactivated) BRP
Catalogue code	Y0000388
Batch number*	1
Assigned value	n/a
Validity	Batch 1 is valid at the printing date: 2014-4-29
Storage conditions	The standard is intended for immediate use. Recommended EDQM storage conditions for unopened containers : -20°C ± 5°C
Safety data	Safety Data Sheet is available from the detailed view or upon request.
Leaflet	Click on the hyperlink to download the leaflet containing the instructions for use, **If available** (Adobe Acrobat Reader version 5 or higher, or the corresponding browser plug-in is needed to open the file) click to download the leaflet

* Sub-batches 1.1, 1.2,1.3, etc., are obtained from the same batch of bulk material.
Notice: the previous classification of the sub-batches 1a,1b, 1c will be gradually replaced with 1.1, 1.2, 1.3 etc.

This statement is valid at the date of printing : 2014-4-29

Conclusion

BSP contributes to QC of IVMPs by

- Standardisation of methods
- Establishment of alternative (3R) methods
- Establishment of reference standards

Thank you for your attention

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