Medicines & Healthcare products Regulatory Agency

Board Meeting

National Institute for Biological Standards and Control (NIBSC) HIGHLIGHTS FROM 2018 - 2019

16 September 2019

Issue/ Purpose: To provide the Board with a summary of NIBSC highlights against its activities for the year 2018/19
Summary: The document provides a summary of the full year's activities within NIBSC against its 2018/19 objectives and also highlights some areas that will be continued into 2019/20. The main focus of the report is the scientific work of the Institute rather than corporate functions, such as finance, governance and risk, workforce analysis which are covered elsewhere as part of general corporate reporting.
Resource implications: **N/A**
EU Referendum implications: Some implications to NIBSC activities mostly in the area of product control work – details provided in the report.
Timings: The report covers the reporting year from April 2018 to March 2019 inclusive.
Action required by Board: To note activities achieved.
Links: Agency Business Plan, NIBSC Business Plan.
Author(s): Marie Donatantonio, Head of NIBSC Corporate Affairs, on behalf of NIBSC Senior Management Team
Which of the five themes in the Corporate Plan 2013/2018 does the paper support? All **If relevant, which Business Plan strategic activity does it support?**
CET Sponsor: Dr Christian Schneider, NIBSC Director

NIBSC Highlights from 2018/19

1. Introduction

The majority of objectives set for 2018/19 were achieved despite an increase in pressure due to unexpected changes and uncertainty. There were inevitably a larger proportion than other years of objectives that will continue into the next year. A large number of objectives this year, as previously, were owned by Programme Boards responsible for the key strands of NIBSC work in the areas of Standards, Control and Research. Others were owned by Committees and separate NIBSC divisions in their areas of responsibility. The following report sets out the achievements of NIBSC and explains some of the issues and reasons for work to continue into the year 2019/20.

2. Standards

The Standards Programme Board (SPB) completed its planned 18/19 work programme to support the clinical safety and efficacy of biopharmaceuticals and standardisation of diagnostic assays through developing biological reference materials. 12 standards were adopted by World Health Organisation (WHO) Expert Committee for Biological Standardisation (ECBS) in October 2018, with 6 being for new WHO standards and 6 for replacements. New units were also assigned to an existing WHO International Standard (IS) and for a replacement seed bank for MRC-5 cells (Medical Research Council cell strain 5 cells commonly utilized in vaccine development) prepared and held by NIBSC.

Another objective to develop/grow the standards programme by initiating projects for the development of innovative standards for biological medicines and diagnostic assays was very successful resulting in 18 new standards being initiated and endorsed by SPB in Q4 resulting in a total this year of 28 new standards projects. These included projects for emerging viral pathogens to make IS urgently needed by WHO and CEPI (Coalition for Epidemic Preparedness Innovations), new standards for next generation sequencing of poliovirus, and a new standard to support analysis of mesenchymal stem cells used in development of advanced therapy products.

A new objective this year had been to grow our standards business, linking in with our targets for increasing income. An external company has assisted in developing an online customer survey to carry out market research to inform standards' strategy development, including standards' distribution. The work on this will continue into next year.

The volume of work in the standards area was higher in Q4 than other quarters with around 48,000 units shipped in Q4 bringing the total standards units shipped up to 175,000 compared to 139,000 in the previous year. A large amount of this was due to sales of influenza reagents which had exceptionally high sales in 2018/19. The number of products available in the NIBSC catalogue increased by 3% and the total number of units in the NIBSC inventory was 921,020 units, a slight reduction in total stock compared to Q3 as a result of discarding some items to intentionally rationalise stock holding.

One objective to review NIBSC's approach to use of distributors for biological standards so that a new policy could be developed and Terms and Conditions be revised where necessary was delayed this year as it is dependent on the outputs of Customer Insight work and this would be carried forward into 19/20.

Finally, under the oversight of the SPB, the objective to develop and deliver a webinar on the use of biological standards for clinical diagnostics was successfully achieved in Q3 and there is now work to consider developing more webinars and associated online content.

3. Biosimilars

Other work on standards across the Institute included promoting the role of biological standards in the biosimilars regulatory framework. Staff attended a large number of international meetings this year, including the "Biosimilars and Biobetters (2019)" conference in London and IRSS meeting in Strasbourg in Q4 to promote the use of International Standards for biosimilar monoclonal antibodies. A collaboration was initiated with A*Star in Singapore to investigate the utility of homogenous glycovariants for structure function studies and reference material production. The program of WHO International Standards for monoclonal antibodies and other biosimilars has progressed well with projects in place to establish WHO International Standards for Darbepoietin, Trastuzumab, Cetuximab and Adalimumab. This will enable manufacturers around the world to create high quality and reproducible biosimilars, providing significant access to cutting edge medicines to patients worldwide. Significant input was provided into the WHO Q&A document on biosimilars to be published on the WHO website and adopted at ECBS 2018 which will assist healthcare providers and patients around the world in their understanding of biosimilars. There was also good work with the cross agency working group looking at alternative approaches to pharmacopoeial monographs with a collaborative plan in development for a study to evaluate the utility of new approaches in this field.

4. Advanced Therapies

The standards objective in the area of Advanced Therapies set out to support and facilitate innovation in the development of safe and efficacious Advanced Therapies through Accession, Characterisation, Banking and distribution of European Union Tissue and Cells Directives EUTCD (Clinical) grade embryonic stem cell lines which can be used to create new medicines for use in clinical trials. This program has progressed well with 10 lines completed by year end, and a further tranche in progress, ahead of the timelines laid out in the Medical Research Council (MRC) program. Completion of this programme of work will enable the UK Stem Cell Bank to provide high quality and reliable starting material for regenerative medicines for UK patients and beyond, with the potential of the Bank becoming an important pillar of the UK Life Sciences infrastructure. Further work has included: initiating the genomics analysis and the cancer panel; populating the individual data portfolios for each line; and initiating the comms/marketing strategy for the Bank.

The UK Stem Cell Bank, which sits in the Division of Advanced Therapies, has been reviewing its options for future funding, given that the funding by the MRC will not be further prolonged. A strategy is being developed further for discussion with relevant bodies for its future set-up, and this will be discussed with CET in autumn 2019. A proposal was put forward in Q2 for a 1-3-year expansion plan for the Advanced Therapies Division, which is by far too small for what would be needed to deliver into the UK and global life science strategies, but due to budget constraints, this has not been possible to progress until the work on science prioritisation has been completed and core funding is available. This has also delayed work in the Cancer Gene Therapy programme of work.

5. Influenza

Vaccine candidate strains and potency reagents have been produced to support timely supply of influenza vaccines for both Northern and Southern Hemispheres. Freeze dried candidate vaccine viruses were made available early in the year with two replacement fills and twelve new viruses added to the catalogue, six being wild type strains and eight high

growth reassortants (HGR). NIBSC produced 2 new HGR viruses (both H3N2), 6 new freeze-dried candidate vaccine viruses, 2 antigen reagents and 2 antiserum reagents, as well as participating in a further 2 calibrations of reagents from other Essential Research Laboratories (ERLs). These reagents enable manufacturers to produce influenza vaccines for the winter season in time.

Principal Scientists from the influenza area have attended key international meetings, including participation in the 'Nagoya Protocol, Pathogens and Public Health' meeting in Egypt. NIBSC contributed to the WHO consultation on the composition of influenza vaccines for the northern hemisphere 2019, followed up by making seven new freeze-dried candidate vaccine viruses including several HGR strains to ensure a good coverage was available.

6. Polio

Significant work took place this year to support the polio eradication programme, ensuring the ability to prepare and distribute suitable reference materials post eradication, and provide vaccine control/vaccine development and environmental surveillance: With polio eradication being an achievable goal, it is essential that residual virus reservoirs can reliably be tested and monitored, and that next generation vaccines are available which will ensure eradication and which can never revert back to a pathogenic virus. Towards the end of Q4 a Phase 2 Clinical Trial of Novel Oral Poliomyelitis Type 2 Vaccine (nOPV2) was started in Panama.

WHO Polio Laboratory Proficiency Testing took place along with sequencing for poliovirus surveillance, helping us to monitor remaining occurrences and move closer to the global eradication target. Vaccines have been tested for the WHO prequalification process; 10 tests were for batch release, research and proficiency tests; 12 vaccines were tested by mutant analysis by PCR and restriction enzyme cleavage (MAPREC) for validation of vaccine seeds for Sabin-Inactivated Polio Virus (IPV) production; and 2 Quality Control tests of the mouse colony from a transgenic mouse supplier were conducted.

Alongside all this NIBSC has trained staff from three overseas establishments on neurovirulence test (TgmNVT) inoculation and clinical scoring and organised the annual training workshop for TgmNVT for WHO, European Directorate for the Quality of Medicines (EDQM), European Official Medicines Control Laboratories (OMCLs) and manufacturers.

Principal scientists attended an on-site visit for accreditation of 4 overseas Reference Polio Laboratories, participated in ECBS; and took part in an ad hoc Small Working Group on the development and evaluation of new polio diagnostic materials and tests.

7. Emerging Infections

Work to develop new reference materials for Emerging Infections such as those identified by WHO, CEPI and the UK's Vaccine Network is hard to predict but this year has included work on the 1st IS for Zika antibody which was submitted and agreed for establishment by ECBS in October 18. There was also participation in a Middle East respiratory syndrome (MERS)-related coronavirus standardisation meeting in Korea; sourcing of material for the 1st IS for Dengue antibody; and 10 new IS proposed for the serology and diagnostics of emerging pathogens. This year has seen closer work with University of Texas Medical Branch (UTMB), with NIBSC hosting a student for 2 months to produce standards for Lassa virus. NIBSC hosted and chaired the first Project Advisory Committee meeting for the Lassa virus project and secured CEPI funding in Q4 which will help fund a project manager to run the programme of work with CEPI task forces for Nipah Virus and MERS projects.

8. Medicine Control Testing

The Control Programme Board (CPB) has been heavily involved in planning for the impact of Brexit on the medicine control testing carried out by NIBSC, and consequently due to the delay in a Brexit outcome by the end of Q4, some of the work was carried forward to the new year. Despite the distraction of this, KPIs were achieved with almost all the 4466 batch release certificates issued within their target turnaround times, apart from two batches in the Haemostasis area exceeding the 15 days limit in Q2. There have been ongoing discussions with manufacturers to try and keep them up to date with changes and maintain a good relationship with them for whatever the future will hold. The CPB have been monitoring batch release levels which dropped by 46% for vaccines and blood products compared to 2017, whereas plasma pool testing was up by 40% in March 2019 compared to March 2018, due to the uncertainty for manufacturers but has seen a significant drop since then. Consequently, this has resulted in a fall in income.

The uncertainty, and finally lack of decision, for Brexit has meant that the objective to increase the strength and breadth of biologics testing capability has been difficult although work has taken place to ensure customers have been made aware of NIBSC testing capabilities. It was recognised that promoting the excellent turnaround times that NIBSC achieves, our technical expertise and quality of kits used would be important. There was an opportunity to highlight these at the Official Medicines Control Laboratory (OMCL) meeting held in London in May 2019.

Staff skills have been reviewed and mapped into a matrix of skills sets for across the batch-releasing Divisions so that there can be flexibility of resources to match any new requirements dependent on the Brexit outcome that will arise in the future. There has been regular input into the agency Brexit discussions ensuring that the monitoring of effects of Brexit on batch release is fed in quickly, given its central role in public confidence in biological medicines, and a business continuity exercise took place to assess the impact on control testing as well as on standards distribution. Pricing strategies for batch release in the event of a no deal or a Brexit deal were developed by the NIBSC Business Development Division.

9. Research

The Research Programme Board (RPB) has monitored the number of scientific publications authored by NIBSC staff this year, reporting that there was an increase to 90 in total compared to 75 in the previous year. This provides an indication of the strength of research within NIBSC.
Three PHD studentships have again been awarded this year following 10 applications that were evaluated by the RPB who were able to rank the applications based upon a number of criteria including Quality of Science, Institute Fit, Supervisory Team, and Training Benefit for the Student. These recommendations were submitted to the Director for endorsement. The three selected projects address scientific issues associated with Gut Microbiome, Japanese Encephalitis virus vaccine and the molecular mechanism of failure of anti-VEGF (Vascular endothelial growth factor) treatment. Recruitment is complete and the successful candidates start in September. These projects will be important contributions to the Institute's future standards pipeline. The RPB has this year reviewed its monitoring of scientific collaborations, maintaining a list of these (with outputs) of its scientists.

10. Refresh of the NIBSC Science Strategy

There has been a focus this year to refresh the NIBSC cross-divisional science strategy, ensuring it underpins NIBSC's mission and vision, making it fit for the scientific needs of the future, taking into account new areas of research and areas identified through horizon scanning, which is now embedded in the agency with the Horizon Scanning Lead role now

being made permanent following a successful trial interim period. The final draft of the science strategy was presented to the NIBSC Science Advisory Committee in Q4, and to CET and the Agency Board in the first half of 2019, and next steps will be to prioritise scientific activities within this, since NIBSC will not be able to deliver all topics at the same time, based on current resource limitations.

11. Antimicrobial Resistance

There are a group of projects for the development of novel vaccines, treatment and diagnostics that address the problems of antimicrobial resistance. A PhD project is in progress to compare biological and chemical conjugation for Group A Streptococcal vaccines which target both polysaccharide and protein antigens from Group A Streptococcus (GAS). In Q4, two novel protective antigens were identified and selected to include in a panel of GAS protein carriers for conjugation to the polysaccharide. Nuclear Magnetic Resonance (NMR) was used to confirm the identity of the GAS cell wall polysaccharide which was then quantified using a colourmetric assay. Preliminary chemical conjugation experiments are currently being undertaken, and work on biological conjugation is set to start Q1 2019-2020. This work will facilitate the development of vaccines against this major pathogen which is still a major burden for public health. For Group B Streptococcus (GBS), work has taken place with Pfizer to evaluate conjugates and measure anti-GBS antibodies in the development of GBS reagents. A technology transfer visit to Pfizer's lab is being arranged to optimise the conjugation method at NIBSC. Such collaborations with industry have been instrumental for NIBSC to contribute to public health, for the common good.

12. Microbiome

Good progress was made this year in the support for microbiome-based therapies. Next generation sequencing was completed for all commercially available microbiome standards and the gut microbiome standard created at NIBSC. Reference materials have also been prepared to support the standardisation of lung microbiome techniques for a multi-centre study led by PHE, analysing how the lung microbiome may influence treatment of chronic obstructive pulmonary disease (COPD). A paper outlining the production of the NIBSC Gut Microbiome DNA Reference reagent has been drafted and has been shared for feedback from authors and collaborators. Work is now taking place with PHE to deliver a manuscript outlining analytical method developments for the lung microbiome. NIBSC's work on the microbiome is targeted at standardising this important treatment modality, and to provide insight into how it works.

The microbiome work has attracted grant funding from Innovate UK allowing the recruitment of two posts, and the group has applied with Warwick University Medical School for a National Institute for Health Research/Medical Research Council (NIHR-MRC) Collaborative Grant. Further collaborative work has taken place with University of Liverpool Centre for Drug Safety Science to investigate checkpoint inhibitor therapy and the microbiome, and we have been successfully awarded a joint MRC-NIBSC funded studentship to expand this area in 2019/2020. NIBSC internal projects have included looking at how the microbiome may impact vaccine efficacy, and also developing a method for manipulating commensal bacteria in the gut. This is a critical step in the field of 'synthetic microbiome' and will assist in future drug delivery and vaccine delivery efforts. We will scope the IP potential for this in Q1 2019/2020.

13. Biological Therapeutics

Work is taking place to establish and evaluate novel paradigms and approaches for evaluating or predicting immunogenicity and immuno-toxicity of biological therapeutics in man. A reduction of unwanted immune responses in patients against a biological therapeutic will reduce side effects and reduce the risk of loss of efficacy. In Q4 work progressed well to

test and investigate the models for immunotoxicology and malaria and to optimise the experiments for engraftment and infection. The major achievement this quarter was the presentation of an initiative at the UK humanised mouse symposium to survey UK researchers conducting experiments using humanised mice to collate their experimental protocols and practices with a view to establish the criteria for harmonised reporting of data and potential standardisation activities in the future. This is a key step for the scientific community towards reproducibility of results for an important model system in medicines development and research.

14. Supporting the Agency

NIBSC worked closely with I,E&S staff in the Agency in support of combatting suspected illegal medicines, and provided analysis that contributed to the successful conviction of the perpetrator, who was sentenced for the manufacture, sale and supply of an unlicensed medicine, Globulin component Macrophage Activating Factor (GcMAF), a product made from human blood that was advertised as a ‘miracle cure’ for a range of conditions including cancer, HIV and autism. Work such as this relies on mass spectrometry equipment and the group have been developing a business case for replacement of the current ageing orbitrap mass spectrometer to be able to reliably continue supporting this work, but this will need to be weighed up against other priorities for NIBSC Capital funding allocation.

15. Financial Sustainability

The long-term financial sustainability of NIBSC has been a key consideration throughout this year, with uncertainty around Brexit and many changes having an impact on NIBSC future income and expenditure. Opportunities for increasing income are essential and work to increase our standards business was referred to earlier. Grant income is also key but has seen a drop this year from £4.2m in 2017/18 to £2.7m in 2018/19. The decrease in grant income for this financial year can be explained by twelve grant funded projects ending in 2018/19. This included a large grant from the US funder the Biomedical Advanced and Development Authority (BARDA). This was awarded to NIBSC at a value of $4,766,049 over 5 years - follow up funding for this grant is currently being discussed. In addition to this the large European Research Infrastructure for Poverty Related Diseases (EURIPReD) project ended in 2017/18. There were three applications in 2018/19 which aimed to provide follow up funding but were unfortunately unsuccessful despite receiving very positive feedback.

Twelve grant funded projects started in the 2018/19 financial year which included two large awards from Innovate UK (£1,999,153) and the CEPI ($1,145,580). However, as these grants began midway through the year the amount claimed on these has been minimal so have not, as of yet, substantially appeared in the income figures. The NIBSC Grants Office is therefore important to highlight relevant new calls for grants to NIBSC scientists, provide more comprehensive information internally on grant funders' requirements, and provide one-to-one support to assist individual scientists with applications, along with improved information available on processes to follow. It is also key to enhance NIBSC’s profile with stakeholders and customers. This work is also in conjunction with the NIBSC Communications Management Group (NCMG) which develops and monitors the communications plan to support the communications and promotion of NIBSC work.

Linked with financial sustainability is also the long-term suitability of the facilities at NIBSC and an Accommodation Strategy has been under development, with reports provided to CET in Q3 and Q4. Options have been proposed and consultation with staff are now helping to refine the possible design. This work has included a review of the long-term replacement plan for the standards production facility as well as several site security projects that are near to completion - there were some delays that resulted in completion targets being pushed into the new year.

Financial pressure continues to be a concern for NIBSC and the balance of Corporate and Transformation costs against money available to continue the science is an area of focus for 2019/20 to ensure the future sustainability of NIBSC.

16. Introduction of new systems and initiatives

New Information Technology solutions were introduced this year. The GS1/PEPPOL system for standards ordering was successfully implemented at the start of the year, and by Q4 continued well but hospitals have not yet been ready to implement the system and trials with them are therefore yet to take place. New General Data Protection Regulations (GDPR) regulations were introduced in May 2018 and there has been continuing work to ensure all is in place; the H&S strategy for the agency was developed and is under consultation with the Health & Safety Strategy Group before wider issue; and the staff engagement plan was launched following last year's staff survey, with an additional survey carried out at NIBSC to dig into some of the areas and understand better staff concerns.

17. Organisational items

NIBSC has managed several internal changes this year. Following the retirement of the Head of Biological Services, that division was combined with Technology, Development and Infrastructure to form a new division called Analytical and Biological Services (ABS) Division. A new Head of Infrastructure and Operations was appointed, and it was agreed that the agency wide H&S function would now permanently report into NIBSC Corporate Affairs. The Head of Viral Vaccines and Head of NIBSC Corporate Affairs posts have been under interim cover while review of the areas took place and will be advertised in the early part of 2019/20. There has been creation of new Divisions of Virology (was Viral Vaccines) and Infectious Disease Diagnostics (was BTPAAD) from a larger Virology Division.