Medicines & Healthcare products Regulatory Agency

Agenda

Title of meeting: MHRA Board meeting (public session)
Date: 23 April 2018
Time: 10.30 a.m. – 12.30 pm
Venue*:* MHRA, (Rooms 501-502) 151 Buckingham Palace Road, London, SW1W 9SZ

Item	Paper number	Lead
1. Apologies and Announcements	-	Chairman
2. Declarations of interest	-	Chairman
3. Minutes of the Board meeting of 15 December 2017	031- 2018	Chairman
4. Declarations of interest	–	Chairman
Discussion items		
5. Brexit – oral update Questions from the public	-	Mr Jonathan Mogford Director of Policy
6. Chief Executive's report Questions from the public	032-2018	Dr Ian Hudson, Chief Executive
7. Horizon scanning - oral update	-	Dr Schneider, NIBSC
8. NIBSC – highlights Questions from the public	034-2018	Dr Schneider, NIBSC
9. Building academic relationships - update Questions from the public	035-2018	Dr Schneider, NIBSC
10. Genomics and companion diagnostics Questions from the public	036-2018	Mr Stephen Lee, Senior Regulatory Policy Manager, Devices Division
11. Key changes introduced in the new EU Device Regulations Questions from the public	037-2018	Ms Gavia Taan, Senior Regulatory Policy Manager, Devices Division
Other business		
12. Any other business		
13. Date of next Board meeting in public session: 22 October 2018		

CPRD NIBSC MHRA

FINAL

MHRA Board (in public session) Part 1

MINUTES OF THE MEETING

15 December 2017

Present:

The Board

Professor Sir Michael Rawlins GBE Kt	Chairman of MHRA
Mr Martin Hindle	Deputy Chairman
Dr Ian Hudson	Chief Executive
Mr Jon Fundrey	Chief Operating Officer
Dr Barbara Bannister MBE	Non-Executive Director
Mr Matthew Campbell-Hill	Non-Executive Director
Professor Bruce Campbell	Non-Executive Director
Mr Stephen Lightfoot	Non-Executive Director
Professor Sir Alex Markham	Non-Executive Director
Ms Deborah Oakley	Non-Executive Director
Professor David Webb	Non-Executive Director

Others in attendance

MHRA executive and supporting officials

Mr Jonathan Mogford	Director of Policy
Ms Rachel Bosworth	Director of Communications
Mr John Wilkinson OBE	Director of Devices
Dr Samantha Atkinson	Director, Business Transformation
Ms Gavia Taan	Senior Regulatory Affairs Manager, Devices
Mrs Louise Loughlin	Head of Science Strategy
Mr Aidan McIvor	Head of Directorate
Ms Jude Thompson	Executive Assistant to the Chairman

Legal Services

Mr Paul Wright	Deputy Director, MHRA, Nutrition and EU Team, DH Legal Advisers, Government Legal Department.

Department of Health

Mrs Carly McGurry	Deputy Director, Medicines Regulation & Prescribing

Item 1: Introductions and Announcements

1.1 Apologies were received from Dame Valerie Beral, Non-Executive Director, and Janet Davies and Ian Thomas of the Welsh Assembly Government

1.2 The Chairman welcomed everyone to the meeting.

Item 2: Declarations of interest

2.1 Two declarations were made:

(i) *Professor Bruce Campbell:* Professor Campbell advised that he has been asked by NICE Scientific Advice to join them in providing advice to Roche Diagnostics about a test used in the management of atrial fibrillation. This is as part of a package, for which companies pay NICE Scientific

Advice. Professor Campbell went on to advise that he would receive a consultancy fee from NICE Scientific Advice for this work.

(ii) *Matthew Campbell-Hill*: Mr Campbell-Hill advised that he has become a member of a governance and strategy advisory board for the remote medical services provider 'Push Doctor', which provide medical appointments by video conference, e.g. Skype.

Item 3: Minutes of the public Board meeting of 20 October 2017

3.1 The minutes of the last public Board meeting, which the Board adopted on 20 November, were noted.

DISCUSSION ITEMS

Item 4: Brexit

4.1 Jonathan Mogford gave an update on Brexit-related work to analyse the best options and opportunities available for the safe and effective regulation of medicines and medical devices in the UK. To inform this work, the Agency has also been working closely with a range of stakeholders, such as the industry trade associations, and with European and international counterparts. Two scenarios are being considered: (a) one where the Agency would continue to work in close regulatory partnership with its EU counterparts and (b) a 'no deal' / 'stand alone' scenario. As part of his update, Mr Mogford also reported on the decision by the European Medicines Agency to relocate to Amsterdam, which was announced on 20 November 2017.

4.2 The Chairman thanked Mr Mogford for the update and invited comments from the Board. These centre on the following areas:

- *Medical devices / Notified Bodies* – The Board asked about the position of the UK's five Notified Bodies post-Brexit. Dr Hudson advised that it was too early to give a view as it would depend on the outcome of the UK's negotiations. Dr Hudson added that UK medical device companies and Notified Bodies are making contingency plans for a possible 'no deal' outcome.

4.3 The Chairman then invited questions from the staff and public observers.

- A member of the Alzheimer's Society expressed concern that post-Brexit could entail delay and additional expense to new treatments due to different regulatory frameworks being in place between the UK and the EU. Dr Hudson advised that the Government's preferred option is for the UK to continue to work closely with European partners and to avoid regulatory hurdles.
- A member of the public asked if medicines would be more expensive after Brexit. Dr Hudson advised that medicines pricing falls outside the Agency's remit, which rests with the Department of Health.

Item 5: Chief Executive Officer's report

5.1 Dr Hudson presented highlights from the Chief Executive Officer's (CEO) report. These centred on the following areas:

- *Reclassification* - An update was given on the reclassification of Viagra Connect (sildenafil 50 mg) in November 2017 as a non-prescription Pharmacy (P) Medicine in the UK.

- *Hormone Pregnancy Tests (HPT)* - An update was given on the report of the Expert Working Group on Hormone Pregnancy Tests, which the Commission on Human Medicines considered in November 2017.

- *Gentamicin* - An update was given on concerns about higher levels of histamine in some batches of gentamicin.

- *Breast implants* – An update was given on recent information that has been provided on Breast implant associated Anaplastic large cell lymphoma (ALCL) via the Agency's webpage on ALCL.

- *Working groups* – An update was given on a new strategic working group that has been set up to further cooperation between the Heads of Medicines Agencies (HMA) and the Competent Authorities for Medical Devices networks at a strategic level. The group met following the recent HMA meeting in Estonia.

5.2 The Chairman then invited questions from the Board, which centred on:

- *Internal Communications awards* – The Chairman noted that Communications Division had won two national awards from the Institute of Internal Communications for best storytelling initiative and as public sector internal communications team of the year. The Chairman congratulated the team concerned.

- *SCOPE* – The Board noted the success of the recent Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Adverse Drug Reaction (ADR) campaign. This involved 19 EU member states, Brazil, New Zealand, as well as various European organisations.

Questions from staff and public observers

5.3. The Chairman then invited questions from the staff and public observers, which centred on:

- Several members of the public shared their own experience of and reflections on their perceptions of the low awareness of the Yellow Card Scheme among healthcare professionals. Dr Hudson explained that the Agency has a programme of engagement with a range of healthcare bodies, including the Royal College of Nursing (RCN) and the Royal College of GPs. Dr Hudson advised that the need to incorporate awareness of the importance of Yellow Card reporting in the curricula for pharmacists and nursing staff is something that is being considered.

- Dr Hudson also mentioned how the Agency has successfully raised awareness of the dangers of buying healthcare products over the internet through television, e.g. Britain's longest-running drama series, Coronation Street.

Item 6: The next Corporate Plan

6.1 Jonathan Mogford presented an update on work to develop the next Corporate Plan. Mr Mogford explained that in view of the large degree of uncertainty that stems from Brexit 2017 was far from an ideal time to prepare a five-year strategic Corporate Plan. That said,

the work on preparing the Corporate Plan is very well advanced, and is closely aligned with that on Operational Transformation. Mr Mogford then outlined the strategic challenges for the Agency that were reflected in the draft Corporate Plan and which will be considered more fully at the Board / CET away day on 29 January.

6.2 The Chairman thanked Mr Mogford for his report and sought the Board's views. These centred on the following areas:

- *Affordability* – The Board advised that a point in time will come when decisions on resources will need to be made, namely what the Agency can afford to do, and what it should stop doing or do less of.

- *Review process* – The Board asked if there were plans to review the Corporate Plan during its life cycle. Mr Mogford advised that this was a feature of the current Corporate Plan and would be applied to the next Corporate Plan. Mr Mogford went on to explain the process for reviewing annual business plans and the mid-life review for the Corporate Plan.

6.3 The Chairman then invited questions from the staff and public observers. These centred on the following areas:

- *Food supplements* – A member of Cure Parkinson's Trust asked if as part of its work on the next Corporate Plan the Agency planned to regulate food supplements. Dr Hudson explained that the Agency does not regulate products that are not medicines or medical devices; food supplements fall within the remit of the Food Standards Agency (FSA). Dr Hudson went on to advise that where something falls on the borderline, the Agency liaises closely with the FSA.

Item 7: Operational Transformation

7.1 Dr Atkinson presented an update on the Operational Transformation (OT) Programme. This included work that has taken place since the Board's consideration of the draft Outline Business Case on 20 November, and further consideration by the Corporate Executive Team at its meeting on 5 December. Dr Atkinson went on to explain that work on OT would be closely aligned with the next Corporate Plan.

7.2 The Chairman thanked Dr Atkinson for her report and sought the Board's views. These centred on the following areas:

- *Opening comments* – The Board welcomed the update and commended Dr Atkinson and colleagues across the Agency for their work so far on Operational Transformation for work on external research and customer insight.

- *Costs* – The Board asked that further work be done on estimating the likely costs and benefits associated with the preferred option (Option 4). Dr Atkinson advised that the Board would receive a costed plan for Option 4, which would include elements from Options 3 and 5.

- *Market research* – The Board asked how the market research would be fed into the model. Dr Atkinson advised that the Agency will carry out further consultation to the test a range of ideas, e.g. IT systems and processes, to ensure that the Agency will make the right choices.

7.3 The Chairman then invited questions from the staff and public observers; none was offered.

7.4 In conclusion, the Board endorsed the overall direction of travel set out in the update.

Item 8: Implementation of EU devices legislation – update

8.1 Ms Gavia Taan presented an update on progress with implementing of new EU Regulations for medical devices (MDR) and *in vitro* diagnostic devices (IVDR), which entered into force on 25 May 2017. As part of her update, Ms Taan outlined progress made with UK and EU implementation, as well as highlighting the need for additional resources within the Agency to meet the range of additional obligations placed on competent authorities by the Regulations. Ms Taan went on to advise that the Agency will continue to engage with industry and work closely with other Member States to ensure that the MHRA and its stakeholders are prepared for the new Regulations.

8.2 The Chairman thanked Ms Taan for her report and sought the views of the Board, which centred on the following areas:

- *Opening remarks* – While noting the wide range of current and planned activity, the Board thought the report could benefit from specific examples on the key changes that the new Regulations will introduce. Ms Taan acknowledged this point and agreed that specific examples would be cited in future updates to the Board.

- *Resourcing aspects* – The Board noted the need for significant additional resources (at para 11) in the paper and asked if this was reflected in the Operational Transformation Programme and the next Corporate Plan? John Wilkinson advised that the resources aspect of the future work has been factored into the Agency's future planning for the next Corporate Plan.

Questions from staff and public observers

8.3 The Chairman invited questions from the staff and public observers; none was offered.

Item 9: Patient Safety and Vigilance Strategy – update

9.1 Louise Loughlin presented an update on the three-project work-streams which underpin the Patient Safety and Vigilance Strategy (PSVS): Project Team 1: incident reporting and signal detection, Project Team 2: risk benefit assessment, and Project Team 3 – safety messaging and risk communication. Among the highlights cited in Ms Loughlin's report were:

- Plans are progressing well with other key partners for the Improving the Impact of Safety Messages Health Summit on 18 January 2018.
- A report regarding the development of methodologies for device signal generation was considered at a workshop in early September 2017. A plan to prioritise and take forward the recommendations and next steps has been drafted and will be discussed at the next PSVS Steering Group meeting.
- The proposed study protocol in relation to use of CPRD data for devices vigilance had been submitted to the Independent Scientific Advisory Committee (ISAC) in December 2017 and the study should begin early in 2018.

- A strategy document for uses of CPRD in relation to devices vigilance is being further developed and will be brought to the next PSVS Steering Group.
- The joint assessment of paraffin-based topical products and fire risk is in progress and will be used as a case-study/opportunity to learn and build from.

9.2 The Chairman thanked Ms Loughlin for her report and sought the Board's views. These centred on the following areas:

- *Electronic reporting* – The Board asked what the Agency was doing to encourage greater uptake in hospital reporting of Adverse Drug Reaction (ADR) reports and linking the ability to report through existing GP and hospital systems. Ms Loughlin advised that this is being considered in conjunction with the Operational Transformation work.

- *Dear Doctor letters* - The Board suggested that these should be sent with a recognisable 'stamp/logo' or be clear that it is from GOV.UK

- *Health Summit* – The Board asked if there was an app and/or website for the Health Summit, and if there are plans to record the summit's discussions. Ms Loughlin advised that a dedicated weblink had been developed and that the summit would be recorded.

Questions from staff and public observers

9.3 The Chairman then invited questions from members of the public and staff. These centred on the following areas:

- A member of public recommended that flat screens in the waiting / public areas of GP surgeries and health centres should be used to promote the use of Yellow Card, and that Yellow Cards should be available for completion at the reception desks in local health centres and GP surgeries. The Chairman thanked the questioner and advised that the Agency would consider her suggestion.

- Another member of the public said that, from her experience, some GPs were reluctant to listen to patients' concerns about possible adverse reactions to medicines. Dr Hudson advised that the Agency is working with a range of healthcare stakeholders, including the Royal College of GPs and the Royal College of Nursing, on this matter. Dr Hudson went on to say that the Agency is very keen to make the reporting of ADRs via Yellow Card as straightforward as possible.

Item 10: Board / Executive interaction - update

10.1 Aidan McIvor presented an update on a range of work that has taken place during 2017 to enhance interaction between the executive and the Board; the update also covered opportunities for Board members to provide advice to the Agency and therein raise the profile of the Board among staff.

10.2 Mr Martin Hindle and Dr Ian Hudson referred to the Board/CET awayday on 29 January, where what improvements could be made to Board/Executive interaction would be considered. Dr Hudson concluded by saying that the Awayday discussion would be informed by a programme of interviews which would take place over the next three weeks with Mr James Humphreys of the Woodnewton Associates Limited.

10.3 The Chairman thanked Mr McIvor for the update and sought the Board's views, which centred on the following areas:

- *Opening remarks* - While welcoming the update, the Board noted that two areas of Board member sponsorship were missing from the update: Dr Bannister's advice to the Agency on vaccines work and Professor Webb's role on relations with the Devolved Administrations. Mr McIvor said he would update the progress report accordingly.

- *Mentoring* – Professor Webb advised that he would like to participate in the mentoring programme for staff. Mr McIvor said he would inform HR.

Questions from staff and public observers

10.4 The Chairman invited questions from members of the public and staff; none was offered.

Item 11: Timetable for the draft Annual Report – to note

11.1 Rachel Bosworth presented the draft timetable for the Annual Report 2017-2018, which the Board noted.

Item 12 Board and Corporate Executive Team awayday – draft programme

12.1 Dr Hudson presented the draft programme for the next Board / Corporate Executive Team awayday, which would be held at the Academy of Medical Sciences on 29 January 2018. The Board endorsed the draft programme, but asked that the item on Artificial Intelligence could be taken in the morning (time to be confirmed) so as to allow one of the Board members to attend a Ministerial meeting. The other items for the awayday: Brexit, the Corporate Plan / Operational Transformation, and Board / Executive interaction would remain unchanged.

Action: Aidan McIvor to circulate a final version of the awayday programme in January.

Item 13: Any Other Business (AOB):

13.1 The Chairman and the Board thanked members of the public and staff for attending the meeting.

13.2 The Chairman then asked if there were any items of AOB; none was tabled.

Date of next public meeting: 23 April 2018

Medicines and Healthcare products Regulatory Agency

23 April 2018

CHIEF EXECUTIVE'S REPORT FOR THE MONTH of MARCH 2018

1. HEADLINES for MARCH 2018

The Department of Health's Regulatory Science Research Unit (RSRU) - NIBSC received the news at the end of March that it had been successful in its bid for a £1m per annum grant for the next five years from the RSRU. NIBSC had previously been awarded this funding of £1 million pa for the previous five years which was secured following a peer reviewed application to DH-Policy Research Programme. The principles of this grant are to provide funding that allow laboratory heads and technical experts time for "regulatory research" that will underpin the Institute's ability to prepare appropriate Standards or establish Control tests, particularly for new products. In particular, it is anticipated that this RSRU funding helps to leverage additional external funding.
The new application for a further £5 million over the next five years was developed in September 2017, and following its submission and external review, confirmation of the contract was received at the end of March.
The application has been made under six areas as follows:

1) Assuring Access to Monoclonal Antibodies as Biological Medicines
2) The threat of Global Infectious Diseases
3) Regenerative and Cell Based therapies - Accelerating access to treatment for Neurodegenerative Disease
4) Using Biologics to overcome Anti-Microbial Resistance
5) Stratified Medicine and Genomics
6) Humanised Mouse Models for evaluating Biologics

2. PRODUCT RELATED ISSUES

Medicines issues

Valproate and risk of neurodevelopmental disorders - The EU wide review completed at the meeting of the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) in March and the EMA published a statement on 23 March. VRMM continued to work with Comms and engage with stakeholders on the plans for implementation and communication of the new contraindications and pregnancy prevention plan. The Minister chaired a meeting with key stakeholders on 14 March. We held a meeting of the Valproate Stakeholder Network (VSN) on 21 March which was attended by 23 different stakeholder organisations, to provide an update on the EU referral, plus our plans for implementation and communication. A meeting of the Commission on Human Medicines Expert Working Group on valproate was held on 29 March to inform UK communication plans. We are in discussion with the Irish regulator and plan to coordinate our communications with them.

Implementation of the recommendations of the Expert Working Group on hormone pregnancy tests – The first meeting of the Cross-Agency Group on the Safety of Medicines in Pregnancy was held on 21 March. The group discussed and agreed the terms of reference and membership and allocated representatives to lead on taking forward each of the recommendations of the Expert Working Group on Hormone Pregnancy Tests. The Cross-Agency Group will meet monthly and will report to the Cross-Sector Steering Group which will be chaired by the Minister.

New licences – new licences were approved in the therapeutic areas of oncology and HIV. The licences are for:
Rubraca (rucaparib) an inhibitor of poly(ADP-ribose) polymerase (PARP) enzymes that blocks the repair of damaged DNA in cancer cells, and, as a result, causes the cancer cells to die for the treatment of relapsed or progressive ovarian cancer. Rubraca was designated as an orphan medicine during its development.
Juluca (dolutegravir / rilpivirine) inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for HIV replication. Rilpivirine activity is mediated by non-competitive inhibition of HIV-1 reverse transcriptase. received a positive opinion for the treatment of human immunodeficiency virus (HIV) infection.

Raxone – Teleconferences have been held with Action Duchenne, DMD Pathfinders, Duchenne UK and Muscular Dystrophy UK to discuss and agree their participation in a patient-focused meeting to consider Raxone and EAMS in light of the recent negative EMA opinion on this product. The patient-focused meeting itself was held on 23 March and was well-attended by three patients and their carers, plus four mothers who have children living with Duchenne Muscular Dystrophy. It provided the CHM members and Licensing colleagues with insight to the likely impact on patients should Raxone no longer be available through EAMS.

Lynparza – on 12th March, AstraZeneca issued a Class 3 Drug Alert to pharmacy/wholesaler level for Lynparza 50mg Capsules. This was due to the level of one of the polymorphic forms of the drug substance (Form L) exceeding the registered specification in one batch of the product. Seven batches were recalled in total as a precautionary measure. This was a Class 3 Drug Alert because although the level of polymorphic form L in the affected batch was above the specification, it was well below the threshold considered to have a clinical impact so the risk to patient safety was minimal. Sufficient stock from alternative batches was available to avoid a shortage.

Mesna – a 2nd Company Led Drug Alert for Mesna 100mg/ml solution for injection/infusion was issued by Claris Lifesciences UK Limited on 28th March. This was due to stability issues which were initially thought to be batch related but on further investigation were found to be formulation related. Manufacture of the product has ceased whilst the product is reformulated. There is no risk of a shortage because Claris had a very small market share and there are a number of alternative suppliers. The product is used in hospitals hence the target recipients were hospital pharmacists.

Devices issues

Medical Device Alerts – There were 2 alerts in March 2018

Number	Title
MDA/2018/009	Bag valve mask (BVM) manual resuscitation system – risk of damage to lungs by delivery of excessive pressure.
MDA/2018/010	All T34 ambulatory syringe pumps – risk of unintended pump shutdown and delay to treatment.

3. REGULATION POLICY AND OTHER SCIENTIFIC TOPICS

European/International TOPICS

Legislation - A statutory instrument with amendments to the **Human Medicines Regulations (HMR) 2012,** is due to come into force on 1 April 2018 (principally independent prescribing by paramedics and distribution of stable iodine in a nuclear emergency). Pressures on parliamentary time mean that these are on the only planned amendments to the HMR in 2018.

International highlights - In March Ian Hudson and Jonathan Mogford visited Health Canada and the FDA to discuss future working. Work to review the MoU with India continues and discussions with FCO colleagues on the implementation plan of the China MoU have started.

UK TOPICS

Corporate and Business Plans – these have now been completed and are due for publication in the near future.

Preparation and Dispensing Errors - On 21 March, the Pharmacy (Preparation and Dispensing Errors – Registered Pharmacies) Order 2018 (Commencement) Order of Council 2018, was signed by the Privy Council.
This commences the Pharmacy (Preparation and Dispensing Errors – Registered Pharmacies) Order 2018 and therefore the legal defences for inadvertent preparation and dispensing errors under section 63 and section 64 of the Medicines Act 1968, made by registered pharmacy professionals working at or from registered pharmacies. The new defences will be available to these professionals from 16 April 2018 onwards, and the Commencement Order is available on the legislation.gov website.
DHSC is in the process of producing a comprehensive FAQ document for distribution to stakeholders ahead of the defences coming into force on 16 April which will provide further details on how the defences can be applied.

Patient Safety and Vigilance Strategy (PSVS) – Central Alerting System (CAS) – we have now completed user acceptance testing for the new Central Alerting System and we are on track to deliver the new platform in April. We have agreed with the business an outage of two working days (Thurs 05 and Friday 06 April), though we will have an emergency process should an alert be required on these dates. We have issued an alert to all our subscribers notifying them of the upcoming changes, and the go live date of 9 April.

Competent Authorities for Medical Devices (CAMD) - Agency colleagues attended the Joint Action on Market Surveillance of Medical Devices (JAMS) Advisory Board to respond to a final update to the four promotional leaflets that outlined the impact for notified bodies, manufacturers, patients and the public, and healthcare professionals. Minor amends were agreed and the leaflets are now nearing completion. The updated website is close to being ready to launch. Current focus is on transitioning users to the new site.

Innovation office – The Innovation Office continues to act as a point of contact for free, consolidated advice. Of the 15 enquiries received in March eight have required collaboration between Licensing Division and other divisions, such as IE&S and Devices and/or other agencies, such as the Human Tissue Authority.
To mark the fifth anniversary of the Innovation office, a meeting was held on 27 March 2018 with the major UK funders of academic research (the National Institute for Health Research, Medical Research Council, Wellcome Trust, Innovate UK, Experimental Cancer Medicine

Centres, UK Stem Cell Foundation and individual medical research charities including British Heart Foundation and Duchenne UK). The aim of the meeting was to raise awareness of the support offered by the Innovation Office, to initiate a mutually beneficial dialogue and to gain feedback from funders on how future efforts should be focused to bring together the research community and regulatory authorities.
The Clinical Trial Unit and Horizon Scanning Lead took an active role in this meeting and are likely to be involved with further meetings with funders and representatives from academia. This was a highly successful meeting consolidating contacts and working relationships with funders, who were keen to actively promote the Innovation Office to the research community, strengthening collaborations with academia. The Innovation Office is looking to work with innovators to provide guidance and identify gaps in regulations and increase outreach events to engage with researchers.
Since the launch of the Innovation Office on 11 March 2013 there have been 570 relevant queries.

Accelerated Access Review (AAR) – Mike Rawlins attended the first meeting of the Accelerated Access Collaborative chaired by Sir Andrew Witty. The focus remains on NHS uptake and adoption, but the licensing process, early access and horizon scanning are also elements of this work. The new pathway will be launched in April 2018 with work beginning now to implement some recommendations and develop others. MHRA also attended a meeting of the steering group that will provide more practical input into the process for designating products. MHRA provided an output of our recent horizon scanning activity and will continue to provide input on the types of advice we can offer developers of medicines and medical devices, as well as experience from designing the EMA PRIME and UK EAMS schemes.

4. MINISTERIAL AND PARLIAMENTARY PRIORITIES

FOI Response Time Compliance: the target for 2017/18 is to ensure that 100% of requests receive responses within statutory limits (20 working days; or exceptionally within 40 days where an extension is required to complete a complex public interest test).

February 2018

as at 05/04/2018	**FOI Requests Received 2017/2018**					
	Q1	**Q2**	**Q3**	**Jan**	**Feb**	**Total**
Received	135	156	123	41	51	**506**
Replies sent on time	134	156	123	40	51	**527**
Replies not yet due	0	0	0	0	0	**0**
Breaches	1	0	0	1	0	**2**
Compliance %	99.3%	100.0%	100.0%	97.6%	100.0%	**99.6%**

5. COMMUNICATION

The main agency-related issues covered in the media in March are as follows:

Press Activities

Comms Division worked with the Investigations Editor of the Evening Standard clarifying statements included in their ‘Opioids Timebomb’ coverage, including advising of an MHRA review into adding stronger warnings to packaging and leaflets.

Slimming pills – Following the Guardian interviewing Danny Lee-Frost last month on our work in enforcement and raising awareness of the dangers of buying slimming pills online, we expect the Guardian's story on slimming pills to be published early April. We also provided statistics and key information to support the story.
Debrief (an online news site with a similar readership to Buzzfeed and an audience profile of ABC1 - further educated, higher earning females in their early 20s), published a story on the dangers of buying slimming pills online which we contributed to with interviews, data and background information.
We have planned an Easter themed animation to be delivered from Sunday 1 April, supported by social media marketing, targeting people who want to get slimmer after Easter treats.
We have prepared an article for *Muscle and Fitness* Magazine, to be published the first week in April, focussing on the risks of dodgy diet pills in sports that require weight loss for competitions. They have a very targeted audience in the fitness and weight lifting industry, with a circulation of 49,000, and 1,121,509 monthly unique website users.

Two devices specialists briefed a BBC journalist for an episode of *Trust Me, I'm A Doctor.* We are also arranged a date for Lynda Scammell of IE&S to be interviewed on the programme.

Other Communications Activities

Medicines Maker power list – We have been liaising with Medicine Maker on their annual Power List. Dan O'Connor has been nominated this year and we worked with him on his response. This is due to be published in the coming weeks.

Contact Lenses – text promoting Yellow Card provided by the MHRA has been published on the General Optical Council's (GOC) website. We have also supported the GOC's 'Love your Lenses' campaign on social media.

Substandard and Falsified (SF) Global Communications programme – Donor funded activity – Following agreement with the Department for International Development (DfID) to support a two-fiscal year funding of campaign activity in five countries Nigeria, Uganda, Ghana, Sierra Leone and Myanmar, we have now commenced developed of the programme. We have issued a RFP (Request for Proposals) for communications insight research in conjunction with WHO procurement teams. We have received a number of quality proposals, agreed a winning bid and are in process of appointing the successful research agency.
Insight gathering will then run in each of the countries to enable us to benchmark current attitudes and behaviours and subsequently be able to measure the impact of the campaign work.

SF Communications Advice Development – We prepared an update report to be presented at the April meeting of the WHO steering group meeting immediately after the Easter break in Geneva.
We are also preparing to run a full one-day communications workshop for the Africa region of WHO member states in Lagos, Nigeria during the week of 16 April.
We continue to develop our multi-lingual "IDEAS" communications framework, which will be further refined in advance of its use live testing at the Lagos SF event. The output from the workshop will be blended with the existing model and then further tested and developed with the programme CWG, prior to soft launch at the November MSM meeting

We continue to collect and curate examples of communications work alongside exploring optimum methods of publishing on the two existing WHO platforms, MedNet and Global Focal Network.

Fake Medicines and Devices Campaign CET agreed that pregnancy, STI and HIV self-test kits as the priority medical products for phase 2; we will also take advantage of media opportunities for erectile dysfunction (ED) products (including a possible documentary with Dr Oscar)

- Condoms could form phase 3 along with ED - if the manufacturer infrastructure is strong enough. To be kept under review.
- CET asked us to review our budget for subsequent activity phases, including the already approved phase 2 budget
- CET asked us to explore whether this activity could be jointly funded with other stakeholders

Customer services - We received customer services enquiries on a "natural" Chinese herbal medicine, Yiganerjing Cream which contained an undisclosed steroid and two antifungal ingredients. We saw an increase in requests for breast implant information held by the Agency following NHS Digital announcement, whilst, enquiries on Tobacco Products Directives (TPD) and Cannabidiol (CBD) are still high.

Agency events programme – Income generated from events in 2017/18 is forecast to be c.£1.35m, this represents an additional £150k income compared to 2016/17. This has been achieved with only c.£40k additional expenditure. We have increased access to some of our most popular income generating events including the GxP series by IE&S, and the Variations/Abridged Applications series by Licensing. In addition, we have started offering webinars, with VRMM delivering two Hot Topics in Advertising webinars this year. We have grown the events programme from an annual income of around £600K in the last five years.

For 18/19 we are developing an events programme which is closely aligned with business objectives, represents value for money, and which continues to meet the modern day expectations of delegates. As a result, the programme will feature: more webinars; more NIBSC events will be income generating to cover costs; a series of exhibitions and speaking engagements by Devices will deliver messages on Yellow Card to audiences who have a low reporting rate. Combined with the ongoing effort from this year, the 2018/19 programme is forecast to generate around £1.5m.

Variations conference - The Variations conference took place on 19 March at BPR. 46 delegates attended the event which generated £11,978.00

6. ORGANISATIONAL TOPICS

MHRA Relocation Move – The move to 10 South Colonnade (10SC) Canary Wharf continues to progress well as we get closer to our physical move in June 2018.
At the end of March, the MHRA Project team physically walked around the fourth floor of 10SC which will be occupied by Ofgem. As predicted, the accommodation design, look and feel was impressive, Ofgem started their occupation over the Easter break and will complete in early April.
Ofgem is of a comparable size to the MHRA and there are several shared accommodation comparisons across the respective floors. For example, the on-top of storage green planting, the extra number of height adjustable desking, the useful nearby project wide light spaces, and the smart welcoming kitchen areas with fully fitted microwaves and tall integrated fridges. There are also on-floor internal integrated coat cupboards as opposed

to the odd shaped coat stands in BPR. This fit-out, look and feel will be the same for the MHRA.
The on-floor building work fit-out to our floors is progressing on time and the IT Telephony piece, as we understand it, will be a temporary solution until we are fully on site; and then will look to make the Telephony more permanent.

Regular meetings on Health & Safety, Security and Business Continuity/Incident Management are now taking place at 10SC before the fortnightly Building User Group (BUG) Meetings. This is great news where all tenant representatives are working more collaboratively together before we all move in; and this gives us better knowledge of our neighbours roles and responsibilities working with the Government HUB team (GHT) should it be needed in any future emergency.

At present, the Agency is looking to engage our own Move Manager so as to help us coordinate and pull the huge physical move piece all together, so all crates and all storage will go to the right places on time. This will take place in April.

All Staff meetings 21-23 March 2018 – Five meeting sessions were held over three consecutive days at BPR and South Mimms. In addition to the Chief Executive update, there were presentations on Brexit, the Corporate Plan and the relocation to Canary Wharf. We used Slido to encourage questions from the audience which worked well.

Changes in the Corporate Executive Team – Gerald Heddell retired as Director of IE&S after fourteen years in post. Dr Sam Atkinson (formerly Deputy Director of IE&S before being seconded as Business Transformation Director leading on the Operational Transformation programme) was appointed as Director in March. John Quinn, director of IMD, will take over leadership of the Operational Transformation programme and will work with Sam to arrange an orderly handover.

Information Management Division Update

- Digital Workplace programme has completed rollout of new laptops at NIBSC. The whole Agency now has new laptops.
- IT delivery as part of the Accommodation delivery plan is progressing.
- IMD-Digital has delivered estimates and plans to inform the OT business case.
- Information Processing Unit's robots went live and the work of the Robotic Processing Automation team was showcased in staff drop-in sessions to "*meet the robots*".

Professor Jeremy Farrar visit to NIBSC – Professor Farrar Chief Executive Officer of Wellcome Trust, one of world's largest and wealthiest research charities, visited NIBSC on 4 April. He requested a visit to see how we interact and collaborate globally for public health impact and to see how Wellcome Trust can support our work and connect us with key groups. He said he was very interested to visit NIBSC for the first time in his career, having sat on committees with various NIBSC staff over the years. He described NIBSC as one of very few truly globally important institutions but is under-appreciated, despite unique contribution to global health.
The meeting heard an introduction from Professor Farrar about his career before and as part of Wellcome Trust, followed by high level outlines of the work of the NIBSC science presented by the Heads of the Scientific Divisions. Around 30 other scientific staff members also attended to hear the topics of discussion which highlighted some key areas that could be taken forward.

NIBSC Second PhD Mini Symposium – On 22 March NIBSC hosted its second PhD Mini Symposium aimed to provide its PhD students with the opportunity to share their work and promote scientific discussion amongst staff. Organised by the Research Excellence Group

(REG), the event featured six oral presentations from PhD students and a poster session, covering the wide range of research topics investigated at NIBSC. A selected panel of NIBSC scientific staff were tasked with judging the oral and poster presentations, and prizes were presented for the best talks and posters on the day. A member of staff from Virology received the prize for the best oral presentation for his talk titled: "Alternative cell-culture strategies for H3N2 influenza – avoiding selection of phenotypic variants which confound the vaccine strain selection process". Three staff members received prizes for their poster presentations. The next NIBSC PhD Mini Symposium is planned for a similar time next year, as these will now be held on an annual basis.

The Influenza Resource Centre (IRC) at NIBSC – the NIBSC Principle Investigator has been awarded a one-year grant by the Bill and Melinda Gates Foundation to support work towards an International Standard for antibody to the influenza virus haemagglutinin stem domain for Group 1 influenza viruses. This grant includes a collaboration (as subcontractor) with the Icahn School of Medicine at Mount Sinai (New York, USA; PI Florian Krammer).

People Survey Action Plans - The Agency's people survey action plan (2017/18), as well as divisional/ centre plans recently signed off by CET are now published on our Civil Service People Survey page.

CEO meetings – On 27 February, Dr Hudson attended the Association of the European Self-Medication Industry conference in Lisbon, and gave a presentation on an update on the Multi-Annual Work Plan and the implications for the area of non-prescription medicines. On 5th March the CEO attended a meeting of CEOs of UK government safety regulators. The following day he attended a roundtable discussion hosted by the BioIndustry Association, chaired by former Life Science Minister and Chair of University College London Hospitals NHS Foundation Trust, Lord Prior, on "How far has the Government delivered on its vision of the Accelerated Access Review".
The Quarterly Accountability Meeting took place on 12th March, which both the CEO and Chair attended. On 27th March, the CEO attended a breakfast event hosted by The House and by Sanofi, to discuss the effectiveness of the Early Access to Medicines Scheme, at the House of Commons.

Employee Benefits – We continue to work with Cabinet Office colleagues on discounted gym memberships. Our discounts portal continues to be a great success, with over 70% of staff utilising the discounts within the 'mylifestyle' benefits portal.

OPERATIONAL PERFORMANCE

New UK Marketing Authorisations (MAs) - New Active Substances - No new active substance applications were assessed in March. The mean assessment time since April 2017 remains at 52 working days or 74 calendar days.

New UK Marketing Authorisations (MAs) - Existing Active Substances - The number (volume) of new MA applications assessed in March was higher when compared with the average number of assessments completed in 2016/17. The numbers of new MA applications determined in March was lower compared with the average monthly figures for 2016/17.

Procedure	**MAA Assessed This Month**	**MAA Assessed 2016/17 Average per month**
National, UK-only	20	34
Decentralised, UK=RMS	34	28
Decentralised and MR, UK=CMS	70	34
Total	124	96

Procedure	**MAA Determined This Month**	**MAA Determined 2016/17 Average per month**
National, UK-only	34	27
Decentralised, UK=RMS	33	24
Decentralised and MR, UK=CMS	33	53
Total	**100**	**104**

Parallel imports (PLPIs) – In March, 70 PLPI initial submissions were received, 143 were assessed and 112 were determined (61, 155 and 124 respectively in February).
Median time from submission to grant was 8.2 months (8.7 months in February).
734 PLPI variation applications were received, 614 were assessed and 653 were determined (585, 593 and 506 respectively in February).
Average time from submission to grant was 3.0 months (3.0 months in February).
Training of the four new assessors is progressing well and service levels are beginning to improve with the completion of the training programme and experience in the role.

Public Assessment Reports (PARs) - 96.3% of UK Public Assessment Reports and Lay Summaries (26/27) completed in March 2018 were published within the 60-day high-level target time from grant of the marketing authorisation. There were 2 updates to PARs (2/2) with non-safety variations of clinical importance (Type II Medical) completed in March 2018.

Clinical Trial Authorisations (CTAs) - There was a total of **96** CTA applications processed this month (***1 March* to *31 March inclusive***) with **96 (100%)** processed within the 30-day target. This included **12** Phase 1 applications processed in an average time of **12.6** days (target 14 days), with **12** (100%) within the 30-day target. Of all other CTAs, **84** were processed with an average time of **24.7** days and **84 (100%)** within the 30-day target.
In the calendar year to date there have been **38** Phase 1 applications processed in an average time of **12.5** days and **199** non-Phase 1 CTA applications processed in an average time of **24.8** days.
In total **1010** applications have been processed in the financial year to date (**+ 55** compared with the same period last year).

Pharmacovigilance Adverse Drug Reactions (ADRs) – During March, the Division continued to meet all Agency targets related to the capture of ADR reports and signal detection. A total of 3221 UK ADR reports were received in March 2018, of which 757 were received from patients, parents and carers. Results against key performance measures for fatal and serious reports were both 100%. 95.5% of UK spontaneous serious ADRs were sent to EMA within the High-Level Target of 11 days and 11 reports were sent to EMA in 12-15 days. Of 114 general enquiries received, 94% were answered within 7 working days and 6% within 10 working days.

Devices adverse incidents - 1,806 Adverse Incident reports received in March (which compares with 1,675 for the same month last year), an increase of 7.8%. The cumulative total for this year is 5,068, which compares with 4,545 for 2017, an increase of 11.5%.

Devices clinical investigations - 100% of clinical investigations have been completed within 60 days and the average review time for the year to date is 53 days. 6 clinical investigations were completed in March and 60 have been completed this financial year.

Biologics batch release – Test release certificates for vaccines and blood products were issued for 90 product batches in March, very slightly up from 77 in February but still showing a general reduction from earlier in the year. The releases this month now included two batches where only a protocol review was carried out which is charged at a new lower cost. There were 218 plasma pool releases in March, a reduction from 299 in February but still

running at a higher level overall than earlier in the year. The target for timeliness of product testing was achieved in March.

7. OTHER INTERNATIONAL TOPICS

Visit from National Drug Authority of Uganda – on 14 March the Agency hosted a visit from Donna Kusemererwa, Secretary to the National Drug Authority of Uganda. Ms Kusemererwa was keen to learn about the roles and responsibilities of the Agency, in particular, the regulation of medicines and medical devices in the UK, ADR reporting and signal management in the UK, and the work of the Agency's inspectorate and enforcement groups. During the presentations and Q&A session, the discussion also covered the Agency's work with international partners to combat the illegal trade in falsified medicines and healthcare products, the Agency's work in supporting the Government's and the World Health Organisation's campaigns against Zika and Ebola, and the Agency's plans to work with the Bill and Melinda Gates Foundation on global health development programmes.

Dr Hudson welcomes Donna Kusemererwa, Secretary to the National Drug Authority of Uganda, to the Agency

Visit from the Russian Ministry of Health – on 7th March, MHRA hosted a visit from delegates of the Russian Ministry of Health (ROH). As part of the visit, the delegates attended the GMP Inspectorate monthly meeting and a Q&A session was held to answer queries on the MHRA's approach to specific aspects of GMP inspections.

Dr Ian Hudson
Chief Executive

Medicines & Healthcare products Regulatory Agency

Board Meeting

NIBSC HIGHLIGHTS FOR 2017/18

23 April 2018

Issue/ Purpose: To provide the Agency Board with a summary of The National Institute for Biological Standards and Control (NIBSC) highlights, against its activities in 2017/18
Summary: The document provides a summary of key achievements by NIBSC through 2017/18 and also highlights some areas that will be continued into the new reporting year.
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 year from April 2017 to March 2018 inclusive.
Action required by Board: To note activities achieved.
Links: None
Author(s): Marie Donatantonio
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: Christian Schneider

NIBSC Highlights from 2017/18

This end of year report on activities from the NIBSC Business Plan 2017/18 shows good achievements in many areas. The Programme Boards for Standards, Control and Research own a proportion of the activities, KPIs and metrics and their reports are provided first, followed by updates from NIBSC divisions and general topics.

The **Standards Programme Board (SPB)** reported on the standards accepted at the WHO Expert Committee for Biological Standardisation held in October 2017, with 23 physical standards accepted, 17 of these being new (i.e. 1st) WHO International Standards or WHO Reference Reagents. These included standards for: monovalent and bivalent Oral Polio Virus (OPV), biosimilars (infliximab and rituximab), typhoid vaccine and antiserum, Respiratory Syncytial Virus (RSV) antiserum, ebola antibodies, activated blood coagulation factor X, factor XII plasma function and antigen, human herpesvirus-6, KRAS mutation panel and malaria antigens. This represents a significant body of work and reflects the diverse work programmes that operate across the Institute.
In addition, the SPB reviewed and endorsed twenty eight new projects for development of reference materials, all for non WHO standards, three of these being for CE-marked in-vitro diagnostics (IVDs) and two for working standards.

The KPI for turnaround time of standards has caused some difficulties this year in terms of analysing the data and reporting the KPI for sales and dispatch. The target set is for a 6.0 day turnaround and this was achieved in all quarters other than Q2, resulting in the overall target just being missed for the full year at 6.1 days. There is a need to manually screen and filter data to account for customer created delays (which might be related to proforma invoices, import permits, authorisation to ship etc.) which are all legitimate reasons for a clock-stop in order to calculate the KPI figure. It was also reported that higher than expected demand during busy periods can make it very difficult to meet the KPI and that despite being busier (and more productive) than usual, sales staff can feel demoralised when the feedback they receive is that targets are not being met. SPB has discussed this and has reconsidered the KPI for 2018/19, to measure the real (unadjusted) time for dispatch of standards as a metric (for example as an average time with min, max and total number of orders processed). This will be easily reported and is arguably more meaningful. SPB also felt that a metric is more likely to be used for monitoring trends as opposed to a KPI where the focus is on met/not met.

The **Control Programme Board (CPB)** reported that the KPIs for turnaround times and workbench reviews had been met. Targets for batch release of products are set as 99% of batches tested and issued under the following categories: 10 days for Plasma Pools and Parenterals, 15 days for Haemostasis products and 60 days for vaccines. Feedback from customers indicates they are very happy with the fast turnaround times achieved by NIBSC. Another target with the CPB is to ensure that 90% of documents such as NIBSC procedures held on the Workbench Document Control system are within their review period and this was achieved for this year. This target is being increased to 95% in 2018/19.

Work to improve communication with manufacturers, especially regarding promotion of control testing capabilities and pricing structures, has increased throughout the year, and the MHRA Licensing Division is now represented on CPB to ensure NIBSC is aware of potential new batch release opportunities. A new Control testing communications group has also been set up this year by the NIBSC Science Communicator, and also the European Working Group looking at Batch Release capabilities included reference to NIBSC in a survey of the Official Medicines Control Laboratories (OMCL) network, ensuring that manufacturers are aware of the tests that can be performed at NIBSC. There have been continued meetings held with

manufacturers this year – some concerns were raised by one about pricing of batches that had been tested previously and only required additional protocol review - pricing was adjusted accordingly and communicated to other manufacturers. There has also been a review of the approach across NIBSC to sharing of batch release data with manufacturers to ensure consistent procedures are followed.

The possible impact of Brexit on batch release testing and planning around this was a trigger to look at flexibility of resources and identify that staff may need to be moved in some areas, depending on the Brexit outcome. Flexibility is supported by CPB and SMT and work has been ongoing to plan for this. Batch release activity is being monitored by CPB, noting that there has been a decrease in batches provided to NIBSC over the year and there is indication that this drop will continue. Work is taking place to consider the effects of different Brexit scenarios for batch release testing.
DH Internal Audit carried out an audit in Q3 of batch release testing activities and a moderate score was given. The audit recommendations and the associated actions for CPB are being progressed and reported on regularly.

The **Research Programme Board (RPB)** reported that within 2017, Institute staff were authors or co-authors on 75 papers published in the year, a slight reduction again from the previous year. The RPB and SMT have discussed possible reasons for this reduction and where there are increased pressures on staff time it is often areas such as writing of research papers and not necessarily the research activity itself that declines because of the disproportionate impact on Grade 6 scientists and above to address other activities. There will be ongoing work to look at ways of mitigating the risk of reduced research outputs.

In the last quarter there was a focus on the submission for the **Regulatory Science Research Unit (RSRU)** programme, which provides £5m from Department of Health over 5 years. Following submission in Q3, a site visit took place in December 17 with DH representatives and external reviewing scientists from Universities of Oxford and Palermo, along with Agency Board member Prof Sir Alex Markham. The Institute received the news in March 18 that the application had been successful which was a fantastic achievement and crucial for maintaining a broad-based research programme which should also provide a platform to attract additional external support and generate further collaborations with key academic partners. The topic areas submitted for the funding were as follows:
1) Assuring Access to Monoclonal Antibodies as Biological
2) The threat of Global Infectious Diseases
3) Regenerative and Cell Based therapies - Accelerating access to treatment for Neurodegenerative Disease
4) Using Biologics to overcome Anti-Microbial Resistance
5) Stratified Medicine and Genomics
6) Humanised Mouse Models for evaluating Biologics

This year's round of applications for **PhD studentships** to commence in 2018 received 13 applications which were reviewed by the RPB in early November 17. Recommendations for support of three studentships were submitted to the Director for endorsement and these were approved as follows:
Kevin Markey - Development and characterisation of a novel vaccine for Bordetella pertussis (whooping cough),
Ally Shaw - Production and analysis of glyco-conjugate vaccine against Group A Streptococcus
Simon Hufton - Optimisation of cross-neutralising nanobodies to influenza haemagglutinin using in vitro molecular evolution
Advertising for these posts has been taking place for a start in September 18.

In the **Virology division**, provision of vaccine candidate strains and potency reagents to support timely supply of **influenza vaccines** for both Northern and Southern Hemispheres was achieved with fills of 3 new reagents in November 2017: 17/220 (H3 A/Singapore - As); 17/218 (H3 A/Singapore - Ag); and 17/214 (B/Phuket - As). The team also participated in or led three calibrations and produced candidate vaccine viruses; H3N2 (3C2a1); NIB104 which were released to manufacturers in response to the Southern Hemisphere strain selection. A reagent fill for 17/246 (H3 A/Singapore-NIB104 - Ag) was completed in January 18.

Good progress has been made on the work towards the **global polio eradication programme** with four 1st WHO International Standards for monovalent and bivalent oral polio vaccines established, and MAPREC (mutant analysis by PCR and restriction enzyme cleavage) testing for Sabin type 2 and 3 Oral Polio Virus (OPV) seeds from Takeda (Japan) completed in February 2018. Following the success of the pilot phase 1 trial of nOPV2, a larger trial is planned for late 2018 and a grant agreement with PATH (originally Program for Appropriate Technology in Health) on “Clinical assessment of nOPV2” has been extended which expands the programme of work and adds a revised total budget of £554,368 until 31st October 2020.

Several papers have been published on the polio work: "Emergence and spread of vaccine-derived polioviruses in Guinea during the Ebola outbreak, 2014-2015" in Emerging Infectious Diseases; “Isolation of vaccine-like poliovirus strains in sewage samples from the UK” in Journal of Infectious Diseases; and finally “Identification and whole-genome characterization of a recombinant Enterovirus B69 isolated from a patient with Acute Flaccid Paralysis in Niger, 2015” in Nature.

There has been good progress in the work around **Emerging Infections, e.g. Ebola, Zika, MersCoV**. A WHO collaborative project to assess serological assays used for the diagnosis and surveillance of Middle East respiratory syndrome (MERS) was completed and two new International Standards (IS) projects for MERS were endorsed by WHO at ECBS in October 2017: 1st WHO IS for MERS CoV NAT Standard and a proposed 1st WHO IS for MERS CoV serum. Also a 1st IS for Ebola antibody was endorsed at ECBS 2017 and a collaborative study for a 1st IS for Zika antibody was completed in Dec 2017. The Zika antibody study was not presented to ECBS because of delays in getting results back from the collaborative study participants and will therefore be presented in the October 2018 meeting. The Ebola Antibody studies were completed in Q4.

Mark Page from this group was appointed as a member on the Coalition for Epidemic Preparedness Innovations (CEPI) standards and assays working group and on a Joint Coordination Group (areas covered MERS, NIpah, Lassa, Chikungunya, Ebola/Sudan/Marburg). Mark Page and Stacey Efstathiou were also awarded a Engineering and Physical Sciences Research Council (EPSRC) grant to support a manufacturing hub in the UK for rapid development of vaccines for Lower Middle Income Countries (LMICs) (£350k over 40 months).

One of the new activities in the **Bacteriology Division** this year was to evaluate and establish novel approaches for studying the role of the gut microbiome in human disease, and a Fellowship post was awarded for this activity. Key deliverables completed this year included development of the 16S V4 rRNA assay and a metagenomics sequencing assay for analysis of the gut microbiome; creation of 20 strain gut microbiome DNA reference material to serve as a control for calibrating gut microbiome analytical techniques; creation of a 10 strain lung microbiome DNA reference material to serve as a control for lung based microbiome diagnostics and lung microbiome research (in collaboration with PHE Colindale and University of East Anglia). Further achievements included the initiation of a large Inflammatory bowel disease (IBD) microbiome study with Warwick Medical School to determine the

bacterial groups associated with the onset of IBD. Results will be used to determine bacterial biomarkers for IBD which may be used in genomic standards. Antimicrobial resistance gene prevalence in the gut will also be analysed as part of this study. Through this work strong collaborations with PHE Colindale and University of East Anglia have been developed, to analyse the lung microbiome of Intensive Care Unit patients and a new reference material was developed as part of this study.

In **Biotherapeutics**, work on developing standards for biosimilars has gone well. The Cross Agency group (NIBSC, BP, IE&S and LD) responded to the external consultation on pharmacopoeial standards with a strategy to establish three working groups to address specific elements of the consultation response. WHO established two International standards, developed by NIBSC for Rituximab and Infliximab. These first-in-class International Standards are now available in the NIBSC catalogue and support the role of public standards in the development and control of biosimilar medicines. A manuscript describing the establishment of an International standard for Rituximab was published and a manuscript describing the infliximab study will be submitted this month. A review describing the use of these important reference materials in the regulatory context of biosimilarity is in preparation.

Following the start of the new Head of **Advanced Therapies** this year a programme of work to increase communication about the work in this area has taken place with the Comms Division. Also, work to support and facilitate innovation in the development of safe and efficacious Advanced Therapies through Accession, Characterisation, Banking and distribution of EUTCD (Clinical) grade embryonic stem cell lines suitable for use in clinical trials was achieved. The cell lines have been identified, scaled, and banked to EUTCD-compliance

In **Technology, Development and Infrastructure (TDI)**, a new Nuclear Magnetic Resonance (NMR) spectrometer was installed, validated and is now supporting safety and efficacy of conjugate vaccines for batch release in line with the Quality System. The greater resolution of the new instrument has improved the signal of the sample and an updated set of reference spectra will now be required.
Bacteriology has developed several physicochemical assays required for assessment of Group B Streptococcus (GBS) conjugated polysaccharides, including assays for molecular size, total & free polysaccharide contents, and NMR identity. NIBSC has prepared and characterised 5 different serotypes of GBS biotin-polysaccharide conjugates and sent them to Public Health England (PHE) for evaluation to facilitate the development and standardisation of an assay to measure antibody response to GBS vaccines. Progress on this work was presented at the Consortium winter meeting at Imperial College in December 2017.
Six of eight candidate antigens plus four sub-domains/non-toxigenic mutants have been purified from E. coli and are being scheduled for endotoxin presence tests and preliminary immunogenicity studies.

A major project this year was the installation of new Materials Requirement Planning (MRP) software in the **Standards Processing Division (SPD)** to make it compliant to EU GS1 (barcoding standards) and PEPPOL (Pan European Public Procurement On-Line) regulations in the NHS. This project has just been achieved and the new system 'Atticus' went live on 9th Apr 2018 following a large amount of work from SPD and IMD colleagues. There will now be some futher work to optimise the system and associated processes.

Work to set up the **NIBSC Grants Office** progressed well this year with both the Grants Manager and administrators now in post. Currently they are focussing on identifying new funding opportunities, providing business input into new grant applications to maximise their chances of success, working with scientific and financial colleagues to

maximise the income claimed from funders, and monitoring and reporting on new and potential future grants.

Following a programme of work and approval by CET and the Board in Q3, the Agency signed up to the **Concordat of Openness with Understanding Animal Research** at the end of Jan 18. The external website was updated to provide more information on the need for animal work and its crucial contribution to public health. A programme of internal communication took place before sign-up and will continue as we review the impact of this greater transparency.

Since the merger of NIBSC with the Agency, there has been a programme of work to bring NIBSC onto the same IT platform, and maximise benefits of the merged organisation. This could not start to be realised until the Agency Digital Workplace Programme (DWP) and Service Transition work reached NIBSC and hopefully result in a shared infrastructure allowing full integration and collaboration. Monitor deployment and laptop rollout has just been completed at end of March 18 and there will need to be continued work for further integration using shared systems.

This year NIBSC has been added to the Agency scope of certification to the new ISO 9001:2015 under BSI. Following its first audit to the new standard in January 2018, three minor non-compliances were cleared and the certificate is now in place for the updated standard.

Medicines & Healthcare products Regulatory Agency

Board Meeting

BUILDING AND MAINTAINING ACADEMIC RELATIONSHIPS - Update

23 April 2018

Issue/ Purpose:
To inform the Board about progress in building and maintaining academic relationships across the Agency.

Summary:
Academic relationships are an agreed and important strategic component of the Agency's current and future work. Academic links have to be maintained after their formal establishment. Previously, the Corporate Executive Team (CET) agreed that academic links should preferably be established at an Agency level in a selected number of areas, which at least in part build on existing links, and which are strategically important both to the Agency and the UK's life science sector.

These areas are:

1. **Regenerative medicine (CET Lead: Christian Schneider)**
2. **Clinical Trial Design (CET Lead: Siu Ping Lam)**
3. **Supporting emergency response to disease (CET Lead: Christian Schneider)**
4. **Use of Real World Data (CET Lead: Janet Valentine)**

This paper provides updates on the 4 areas listed above, as well as an update on **Stratified Medicine/Pharmacogenomics** and **the Innovation Office & Academic Hubs**. In addition, this paper covers outcomes from discussions with the academic relationship leads for each area of the Agency, as to whether a cross-agency group can in some way support these academic links/collaborations at an Agency level.

Resource implications:
None

EU Referendum implications:
Academic relationships will help the Agency strengthening its network with scientists, provide access to specific expert knowledge, and thereby may help facilitating creating a permissive and fruitful regulatory environment for development and licensing of medicines in the UK.

Timings:
Immediate

Action required by Board:
To note and comment on the progress in building and maintaining academic relationships across the Agency.

Author(s): Jenny Buckland and Christian Schneider

Which of the five themes in the Corporate Plan 2013/2018 does the paper support?
Supporting Innovation

If relevant, which Business Plan strategic activity does it support?
CET Sponsor: Christian Schneider

Introduction

Since 2015, the CET and Board have been regularly updated on progress on the Agency's active relationships with the academic life sciences community, which were agreed to be of high value both to the Agency and its academic partners:

CET agreed that academic links should preferably be established at an Agency level in a selected number of areas, which at least in part build on existing links, and which are strategically important both to the Agency and the UK's life science sector.

These areas are:

1. Regenerative medicine (CET Lead: Christian Schneider)
2. Clinical Trial Design (CET Lead: Siu Ping Lam)
3. Supporting emergency response to disease (CET Lead: Christian Schneider)
4. Use of Real World Data (CET Lead: Janet Valentine)

In extension to a previous CET paper (**CET/17/147**), this paper provides a short update to CET, and also covers outcomes from discussions with the academic relationship leads for each area of the Agency, as to whether a cross-agency group, can in some way support these academic links/collaborations at an Agency level or whether this is really just a local 'business as usual' activity.

1. Discussions with the academic relationship leads for each area of the Agency (Jenny Buckland)

The academic relationship leads for each area of the Agency met with Jenny Buckland on Tuesday 9th January 2018 to discuss whether a cross-agency group can in some way support academic links/collaborations at an Agency level.

Attendees: Phillip Bryan, Katherine Donegan, Nathalie Gilmore, Andrew McGuigan, Puja Myles, Mark Page, Krishna Prasad, Jack Price, Michael Whaley.

We agreed that we did not think it would be useful to have an agency-wide overarching strategy for establishing and maintaining academic relationships, as the best approach would differ for different centres and divisions, and for different collaborations.

We agreed that academic relationships are key for the Agency and that these should be visible to, and supported by, senior managers.

We agreed that, academic relationships are best managed on an individual level rather than at an Agency level, but there are a number of areas that could potentially be developed to further support these relationships:

- Training: investigate additional opportunities to support Masters/PhD students as well as internships about regulatory science at the Agency
    - Investigate putting in place an Agency-level approach for these programmes, so there is a process/guidelines to follow with regards to how to set these up (to cover issues relating to insurance, security clearance etc.).
    - Consider establishing a regulatory science course, in association with an academic partner such as Kings College London or University College London (UCL), as such courses are rare and we would be an ideal partner for this. Topics such as clinical trial design, ethics of

medicines, research required to bring a product to approval, assay development etc. could be considered.

- Grant funding: advice regarding eligibility/opportunities for grant funding for collaborative projects would be valuable across the Agency
- Horizon scanning activities could feed into this, helping us to find the key academics to be connecting with at an early stage of a project
- Promote internal information sharing about key collaborators/relationships, so we know who our colleagues are partnering with for different areas, to ensure we find the right partners for the right projects
- Consider raising the visibility of the Agency as an employer of choice through strong academic relationships and a presence at appropriate careers events

2. Update on progress in the four focus areas

2.1 Regenerative Medicine (CET Lead: Christian Schneider)

The Agency has numerous pre-existing productive academic links in this area, both nationally and internationally, which should and will be maintained.

2.1.1 The UK Stem Cell Bank (UKSCB) (Elsa Abranches and Jack Price)

The UKSCB, led by Jack Price and Elsa Abranches, are involved in numerous collaborations in this area.

- Under the UKSCB Medical Research Council Phase V grant, the team are involved in maintaining relationships with UK derivation centres (University of Sheffield, Newcastle University, Roslin Cells Limited, Kings College London, Manchester University) and requestors (extensive list) of human embryonic stem cell (ESC) lines
- UK Regenerative Medicine Platform/Pluripotent Stem Cell Project: interaction with all members of the Pluripotent Stem Cell (PSC) Platform hub headed by Dr Peter Andrews, and direct collaboration with the University of Loughborough on a standardisation project (Dr David Williams and Dr Mark McCall) (http://www.ukrmp.org.uk/hubs/pscp/)
- Stem Cell COREdinates consortium: We have recently been invited to participate and have started to collaborate with this consortium, composed of human PSC-focused groups (http://coredinates.org/)
- University of Suffolk, student placement: We have recently started discussions about firming a scheme for student placement with Dr Federica Masieri (https://www.uos.ac.uk/people/dr-federica-masieri)
- Flow cytometry standardisation project: We have established several connections with academic groups regarding the development of PSCs and mesenchymal stem cells (MSCs) flow cytometry standards, namely with Dr John Girdlestone (NHSBT Stem Cells and Immunotherapies Department at the John Radcliffe Hospital, Oxford), Dr Mark Lowdell (Royal Free Hospital , University College London), Dr Claudia Lobato da Silva (University Lisbon, Portugal), Dr.Simone Haupt (University Bonn), Dr Zoe Hewitt (University Sheffield)
- Training courses: the UKSCB has ongoing collaborations with the Harvard Stem Cell Institute (Dr Laurence Deheron, Dr William Hendrix) and The Wellcome Trust Sanger Insitute (Dr Minal Pattel) for running training courses on the PSC field

- EBiSC project: ongoing connections with academic partners of the European Bank for induced PSCs (https://www.ebisc.org/)
- ISCBI: active member of the International Stem Cell Banking Initiative composed mostly of biobanks and industry people, but also some academic partners
- The UKSCB is also currently involved in three EU Innovative Training Network grant applications:
    - iPATH is a joint proposal led by Dr Moroitz Rossner of the Max Planck Institute, Gottingen, including the University of Utrecht and King's College London
    - New-Cadre is led by the Klinikum der Universitat, Loln, and includes the University Medical Centre, Utrecht, Imperial College London, and the Technische Universitat, Dortmund
    - EmINeNT involes the University of Barcelona, the Karolinska Institute, Aarus University, the University of Exeter, and King's College London
- In addition, the UKSCB is a partner on a Medical Research Council (MRC) Mental Health Data Pathfinder Grant Application, which is led by the Centre for Neuroscience and Mental Health Research Institute and the MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff.

2.1.2 The Cell Biology Group (Ross Hawkins)

The Cell Biology Group, led by Ross Hawkins, in the Advanced Therapies Division at NIBSC, has several collaborations to develop novel genomic standards and improve their use in diagnostics and clinical decision-making.

- In 2017, we initiated a collaboration with Prof Mikael Kubista and Dr Anders Ståhlberg of the TATAA Biocenter (Gothenburg, Sweden) to use genomic standards to analyse the ability of next generation sequencing to accurately measure levels of mutations in human genomic DNA.
- We are collaborating with the European quality network IQNPath to co-host a workshop on the standardisation of cancer diagnostics in 2018. We also are working with other quality networks EMQN and UK NEQAS (Mol Genet) to develop partnerships with key European stakeholders.
- A long-standing relationship between Prof Nick Cross and Dr Helen White of Southampton University and also with Dr Philip Beer of Leeds University continues to develop approaches to improve measurement standardisation in leukaemias.
- We work with Dr Joanna Bridger at Brunel University London to explore the effects on whole genome organisation of chromosomal aneuploidies in embryonic stem cells.
- We are part of an academic consortium led by Prof Gábor Méhes (Debrecen, Hungary) that has applied for Horizon 2020 funding for the CEPOMICS project on precision oncology.

2.1.3 Other

- Also part of the Advanced Therapies Division, Yasu Takeuchi is in discussion with several academics in Europe to try to secure EU funding for xenotransplantation using genetically modified pigs. This is for R&D towards Phase I clinical trials for pig-to-human transplantation of organs (kidney/heart) as well as tissues/cells (pancreatic islets).

- In addition, as part of the NIBSC/UCL MOU on advanced therapies, NIBSC partnered a CPD course, run by UCL on regulatory science for advanced therapy, second time in July 2017: http://www.ucl.ac.uk/lifelearning/courses/regulatory-science-advanced-gene-cell-therapy This will be repeated in July 2018.

2.2. Clinical Trial Design (CET Lead: Siu Ping Lam)

The Licencing division has made progress in forging stakeholder input including academic interactions in several areas in line with the objectives of the CET paper. The principal areas of interest where stakeholder and especially academic institutions of excellence contribute to the work of the Licencing division are through the Commission of Human Medicines (CHM) and its expert advisory groups providing advice on the evaluation of medicinal product applications where innovative products are discussed. The academic groups involved include Universities of Edinburgh, Liverpool, London, and NHS trusts. There is representation from other universities on the expert advisory groups to a lesser extent. The individual and collective expertise of the expert advisory groups provide specialist advice to the CHM and MHRA assessment teams, including innovative technologies presented in marketing authorisation applications as well as those applications in the Early Access to Medicines Scheme (EAMS), in accordance with the Agency's role in protecting and enhancing public health.

In addition to the above regular ongoing interaction through the existing expert advisory groups, there is additional work in the areas of novel clinical trial designs, pharmacogenomics and stratified medicine, and companion diagnostics. The interactions also extend to areas of manufacturing and quality aspects.

As an update to the previous CET paper (**17/147**) several actions have been completed with plans to enhance existing collaborations through partnerships and meetings and workshops.

A commitment to building these links will require dedicated research time for staff, and may involve contractual obligations to collaborating institutions. Medium to long term implications of any research project work and its impact on day-to-day regulatory activities will need detailed evaluation. As an aside, the CET should be aware that the SMT are actively running recruitment exercises and are evaluating the need for resource in the impending Brexit discussions. The recruitment exercises have been successful to a good extent. Current focus would be efficient training for new assessors and subsequent development of research interests and activities. The division is encouraging staff from all disciplines to develop these ideas and is exploring options for research collaboration in different areas, including development of the concept of regulatory science, engagement with the EU network, as well as global regulatory efforts (International Coalition of Medicines Regulatory Authorities, ICMRA) on enhancing and supporting innovation.

2.2.1 Novel Clinical Trial Designs: (Krishna Prasad/Rob Hemmings/Martin O'Kane)

The area of novel clinical trial approaches is an area of special interest to the Licencing division. The MHRA has existing collaborations with the Association of the British Pharmaceutical Industry (ABPI) and with academic institutions including the commissioners and MRC to discuss approaches to novel trial designs and their integration into the regulatory framework. The 10th Ministerial Industry Strategy Group (MISG) meeting discussed use of novel clinical trials designs, and their regulatory requirements. These novel designs will have an important role in the

coming years. The meeting report has been published on the ABPI website (not published on MHRA website due to civil service restrictions): http://www.abpi.org.uk/our-work/library/industry/Pages/MISG-New-Technologies-Forum-Report-Umbrella-Basket-Protocols.aspx

A follow-up meeting took place on the 8th May 2017 at the ABPI offices to take forward the recommendations from the previous meeting and is focussed on identifying areas of action that initiate academic/regulatory/industry collaborations. The ABPI are generating a report from this initial meeting, which will enable and help formulate a series of workshops between academia (many clinical trialists/investigators), industry and the MHRA. The work that is being carried out may lead to research fellows working more closely with the MHRA on specific projects. Several MHRA personnel are involved (Krishna Prasad/CTU/Stats Unit)

Efforts are underway for a symposium/workshop (½ to ¾ of a day) with the various (funding) Charities that support clinical research to enhance awareness of regulatory requirements for clinical trial conduct, and to influence design of studies in the clinical research that could form the platform for subsequent development of drugs and devices. The workshop will include delegates from non-commercial organisations that support or conduct clinical trial research (MRC, Cancer Research UK [CRUK], the British Heart Foundation [BHF], UCL, Oxford trials Unit etc.). It is recognised by all stakeholders that enhanced regulatory interaction is beneficial to academia and funding organisations.

There is ongoing discussion with CRUK and the MRC to set-up a bilateral meeting to discuss ongoing clinical trial applications, and the regulatory requirements. (CTU/Stats/ Krishna Prasad)

2.2.2 Collaborative project on Patient Reported Outcomes (PROs) in clinical trials (Martin O'Kane/ Lisa Campbell/ Beatrice Panico from CTU).

This is work in collaboration with Prof Melanie Calvert from University of Birmingham on use of PROs in clinical trial as endpoints. Prof Calvert has initiated a nationwide study into PRO's and her department are in the process of developing PRO specific guidance for trial protocol writers. The project outcomes were presented at the culmination meeting in May 2017 and Lisa Campbell participated as a key stakeholder; this work, which also actively involved Dan O'Connor, is due to be published in the *JAMA* on the 6th February, entitled "Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension".

Also related to PROs, Dan O'Connor contributes to the Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) Consortium, which aims to develop recommendations for standardising the analysis and interpretation of PROs and quality of life data in cancer randomised trials.

***2.2.3 Adaptive Clinical trials* (Rob Hemmings)**
There is ongoing work on adaptive clinical trials in collaboration with MRC methodology unit and University College London (Prof Deborah Ashby).

2.3. Supporting emergency response to disease (CET Lead: Christian Schneider)

The Agency played a key part in the Ebola response, and won considerable praise for its strong support for experimental vaccine developers, its pragmatic and rapid review of trial applications, and its work to develop international standardisation of

disease monitoring methods. That said, there are clear opportunities to work with the research and development community to support development of technologies and products that may be needed for emergency responses in future.

2.3.1 Emerging pathogens (Mark Page and Neil Almond)

- Mark Page from NIBSC is the Agency's contact person for the Coalition for Epidemic Preparedness Innovations (CEPI), now being our representative for the CEPI Standards and Assays Working Group and their Joint Coordination Group; through this involvement NIBSC can make and build on existing relationships with relevant parties including vaccine developers and academia.
- Mark Page has recently established a link with the University of Oxford through Professor Peter Horby (https://www.ndm.ox.ac.uk/principal-investigators/researcher/peter-horby) who leads the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC), which will enable NIBSC scientists to access source materials for emerging pathogens. Mark and colleagues have submitted a grant application to NIHR to support this framework.
- Mark and other NIBSC colleagues are part of a large collaborative research hub led by Professor Robin Shattock at Imperial College London (http://www.imperial.ac.uk/people/r.shattock) to produce standards and regulatory science for nucleic acid based vaccines (the grant has a value £350k over 40 months) and are also part of a Dengue hub led by Professor Nguyễn T. K. Thanh at University College London (http://www.ucl.ac.uk/cmr/staffprofiles/TTKNG00). In addition, they have set up a quarterly meeting with the virus pseudotype unit (Kent University and Sussex University) who we work closely with to develop pseudotypes for emerging viruses and their use in neutralisation assays.
- In terms of grants, NIBSC scientists have an ongoing Small Business Research Initiative (SBRI) Innovate UK grant, led by Neil Almond, to investigate how the reference reagents that NIBSC has produced for MERS, Ebola and Zika viruses can be used in animal models of infection to assign protective antibody titres (expressed in units) so that they can be related and applied to human vaccine studies. NIBSC scientists are also included as subcontractors on a second successful SBRI application in which they are performing passive transfer protection studies using anti-CHIKV sera derived from Phase 2 Clinical Trial materials.
- Mark Page and colleagues have also submitted two grant applications in association with the University of Nottingham, led by Associate Professor Janet Daly (https://www.nottingham.ac.uk/Vet/People/janet.daly).

2.3.1 Other – the importance of standards, developing assays and participating in collaborative studies

Publicising the importance of producing standards for emerging pathogens is key and NIBSC staff are increasingly being asked to speak at consultation meetings (organised by the FDA, NIH, WHO, Wellcome Trust), which reflects the better awareness of the vaccine community for the need to harmonise and calibrate assays. The outcome of these meetings is that NIBSC is often approached to work with academic institutions in developing assays and participating in collaborative studies.

2.4. Use of Real World Data (CET Lead: Janet Valentine)

2.4.1 VRMM (Katherine Donegan and Phil Bryan)

Real world data is pivotal for assessing the safety of medicines and vaccines post-licensing. VRMM recognises the vital contribution that academic organisations make in developing methodologies for data collection and analysis, generating data on the safety profile of individual medicines and vaccine, and monitoring the use of medicines in clinical practice.

As seen elsewhere in the Agency, academic researchers contribute directly to regulatory decision making through the Commission of Human Medicines (CM) and its expert advisory groups (EAGs), particularly the Pharmacovigilance EAG. Further, there are a number of projects that are ongoing, or have recently concluded, where collaboration with national and international academic organisations related to the use of real world data throughout the pharmacovigilance lifecycle.

- **Reporting of adverse event and signal detection**

Spontaneous reporting remains the cornerstone of pharmacovigilance and new technologies and Big Data are offering increasing opportunities for identifying individual adverse events potentially causally associated with a medicine or vaccine. VRMM has worked extensively with academic groups over the years in this field and more recently through its leadership role in both the SCOPE (Strengthening Collaboration for Operating Pharmacovigilance in Europe) Joint Action and the Innovative Medicines Initiative (IMI) WEB-RADR projects.

In SCOPE, which aimed to help medicines regulators operate pharmacovigilance systems to the EU legislative requirements, the University of Groningen contributed to a collaborative analysis of healthcare professional awareness of ADR reporting schemes and their communication preferences, while the WHO's Uppsala Monitoring Centre (UMC) participated in analysis of ADR reporting systems.

Within IMI WEB-RADR, the UMC led the investigation of analytic techniques for social media data, while the University of Groningen considered patient and healthcare professional perceptions of mobile apps and the Yellow Card app specifically, working with the Institute of Child Health at UCL. Additionally, the University of Liverpool studied the value of these novel data sources to pharmacovigilance, when compared to traditional data sources.

- **Vaccine pharmacovigilance**

The MHRA plays an important role in the proactive surveillance of vaccines used as part of the National Immunisation Schedule. For the introduction of each new vaccine VRMM work closely with academic researchers within Public Health England. This work has generated important new safety data on several vaccines which has been published in the peer-reviewed literature. VRMM has also provided input into an ongoing project with PHE and the London School of Hygiene and Tropical Medicine (LSHTM) which is being conducted within the NIHR Health Protection Research Unit in Immunisation which has looked at the use of CPRD for near real-time monitoring of vaccine safety. VRMM are also currently involved in the IMI ADVANCE (Accelerated development of vaccine benefit-risk collaboration in Europe) project which includes several EU academic partners.

- **Pharmacoepidemiology research**

The Pharmacoepidemiology Unit within VRMM conduct research using data from the CPRD to support wider decision-making across the division. Much of this work includes collaborating with a range of academic groups on individual studies. Recent examples include collaborations with the University of Manchester, UCL, LSHTM, and the University of Sussex. These include studies measuring outcomes and monitoring the impact of regulatory action.

Individuals within VRMM also have a number of links with national disease registries including, for example, the British Society for Rheumatology Biologics Registers, operated through the Arthritis Research UK Centre for Epidemiology at the University of Manchester, as a member of their research advisory group.

- **Teaching and outreach**

Individuals within VRMM contribute to delivering training modules as part of a number of academic courses for example, an MSc course at the University of Hertfordshire and a summer course at Oxford University as well as courses run by the Drug Safety Research Unit through the University of Portsmouth. In particular, a number of lectures are provided on the LSHTM Certificate in Pharmacoepidemiology and Pharmacovigilance and VRMM sit on the course committee. VRMM also host, during the summer period, MSc Students from the University of East London for work experience. There is also active outreach through national and international conferences (e.g. those run by the International Society of Pharmacovigilance and the International Society of Pharmacoepidemiology) which have large academic participation, promoting the research work conducted with the Agency and helping to build relationships with potential academic partners.

2.4.2 CPRD (Rachael Williams and Puja Myles)

Approximately 50% of CPRD clients are academic researchers. Close engagement with the academic community is essential for CPRD to provide both a high-quality client research service and for the professional development of CPRD staff. CPRD engages directly with the academic research community on a routine basis in the following ways:

- Delivering training modules as part of academic courses, for example, MSc courses at King's College London, Oxford University and the University of Hertfordshire, and short courses for the Farr Institute of Health Informatics Research and the London School of Hygiene and Tropical Medicine
- Delivering bespoke training in the use of CPRD data to academic clients who hold an annual institutional license
- Collaborating in joint academic research proposals using CPRD data which invariably result in peer-reviewed publications with CPRD co-authorship
- Holding CPRD User Group Meetings where academic researchers can network with CPRD staff and discuss potential research proposals
- Hosting expert meetings with academics to help shape CPRD developments, for example, the recent stakeholder engagement workshops on machine learning and data mining
- Sponsoring joint sessions at conferences, for example, the recent symposium by CPRD and Manchester University on the role of epidemiology in optimising pragmatic randomised clinical trials at the 2017 International Conference for Pharmacoepidemiology
- CPRD research staff undertaking PhDs and therefore also being registered as students at academic institutions. Currently four CPRD staff members are undertaking part-time PhDs with academic institutions in the UK and in the Netherlands.
- Conversely, full time external PhD students are sponsored by CPRD and carry out placements with CPRD on shared projects.
- CPRD staff frequently form academic collaborations to assist in the characterisation and validation of newly developed CPRD research products, such as the recently developed pregnancy register

Other areas which may be fruitful in the future include developing a more formal arrangement with established academic consortia and networks such as the Farr Institute of Health Informatics Research and the NIHR School of Primary Care Research.

3. Update on Stratified Medicine/Pharmacogenomics and the Innovation Office & Academic Hubs

3.1 Stratified Medicine/Pharmacogenomics (Steve Lee & Krishna Prasad)

3.1.1 UK Pharmacogenetic and Stratified Medicine network (UK-PSMN)

As previously detailed, the major point of interaction for stratified medicine with the academic community is through the UK-PSMN, based at University of Liverpool (Prof Sir Munir Pirmohamed).

The membership of this network is primarily based in academic institutions and NHS trusts with a specific interest in genomic and pharmacogenomics. MHRA is an active member of this group and Krishna Prasad is a member of the steering group. The network steering group meets 2-3 times/year planning for symposia, forums and the annual meeting. The network is aimed at raising awareness about stratified medicine, ongoing work/research, establish research collaborations and organise workshops to discuss key issues affecting the field and its implementation in the NHS. There have been > 6 workshops organised by the network in 2016.

MHRA (Steve Lee & Krishna Prasad) in collaboration with the UK-PSMN held a Workshop on Regulation of Genomic Tests on the 9th of June 2016 at Skipton House. The attendees included academics, NICE, NHS trusts and Industry representatives (devices and pharma). The workshop discussed the aspects of genomic tests, standardisation of clinical tests, the regulatory requirements and impact. The meeting report is published on the network website (publication was delayed due to purdah and embargo arising from the referendum and subsequent general election).

A follow-on workshop to generate a co-ordinated set of actions and processes for handling genomic tests is planned for May 2018 and planning is in progress.

Additionally, the agency and LD in collaboration with Devices is taking a lead in engaging stakeholders in the dialogue which will influence the Genomic strategy for devices as well as genomic therapy regulation. The agency might need to consider the relevance of this in the context of opportunities afforded by Britain's exit from EU links.

3.1.2 UK *Genomics for Diagnostic Forum (*Krishna Prasad and Liz Baker)

The genomics diagnostic forum an agency wide forum led by Devices and NIBSC and (with LD reps- Krishna Prasad and Liz Baker). The forum draws academic input from the Royal College of Pathologists, University of Liverpool/ NHS chair of Pharmacogenetics, Genomics England, UK Gene Therapy network and Department of Health (DH). It offers a collaborative group of stakeholders that help in identifying difficult aspects of development of diagnostics for genomics, agreeing methods of establishing standards, quality control mechanisms and regulatory requirements of diagnostics. These meetings currently take place at 6-monthly intervals.

3.1.3 UK *Interaction with SMIP and Catapult initiative*

The agency was involved with the Strat-Med innovation platform initiated by Innovate UK(Krishna Prasad / Shirley Hopper) and supported by 7 funding organisations; including MRC, CRUK, ARUK, the NIHR Office for Clinical Research

Infrastructure (NOCRI), plus DH and, the more recent Catapult Initiative. There is enhanced interaction with a variety of Catapults (Precision medicine, Cell therapy etc.) with links to academic hubs (Cambridge University, Liverpool University). The agency supported the research initiatives in the context of providing input and advice to these catapults on methodology, trial designs, and data generation. These interactions permitted the agency and assessors to gain experience and knowledge of recent developments as well as tap in to expert opinions as needed. This project is now complete.

3.2. Innovation Office & Academic Hubs (Julian Bonnerjea and Nathalie Gilmore)

The Innovation Office is an opportunity for the MHRA to establish collaborative work with academic hubs in order to provide support to innovations in drug and device development. The Innovation Office lead (appointed recently) initiates liaisons with established contacts and works to identify new contacts. There is ongoing work in this area with the Precision Medicine and Regenerative Medicine catapults and many other stakeholders.

An Innovation Steering Group has been established, with representatives from Licensing Division, IE&S, Devices, Comms and NIBSC, to promote awareness of the work of the Innovation Office, both internally within teams and externally at stakeholder events. This group will also have a key role in establishing the strategy for the Innovation Office to broaden the support currently offered to stakeholders.

The Innovation Office has established links with the agency's Horizon Scanning Working Group – the innovation office team participate in the group and the Horizon Scanning Working Group Chair, Jenny Buckland, is a member of the Innovation Steering Group. Through this close collaboration it is envisaged that comprehensive support will be offered to innovators, innovative technologies and the Agency's horizon scanning capability will be augmented.

A meeting with the major funders of academic research (the National Institute for Health Research [NIHR[, the Association of Medical Research Charities [AMRC] and several of the medical research charities) in scheduled for March 2018 to raise awareness of the support offered by the Innovation Office, to initiate a mutually beneficial dialogue and to gain feedback on how future efforts should be focused to make the maximum impact. CTU staff will have an active role in this initial meeting and, dependent on the steer given by the funding bodies, are likely to be involved with further meetings with funders and representatives from academia.

Staff at the MHRA continue to raise awareness of the agency's support for innovation through events such as the recent Festival of Genomics. Many staff have links and take on training / lecturing roles (such as University College London on regulatory options or requirements) and participate in many Student MSc and staff training courses.

The Innovation Office has interacted with many academic institutions providing written and face to face advice on a wide range of subjects, often involving collaboration across divisions or with other agencies. One example worth highlighting is the series of meetings with participants in the REMEDIES (RE-configuring MEDIcines End-to-end Supply) Project. This is an industry/academic collaboration investigating how medicines manufacture can be shaped to better meet the needs of patients. A project specific meeting is scheduled on 8 February 2018.

Innovation Steering Group members are also involved in the Horizon 2020 CSA on training academia in regulatory science being administered by the EMA. MHRA focussed on the workstream to define a strategy for training programmes to strengthen the ability of academia to engage in *regulatory science* and to improve support for successful regulatory *Scientific Advice* and *Protocol Assistance initiatives* based on identified best practices. In is anticipated that through participation in this scheme an insight will be gained into the work being carried out by other agencies across Europe and best practices will be more easily identified. This is also a useful opportunity to collaborate with innovation offices from other EU agencies and learn together through shared experience.

Conclusion and recommendations

The Agency's relationships with the academic life sciences community are of high importance to the Agency and, based on the notes above for the priority areas identified, appear to be thriving.

The academic relationship leads for each area of the Agency agree that such academic relationships are key for the Agency and that these should be visible to, and supported by, senior managers. The group agree that these relationships are best managed/supported on an individual level rather than at an Agency level. An Agency-wide overarching strategy for establishing and maintaining academic relationships was not thought to be useful, as the best approach would differ for different centres and divisions, and for different collaborations. However, some areas were identified that could be developed to further support academic relationships across the Agency and we ask for your feedback/comments about these please and whether these should be taken forward in some way.

Medicines & Healthcare products Regulatory Agency

Board Meeting

GENOMICS AND COMPANION DIAGNOSTICS

23 April 2018

Issue/ Purpose: The Board continues to review MHRA approach to genomics and companion diagnostics. This paper is intended to update the Board on progress.

Summary:
The paper provides updates on implementation activities around the new regulations for in vitro diagnostic medical devices (IVDs) that are relevant to genomics and companion diagnostics including:

- MHRA draft guidance on application of the health institution exemption for medical devices and IVDs.
- Challenges in the regulation of bioinformatic software
- Ongoing work to address the regulation of companion diagnostic IVDs in the new regulations

Resource implications: None

EU Referendum implications: None

Action required by Board: To note

Author: Steve Lee

Which of the five themes in the Corporate Plan 2013/2018 does the paper support?
Innovation

If relevant, which Business Plan strategic activity does it support?
Develop Agency wide genomics strategy, and define mechanisms for supporting genomic/companion diagnostic proposals – presenting business case for strategy development to the Agency's Corporate Executive Team by end Q2. Then, initiate the process of developing a strategic Agency plan on dealing with companion diagnostics in the context of new IVD regulations, EAMS and the new clinical trial regulations following on from that.

CET Sponsors: John Wilkinson, Siu Ping Lam

Background

Health Institution Exemption

The Chief Medical Officer's annual report[i] (Generation Genome) recommends that NHS England continues to recommission genomics services with centralised laboratories and regional hubs. CMO also recommends to MHRA that the new IVD regulations are 'applied appropriately'.

In order to meet this recommendation, we can anticipate that much of the NHS England work on gene sequencing and bioinformatics will continue to happen within the exemption for health institutions and therefore the provisions for health institutions in the new regulations are key.

The new EU regulations for in vitro diagnostic medical devices (IVDs) and medical devices (MDs) will continue the exemption for manufacturing or modifying and using IVDs or MDs within the same health institution in Member States (also known as 'in house manufacture'). Health institutions wishing to apply the exemption in the new regulations will need to ensure that products meet the relevant General Safety and Performance Requirements of the new regulations. In addition, health institutions will need to have:

- an appropriate quality system in place;
- a justification for applying the exemption;
- technical documentation in place.

Some of this information will need to be publicly available.

MHRA have worked with a range of stakeholders to develop a simple process with associated guidance that UK health institutions could use to apply the exemption. Although the formal transition to the new regulations for Member States ends in May 2022 (IVDR) and May 2020 (MDR), we are actively working on the draft guidance so that health institutions here have sufficient time to consider the new requirements before the end of any relevant transition period.

The simple process and guidance have been published as a MHRA consultation[ii] with a long consultation time (til March 2019) to allow health institutions plenty of time to understand what needs to be done to comply with the new requirements. We are actively working with health institutions who wish to act as early adopters and pilot sites for the new requirements.

Regulation of bioinformatics software

We recognise that the appropriate regulation of bioinformatics software is critical to the success of a genomics strategy. In particular, regular significant updates, the use of open source software and reliance on equivalence are all challenges for the development of bioinformatics software in commercial and health institution settings. We continue to work with the UK bioinformatics community to develop tactics for appropriate application of the IVD regulations.

Companion Diagnostics

Licensing and Devices Divisions have previously defined policies around the regulation of diagnostic devices in clinical trials using the IVD Directive. Now we are looking at defining policies under the new IVD Regulations.

Under IVDR, clinical performance studies of companion diagnostic IVDs (as well as other interventional IVD performance studies) will need to be assessed by a Devices Competent Authority prior to the start of the study. The IVD clinical performance study can be part of the clinical trial of the corresponding medicinal product (eg co-development) or they can be separate (eg IVD follow-on study).

Prior to CE marking a companion diagnostic, the IVD manufacturer will apply to a Notified Body who as part of their overall assessment will seek the opinion of EMA or the relevant medicines competent authority before the NB grants a certificate to the manufacturer.

A joint task force of the Commission's IVD and clinical investigations working groups has been set up and will begin discussions on providing guidance on IVD performance evaluation studies including companion diagnostics. The joint task force will include EMA and pharma industry in the companion diagnostic aspects of the discussion and will bring in the EMA concept paper on predictive biomarker-based assay development in the context of drug development and lifecycle. The joint task force can also begin to facilitate a discussion between EMA and Notified Bodies.

The formal application process for competent authority assessment of a companion diagnostic clinical performance study will depend on the implementation of EUDAMED (expected 2020). In the meantime, MHRA continue to determine the need (and capacity) for an informal process which MHRA might wish to develop before 2020 for study sponsors who wish to claim IVDR compliance.

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[i] Annual Report of the Chief Medical Officer 2016, Generation Genome
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/624628/CMO_annual_report_generation_genome.pdf

[ii] Open consultation: Health institution exemption for IVDR/MDR
https://www.gov.uk/government/consultations/health-institution-exemption-for-ivdrmdr

Medicines & Healthcare products Regulatory Agency

Board Meeting

KEY CHANGES INTRODUCED IN THE NEW EU DEVICE REGULATIONS

23 April 2018

Issue/ Purpose: To provide a summary of the key changes introduced by the new EU Regulations on medical devices and in vitro diagnostic devices, as background for future updates on related implementation work.

Summary: The new EU Regulations for medical devices (MDR) and *in vitro* diagnostic devices (IVDR) entered into force on 25 May 2017. These Regulations introduce many changes, which will have a significant impact on the way in which we regulate medical devices and IVDs.

As we progress with our implementation work, we will continue to engage industry and work closely with other Member States in order to ensure that the MHRA and our stakeholders are prepared for the new Regulations.

Resource implications: We anticipate a requirement for significant additional resourcing due to the impact that the new requirements will have on the Devices Division.

EU Referendum implications: Elements of the new regulations have been applied directly in UK law since May, meaning devices can now be legally placed on the UK market if they are in conformity with the new regulations, invoking all relevant requirements. As it stands, the EU (Withdrawal) Bill would maintain this position beyond March 2019.

Action required by Board: For information

Author(s):
Gavia Taan – Senior Regulatory Policy Manager, Devices Regulatory Affairs

Which of the five themes in the Corporate Plan 2013/2018 does the paper support?

Theme 2: Bringing innovation safely to market
Theme 5: Achieving excellence – a well-run, efficient and effective organisation

If relevant, which Business Plan strategic activity does it support?

Aim 2: Enabling innovation Aim 3: Vigilance Aim 4: Secure global supply chains
CET Sponsor: John Wilkinson

Key changes introduced in the new EU Device Regulations

Purpose

1. The new EU Regulations for medical devices (MDR) and *in vitro* diagnostic devices (IVDR) entered into force on 25 May 2017. This paper sets out the key changes between the new Regulations and the current Directives for medical devices (MDD), *in vitro* diagnostic devices (IVDD) and active implantable medical devices (AIMDD).

Background to legislation

2. The date of entry into force marked the beginning of the three- and five-year transition periods. Therefore, the MDR and IVDR will fully apply in EU Member States from 26 May 2020 and 2022 respectively.

3. During the transition period, devices can be placed on the market under the current EU Directives, or the new Regulations (if they fully comply with the new Regulations).

4. Once the new Regulations are fully applied in the EU, devices previously placed on the market in accordance with the current EU Directives may continue to be placed on the market until May 2024, as long the certificate remains valid and certain other requirements are met.

Key changes

5. Increased scope and changes to risk classification. The new legislation will regulate certain groups of products without an intended medical purpose, listed under Annex XVI of the MDR, as medical devices (for example, non-corrective contact lenses, dermal fillers, and brain stimulation devices). This will be a new stakeholder group to regulate and we will be conducting extensive communications campaigns over the coming months.

   In addition, the Regulations introduce new classification rules, meaning that certain devices (such as certain categories of software and devices containing nanomaterials) will be reclassified into high risk categories, and thus will require a more stringent assessment. Furthermore, devices that are manufactured and used within health institutions will no longer be excluded from regulatory oversight and will need to meet certain requirements set out in the Regulations.

6. Increased traceability of devices and incidents. The Commission is responsible for significantly overhauling the existing Eudamed database. It will be expanded to capture more complex data on devices. This includes information regarding economic operators, notified bodies, certificates, clinical investigations, vigilance and market surveillance. It will also enable more accurate trend reporting analyses. Much of this information will be made available to the public.

   The new Regulations also place a greater emphasis on traceability throughout the whole supply chain through the introduction of a unique device identification (UDI) system, which manufacturers must include with their devices, enabling greater control over safety alerts, potential recalls and surveillance tasks.

However, these changes, particularly assignment of UDI, will incur significant costs, and can be expected to take several years to fully embed. If the Commission has not readied the new Eudamed in time, then these provisions will also be postponed accordingly.

7. Increased scrutiny, particularly of higher risk devices. The notified body requirements in the MDR largely build on those already established by the EU Joint Plan following the PIP scandal. This has resulted in a strengthened notified body system, enabling joint inspections, unannounced factory inspections and the physical or laboratory testing of devices.

   The Regulations introduce pre-market clinical scrutiny of selected high risk, novel devices. These will be performed by 'Expert Panels' to be administered by the European Commission.

   A key impact on Competent Authorities is the enhanced market surveillance responsibilities, resulting in clearer obligations for Competent Authority to conduct inspections on manufacturing and clinical investigation sites. This will have a significant resourcing impact on the Devices Division.

8. Changes to obligations for economic operators. The Regulations introduce clearer obligations for those involved in manufacturing and supplying devices, with importers and distributors being regulated for the first time. In addition, manufacturers and authorised representatives will now be required to have at least one person responsible for regulatory compliance.

   The MDR and IVDR set out more rigorous vigilance reporting requirements and introduce an ongoing assessment of potential safety risks with requirements for manufacturers to produce mandatory post-market clinical follow-up (PMCF) and periodic safety update reports (PSURs).

   Manufacturers will also be obliged to prepare annual PSURs and report on trends, and the time period within which manufacturers must report serious incidents to competent authorities will be reduced to 15 days.

   Due to the extent of changes to economic operator obligations, implementation of the new Regulations will require significant development of both existing and new stakeholder engagement and communications activity.

9. Changes to clinical and performance evidence requirements. The up-classification of many devices, and the new standards for clinical and performance evidence in conformity assessment, means we can expect a significant increase in the number of clinical investigations and performance studies; MHRA will need to assess and approve those in the UK.

10. Changes specific to IVDs. Both the MDR and IVDR are broadly similar, but some aspects are necessarily different for the IVDR. The five-year transition period is primarily because of the overhaul of the IVD risk classes, which will result in a huge increase in the number of IVDs requiring notified body assessment.

    The new Regulations also call for a network of EU reference laboratories to be set up to provide advice on, verify the performance of, and test Class D IVDs.

11. Increased coordination and collaboration. The Regulations encourage better collaboration between Member States, and with the Commission, as well as streamlining and facilitating the flow of information between economic operators, notified bodies or sponsors and Member States. This is to enable Competent

Authorities to develop a clearer picture of the market, ensure high levels of safety across the EU, and to avoid the repetition of serious incidents, such as the Poly Implant Prostheses (PIP) scandal. In addition, joint working, coordination and communication of activities is expected to lead to more efficient use of resources and expertise at a national level.

Conclusion and next steps

12. The new EU Regulations introduce many changes, which will have a significant impact on the way in which we regulate medical devices and IVDs. We are working closely with the Policy, Legal and Finance teams in order to understand and plan for these changes.

13. As we progress with our implementation work, we will continue to engage industry and work closely with other Member States in order to ensure that the MHRA and our stakeholders are prepared for the new Regulations.