Human Rabies Vaccines Part I
Switching from *in vivo* to *in vitro* potency testing

Patrice Riou

Global Analytical Strategy and Regulatory Compliance
R&D
Sanofi Vaccines
Contents

01  Context

02  ELISA development/validation
    - mAb choice
    - Assay development & validation

03  Potency acceptance criteria
    - Case of a new vaccine
    - Case of a registered vaccine

04  Conclusions
 Contents

01 Context

02 ELISA development/validation
   - mAb choice
   - Assay development & validation

03 Potency acceptance criteria
   - Case of a new vaccine
   - Case of a registered vaccine

04 Conclusions
Sanofi Human Rabies Vaccine Portfolio

1977
- Wistar Rabies PM:WI 38 1503-3M
  inactivated with Beta-propiolactone (BPL)
  Human diploid Cells (MRC5)
  Small scale vaccine

1985
- Vero Rabies Vaccine global
  Vero continuous cell Line

2027+
- Large scale Purified vaccine
- Large scale Highly purified vaccine
Rabies Vaccine Potency Assays

**NIH in vivo potency assay**
- Immunization followed by lethal challenge in mice with IC injection of virulent rabies suspension (CVS strain)
- Developed in 1966\(^{(1)}\) and used for more than 50 years to release rabies vaccines
- Compendial test described in WHO TRS 941 & Ph. Eur. 0216
- High variability observed & use of a large number of animals per test

**Objective**
- REPLACEMENT of animal model

<table>
<thead>
<tr>
<th>Current Method</th>
<th>Regulatory context</th>
<th>New method</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH in vivo Potency test</td>
<td>• DIRECTIVE 2010/63/EU on the protection of animals used for scientific purposes</td>
<td>ELISA in vitro Potency test</td>
</tr>
<tr>
<td></td>
<td>• Ph. Eur. 0216 – Rabies vaccine for human use</td>
<td></td>
</tr>
</tbody>
</table>

\(^{(1)}\) Seligmann EB Jr. Laboratory techniques in rabies. Potency-test requirements of the United States National Institutes of Health (NIH). Monogr Ser World Health Organ. 1966;23:145-51
G protein ELISA – Good surrogate of potency !?

Major correlate of protection is due to glycoprotein G neutralizing antibody


≈ 83% of human rabies neutralizing Abs are against G protein domain III


The protection mainly depends on the preservation of its three-dimensional structure

- Bunschoten et al, J Gen Virol. 1989 Jun;70 ( Pt 6):1513-21

Denatured glycoproteins are shown to be poorly immunogenic

- Gamoh et al, Biologicals 1996;24:95-101

Initial studies indicate good agreement between NIH test and the ELISA antigen content

- Perrin et al, Biologicals, 18 (1990), pp. 321–330
- Gibert et al, Vaccine. 2013 Dec 5;31(50):6022-6029
Contents

01  Context

02  ELISA development/validation
    - mAb choice
    - Assay development & validation

03  Potency acceptance criteria
    - Case of a new vaccine
    - Case of a registered vaccine

04  Conclusions
### Rabies G protein ELISA – monoclonal Antibodies

**Quantitative sandwich direct ELISA method using two monoclonal antibodies against specific rabies G protein epitopes**

**Capture mAb 1112-1**  
(Wistar Institute, Philadelphia, PA, USA)  
- IgG1 isotype: neutralizes all genotype 1 strains  
- Against the **antigenic site II** of the glycoprotein  
- Recognizes **conformational and discontinuous epitopes** (aa 34-42 and aa 198-200 associated by S-S bridge)  

*Dietzschold et. al. (1992) PNAS 89(15):7252-7256*

**Detection Biotinylated mAb D1-25**  
(Pasteur Institute, Paris)  
- IgG1 isotype: neutralizes genotype 1 (PV, CVS, PM and Flury LEP strains) and genotype 6 (EBL2 strain)  
- Against the **antigenic site III** of the glycoprotein  
- Recognizes **conformational epitope** of the glycoprotein (aa 330-343)  

*J. Fournier-Caruana et al. (2003) Biologicals 31:9-16*

**Figure:**
- 1112-1 (Capture mAb)  
- D1-25 (Detection mAb)  
- Antigenic sites I, II, III, and IV

*Sanofi*

**Graphical Representation:**
- Antigenic site I: 226-231
- Antigenic site II: 34-42 + 198-200
- Antigenic site III: 330-338
- Antigenic site IIIa: 342-343
- Antigenic site IV: 251-264

*Bakker et al. (2005) J. Virol., 79: p9062*
Rabies G Protein ELISA – Functional Monoclonal Antibodies

Neutralizing activity using Rapid Focus Fluorescent Inhibition Test (RFFIT)

<table>
<thead>
<tr>
<th>mAb</th>
<th>Neutralizing activity (IU/µg mAb)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CVS11 strain</td>
</tr>
<tr>
<td>D1-25</td>
<td>0.079</td>
</tr>
<tr>
<td>1112-1</td>
<td>3.22</td>
</tr>
</tbody>
</table>

Chabaud-Riou M et al, Biologicals 46 (2017) 124-129

- Both D1-25 and 1112-1 mAbs show similar neutralizing activity against the 3 rabies strains CVS11, Pitman More and Flury LEP
- 1112-1 mAb has superior neutralizing activity compared to D1-25 mAb
Rabies G protein ELISA*

- Develop *in vitro ELISA potency* test for the detection of Rabies G protein
- Generate data to support the NIH test replacement on the next generation of rabies vaccine VRVg

- Quantitative *sandwich direct ELISA* method
- Use of two neutralizing monoclonal antibodies against specific rabies G protein epitopes
- Titration relative to an internal reference calibrated in IU against the 6th WHO IS

**Implementation of the in vitro ELISA potency assay**
1. Next generation of rabies vaccine VRVg
2. Commercialized rabies vaccine

Sanofi Rabies G Protein ELISA : Stability Indicating Assay

**Strategy**
- Set up experimental conditions to produce altered / degraded rabies virus
  (Chabaud-Riou M et al, Biologicals 46 (2017) 124-129)

**Heat degradation**
- Loss in ELISA signal after several days of heating

**Reduction / alkylation degradation**
- **Sample**
  - Initial: 28.0
  - Control (non reduced / alkylated): 21.1
  - Reduced & alkyated: < LLOQ

**Hyperinactivation with BPL degradation**
- Loss of ELISA signal after Inactivation with an excess of BPL: Alteration of G protein antigenic sites (2)

The Sanofi Pasteur rabies G protein ELISA detects the alteration of the G protein and is a stability indicating assay

---

(2) Morgeaux et al. (1993), Vaccine 11-1:82-90
Rabies G protein ELISA agreement with NIH ...

...but more discriminative

G protein ELISA is more discriminant than *in vivo* NIH test

Based on Ph. Eur. 5.2.14: Substitution of *in vivo* method(s) by in vitro method(s) for the quality control of vaccines

<table>
<thead>
<tr>
<th>Sub-potent lots by thermodegradation (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Assay</strong></td>
</tr>
<tr>
<td>Intact vaccine</td>
</tr>
<tr>
<td>ELISA - UI/dose</td>
</tr>
<tr>
<td>NIH - UI/dose (IC95 interv)</td>
</tr>
</tbody>
</table>

ELISA is able to discriminate intact vaccine, heat-treated vaccine and mixed sub-potent lots

<table>
<thead>
<tr>
<th>Sub-potent lots by sub-formulation (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VRVg</strong></td>
</tr>
<tr>
<td>ELISA</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

Agreement between G protein content by ELISA & NIH results

<table>
<thead>
<tr>
<th>Sub-potent lots by hyperinactivation (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VRVg</strong></td>
</tr>
<tr>
<td>ELISA</td>
</tr>
<tr>
<td>V4000</td>
</tr>
</tbody>
</table>

ELISA can discriminate sub-potent lots obtained after hyperinactivation

Rabies G protein ELISA is a good candidate to replace NIH potency test

(1) Chabaud-Riou M et al, Biologicals 46 (2017) 124-129
(2) Toinon A et al, Biologicals 60 (2019) 49-54
### Sanofi Rabies G protein ELISA - ICH Validation

The method is validated at the Drug Substance (DS) and Drug Product (DP) stages for both vaccines according to ICH principles.

#### Specificity
- **Vaccine matrix**

#### Linearity range
- **DS**: [1.0 – 323.9] IU/mL
- **DP**: [0.62 – 11.15] IU/dose

#### Accuracy
- **DS**: [95% – 102%]
- **DP**: [93% – 104%]

#### Intermediate precision
- **DS**: x/± 1.08
- **DP**: x/± 1.12

### Critical parameters identified and evaluated during robustness studies
Sanofi Rabies G protein ELISA

Sanofi Rabies G protein ELISA is a good candidate to replace NIH potency test

1. Uses 2 different neutralizing mAbs
   - Targeting 2 conformational epitopes of the G protein

2. Is fully Validated
   - ELISA validated according to ICH Q2R1 principles
   - ELISA results are more consistent and precise than NIH

3. Is a Stability indicating assay
   - As it can detect G protein degradation

4. Is in Agreement with NIH
   - Similar trend can be observed between NIH and ELISA tests results

5. Discriminates sub-potent vaccines
   - More discriminant than NIH
Dose dependent relationship between Rabies G Protein Content (by ELISA) & Human immune response (GMT)

**VRV11 Phase II dose-ranging clinical study**


---

**VRV11 Study**: Agreement between human immune responses (GMT) & **ELISA titers**

**VRV11 Study**: Low agreement between human immune responses (GMT) and **NIH titers**
Contents

01 Context

02 ELISA development/validation
   - mAb choice
   - Assay development & validation

03 Potency acceptance criteria
   - Case of a new vaccine
   - Case of a registered vaccine

04 Conclusions
Sanofi Rabies G Protein ELISA
Support to VRVg process development

- Rabies G protein ELISA implemented on DS process intermediates:
  - To monitor process yields/losses
  - To ensure consistent quality along DS process

- Rabies G protein ELISA used to **formulate** VRVg FBP

- Rabies G protein ELISA used to monitor VRVg DS and DP **stability**

- VRVg DP **Clinical dose(s)** expressed in ELISA units since phase 1 and all along clinical development
  - NIH test performed on DP as a specification test in parallel to ELISA on all clinical DP batches
Strategy for New Vaccine (e.g. VRVg)

DP in vitro potency (ELISA) Potency acceptance criteria

- For CTD submission: To define acceptance criteria supported by clinical data
- For life-cycle management: to define in-house action limits based on process consistency

**CTD submission strategy**

- **ELISA Release Upper acceptance criteria**: Maximal ELISA dose demonstrated to be safe
- **Acceptance criteria range**: ELISA Release and Stability Lower acceptance criteria
- **ELISA Release and Stability Lower acceptance criteria**: Minimal ELISA dose demonstrated to be efficacious

**Life-Cycle Management**

- **ELISA Release Upper acceptance criteria**: ELISA Upper limit
- **In house limits based on consistency approach**: ELISA Lower limit
- **Release and Stability lower acceptance criteria**
ELISA Potency acceptance criteria for VERORAB™ DP

**Strategy**

Consistency approach of the VERORAB™ product with the *in vitro* ELISA

Calculation of the new acceptance criteria: mean ± 3 standard deviations

**Results**

Representative batches of VERORAB™ vaccine production (*i.e.*, well-established safety and efficacy profile, with consistent manufacturing)

<table>
<thead>
<tr>
<th></th>
<th>1.9 UI/dose</th>
<th>4.3 UI/dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELISA units (U)</td>
<td>2.0</td>
<td>3.5</td>
</tr>
</tbody>
</table>

279 batches covering 3 years of manufacturing

**Agreement Study**

Assess the proposed acceptance criteria with sub-potents batches tested in both NIH & ELISA
G protein ELISA for DP formulation and DS monitoring

New ELISA potency on DP is associated with:

- New DP ELISA formulation target (replacement of SRID)
  - To match DP acceptance criteria and taking into consideration F&F and shelf-life losses

- Implementation of ELISA on VeroRab™ DS (replacement of SRID)
  - To monitor DS stability

- Implementation Of G rabies ELISA on VeroRab™ DS intermediates
  - ELISA has a wider linearity range and is less sensitive to matrix interference
  - Better monitors process yields/losses to ensure consistency
Contents

01 Context

02 ELISA development/validation
   - mAb choice
   - Assay development & validation

03 Potency acceptance criteria
   - Case of a new vaccine
   - Case of a registered vaccine

04 Conclusions
Conclusions

Replacement of *in vivo* method by *in vitro* method and setting specifications

- *In vitro* method suitability & validation package is key
- Consider implementing in vitro method not only at DP stage but also in upstream intermediates (DS intermediates, DS, FBP, Filled Product) and for stability studies

**For new products**
- Clinical trial design is critical in order to have clinical data supporting potency acceptance criteria
- Defining the DP dose for phase 1/2 dose ranging and for phase 3 efficacy studies is important
- F&F product losses and product stability should also be taken into consideration

**On already commercialized product**
- Consistency approach requires to set product specific criteria calculated using a set of batches representative of manufacturing variability
- Implementation of *in vitro* method not only on DP but also in intermediates
Acknowledgements

Françoise Guinet-Morlot
Carole Bourot
Elisabeth Niogret
Sebastien Gaudin

Emmanuelle Coppens
Benedicte Mouterde
Audrey Toinon
Sylvie Uhlrich
Disclosure and Funding

Patrice Riou and contributors (listed in acknowledgment) to this study are sanofi employees and may hold sanofi shares

This study was funded by sanofi
Thank you
THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)
Case study: Human rabies vaccines
Switching from *in vivo* to *in vitro* potency testing

*Part II : towards a global harmonised change*

Eriko TERAO
Council of Europe
European Directorate for the Quality of Medicines & HealthCare (EDQM)
Biological Standardisation Programme

*Transition to non-animal based vaccine batch release testing, HSI Webinar 27th March 2024*
Rabies vaccines – from *in vivo* to *in vitro* potency testing

- *European Convention for the protection of vertebrate animals used for experimental and other scientific purposes* (ETS No. 123, Council of Europe, 1986)

**International initiatives for the development of an alternative *in vitro* method for the potency control of human rabies vaccines conclude on the feasibility of an ELISA approach**

2010: workshop on the consistency control of vaccines (Strasbourg, FR)
2011: workshop on alternate rabies virus vaccine potency test development (Ames, USA)

→ Despite the development of various alternative approaches, the global acceptance for the replacement of the NIH test by an *in vitro* method is hindered by the absence of a common standardised method
Establishing a common standardised replacement method

Advantages
- acceptance at large (global) level
- no need to maintain multiple validated methods for lot release testing
- increased proficiency of operators
- higher precision & shorter lead times of an ELISA approach
- optimised resources
- cost effective

Pre-requisites of the method
- no proprietary rights on method
- accessible reagents and equipments
- applicable to most products
- transferable and robust method

→ international initiative
→ international collaborative project
Rabies vaccines – from *in vivo* to *in vitro* potency testing

Step 1
- what methods are available?
- which to select?

Step 2
Is the selected method suitable for global use?
- transferability
- applicability to routine release testing

Step 3
International agreement & implementation
Rabies vaccines – from *in vivo* to *in vitro* potency testing

**Step 1**
- what methods are available?
- which to select?

**EPAA project**
Step 1: selection of a candidate method: EPAA project

**European Partnership for Alternative Approaches to Animal Testing (EPAA)**

**Vision**  Replacement, reduction and refinement (3Rs) of animal use for meeting regulatory requirements through better & more predictive science

**a collaboration between**

- **European Commission**  5 Directorate General: DG GROW, DG ENV, DG SANTE, DG JRC, DG RTD including Partner Agencies: ECHA, EFSA, EMA
- **Industry stakeholders**  39 companies & 9 associations from 8 industrial sectors

* Steering Committee

* Advisory body (Mirror Group)  representatives of civil society, including academia, animal welfare and 3Rs centres, acting as a consultation forum in an advisory capacity to the steering committee

* Secretariat  GROW-EPAA@ec.europa.eu
Step 1: selection of a candidate method: EPAA project

✓ 2012 EPAA Workshop 1 (Arcachon-1 meeting)

• creation of an international Working Group including - public laboratories & manufacturers
  - from Europe, Americas, Asia
  - academia, WHO, EDQM

• Scientific coordinator: JM Chapsal (independent, EPAA)

→ inventory of available sandwich ELISA methods
  using well-characterised monoclonal antibodies
  recognising the protective trimeric form of the rabies glycoprotein

→ launch of an inter-laboratory study to select an appropriate ELISA method
Step 1: selection of a candidate method: EPAA project

- 5 laboratories: 2 manufacturers & 3 NCLs
- 3 ELISA methods: from 2 manufacturers & 1 NCL
- 3 products, 3 virus strains (PM, Flury-LEP, PV)
- 7 samples: intact (N), heat degraded (Degr), mix of 50% intact-spiked degraded (50%)
- WHO Rabies vaccine IS as reference standard to express results in IU

<table>
<thead>
<tr>
<th>Method</th>
<th>Lab</th>
<th>Coating Ab (clone)</th>
<th>Detection Ab (clone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>mAb (D1)</td>
<td>mAb (D1)</td>
</tr>
<tr>
<td>B</td>
<td>3</td>
<td>mAb (1112-1)</td>
<td>mAb (D1)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>2</td>
<td>polyclonal</td>
<td>mAb (TW 17)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Step 1: selection of a candidate method: EPAA project

☑️ **2015 EPAA Workshop 2 (Arcachon-2 meeting)**

The Working Group determined that the GP ELISA (method B, Sanofi Vaccines) is the most promising method for further evaluation in a wider collaborative study.

- no proprietary rights by the developer of the selected method
- highly characterised specific monoclonal antibodies owned by public laboratories
- recognises at least 3 virus strains used for vaccine production (data from 2015; at least 6 strains by 2022)
- preliminary data support good transferability of the method

*Morgeaux et al*  
*Vaccine 2017;35(6):966-71*

→ Step 2
Rabies vaccines – from *in vivo* to *in vitro* potency testing

**Step 1**
- what methods are available?
- which to select?

**Step 2**
Is the selected method suitable for global use?
- transferability
- applicability to routine release testing

**Step 3**
International agreement & implementation

---

**EPAA project** (2012–2016)
→ selection of the GP ELISA

**BSP148 project**
Step 2: evaluation of the selected method for global use

**Biological Standardisation Programme (BSP)**

A programme co-funded by the • Council of Europe/EDQM  
• Commission of the European Union

- organises international collaborative studies for the  
  - establishment of common reference materials and critical reagents  
  - evaluation of the transferability and robustness of common (new/improved) testing methods

* Steering Committee  
  Chairs of the Ph. Eur. Groups of Experts for biological products (human & vet.)  
  EU Commission, European Medicines Agency & WHO representatives  
  ad hoc specialists from public institutions

* coordinated by a technical secretariat based at the EDQM/Council of Europe

• is independent: no financial interest, neutral focal point for open discussions  
• holds discussions with all interested parties **worldwide** (NCLs, manufacturers, WHO, WOAH, pharmacopeia,...)  
• works for the improvement of international harmonisation (e.g. joint studies with other organisations)  
• ensures a link to the Ph. Eur. texts (e.g. via Ph. Eur. Groups of Experts and Ph. Eur. Commission)
Step 2: evaluation of the selected method for global use

2016: Launch of the joint EDQM/BSP – EPAA project: BSP148

Project Leaders
S. Morgeaux (ANSM, FR) & JM Chapsal (Independent, EPAA)

Scientific coordinator
E. Terao (EDQM/BSP, Council of Europe)

→ Is the selected method suitable for global use?
  • transferability
  • applicability to routine release testing

  o Phase 1. preparatory phase
  o Phase 2. collaborative study
  o Phase 3. reporting study
Step 2: evaluation of the selected method for global use (BSP148)

Phase 1. preparatory phase (project management team)

- Licensing agreements established by the owner institutes of the antibodies (Wistar Institute, Institut Pasteur) with 2 commercial suppliers (2016-2019)

- Procurement of test samples
  - 7 manufacturers worldwide, 11 samples
  - 5 virus strains (PM, PV, Flury-LEP, aGV, CTN)
  - various potencies (low, medium, high)

- Pre-testing by 2 laboratories
  - determination of the pre-dilutions of the samples
  - qualification of lots of critical reagents

- Determination of the statistical data analysis models
- Elaboration of a detailed SOP, study design & study protocol
Step 2: evaluation of the selected method for global use (BSP148)

Determination of the statistical analysis models for data analysis

- full dose-response curves (12 dilution points)
- fitting of 2 statistical models to the data
  - 5 parameter logistic (5PL) model (asymmetrical sigmoid curve)
  - parallel line (PL) model (linear part of the dose-response curve)

Study & assay design

- Selection of 8 dilution points - covering the linear range + lower/upper points
- optimised pre-dilutions of samples & standard
- duplicate testing (using independent predilutions)
- WHO 7th IS for rabies vaccine in each plate to express results in IU/mL
- blank wells for assessment of assay quality
- 3 independent assays, balanced plate layout
Step 2: evaluation of the selected method for global use (BSP148)

Phase 2. Collaborative study outline

- **Participants**
  - 31 laboratories: public/NCLs & manufacturers
  - Europe, North & South Africa, North & South America, Asia

- **Test samples & ref. standard**
  - set of 11 marketed vaccines covering 5 virus strains and various potencies
  - WHO IS for Rabies vaccines (inactivated, non-absorbed – 7th IS)

- **Study protocol**
  - Common ELISA SOP with standardised critical reagents (antibodies & detection conjugate)
  - optional, as available: *in-house* ELISA method
  - Standard reporting sheets
  - Central statistical analysis
Step 2: evaluation of the selected method for global use (BSP148)

Phase 2. Collaborative study outline

2020/12-2021 • dispatch of samples to participants
  • technical support for method transfer (trouble-shooting and adjustment of testing conditions)

2022/02 • 25/31 laboratories reported results for 10 samples
  • 10 laboratories reported results for an additional 11th sample (procured in 2021)

2023/04 • central data analyses & Phase 2 report
  - 2 analysis models: all datapoints (5PL), linear part of dose-response curves (PL)
  - all datasets & subset of datasets from assays complying to the SOP
  - evaluation of possible assay suitability criteria (slope, inflection point, OD50,...)

**NOTE:** due to the limited availability of the samples, the study timeline and the pandemic context, some reported data were generated from sub-optimal assays
Step 2: evaluation of the selected method for global use (BSP148)

Phase 2: Collaborative study overview of results
Step 2: evaluation of the selected method for global use (BSP148) . Phase 2 conclusions

- **Applicability**
  - to all tested strains: PM, PV, Flury-LEP, aGV, CTN (and at least 1 additional strain)

- **Potency estimates**
  - similar between participants’ and centrally calculated values

- **Assay precision**
  - all confidence limits within 80-125%
  - satisfactory despite sub-optimal method transfer

- **Assay repeatability**
  - Mean variation (gCV) <15% for most laboratories*
   - <1-2% in some laboratories
  - largest variation for laboratories optimising testing conditions in-between reported assays
  - satisfactory intra-laboratory variation despite limited proficiency in method

- **Assay reproducibility**
  - inter-laboratory variation of gMeans: 5.9-12.9%* depending on sample
    - higher variation with some samples requiring higher pre-dilutions
    - linked to the efficiency of method transfer & proficiency
    - satisfactory inter-laboratory variation despite sub-optimal method transfer
Step 2: evaluation of the selected method for global use (BSP148)

Phase 3. Reporting phase: applicability to routine batch testing

Launched 2023/12

'simulation of a real life situation'
→ testing of as many batches of different products as possible with the standardised GP ELISA to generate data supporting the discussions on future specifications & assay validity criteria

Participants
- 19-25* laboratories: public/NCLs & manufacturers, in all regions
  - access to routine batches of marketed vaccines
  - fully transferred GP ELISA
* including 4 new study participants

Method
- GP ELISA SOP used in routine (no imposed lot of critical reagents)
- WHO 7th IS as standard to express results in IU

Test samples
- non-expired lots from routine production (no sample provided by EDQM)

- data reporting by 12/2024
- central data analysis at EDQM & study report elaboration
Step 2: BSP148 project timeline

✓ Phase 1 (preparatory phase) 2016-2020
✓ Phase 2 (collaborative study) 2021-2023
  ✓ Technical workshop (study participants) 2021-2023

➤ Phase 3 (reporting phase) 2024-2025
  o Publication of the BSP148 study outcomes
  o Symposium - for discussions on method implementation 2025
  o Proposal for the global replacement of the in vivo potency test by a standardised ELISA (revision of compendial texts & WHO guidelines)
BSP148 study participants

19 official control & public laboratories and 12 manufacturers
additional 4 laboratories joining after Phase 2
Thank you for your attention

Stay connected with the EDQM

EDQM Newsletter: https://go.edqm.eu/Newsletter
LinkedIn: https://www.linkedin.com/company/edqm/
X: @edqm_news
Facebook: @EDQM_CouncilofEurope