New Frontiers in the Quality of Medicines

Workshop
European Biological Standardisation Programme (BSP)

Moderators:
Dr Roland Dobbelaer
Dr John Purves

EDQM International Conference
13-15 June 2007
Strasbourg, France
European Biological Standardisation Programme (BSP)

Co-operation and collaboration EDQM / EMEA in the biological field

New Frontiers in the Quality of Medicines

John Purves
European Medicines Agency (EMEA)
14th June 2007

Overview of Presentation

- Introduction and general background
  - Legislation – 1965 through to 2007
  - Integrated Quality Management System (I.Q.M.S.)
  - Collaborations – Global - European
- EDQM and EMEA Activities
  - BSE, v-CJD, and Blood Products
  - Regulatory Procedures in the event of an influenza pandemic
  - Comparability of biotechnological products
  - W.H.O.
- Conclusions
40 Years of Harmonisation

- 1965 - First Directive set out basic principles
- 1975 - Experience consolidated and original CPMP created
- 1981 - Specific veterinary legislation and old CVMP created
- 1985 - “1992 Single Market” project started
- 1995 - EMEA officially opens
- 2001 - Review of the legislation

Enlargement

EMEA Mission Statement Summary

“The mission of the European Medicines Agency is to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health”. For example, we:

- Mobilise scientific resources in the EU to provide high quality evaluations, advice on R&D programmes and information to users and health professionals
- Develop efficient procedures to allow timely access to innovative medicines through a single European marketing authorisation
- Reinforce the safety of medicines for humans and animals through pharmacovigilance and MRLs for residues in food-producing animals
- Evolution of the review procedure, CHMP and its Working Parties

Important Factors for the EMEA

Integrated Quality Management System

- EMEA Mission Statement & Quality Policy
- EMEA Policies
- EMEA Core & Key Tasks (Process Maps/Flowcharts)
- EMEA SOPs
- EMEA Forms
- Standard Documents
- Templates

International Co-operation (1)

EMEA Road Map to 2010: Preparing the Ground for the Future (2005)

Implementation plan (Chapter 6)

- Strengthen the EMEA’s international collaboration with non-EU Regulatory Authorities including:
- Scientific evaluation of human medicines for non-EU countries
- Review interaction between EMEA and FDA in context of Confidentiality Arrangements
- Explore extension of international cooperation
International Co-operation (2)

Status report on Implementation of the EMEA Road Map (2006)

- Good progress with interactions between EMEA and FDA in the context of the EU/FDA Confidentiality arrangements

EMEA Work Programme 2007

- International Conference on Harmonisation (ICH)
- WHO (e.g. medicines for use in developing countries)
- Co-operation with FDA – consolidate procedures for parallel scientific advice
- Explore co-operation agreement with Japan

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE
ICH

Collaboration of the regulatory authorities of

- Europe
- Japan
- United States

And the pharmaceutical trade associations

- European Federation of Pharmaceutical Industry – EFPIA
- Japanese Pharmaceutical Manufacturer’s Association - JPMA
- Pharmaceutical Research and Manufacturers of America - PhRMA

ICH Topics

- Quality by Design / Process Analytical Technology

- E2E Pharmacovigilance planning (finalised) – links to EU Risk Management Plan
EMEA - “Euro-partners” and International Network

- European Commission (DG Enterprise, DG Research and DG Sanco)
- European Parliament
- National competent authorities (human and veterinary)
- 2,300 European experts
- European Pharmacopoeia (Council of Europe)
  » EDQM and Biological Standardisation Steering Committee
- Medicines Control Laboratories Network
- I.C.H. – F.D.A. and Japan

EDQM - EMEA joint forum

- Joint forum for discussions between EMEA and its scientific committees and the European Pharmacopoeia

- Purpose: to identify and discuss issues of common concerns

- Sharing of work programs, discussion on specific topics and organisational matters
EDQM-EMEA joint forum

- Meets every year; chaired by CHMP Chair and EDQM Director

- Participants: representatives (chairs, secretariats) from EDQM, EMEA, Ph.Eur. Commission, OMCL, CHMP, CVMP, HMPC, QWP, BWP, VWP, GTWP, CPWP, IWP

- European Commission is informed

EDQM-EMEA joint forum: topics

- Biologicals (incl. Biotechnology, Blood, related OMCL issues). Ex: NAT testing of plasma pools

- Advanced Therapies (gene and cell therapies). Ex: PhEur work and EMEA guidance

- Vaccines. Ex: general vaccine monograph

- OMCL related issues. Ex: interaction between OMCLs and licensing authorities
EDQM-EMEA joint forum: topics

- Quality and Inspections related matters. Ex: chapters on microbiological contamination of non-sterile products

- Herbal medicinal products. Ex: family monographs for extracts

- Veterinary medicinal products. Ex: compliance of veterinary vaccines with veterinary vaccine monographs

Building up EU Collaboration
BWP Experience

- Ad Hoc Pharmacy and Biotechnology Working Party set up in 1986

- Chairmen – G Schild, G Vicari, J-H Trouvin

- Now called Biologics Working Party

- All EU Member States

- EDQM regular participation
### Building up EU Collaboration

#### BWP Experience

- Legislation
- Science
- Advice to CHMP
- Product evaluation
- Guidelines
- Common objectives

- Member States – initially strangers
- 2-day meetings
- Exposed to each other’s Assessment Reports
- Lively discussions
- Agreement and drafting of recommendations

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### Building up EU Collaboration

#### BWP Experience

- Eating and drinking together

- Got to know each other – and the Commission

- This knowledge resulted in national barriers dropping

- Result – we worked very much together from the early days
Experience – past and current

- TSE guideline and Certification
- v-CJD and blood products
- Commission Decision regarding the ban on specified risk materials
- BWP / EDQM discussions, the concept of certification and the implementation – reflection of European team-work
- Influenza pandemic
- Biosimilars
- Advanced Therapies
- Outcome - positive

Current Co-operation and Collaboration - EDQM-EMEA

- Concomitant revision of the:
  - Note for Guidance on Allergen Products (CPMP/BWP/243/96)
  - Ph. Eur. Monograph on Allergen Products (01/2005:1063)
- EMEA and some national experts involved in the ongoing revision of the N.f.G. invited to the EDQM Allergens Working Party
- Purpose: to ensure consistency and complementarity between the revised N.f.G. and the revised Monograph
- Plan to release the two draft revised documents for public consultation at close intervals
EMEA and Council of Europe

Complementary activities of EMEA and European Directorate for Quality of Medicines (EDQM) and HealthCare with respect to the quality of medicines, including:

- Ph. Eur. monographs mandatory for medicinal products authorised in the EU
- European standards and reference materials
- Medicines sampling and testing programme
- Co-ordination of Official Control Authority Batch Release (OCABR) for blood products and vaccines
- Blood transfusion – Council of Europe guide

Plasma-derived medicinal products

- Close liaison between EMEA’s BWP and Blood Products Working Party and Group 6B of the Ph. Eur.

Examples

- Nucleic acid amplification techniques (NAT)
- CHMP recommendation for plasma pool testing for hepatitis C virus RNA by NAT from July 1999.
- As a consequence, Ph. Eur. monograph for Human Plasma for Fractionation modified to make testing mandatory.
**Plasma-derived medicinal products**

**Examples**
- On-going discussion on parvovirus B19 NAT testing of plasma pools.
- Freezing conditions of plasma
- Different interpretations of monograph requirements identified by EMEA from inspections linked to Plasma Master File evaluations.
- Referred to Group 6B, who reviewed available data and made new recommendations, adopted by Pharmacopoeia Commission in Nov 2006

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**CHMP Scientific Opinions for non-EU Countries**

- CHMP opinions, in co-operation with WHO, on medicinal products for human use that are intended exclusively for markets outside of the EU (Article 58. of Regulation (EC) No 726/2004)
- Procedure for medicines to prevent or treat diseases of major public health interest e.g. vaccines, medicines for HIV/AIDS, malaria or tuberculosis.

Conclusions

- Looking back at the experience gained, the outcome was positive
- Reflecting on our current activities and steps taken to further strengthen our interactions, we have put in place mechanisms to share information, experts and attend EDQM Group meetings / EMEA Working Parties
- New Frontiers – will include sharing of Work Programmes for coming years, identify new issues we need address together in a complimentary manner and envisage longer term plans by means of sharing “Road Maps”

Thank you for your attention!

- For your information:
  - EMEA Website: http://www.emea.eu.int
  - John.Purves@emea.europa.eu
  - Direct line: +44 (0) 20 7418 8402
International Cooperation and Standardization in the Field of Blood Products

COE/EDQM & Health Care
14 June, 2007
Mark Weinstein, Ph.D.
Office of Blood Research and Review
CBER, FDA

Topics

• Benefits of international cooperation in setting standards for blood products
• FDA interactions with international standard setting organizations
• Recent standards development
• Future directions and challenges
Importance of Biological Standards Program

- Physical standards produced in collaborative studies
- CBER product testing, research labs, clinical and product expert reviewers all participate
- Critical role and need for scientific and technical expertise
- Growing interest in outside standards setting organizations & activities, frequently global
- In FY 2006, 86 CBER staff participated in
  - 76 standards activities
  - with 28 organizations
  - In all portfolio areas: blood, vaccines, C&GT, IT

Benefits of Developing International Blood and Plasma Reference Standards

- Improves communication and input to enhance blood collection practices worldwide
- Improves consistency of reference standards and assay results which helps to ensure consistency for manufacturing and clinical trials for biological products
- Reduces time, frequency, and cost of standards development
- Allows comparison of results among different assays
- Supports harmonization of international regulations
- Facilitates development and availability of diagnostic and therapeutic products in a global market
FDA Collaborations

• World Health Organization
  – Expert Committee on Biological Standardization (ECBS)
    • Establishes international standards and reference materials; provides advice about blood
  – Collaborating Center for Biological Standardization
    • FDA laboratories work collaboratively on standards development for in vitro diagnostic devices including NAT, plasma proteins, blood grouping reagents, and reference materials for the study of TSEs

• National Institute of Biological Standards and Control (NIBSC)
  – UK institute; main source for preparation of potency reference materials and organizer of international collaborative studies on reference preparations. Presents data to ISTH for consideration

• Paul Ehrlich Institute (PEI)

• International Society on Thrombosis and Hemostasis (ISTH), Scientific and Standardization Subcommittee (SSC)
  – potency standards, clinical trial designs, patient registries, surveillance. Evaluates candidate reference standards for consideration by ECBS

• WHO-ISTH Liaison Group
  – new WHO guidelines; prioritization, development and establishment of WHO standards, review of WHO collaborative studies considered by SSC
FDA Collaborations

- International Conference on Harmonization
  - Guidance for Biotech products, e.g. format of data submission, stability testing, principles for assessing comparability of biotech products before and after manufacturing changes

- Council of Europe/ European Directorate for the Quality of Medicines, European Pharmacopoeia Commission & Health Care (COE/EDQM)
  - Group of Experts 6B FDA Observer input helps to harmonize plasma derivative analytical assay methods and working potency standards used in Europe and the US
  - TS-GPUQA Working Group Guide to the Preparation, Use and Quality Assurance of Blood Components

Areas of Standards Development in CBER Specific to Blood and Blood Products

- In vitro diagnostic (IVD) reference preparations
- Blood grouping reagents and blood group substances
- Software standards
- Coagulation proteins
- Other plasma proteins, e.g. albumin, immune globulins
## Current Projects

### IVD Related

<table>
<thead>
<tr>
<th>Organization</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO</td>
<td>HBsAg reference panel, Anti-HCV monospecific reference panel, Anti-HIV subtype panel, International Standard for HBV DNA NAT</td>
</tr>
<tr>
<td>WHO, NIBSC</td>
<td>TSE reference materials</td>
</tr>
<tr>
<td>NIBSC</td>
<td>WNV panel, HIV-2 RNA panel, HIV non B subtype panel</td>
</tr>
<tr>
<td>ISO</td>
<td>ISO/TC212/WG3 – labeling standards for IVDs</td>
</tr>
</tbody>
</table>

### Blood Product Labeling

<table>
<thead>
<tr>
<th>Organization</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICCBA</td>
<td>Uniform Labeling of Blood and Blood Components using ISBT 128</td>
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</table>

### Blood Grouping

<table>
<thead>
<tr>
<th>Organization</th>
<th>Description</th>
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<tbody>
<tr>
<td>WHO (NIBSC, CLB, IGBRL)</td>
<td>Blood Grouping Reagents, Anti-D, Anti-A, Anti-B, Anti-IgG. Standardize Anti-D for evaluation of QC and proficiency. Immunohematology enzyme standard</td>
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</tbody>
</table>

### Software

<table>
<thead>
<tr>
<th>Organization</th>
<th>Description</th>
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</thead>
</table>
## Current Projects

### Plasma Derivatives

<table>
<thead>
<tr>
<th>Organization</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>EDQM, NIBSC</td>
<td>Reference reagents to standardize the assays for anti-A and anti-B hemagglutinins and to control the levels in immunoglobulin products. Immune globulin standards to control potencies of anti-polio, anti-measles, anti-HBs and other surrogate markers for immune globulins. New Reference Hepatitis B Immune Globulin.</td>
</tr>
<tr>
<td>WHO NIBSC</td>
<td>Validation studies of plasma-derived Alpha-1-Proteinase Inhibitor for use with recombinant analogues.</td>
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## Coagulation Factor Standardization

<table>
<thead>
<tr>
<th>Coagulation Factor</th>
<th>Standard</th>
<th>Year</th>
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<tbody>
<tr>
<td>FIX</td>
<td>US/ Ph. Eur. /WHO 3rd</td>
<td>1996</td>
</tr>
<tr>
<td>FVIII</td>
<td>Mega 2/ Ph. Eur. 3</td>
<td>2001</td>
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<tr>
<td>vWF</td>
<td>WHO 1st</td>
<td>2001</td>
</tr>
<tr>
<td>Thrombin</td>
<td>Lot K/WHO 2nd</td>
<td>2003</td>
</tr>
<tr>
<td>FVIII</td>
<td>WHO 7th</td>
<td>2003</td>
</tr>
<tr>
<td>FIX</td>
<td>US/ Ph. Eur. /WHO 3rd</td>
<td>2007</td>
</tr>
</tbody>
</table>
Future Directions and Challenges
New Standards: New Blood Products, Tests, or Technologies

- Analogues with newly engineered properties, e.g. new forms of factor VIII or ATIII
  Does each new form require its own standard?
- New references for new technologies
  - Example: DNA microarray technology
- Potentially new analyte standards for immune globulin products
- Reference standards and assays for blood products may intersect with those for vaccines, bone marrow, tissues, and organs

Future Directions and Challenges
New Standards: Threats to the Blood Supply

- Assays for infectious diseases, e.g. malaria and Chagas disease, including emerging infectious diseases, e.g. vCJD, West Nile Virus, require new reference panels
- Reference standards for bioterrorism threats
  - Needed for potency determination of potential therapeutics, e.g. vaccinia immune globulin
  - Assess amount of toxin or infectious agent in blood, e.g., anthrax
Future Directions and Challenges

Old Standards With New Uses

• Evaluate newly recognized activity
  – von Willebrand factor binding of collagen

• Evaluate sites important for in vivo circulatory lifetime
  – tyrosine sulfation for Factor IX

• New assays
  – proteomics may use the present plasma reference standard

Challenges

• Limited resources. Need to prioritize and leverage

• Need to engage appropriate personnel in international standard setting activities

• Time to renew references difficult to estimate because of changes in demand
  – Decrease in number of fractionators, plasma collection facilities, amount and diversity of products in the US
  – Increase in fractionators, regulatory authorities in other countries, e.g. China?

• Should we standardize methodology in addition to reference preparations?
  – Standard assay methodology would be very useful for some proteins, e.g. Factor VIII
Summary

• Collaborations in the development of international standards and reference materials provide many benefits to participants, regulators, industry, and the public

• FDA interacts with many standard-setting organizations and is engaged in multiple collaborative studies

• New physical standards are needed to replace dwindling supplies of existing materials and to meet future challenges

• Common written standards for product manufacturing and control help to facilitate product development globally
Newcastle Disease Vaccine: Management of the project and the methodology used

Riks Maas, Catherine Milne, Ivo Claassen


Potency test for inactivated NDV vaccines

- History and scientific basis for the NDV assay
- Validation of the candidate potency test
- Results and Conclusions
- Critical success factors
Scientific basis for NDV antigen ELISA

- Currently described potency assays for inactivated ND-vaccines are vaccination/serology or vaccination/challenge experiments

- Antigen specific antibodies are a correlate of protection

- Inactivated ND vaccines are a homogenous group (single serotype; comparable adjuvant)

- Early research indicated a strong correlation between antigen content and antibody response in experimental vaccines

Principle of the quantitative NDV-HN ELISA

- Extract the antigen from the vaccine emulsion

- Dilution series of the NDV antigen

- Dilution series of the NDV reference

- Antigen content is calculated by parallel line analysis using Combistats (relative potency)
Validation (1): In house validation

- Specificity for NDV
- Recognition of different NDV vaccine strains
- Influence of antigens in multivalent vaccines
- Influence of method of inactivation (βPL/formalin)
- Validation of the extraction method
- Precision
- Accuracy
- Robustness
- Transferability
Available: 5,000 ampoules of each reagent (lyophilised), allowing analysis of 45,000 samples.

Preparation of large and well defined stocks of reagent

Stability studies on the lyophilised stocks

- Reactivity after storage at -20°C, 4°C, 20°C, or 37°C for 2 months of each of the lyophilised reagents: no measurable reduction in reactivity

- Monitoring of the consistency of the reactivity of the reference preparation in 90 tests performed over a period of one year
Transferability in co-operation with EDQM

- The relative potency of 5 inactivated ND-vaccines and one control vaccin was determined by 3 laboratories:
  - State Quality Control and Standardization (ID-Lelystad)
  - QC (vaccine production) (ID-Lelystad)
  - IVI (Switzerland)
- Each lab performed two tests: in each test both antigen extraction and HN-ELISA
- Protocols and reagents were distributed without additional information

Transfer study candidate NDV potency assay

E: w/o Gumboro vaccine
Dossier submission to group 15V

- Relevant scientific background
- In house validation data
- Preparation and stability data on reference and reagent stocks
- Transferability

- Go/no go

- 15V advice was positive but insisted that correlation between in vitro and in vivo tests should be confirmed in other laboratories

Prevalidation: BSP055-1 (Biological Standardisation programme)

- Feasibility study to evaluate the correlation between results of a candidate in vitro assay and established in vivo assays for potency determination of Newcastle disease vaccines (Pharmeurope Bio)
- Three OMCLs performed vaccination/challenge, vaccination /serology and NDV ELISA on a set of regular vaccines

- Results between labs were comparable for in vivo and in vitro assays
- One vaccine batch was found to be below release level for all assays in all OMCLs
Validation study: BSP055-2

- Validation study to evaluate
  (1) the reproducibility of a candidate in vitro potency
  assay of Newcastle disease vaccines and
  (2) to establish the suitability of a candidate biological
  reference preparation. (Pharmeurope Bio)
- Nine vaccines were tested by 14 laboratories (OMCLs
  and vaccine manufacturers)
- Outcome was statistically evaluated by EDQM (A.Daas)
- All laboratories were able to identify subpotent vaccines

BSP055 Results Validation s
Milestones in NDV-ELISA validation

- 1997-1999: Research on ND-vaccines and development of NDV-antigen quantification assay
- 2000: Large stocks of lyophilised test reagents and reference materials were made
- 2000: In house validation and transferability
- 2000 (December): A dossier regarding this assay was submitted to and reviewed by group 15V
- 2001: International transferability study
- 2001/2002: Pre-validation study in collaboration with EDQM (BSP055-1)
- 2003: Validation study in collaboration with EDQM and 14 European Laboratories (BSP055-2)
- 2004/2005: Adoption of the assay by group 15V
- Technology transfer at ECVAM training course for new member states (PEI, Langen 2004)
- 2006 Incorporation in monograph for inactivated ND-vaccines

Conclusions

- NDV antigen ELISA can be used for batch release testing for all inactivated NDV vaccines that are currently on the EU market
- NDV antigen ELISA was adopted by group 15V
- Reference obtained an official status
- References and reagents were transferred to EDQM
- The assay is included in the NDV monograph
**Kit with test reagents and BRP is available at EDQM**

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<thead>
<tr>
<th>Catalogue Number</th>
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<tbody>
<tr>
<td>Name</td>
<td>Newcastle Disease Vaccine BRP</td>
</tr>
<tr>
<td>Current batch number</td>
<td>1</td>
</tr>
<tr>
<td>Unit quantity</td>
<td>4 uc</td>
</tr>
<tr>
<td>Sale unit</td>
<td>1</td>
</tr>
<tr>
<td>Usage</td>
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</tr>
<tr>
<td>Used in monograph(s)</td>
<td>See leaflet</td>
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<tr>
<td>Additional information</td>
<td>The kit contains : 1 vial BRP1 NDV reference antigen, 1 vial BRP1 NDV control antigen, 1 vial BRP1 NDV coating antibody, 1 vial BRP1 NDV conjugated, detection antibody</td>
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<tr>
<td>MSDS</td>
<td><a href="#">click to download Material Safety Data Sheet</a></td>
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<tr>
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<td><a href="#">click to download the leaflet</a></td>
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<tr>
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<td>Dispatching conditions</td>
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<tr>
<td>Price</td>
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**Publications on ND-antigen quantification**


## Critical Success Factors in this project

- Homogenous group of vaccines
- Sound scientific research
- Extensive In house validation
- Large stocks of well defined reagents and reference used for all collaborative studies
- Collaboration with EDQM
- Good project management
- Help from other OMCLs and vaccine manufacturers
- Money
- Luck

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**End**