Medicines & Healthcare products Regulatory Agency

NIBSC
Confidence in Biological Medicines

Update from NIBSC Standardisation Activities

Elaine Gray

JCTLM 30 November -1 December 2015

NIBSC now in the MHRA Family

Executive agency

- Medicine and Healthcare products Agency is an executive agency of the UK Department of Health

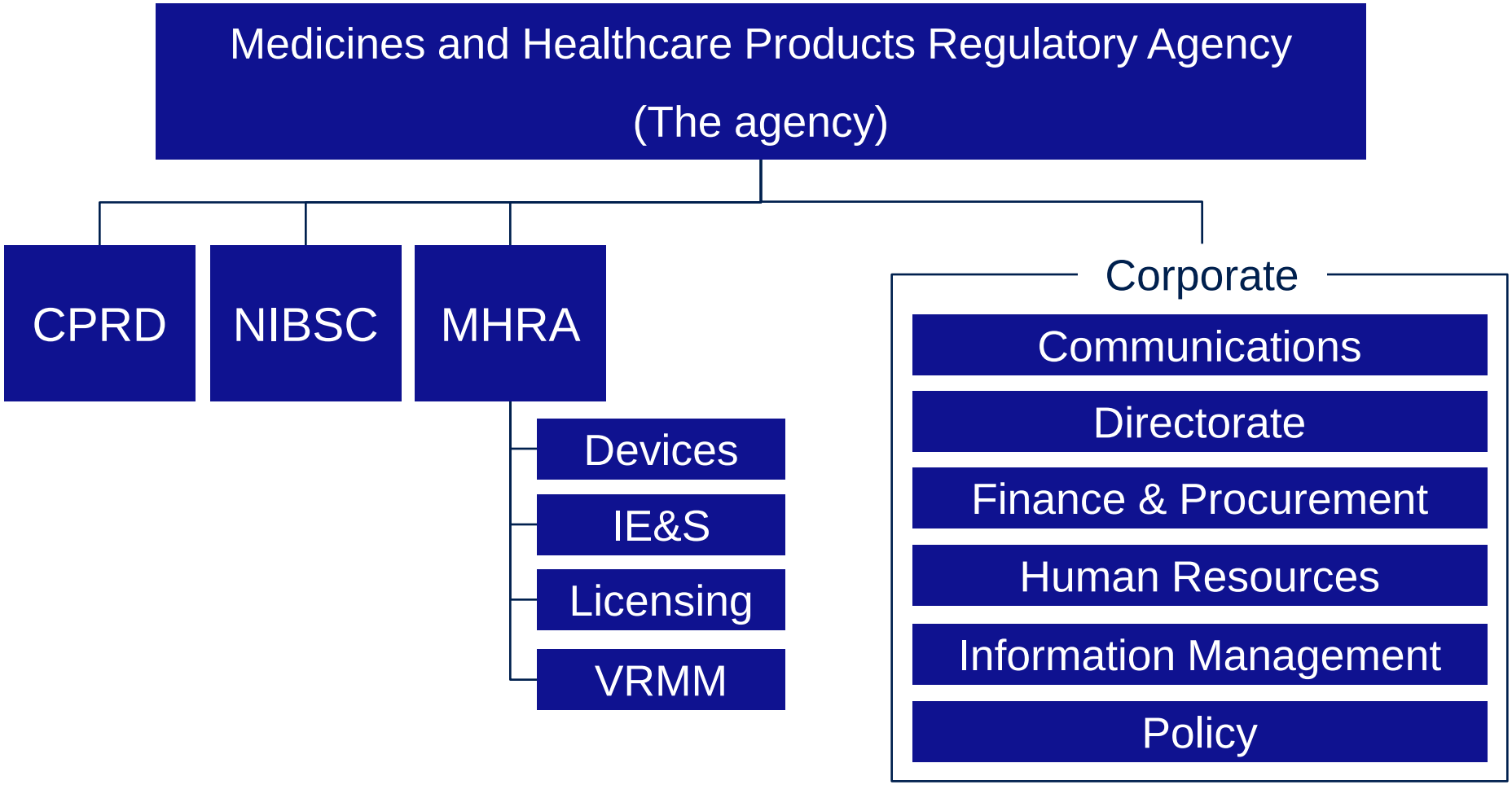
Size

- Around 1225 staff, with a total budget of approximately £140 million

Location

- Head office at 151 Buckingham Palace Road, London
- NIBSC based at South Mimms, Hertfordshire
- A regional office at York
- British Pharmacopoeia and MHRA laboratories based at LGC in Teddington

Organisational structure



NIBSC is the WHO International Laboratory for Biological Standards with a remit to produce WHO International Standards

ECBS (Expert Committee on Biological Standardization of WHO) reviews and adopts/endorses NIBSC proposals for International Standards.

- Completed projects for formal endorsement as WHO International standards, reference reagents, panels or other types of reference standard
- Proposed future projects to commenced, leading to eventual adoption as WHO standards

Catalogue	1980 126 WHO Standards	2010 303 WHO Standards
Analyte Range	Antisera, hormones Clotting factors, vaccines	These plus the biotechnology range: cytokines, growth factors, recombinant enzymes, DNA, RNA, TSE's, cells, tissues, Pathogens, Gene therapy
Supported Technology	In vivo bioassays In vitro bioassays Immunoassays	These plus: Physico-chemical methods Genetic testing NAT tests Genomics Proteomics Infectivity Cell responses (Proliferation, Survival chemotaxis etc) Flow cytometry

ECBS 2015

Standards established:

4 replacement IS's
13 new IS's

Future projects endorsed

5 replacement IS's
22 new IS's

17 in the area of diagnostic serology
5 in Biotherapeutics,
2 in Haemostasis
3 in Vaccine science

Vaccines and related substances

Preparation	Activity	Status
Antibodies, human, to enterovirus type 71	14/140 : 1,000 IU per ampoule 13/238 : 300 IU per ampoule	**1st WHO International Standard** **1st Reference Reagent**
Meningococcal Serogroup A Polysaccharide	0.828 ± 0.084 mg MenA PS per ampoule	**1st WHO International Standard**
Meningococcal serogroup X Polysaccharide	0.775 ± 0.090 mg MenX PS per ampoule	**1st WHO International Standard**
Diphtheria Toxoid	**1870 Lf per ampoule**	**3rd International Standard for use in the Flocculation Test**

Biotherapeutics

Preparation	Activity	Status
Tumour Necrosis Factor receptor Fc fusion protein (Etanercept)	10,000 IU per ampoule	**1st WHO International Standard for assay of anti-tumour necrosis factor biological function**
Antibodies against Erythropoietin	**No unitage assigned**	**1st WHO monoclonal antibody reference panel for standardization of tests for human antibodies to erythropoietin**

Blood Products and related substances

Preparation	Activity	Status
anti-A and anti-B in serum and plasma	DRT titres 128 for both anti-A and anti-B, IAT titres 256 for both anti-A and anti-B	**WHO Reference reagents for anti-A and anti-B for use in haemagglutination assays**
Blood Coagulation Factor IX, Concentrate	10.5 IU per ampoule	**5th International Standard**
Blood Coagulation Factor IX	**Assignment of a Factor IX antigen value of 0.9 IU/ampoule**	**4th WHO International Standard for FII, VII, IX, X, Plasma, 09/172**

In vitro diagnostic device reagents

Preparation	Activity	Status
JC polyomavirus DNA	7.0 $\log_{10}$ IU/ mL	**1st WHO International Standard for NAT**
BK polyomavirus DNA	7.2 $\log_{10}$ IU/ mL	**1st WHO International Standard for NAT**
Hepatitis C Virus RNA	5.0 $\log_{10}$ IU per mL	**5th WHO International Standard**
Antibodies, human, to Toxoplasma gondii	160 IU per ampoule	**4th WHO International Standard**
Vitamin B12 and folate	107 pmol/L per ampoule	**1st WHO International Standard**
Insulin C-peptide	8.64 µg per ampoule	**1st WHO International Standard**
Ebola antibodies	1 u/ml	**1st WHO International Reference Reagent**
Ebola RNA	Ebola NP-VP35-GP-LVV: 7.5 Log10 Units/ml Ebola VP40-L-LVV: 7.7 Log10 Units/ml	**1st WHO International Reference Panel for Ebola NAT**
Bacteria strains	**Extension by 10 bacteria strains**	**1st WHO Repository of Platelet Transfusion-Relevant Bacterial Reference Strains****

Innovative standardisation: Completed projects for 2015

- Etanercept standard
  - First MAb-derived product. First standardization of an immuno-modulatory blocking activity (TNF blocking)
- Anti EPO panel
  - first materials for standardization of assays for immunogenicity of therapeutic products
- Men A/Men X vaccine standard
  - First standardization using qNMR as a SI-traceable reference method
- EV71 International standard
  - Addressing a serious problem in China
  - Successful co-development with NIFDC
- Adventitious agent detection
  - First steps in standardizing deep sequencing as a regulatory technology

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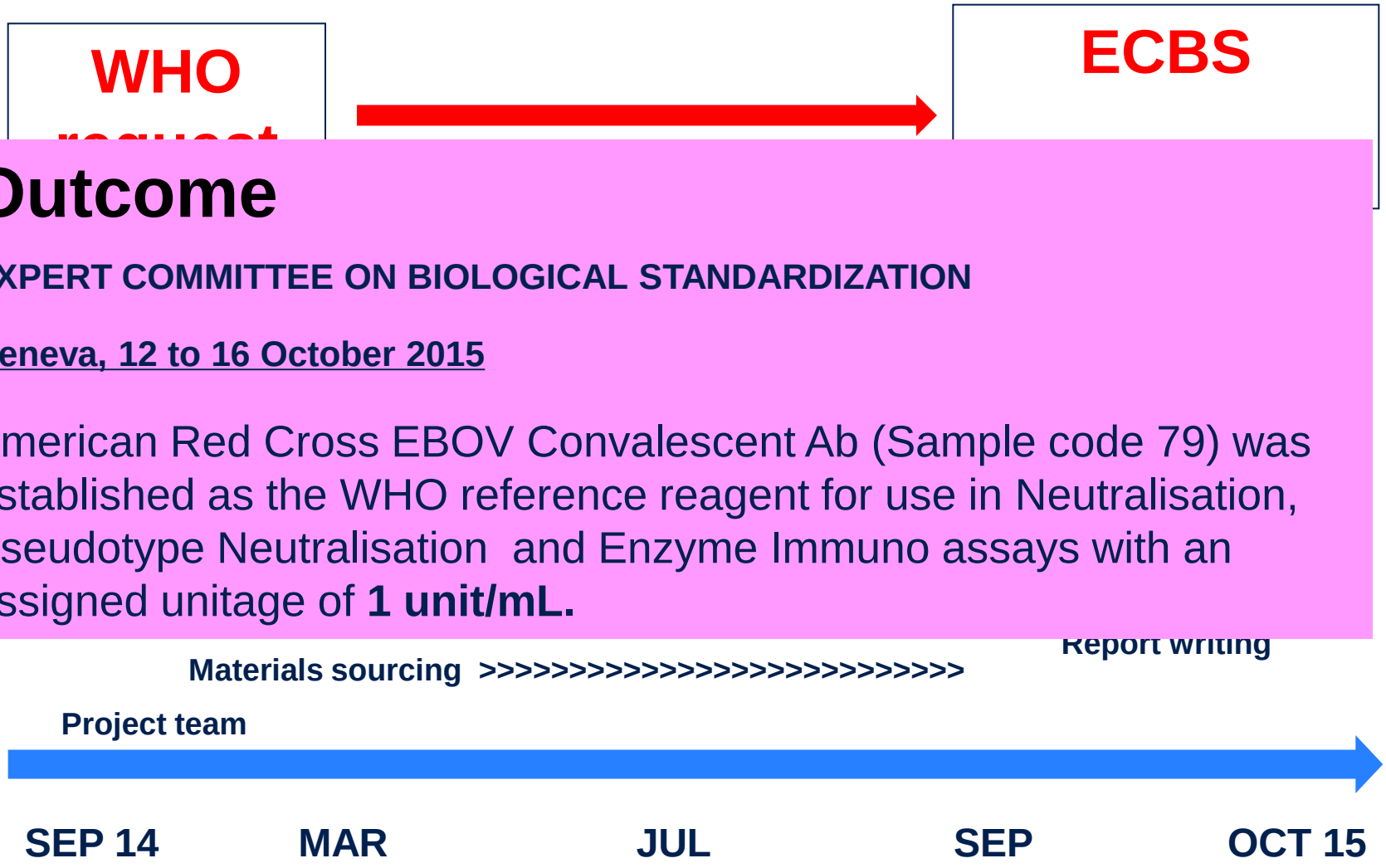
Reference materials for Ebola

(in collaboration with PHE for supply and handling of materials)

Phil Minor/Mark Page

Project timelines



Innovative standardisation: New proposals for 2015

- The proposed standard for TGN1412 supports new methods for pre-clinical immuno-toxicity testing
- Darbopoietin-First standardization of a 2nd generation sequence variant activity
- Pro-coagulant IgG panel- First establishment of standard run controls of known contaminated medicines
- The KRAS genetic test standard proposes the use of a new format (Gentegra) for PCR standards

World Health Organization

WHO/BS/2015.2255 Add
ENGLISH ONLY

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION
Geneva, 12 to 16 October 2015

Evaluation of candidate International Standards for Meningococcal Serogroups A and X polysaccharide

Caroline Vipond[1#], Carolyn Swann[2], Thomas Dougall[3], Peter Rigsby[3], Fang Gao[1], Nicola Beresford[1], Barbara Bolgiano[1] and the MenA/MenX IS Working Group*

Meningococcal Polysaccharides

Route of value assignment – qNMR by 4 laboratories

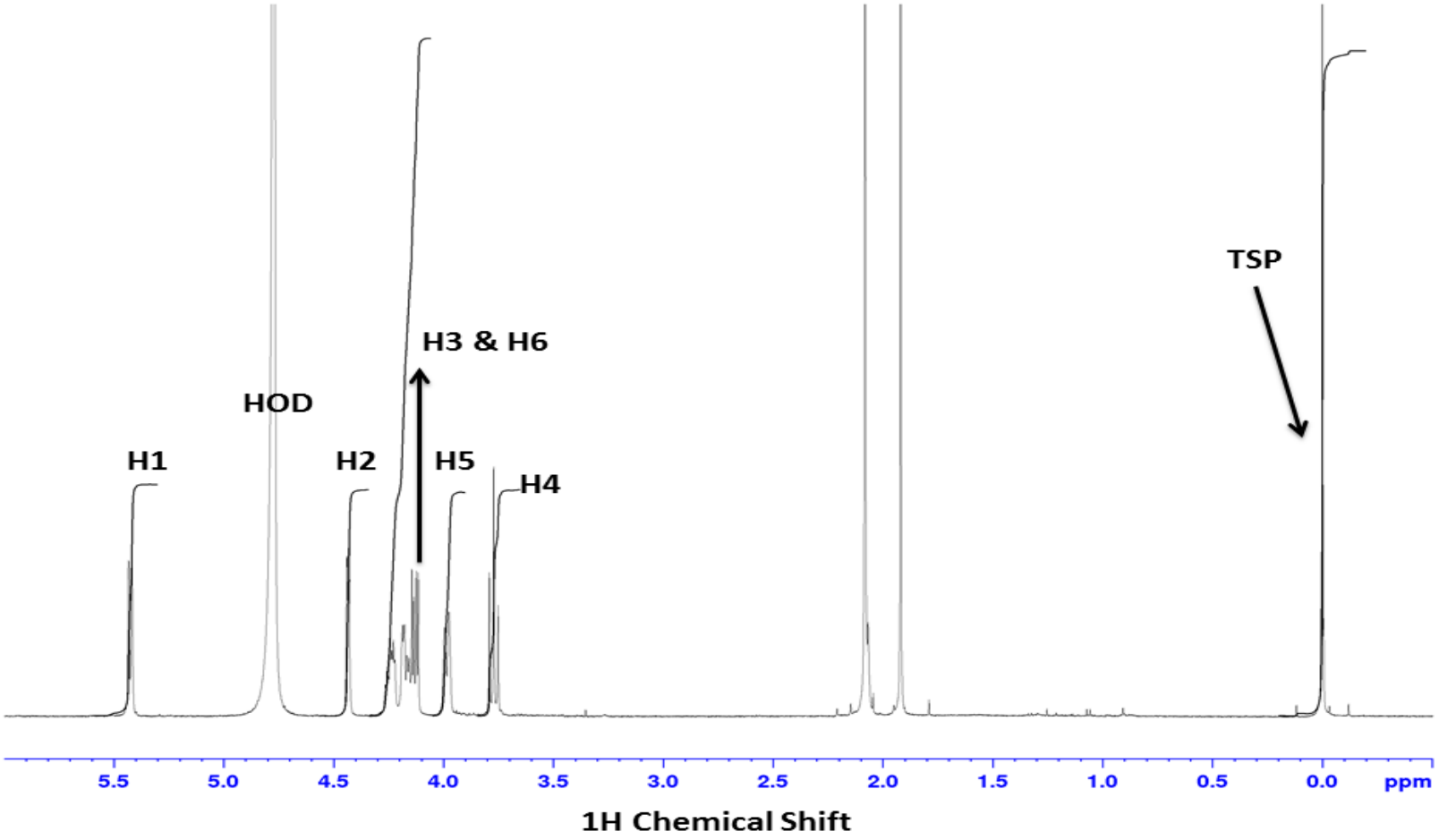
End users - vaccine manufacturers and control laboratories

Proposed reference materials will enable standardisation of MenA and MenX PS content of licensed and new vaccines

1. Reference standard to quantify MenA PS in potency assays using colorimetric, chromatography, spectroscopy (ICP) and ELISA methods.

2. Calibration of in-house reference standards

qNMR: Five resonances were chosen from the ^{1}H spectrum and integrated with specific integral regions to give an accurate calculation of the Men A content. A fix integral region for the TSP-d_4 at 0ppm was chosen



13/246: The 1st International Standard for the Meningococcal Serogroup A polysaccharide

Value assigned: 0.845 ± 0.043 mg MenA PS per ampoule (expanded uncertainty with coverage factor of k=2.45 taken to correspond to a 95% level of confidence), as determined by quantitative NMR

Method	Sample A (Men A)	
	Average mg/ampoule	CV (%)
NMR	0.845 (n=4)	3.2
Phosphorus	0.915 (n=11)	8.3
HPAEC-PAD	1.076 (n=3)	13.3

Caroline Vipond, Carolyn Swann, Tim Rudd

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Thank you for your attention

Our organisation

Medicines and Healthcare products Regulatory Agency

- Incorporates the 3 business centres and is supported by 6 corporate divisions: communications, directorate, finance and procurement, human resources, information management and policy

Medicines & Healthcare products Regulatory Agency

Our organisation

Medicines and Healthcare products Regulatory Agency (MHRA)

- Regulates medicines and medical devices, ensures that they work, and are acceptably safe; focuses on the core activities of product licensing, inspection and enforcement, and pharmacovigilance

Our organisation

Clinical Practice Research Datalink (CPRD)

- Gives access to an unparalleled resource for conducting observational research and improves the efficiency of interventional research, across all areas of health, medicines and devices

CPRD