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 Biological Standardisation Programme (BSP)

Workshop on a novel *in-vitro* model as alternative to *in-vivo* toxoid vaccines testing: *Clostridium septicum* vaccine as proof of concept

9-10 March 2021

Dr Catherine Milne,
Department of Biological Standardsiation, OMCL Network and HealthCare (DBO), EDQM, COE

EDQM Biological Standardisation Programme (BSP)

- Exists since 1991
- Contract with EU since 1994 - coincides with the creation of the Official Medicines Control Laboratory (OMCL) network
- Sponsors
  - Council of Europe /EDQM
  - EU Commission

Funded by the European Union and the Council of Europe

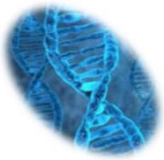
EUROPEAN UNION

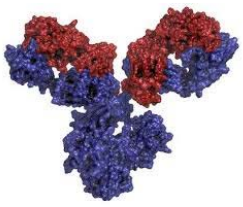
COUNCIL OF EUROPE

CONSEIL DE L'EUROPE

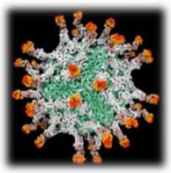
Implemented by the Council of Europe

Scope





- Biotech products (Group 6, (MAB, P4BIO))
  (hormones, cytokines, anticoagulants (heparins), mAbs…)
- Blood derived medicinal products, contaminants (Group 6B)
  (immunoglobulins, coagulation factors…)
- Vaccines, sera for human use (Group 15)
- Vaccines, sera for veterinary use (Group 15V)
- Miscellaneous (specific working groups)
  (allergens, endotoxins, mycoplasma…)



The BSP in Brief

Supports Standardisation in Quality Control of Biologicals

- Establishment of Ph. Eur. working standards (BRP) & reagents (BRR) for use in the context of the Ph. Eur.
- Standardisation of methods for Ph. Eur.
- Application of 3R concept (refine, reduce, replace) to Ph. Eur. methods
- International harmonisation: collaboration with WHO, OIE and national authorities

The BSP Programme oversight

Overseen by a Steering Committee

- Chairs of Ph. Eur. expert groups in relevant fields
- Ad hoc experts (human vaccines, veterinary vaccines, human blood derived medicinal products, biotech)
- EMA (IWP, BWP), WHO (observers)
- EU Commission representative
- EDQM Director's representative

Secretariat and Program Administrators

- EDQM – Department of Biological Standardisation, OMCL network and HealthCare (DBO), BSP Team

Provides an expert panel with varied and specific expertise and links to Ph. Eur. expert groups and international partners for advice and decisions on projects

How Does the EDQM BSP Help?

- Provides a 'neutral' independent space for exchange
  (anonymised participants /samples, central calculation)

  For:
  - Independent laboratories from national authorities e.g. OMCLs
  - Laboratories from different manufacturers
  - Qualified academic/other labs
  - National authorities and experts
- Uses large scale collaborative studies to:
  - Demonstrate the general applicability and recommended use of methods already validated in a 'product specific and/or local' context
  - Establish commonly assigned values for Ph. Eur. reference standards
- Provides a key link between practical work of laboratories and the Ph. Eur.
  - Successful methods and standards are included in the Ph. Eur. and have a legal standing
- Focus on the European market with an eye on global participation and acceptance (common reference material and method recognition where possible)

What EDQM BSP Does Not Do

- Method validation outside the QC field
- Method development from scratch
- Complete validation for individual products
- Method validation for single products or single manufacturers
- Work outside the scope of the Ph. Eur.

Method of Work - Overview

1. Proposal for new BRP/method (from Expert Group, OMCL, manufacturer…)
   - ✓ Relevant to the Ph. Eur.
   - ✓ Mature method with validation package (no additional research/development required)
   - ✓ Applicable to most products
   - ✓ No proprietary method/reagents – reagent accessibility assured for future use
2. Decision by Steering Committee
   - ✓ Start of the project (if possible run jointly with WHO, US-FDA, USP to established harmonised/common reference standards and methods)
   - ✓ Nomination of external expert as Project Leader
3. Launch of BSP project including collaborative study
4. Reporting and updates on project to BSP SC for advice and decisions on critical steps
5. Approval of final report by BSP SC, Group of Experts
6. Adoption by Ph. Eur. Commission (for BRP) – considered for Ph. Eur. experts for inclusion in Ph. Eur. texts
7. Publication in Pharmeuropa-Bio & SN

Focus on Step 3: Project Launch and Collaborative Study

Preparative phase - with the project leader(s)

- Procurement of a starting material for the candidate and study samples
- Production of batch(es) of candidate standard
- Pre-testing by a few laboratories – verifying method details
- Stability study (thermal stress)
- Elaboration of a study protocol for the study
- Invitations to laboratories : OMCLs, manufacturers from EU and other regions
- Preparation of the shipments (import permits,...)

Running the collaborative study – with all participating laboratories

- distribution of a common panel of samples
  - calibrants : current WHO IS and/or Ph. Eur. Ref. Standard
  - candidate replacement batch(es)
- distribution of a common study protocol
  - materials and methods
  - special instructions
  - reporting sheets
  - deadlines and contact details
- Return of results and central statistical analysis
  - Assignment of a unitage (IU where possible)
  - Evaluation of assay variation
- Draft study report - anonymised data sets
  - Shared with participants for data check and comment before further dissemination

Reporting phase (optional) - usually with manufacturers

- data from routine production lots with a new method or ref. standard

Dissemination of Results

BSP studies results are:

Reported to:

- Study Participants - pre-check before further distribution
- BSP Steering Committee
- Involved Expert Groups
- Ph. Eur. Commission

Published in:

- Pharmeuropa-Bio & Scientific Notes
- Peer reviewed scientific journals (some studies)

In some cases (e.g. new methods, issue of global interest) a symposium is organised by EDQM

Ultimate goal inclusion in the Ph. Eur. and widespread implementation

FREE ON-LINE ACCESS
https://pharmeuropa.edqm.eu/home

Examples of BSP Projects Past and Present (1)

163 BSP projects

125 projects on BRP/CRS/BRR establishment
> 130 batches of more than 60 different BRP/CRS
BRPs/CRS monitored throughout their lifetime

ALL BRP/CRS prepared for use in context of Ph. Eur. texts

• Human vaccines	Antigens, toxoids, toxins Antisera,…	mumps, …, acellular/whole cell pertussis, …influenzae b, poliomyelitis (OPV, IPV), …HBV, HCV,…
• Veterinary vaccines	Antigens Cha… …tisera,…	rabies, equine influenza, clostridia swine erysipelas, Newcastle disease, tetanus toxoids,…
• Blood pro…	…mmunoglobulins Clotting factors Contaminants,..	normal and specific Ig (tetanus, hepatitis,…) coagulation factors VII, VIII, IX, albumins,… HAV & HEV RNA, prekallikrein…
	…iotech products	Erythropoietin, somatropin, heparins, etarnercept, infliximab…
• Miscellaneous	Mycoplasma strains, allergens, endotoxins…	

Examples of BSP Projects Past and Present (2)

Validation of improved & alternative 3R methods

44 projects on method validation

>25 projects on 3R methods - to refine , reduce, replace animal use

- Human vaccines — serology methods, alternative
  - diphtheria, tetanus …d,…
  - hepatitis A, …
  - Inacti… …munogenicity & antigen content,…
- Veterinary vacci… …s, alternative 3R *in vitro* assays
  - …, Clostridia, swine erysipelas, Newcastle disease,…
  - improved agglutination method, alternative 3R potency assays
  - isoagglutinins direct method, Tetanus immunoglobulins,…
- Biologicals — alternative 3R & improved physico-chemical tests
  - somatropin, heparins, erythropoietin, INF alfa-2,…

Successful candidate methods included in Ph. Eur. texts by Ph. Eur. expert groups

How to Participate in a BSP Project ?

✓ *evaluate a proposed new method/standard*

✓ *contribute to the calibration of a new batch of reference standard*

- As participant
  - laboratory from manufacturer / OMCL
    - if you perform the test
    - if you use the Ph. Eur. RS
- As project leader
  - expert in the field
    - with access to a laboratory
    - with wide knowledge of products / methods
    - if you developed a new method
- As donator of starting material
  - manufacturer

→ Check the EDQM website for ongoing / future studies (BSP work programme)

→ Contact the EDQM/DBO/BSP (via Helpdesk on the EDQM website or direct contact)
e.g. with mature project proposals, candidate BRP/CRS material, interest in study participation, requests for information

Many Thanks to All Supporters

Past and Present

BSP Steering Committee Members
Project Leaders
Project Participants
Donators of Material
International Collaborators

EDQM DBO Team

Scientific Project Administrators: Marie-Emmanuelle Behr-Gross, Angèle Costanzo, Sébastien Jouette, Natalia Sinitskaya, Eriko Terao
Assistant: Sally Woodward
Statisticians: David LeTallec, Elena Regourd
Head of Section: Catherine Milne
Head of Division: Michael Wierer
Head of Department: Laurent Mallet

..and internal EDQM collaborators
DLab, DRSL, DAF, ITPD, PRDD….

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**