Medicines & Healthcare products Regulatory Agency

Public Board Meeting

16 December 2019

INTERIM CHIEF EXECUTIVE'S REPORT FOR OCTOBER AND NOVEMBER 2019

1. HEADLINES for October and November 2019

BREXIT
No Deal: The No Deal correcting Statutory Instrument (SI) has been made. The Agency remains in a state of readiness for a No Deal outcome.
Communications – A large amount of Brexit-related guidance was cleared and published. Communications Division provided an audit of all content which will be impacted by a no-deal Brexit to Government Digital Service (GDS), to help with cross-government resource planning. A global email to staff was issued and a piece published on INsite from our Chair Sir Michael Rawlins passing on thanks from our Minister for all the hard work done by the Agency over the past year, with a particular focus on those working on Brexit.

MHRA Annual Lecture 2019 – Sir John Bell, Regius Professor of Medicine at Oxford University and the government's Life Sciences Champion, delivered the Agency's 14th Annual Lecture at the King's Fund, London. Sir John's lecture was entitled "The future of life sciences: keeping the UK at the forefront of medical and scientific excellence" in which he outlined his perspective on the life sciences industry and the role the UK will play in it. Sir John said the UK has a unique opportunity to lead the field in life sciences, with an exciting and important enabling role for the MHRA. In his speech to an audience of over 200 healthcare and industry leaders, patient group representatives and Agency colleagues, Sir John set out how he would like to see the UK establish three new life science industries: genomics, digital health and early diagnosis. These new industries will come with their own regulatory challenges but will be critical to the UK continuing to lead in the field of life sciences. Sir John told the audience that the MHRA has a unique opportunity to challenge the status quo in regulation and play a leading role in a life science strategy driven by academia, industry, government and the NHS.

Feedback has been very positive; the post event survey has been sent out to all delegates who attended, the results of which are in the process of being analysed for the evaluation report. An edited video of the lecture was published on YouTube and promoted on social media. An updated Agency showreel was launched at the Annual Lecture and will feature at future events and displayed on the screens on the fifth floor. The video showcases the key successes of our expert centres, demonstrating their brands, but also in keeping with the wider Agency brand look and feel. The video will also be edited for use on social media.

Awards - Our 'Shaping our Future' campaign won the Staff Engagement category at the 2019 Public Relations and Communications Association (PRCA) awards ceremony in London earlier this month. We also received a Bronze Award for our #fakemeds campaign in the Public Service Communications Excellence Awards 2019 – the third year in a row that our work has been recognised in these awards. Comms also reached the final of this year's PR Week awards in the in-house team of the year (public and third sector) category. Unfortunately, we did not win this time and the award went to Transport for London – but we were delighted to reach the final shortlist against tough competition.

Yellow Fever Vaccine and YEL-AND and YEL-AVD – The third and final meeting of the Expert Working Group (EWG) on Yellow Fever Vaccine took place on 4 October. The Group concluded that the balance of benefits and risks of yellow fever vaccine remains favourable for most travellers when used in accordance with the current indications but that additional measures should be put in place to minimise the risk of two very rare but potentially fatal adverse effects, viscerotropic disease (YEL-AVD) and neurotropic disease (YEL-AND) particularly in those with a weakened immune system and those over the age of 60 years. The conclusions and recommendations of the EWG were fully endorsed by the CHM. The CHM advice has been communicated to the lead Member State (Germany) and the marketing authorisation holder, and both have agreed to take these forward. This includes implementing a statutory screening checklist in the Risk Management Plan. The MHRA has worked closely with all parties, including Public Health England (PHE) and the national travel health networks, on communicating the new measures through a joint letter and a DSU article to support implementation into clinical practice.

The recommendations of the Expert Group have now been communicated to yellow fever vaccine clinics through a letter co-signed by the MHRA, Public Health England, National Travel Health Network and Centre (NaTHNaC) and Health Protection Scotland (HPS). An article in the MHRA's safety bulletin has also been published and is available here: https://www.gov.uk/drug-safety-update/yellow-fever-vaccine-stronger-precautions-in-people-with-weakened-immunity-and-in-those-aged-60-years-or-older. A link to the letter and to the detailed public report can also be found in the bulletin.

E-cigarettes and reports of lung adverse reactions– the MHRA is investigating reports of lung adverse effects linked to vaping. These are primarily from the USA and associated with vaping cannabinoids. Advice has been sought from the Commission on Human Medicines (CHM) Expert Group on E-cigarettes and from CHM in November. Vigilance and Risk Management of Medicines (VRMM) is also working with Public Health England and other stakeholders to strengthen surveillance in the UK.

Independent Medicines and Medical Devices Safety (IMMDS) Review – The Cumberlege Review Team has continued to focus on analysing the evidence and preparing the report which is expected to be published in March. The Review Team has published the timelines of events for sodium valproate and pelvic mesh on their website. The MHRA is working with DHSC and other healthcare partners on the emerging themes from the Review.

Ranitidine and nitrosamine impurities – In October the MHRA issued an alert to healthcare professionals, following action taken by Teva to recall all unexpired stock of certain batches of 2 types of ranitidine medicines used to treat conditions such as heartburn and stomach ulcers because of nitrosamine impurities. Healthcare professionals were told to stop supplying the two products immediately and to quarantine and return remaining stock. Patients in the UK were advised not to stop taking their medication, and that a treatment review was not necessary until the next routine appointment. The recall was undertaken as a precautionary measure due to possible contamination of the active substance, ranitidine, with an impurity called NDMA (N-nitrosodimethylamine) which has been identified as a risk factor in the development of certain cancers. The MHRA is actively involved with the European Medicines Agency (EMA) and other medicines regulators to determine the impact of what is an ongoing, global issue. On 8 October, a drug alert was also issued regarding the withdrawal of four types of prescription-only ranitidine products.

Metformin diabetes medicines and nitrosamine impurities – Outside the UK very low amounts of an impurity, N-nitrosodimethylamine (NDMA), have been found in some metformin diabetes medicines. Patients in the UK have been advised to continue taking their metformin medicines as usual. The risks from not having adequate diabetes treatment far outweigh any

possible effects of the low levels of NDMA seen in metformin medicines outside the UK. The MHRA is working closely with the European Medicines Agency (EMA) and other regulatory authorities to determine whether any further action is required and will continue to keep patients updated as more information becomes available. The levels of NDMA seen in the affected non-UK metformin medicines are very low and appear to be within or even below the range that people would normally be exposed from other sources, including food and water. We managed multiple communications, handling approaches with social media and press activity that has led to widespread coverage.

Emerade Adrenaline Autoinjectors – The MHRA and EMA were recently informed that the company's ongoing investigations of Emerade Autoinjectors had shown that an error in one component of the autoinjector was believed to cause some pens to fail to activate. On 28 November following information from DHSC that sufficient stocks of alternative brands of adrenaline autoinjectors were available, a Class 2 recall to wholesaler and pharmacy level was initiated to prevent additional Emerade devices being supplied to patients. The recall also included further advice to patient related to the environmental factors: avoiding exposure of pens to temperatures above 25°C as this may increase the likelihood of the fault occurring. The alert also reiterated the existing important advice that patients should carry two pens at all times. This recall was communicated to DHSC, patient groups and the ministerial team. https://www.gov.uk/drug-device-alerts/class-2-medicines-recall-emerade-150-300-and-500-microgram-solution-for-injection-in-pre-filled-syringe-mdr-57-08-19

2. PRODUCT RELATED ISSUES

Medicines issues

Medicines in pregnancy and data – The Commission on Human Medicines (CHM) Expert Working Group (EWG) on optimising data on medicines used in pregnancy, which comprises key data holders, researchers and experts in teratology, maternal health and epidemiology met for the second time in October to map currently available relevant data sources in the UK, identify gaps in the available data and consider how data quality could be further improved.

ADHD and paracetamol use during pregnancy – The Pharmacovigilance Expert Advisory Group (PEAG) considered the findings of a prospective cohort study (published in October in JAMA Psychiatry) for an apparent dose-related association between cord biomarkers of foetal exposure to acetaminophen/paracetamol and increased risk of physician-diagnosed Attention Deficit Hyperactivity Disorder (ADHD), Autistic Spectrum Disorder (ASD), and other developmental delays (DDs). The PEAG considered that the study adds to the growing evidence base for a possible effect of paracetamol on neuropsychiatric development of the foetus but because of a number of important limitations, including the lack of a control group, poor exposure data and a potentially biased sample population, it does not contribute significantly more than those studies reviewed by the EU Pharmacovigilance Risk Assessment Committee in a 2018 review and the UK ALSPAC cohort study considered by PEAG in September 2019. The PEAG advised that the study did not warrant any update to current product information.

Calea UK Limited and sterile product supply – In November 2019, a meeting with the company was held at MHRA offices to discuss proposed action plans and how they are to be successfully implemented. Ongoing media handling of the Calea supply issue has continued, including managing responses to BBC Radio Wales Eye on Wales documentary broadcast on 16 October.

Medical Devices issues

Surgical mesh for the treatment of hernias (including inguinal) – Increasing concerns relating to hernia mesh complications (chronic pain) are being observed. We are continuing to interact with key stakeholders in the UK, largely with the British Hernia Society, to keep abreast of issues relating to use of surgical mesh for the treatment of hernias and to share information as appropriate.

Breast Implants and Anaplastic Large Cell Lymphoma (BIA-ALCL) – We emailed stakeholders to raise awareness of regulatory action being taken by the Therapeutic Goods Administration on breast implant products available in Australia.

Acuvue contact lens – Johnson and Johnson initiated a voluntary product recall of specific lots of Acuvue daily disposable contact lenses. The affected lots may have had particles on the contact lens or in the contact lens blister solution. If the particles are not noticed before insertion into the eye, this could cause eye redness or discomfort or corneal abrasion (damage to the surface of the eye). The Agency handled communications around the Acuvue contact lens recall, which included liaison with Johnson and Johnson; proactive press release sell-in, web content, and social media activity including graphics. This secured coverage in a range of online publications, including the Sun, Mirror, and Mail.

Medical Device Alerts There were eight alerts in October 2019:

Number	Title
MDA/2019/032	Deltec Gripper non-coring needles and PORT-A-CATH trays containing Gripper needles – recall due to risk of needle occlusion.
MDA/2019/033	Anaesthetic face masks – Specific Intersurgical Economy 22F taper connection may be oversized and leak or disconnect from the breathing circuit.
MDA/2019/034	Intraoperative probe cover with long Surgi-tip – risk of infection due to manufacturing failure - manufactured by Ecolab/Microtek Medical Malta Ltd.
MDA/2019/035	Rocket and NuSurgix fetal blood sampling (FBS) amnioscopes and FBS kits – stop using ethyl chloride spray during the fetal blood sampling procedure with these devices.
MDA/2019/036	Specific Hudson RCI Sheridan endotracheal tubes and connectors - 15 mm connector may detach from the tube before or during use - manufactured by Teleflex Medical.
MDA/2019/037	Prismaflex haemofiltration systems installed with software versions 8.10, 7.20 and lower – risk of unexpected machine shutdown during treatment.Manufactured by Baxter
MDA/2019/038	Syringe driver pumps: T34™ 3rd edition models only – stop using the pump until updated instructions for use and BodyComm™ V3.0 software are released.
MDA/2019/039	Professional use defibrillator/monitor: Efficia DFM100 – risk of failure to switch on or unexpected restart.

There was one alert in November 2019:

Number	Title

MDA/2019/040	Alaris™ Gateway Workstation and Alaris™ Gateway Workstation web browser user interface.

Targeted Letters: There were five targeted letters sent in October 2019:

- AngioDynamics Solero microwave tissue ablation system - revised instructions for use to ensure the system is properly functioning prior to the surgical preparation of patients, to avoid a delay in providing therapy.
- Recall of Rocket Medical LLETZ diathermy loop extensions - a partial connection could result in a diathermy burn to the patient during a procedure.
- Recall of Pulsante® SPG microstimulator systems, which were not properly validated.
- Gentherm Medical Norm-O-Temp hyperthermia system – update to instructions for use to warn users that exceeding 40oC for extended periods may cause tissue damage.
- Medisoft nitric oxide analyser – risk of overheating of battery if left on charge for prolonged periods.

There were no Targeted Letters in November.

Devices Apprentices – Devices has three apprentices undertaking a masters level apprenticeship standard in regulatory affairs, which is delivered by The Organisation for Professionals in Regulatory Affairs (TOPRA). One apprentice met Sir John Hayes, former Minister of State for Further Education, who was previously involved in development of apprenticeships during his time in office. It was an opportunity to discuss his work, its impact on the availability and usefulness of apprenticeships now, the new Regulations and the value of developing regulatory skills through apprenticeships.

REGULATION POLICY AND OTHER SCIENTIFIC TOPICS

European/International Highlights

International Coalition of Medicines Regulatory Authorities (ICMRA): A Summit meeting held in Rome which was attended by the CEO and Policy Director. A number of bilateral meetings were also held to continue discussions regarding collaboration after Brexit. An ICMRA Executive Committee telephone conference took place on 25 November.

UK TOPICS

The Innovation Office – continues to act as a valuable point of contact for free, consolidated advice and 16 new enquiries were received in October. As well as responding to written enquiries, eight face-to-face or teleconference meetings were held in October. In November 2 new enquiries were received. As well as responding to written enquiries, seven face-to-face or teleconference meetings were held in November. Since the launch of the Innovation Office on 11 March 2013 there have been 912 relevant queries.

Partnership – We continue to build effective working relationships with relevant bodies across Government, the health sector and industry.

Business planning – We are beginning work to prepare the Agency's business plan for next year alongside action to sharpen up quarterly reporting against business plan priorities.

4. MINISTERIAL AND PARLIAMENTARY PRIORITIES

FOI Response Time Compliance – The table below shows FOI activity and compliance for requests received at 30 September. Figures are shown in arrears for the previous month. This

is because the 20-day deadline means most cases are still live during a given month and therefore we are unable to calculate compliance accurately.

Rolling FOI KPI total

September 2019

as at 30/09/2019	FOI Requests Received 2019/2020				
	Q1	**Jul**	**Aug**	**Sep**	**Total**
Received	137	61	58	50	**306**
Replies sent on time	136	61	58	50	**305**
Replies not yet due	0	0	0	0	**0**
Breaches	1	0	0	0	**1**
Compliance %	**99.3%**	**100.0%**	**100.0%**	**100%**	**99.7%**

Rolling FOI KPI total

October 2019

as at 31/10/2019	FOI Requests Received 2019/2020			
	Q1	**Q2**	**Oct**	**Total**
Received	137	170	60	**367**
Replies sent on time	136	169	60	**365**
Replies not yet due	0	0	0	**0**
Breaches	1	1	0	**2**
Compliance %	99.3%	99.4%	100.0%	**99.5%**

5. COMMUNICATION

All Staff Meetings – The third All Staff Meeting of the year took place on 15 October and over 200 colleagues joined the meeting remotely via Zoom, with nearly 400 people in the various rooms. A full transcript of the Q&As was published on INsite.

CPRD – The CPRD database has reached 20% population coverage and is receiving data for 13 million currently registered patients; an update was published on INsite for staff. CPRD exhibited and gave a presentation at the Royal College of GPs annual conference in Liverpool, to publicise the benefits of joining and contributing data to CPRD and how the data is used in research. A research poster was presented at the International Clinical Trials Methodology Conference (ICTMC) in Brighton.

The latest CPRD bulletin was distributed to GP practices that contribute data, with an update on recently published research papers using CPRD data. Across the UK, more than 1,700 practices now contribute data to CPRD.

Digital Health Software Algorithms – Sensyne Health announced a research collaboration with the MHRA to validate digital health software algorithms. We provided communications advice about the announcement. We responded to some trade press enquiries, and one from the Wall Street Journal.

Finance and Procurement – Withdrawal of cheque payments has been communicated by Finance to all organisations using this form of payment. On 1 November an update was placed on GOV.UK.

Interview with BBC Defenders programme – An interview with the BBC Defenders (a BBC programme following the work of enforcement officers as they battle to protect the public) took place at NIBSC; a member of MHRA Enforcement was interviewed regarding the Operation Upana case.

NIBSC Website activity has increased overall in October 2019 as compared to September 2019, driven by new content generation and social media referrals. Audience numbers remain stable monthly.

Patient/public engagement consultation – We carried out final promotion of the patient and public engagement (PPE) consultation, which closed on 7 October. A total of 807 responses were received to the questionnaire, which far exceeded our targets. We delivered a Northern Ireland public engagement event and Patient Group Consultative Forum (PGCF) meeting to support the consultation. We participated in a panel on PPE with regulators (MHRA and NICE) at the Genetic Alliance UK annual conference.

Events programme:

- **GMDP London** – this 4-day event was held at the Novotel Hammersmith from 11-14 November 2019. A total of 1138 paying delegates attended, with a target of 1093 over the 4 days. Ticket sales are currently showing that we have exceeded the target. The initial feedback has been very positive with a number of delegates saying that this year's event was the best one yet. The post event survey has been sent out to all delegates, the results of which should be available for us to review in approximately four weeks.

- **NIBSC Webinar** – a joint webinar with IBMS was held on 21 November. A total of 87 paying delegates registered, with 80 people logging onto watch. The financial report will be sent to us in due course, but ticket sales to date have exceeded the target. A survey has been sent out to all delegates, the results of which should be available for us to review in approximately 4 weeks. We have already received some positive feedback on how the webinar ran and how engaged the audience were.

In October, the recently appointed Science Coordinator for NIBSC, has been active in ensuring news stories are being put onto the NIBSC website as soon as possible. The co-ordinator has also started to work closely with NIBSC staff in ensuring the website content is being reviewed and starting to make changes in content to make it more useful and relevant to readers.

Website usage: There were 13,029 users of the NIBSC website this month which represents a 16% increase compared to last month and an 11% increase compared to the same period last year.

News stories: Two stories from last month were posted on the 'Latest news' section of the NIBSC website in October. The first was the story about colleagues representing NIBSC at the Institute of Biomedical Science (IBMS) congress in Birmingham at the end of September. This biennial event is the biggest biomedical science conference in Europe. The story outlined the sessions that NIBSC participated in and also advertised an upcoming webinar being run jointly with IBMS that is due to take place on 21 November. This story received a total of 42 unique page views in the month following its publication. For this event, six leaflets were designed in-house by event organisers Clare Morris and Neil Almond from Infectious Disease

Diagnostics Division, along with scientists from the division. These leaflets are now available for customers to access on the website: www.nibsc.org/leaflets.

The second story was following the WHO Consultation and Information Meeting on the Composition of Influenza Virus Vaccines for Use in the 2020 Southern Hemisphere Influenza Season. The story outlined NIBSC'S role at this meeting as an Essential Regulatory Laboratory and listed the strain recommendations with a link to the Influenza Resource Centre reagent list. This story received a total 121 unique page views in the month following its publication.

Website updates: The control testing webpage was updated to include a new graph and table that highlights the fast turnaround times that NIBSC offers for this service.

The Director's NIBSC-authored Paper of the Month for October 2019 (from those published/indexed on Pubmed in September) was: "The recent emergence of a highly related virulent Clostridium difficile clade with unique characteristics".

Shaw HA, Preston MD, Vendrik KEW, Cairns MD, Browne HP, Stabler RA, Crobach MJT, Corver J, Pituch H, Ingebretsen A, Primohammed M, Faulds-Pain A, Valiente E, Lawley TD, Fairweather NF, Kuijper EJ, Wren BW.
Clin Microbiol Infect. 2019 Sep 13. pii: S1198-743X(19)30489-6. doi: 10.1016/j.cmi.2019.09.004.
Selected for being a highly collaborative and clinically-relevant research paper

Summary: Clostridium difficile is a major global human pathogen divided into five clades, of which clade 3 is the least characterised. Here, the authors analysed the clinical presentation of C. difficile RT023 infections in comparison with known "hypervirulent" and non-hypervirulent strains, using data from the Netherlands national C. difficile surveillance programme. Clinical presentation of C. difficile RT023 infections show severe infections akin to those seen with "hypervirulent" strains. Given their recent emergence, virulence and genomic characteristics, the surveillance of clade 3 strains should be more highly prioritised.

The paper was selected from the following Original Research Papers.
1. A WHO Reference Reagent for lupus (anti-dsDNA) antibodies: international collaborative study to evaluate a candidate preparation.

Fox BJ, Hockley J, Rigsby P, Dolman C, Meroni PL, Rönnelid J.
Ann Rheum Dis. 2019 Sep 5. pii: annrheumdis-2019-215845. doi: 10.1136/annrheumdis-2019-215845.

2. Novel clinically relevant antibiotic resistance genes associated with sewage sludge and industrial waste streams revealed by functional metagenomic screening.

Zhang L, Calvo-Bado L, Murray AK, Amos GCA, Hawkey PM, Wellington EM, Gaze WH.
Environ Int. 2019 Sep 2;132:105120. doi: 10.1016/j.envint.2019.105120

3. Genetic diversity in the env V1-V2 region of proviral quasispecies from long-term controller MHC-typed cynomolgus macaques infected with SHIVSF162P4cy.

Capone A, Lo Presti A, Sernicola L, Farcomeni S, Ferrantelli F, Maggiorella MT, Mee ET, Rose NJ, Cella E, Ciccozzi M, Ensoli B, Borsetti A.
J Gen Virol. 2018 Dec;99(12):1717-1728. doi: 10.1099/jgv.0.001159. Epub 2018 Oct 12.

4. Comparative fitness analysis of D-cycloserine resistant mutants reveals both fitness-neutral and high-fitness cost genotypes.

Evangelopoulos D, Prosser GA, Rodgers A, Dagg BM, Khatri B, Ho MM, Gutierrez MG, Cortes T, de Carvalho LPS.
Nat Commun. 2019 Sep 13;10(1):4177. doi: 10.1038/s41467-019-12074-z.

5. Collaborative study for the calibration of the replacement International Standard for pertussis toxin for use in histamine sensitisation and CHO cell clustering assays.

Douglas-Bardsley A, Asokanathan C, Tierney S, Hockley J, Markey K.
Biologicals. 2019 Sep 13. pii: S1045-1056(19)30086-7. doi: 10.1016/j.biologicals.2019.09.001.

Reviews/other publications

WHO international standard for anti-rubella: learning from its application.

Kempster SL, Almond N, Dimech W, Grangeot-Keros L, Huzly D, Icenogle J, El Mubarak HS, Mulders MN, Nübling CM.
Lancet Infect Dis. 2019 Sep 6. pii: S1473-3099(19)30274-9. doi: 10.1016/S1473-3099(19)30274-9. [Epub ahead of print] Review.
PMID: 31501007

The Standardisation Science group at NIBSC have had a publication accepted based around a collaboration with two PhD students of Prof Yvonne Perrie of Strathclyde University – entitled “Freeze drying cycle optimization for the rapid preservation of protein-loaded liposomes” - now available in press in the International Journal of Pharmaceutics https://doi.org/10.1016/j.ijpharm.2019.118722

In November the Science Coordinator for NIBSC has summarised Communications activities supporting NIBSC this month.
1) Website usage: There were 11,929 users of the NIBSC website this month. This is a 8% decrease compared to last month but a 5% increase compared to the same period last year.

2) NCMG: The NIBSC Communications Management Group has been relaunched with a new format. NIBSC champions have also been appointed to represent their divisions at meetings based around 4 key communication themes: website/INsite, events, publications and thought leadership. The first meeting is scheduled to take place on 10 December.

3) News stories: As part of efforts to increase internal awareness of the work being carried out at NIBSC a story was posted on INsite about the institute’s involvement in the Global Polio Eradication Initiative. This piece received very positive feedback from colleagues across the MHRA.

On Thursday, 21 November, members of the Infectious Disease Diagnostics (IDD) divisions of NIBSC, joined by two external speakers from Viapath and United Kingdom Accreditation Service (UKAS), delivered the second in a series of webinars from this group. The webinar was delivered in conjunction with the Institute of Biomedical Scientists (IBMS) and was designed to engage with IBMS members and NIBSC customers. The webinar was entitled “Assay and device validation and verification with respect to ISO 15189”. There were over 90 paying attendees to the webinar, which received excellent feedback as well as nearly 40 questions indicating that the subject was of interest to the audience and that they were highly engaged throughout. The IBMS were delighted with the response with thanks to Sach Sandhu and NIBSC aim to deliver the third webinar in this series in March 2020. The ticket sales indicate that this event has well exceeded its target income.

NIBSC-authored Papers November 2019

Two papers were selected as the Director's NIBSC-authored Paper of the Month for November 2019 (from those published/indexed on Pubmed in October), both related to the work at NIBSC on Zika virus, recognising NIBSC's work in this new and important area of emerging viruses, which cover both establishment of relevant standards and research. The papers were:

1. High susceptibility, viral dynamics and persistence of South American Zika virus in New World monkey species.

Berry N, Ferguson D, Ham C, Hall J, Jenkins A, Giles E, Devshi D, Kempster S, Rose N, Dowall S, Fritzsche M, Bleazard T, Hewson R, Almond N.

Sci Rep. 2019 Oct 10;9(1):14495. doi: 10.1038/s41598-019-50918-2

Summary: South American Zika virus (ZIKV) recently emerged as a novel human pathogen, linked with neurological disorders. However, comparative ZIKV infectivity studies in New World primates are lacking. Here, the authors studied zika infection in common marmosets and red-bellied tamarins and found both species to be highly susceptible to sub-cutaneous challenge with the Puerto Rico-origin $ZIKV_{PRVABC59}$ strain, having a higher viraemia than Old World species. Tamarins and rhesus macaques shoed symptoms of compromised blood-brain barriers 3 days post-ZIKV exposure and early, widespread dissemination across multiple anatomical sites. Therefore, Tamarins and marmosets represent viable New World models for ZIKV pathogenesis and therapeutic intervention studies, including vaccines.

2. Harmonization of Zika neutralization assays by using the WHO International Standard for anti-Zika virus antibody.

Mattiuzzo G, Knezevic I, Hassall M, Ashall J, Myhill S, Faulkner V, Hockley J, Rigsby P, Wilkinson DE, Page M; collaborative study participants.

NPJ Vaccines. 2019 Oct 14;4:42. doi: 10.1038/s41541-019-0135-3. eCollection 2019

Summary: In this study, the authors show how the 1st WHO International Standard for anti-Zika antibody was able to harmonize the neutralization titres of a panel of serological Zika-positive samples from laboratories worldwide. Expression of the titres in International Unit per millilitre reduced the inter-laboratory variance, allowing for greater comparability between laboratories. We advocate the use of the International Standard for anti-Zika virus antibodies for the calibration of neutralization assays to create a common language, which will permit a clear evaluation of the results of different clinical trials and expedite the vaccine/treatment development.

The papers were selected from the following Original Research Papers.

3. Towards quantification of protective antibody responses by passive transfer of the 1st WHO International Standard for Ebola virus antibody in a guinea pig model.

Dowall SD, Kempster S, Findlay-Wilson S, Mattiuzzo G, Graham VA, Page M, Hewson R, Almond N.

Vaccine. 2019 Oct 24. pii: S0264-410X(19)31372-6. doi: 10.1016/j.vaccine.2019.10.009.

4. Biosafety risk assessment for production of candidate vaccine viruses to protect humans from zoonotic highly pathogenic avian influenza viruses.

Chen LM, Donis RO, Suarez DL, Wentworth DE, Webby R, Engelhardt OG, Swayne DE.

Influenza Other Respir Viruses. 2019 Oct 28. doi: 10.1111/irv.12698.

5. Clostridium difficile clade 3 (RT023) have a modified cell surface and contain a large transposable island with novel cargo.

Shaw HA, Khodadoost L, Preston MD, Corver J, Mullany P, Wren BW.

Sci Rep. 2019 Oct 25;9(1):15330. doi: 10.1038/s41598-019-51628-5.

6. Complete Genome Sequence of Original Material Used To Derive the WHO International Standard for Human Polyomavirus BK DNA.

Jenkins A, Govind S, Morris C, Berry N.

Microbiol Resour Announc. 2019 Oct 24;8(43). pii: e00911-19. doi: 10.1128/MRA.00911-19.

Reviews/other publications

7. Quantification of Pancreatic Islets: Using Image Analysis Tools.

Harikumar PE.

Methods Mol Biol. 2020;2076:215-229. doi: 10.1007/978-1-4939-9882-1_12.

6. ORGANISATIONAL TOPICS

Human Resources – We celebrated Black History Month with a host of information and stories from staff daily throughout the month on Insite and screens, and were delighted to host John James OBE, Chief Executive of the Sickle Cell Society, who delivered a talk to staff about sickle cell disorder - what it is, treatment, keeping well and supporting others. The Sickle Cell Society is celebrating 40 years in 2019. We also promoted the range of financial wellbeing information and support for staff – help with budgeting, debt management and saving. We celebrated Carers Rights Day, promoting the Civil Service carers passport, a communication tool to enable a carer and their manager to discuss and record the flexibilities needed to combine caring and work. We also reminded carers of the support available to them through our commitments to health and wellbeing, our employee assistance programme, the availability of emergency carers leave and 'For you, by you, the Charity for Civil Servants.

The WHO Expert Committee for Biological Standardisation, the highest body to approve (or not) International Standards, held their annual meeting in October. A number of novel standards were endorsed or approved, and full details will be published in due course.
In addition, the WHO announced eradication of two of three wildtype polio viruses and NIBSC have contributed greatly to this achievement. There will be more information on this as we publish further communications on the subject.

NIBSC was part of a successful grant application to a Medical Research Council and Japan Agency for Medical Research and Development (MRC – AMED) joint call for proposals. The project will be led by Dr Yohei Yamauchi from the University of Bristol and will investigate the need for host factors in the entry of influenza viruses into cells. This research may lead to new pathways for attenuating influenza viruses.

The principal Scientist from the Bacteriology Division has been awarded a joint Bill & Melinda Gates Grant with Ravi Ganapathy of the International Vaccine Institute (Seoul Korea) and a colleague from Bioconsult (New York City, USA) to develop critical reagents for the potency assay of oral inactivated cholera vaccines. NIBSC will receive approximately £197k to develop and produce a recombinant monoclonal antibody against O1, as well as other reagents, which will help to standardise this batch release assay.

As part of a project to reduce storage costs, and in particular reducing the need for off-site storage, contingency stocks of standards that were being stored by an external repository have been brought back to the South Mimms site. This is part of an OT project and this move will save around £20,000 per year in storage fees. The project has also had to consider the business continuity aspects of ensuring that stocks are not all held in the same location so storage on site has had to take this into account.

The Dispatch Manager in the Standards processing Division qualified this month as Dangerous Goods Safety Advisor (DGSA) for NIBSC. This required a huge amount of work and is a great achievement. He will be developing his role throughout NIBSC, providing advice and updating guidance and policies as required. He will gradually be considering the wider

requirements for the Agency through the H&S team to ensure all risks are covered for activities across the organisation.

Licensing staff presented at 5 external meetings during October:

Name of Event & Location	Title of Presentation
Joint Pharmaceutical Analysis Group (London)	Mutagenic impurities: a regulatory overview
Cell & Gene Therapy Congress (London)	Cell & Gene Therapy Congress
Combination Products 2019 (Berlin)	Medicine Regulation
Wearable Injectors and Connected Devices (London)	A regulatory outlook of Wearable Injectors and Connected Drug Delivery Devices
SMi's 9th Annual Orphan Drugs & Rare Diseases Conference (London)	Impact of Brexit on rare disease research

Licensing staff presented at 5 external meetings during November:

Name of Event & Location	Title of Presentation
Visad Annual Meeting (Turkey)	Overview of GMP Inspections in Europe
Early Phase Clinical Development (Barcelona)	Regulatory perspective on Innovative Protocol Designs in Early Phase Designs: Basket, Umbrella and Platform designs
Early and Managed Access Programmes (London)	Navigating the Current and Future Regulatory Landscape of Early and Managed Access Programmes
Ophthalmic Drugs Conference (London)	Regulatory outlook on ocular drug clinical development
Pharmaceutical Aerosols, Dry Powder Inhalation Systems and Nasal Delivery Devices (London)	Regulatory Considerations for Inhaled Delivery Devices

Medical Devices Safety Officers webex – This month the Medical Devices Safety Officers webex focussed on the BD T34 syringe pump, which is the first time one specific device has been discussed in the such detail. However, there are many issues with this pump that affect most MDSOs. MSOs were also invited to attend – there were over 150 attendees.

The Polio group at NIBSC hosted two workshops in November:
The first was the 13th joint NIBSC/EDQM (European Directorate for the Quality of Medicines and Healthcare) workshop on Training and implementation of the Transgenic Mouse Test for Oral Polio Vaccine. It took place on 12-13 November 2019 NIBSC. The workshop was designed to allow scorers of the Oral Poliomyelitis Vaccine (OPV) Transgenic Mouse Neurovirulence Test (TgMNVT) a hands-on opportunity to compare practices and to discuss technical and practical issues specific to the test. The workshop participants included EU Official Medicines Control Laboratories (OMCLs) and manufacturers. In view of the expanding interest of the application of the TgMNVT in some non-EU countries, EU OMCLs and manufacturers considered it beneficial to extend the

exchange and invite non-EU participants from both control authorities and manufacturers since 2016.

The second workshop was on the Standardization and Quality Control testing of Sabin Inactivated Polio Vaccines (sIPV). This was also held at NIBSC on 18- 27 November and was organised by colleagues from the Polio Group. The background to this is as follows: In order to produce IPV more safely, several manufacturers are producing IPV using Sabin poliovirus strains rather than the usual wild type strains that have been used for conventional IPV (cIPV) for more than 50 years. As many as 17 new manufacturers are producing or plan to produce Sabin IPV (sIPV) in the near future. The potency of cIPV and sIPV is measured in vitro using a validated ELISA (enzyme-linked immunosorbent assay) test with suitable reference preparations and it is expressed in D-Antigen units (DU). The study outcomes strongly suggested that assay validity and between-laboratory variability for in-house methods improved when a sIPV sample was used as a reference to determine the potency of sIPV study samples. Because of this it is very important that suitable reference standards and methodologies to assess the quality of sIPV products are available to meet the increasing demands, and hence the need for a sIPV International Standard (IS).

The 1st International Standard for sIPV was endorsed by WHO in 2018 with the new unitage SDU (Standard D-antigen Units). In order to try and harmonise methods (in vitro and in vivo) and promote the use of the new IS, NIBSC was asked to organise a number of workshops for manufacturers and National Control Laboratories. This workshop included 10 participants from Chinese producers. The aim of the workshop was to provide support by practical activities and lectures on topics related to the Quality testing /standardisation required, and to promote understanding of how to calibrate current references using the new IS and SDU units. The workshop was highly successful with excellent feedback. It has helped strengthen and harmonise methodology as well as initiating collaboration and discussion between participants and NIBSC.

CEO meetings in October 2019

On the 2nd of October the CEO met with Raj Long of the Gates Foundation; and on the 4th October attended the CHM Expert Working Group meeting on Yellow Fever Vaccine. On the 7th October the CEO and Chairman had a meeting with Baroness Blackwood to discuss Brexit; following this Dr Raine joined a Life Sciences EU Relationship Group teleconference hosted by the Office for Life Sciences. The CEO had a teleconference with Professor Donal O'Donoghue from the Royal College of Physicians on the 9th of October, regarding the MHRA's approach to Artificial Intelligence regulation; this was followed by the MHRA Annual Lecture at the King's Fund, delivered by Sir John Bell. On the 10th October the CEO attended a meeting at DHSC with Sir Chris Wormald, DHSC Permanent Secretary. On the 11th October the CEO met with the new Chief Medical Officer Chris Whitty for an introductory meeting.

On October 16th the CEO gave a keynote talk on '*Regulation & delivering innovative therapies to patients'* at the ABPI Ethics and Regulation of Innovation conference. A meeting was held with Sir Andrew Dillon, Chief Executive of the National Institute for Health and Care Excellence, to discuss Brexit. Dr Raine attended the MDEpiNet (the FDA Medical Devices Epidemiology Network) meeting in Washington on the 22nd of October and gave a presentation on '*International Collaborations and Partnerships int eh Regulatory Setting: a UK perspective'.* On the 23rd October the CEO and Chairman attended the Accelerated Access Collaborative Board meeting.

There was an ICMRA summit held in Rome over 28-30th October, which the CEO and Director of Policy attended. The CEO chaired a session on clinical trials in special populations and gave a presentation on medicines in pregnancy. On the 31st October a meeting with the European Medicines Group was held at the MHRA offices in Canary Wharf; this was followed

by the MHRA's Annual Accountability Review Meeting at the House of Lords which the CEO and Chair attended.

CEO meetings in November 2019

On the 1st November, the CEO attended a meeting with Professor Lesley Regan, the president of the Royal College of Obstetricians and Gynaecologists to discuss women's health. Following this Ian Trenholm, CEO of the Care Quality Commission, visited MHRA to meet with the CEO, and the Directors of VRMM and Devices divisions; then Dr Raine met with the Chief Medical Officer. On the 8th November Dr Raine attended the NIBSC Scientific Advisory Committee meeting, followed by a visit to the UK Stem Cell Bank at NIBSC. On The 12th November the CEO attended a meeting with Jonathan Marron, Director General of Community and Social Care at DHSC. The DHSC Audit and Risk Committee meeting took place on the 13th of November, followed by the Whitehall Responsible Officer meeting on the 14th. The CEO attended the IMMDS steering group meeting at DHSC on the 15th November. On the 19th November the CEO attended a viewing at the Science Museum's *Medicine: The Wellcome Galleries* exhibition where there is an exhibit featuring the Yellow Card; and following this had a teleconference with Professor Peter Borriello, CEO of the Veterinary Medicines Directorate, to discuss how the VMD and MHRA work together.

On 27th November the CEO attended an introductory meeting with Matthew Gould, the CEO of NHS X: a joint unit between the Department for Health and Social Care and NHS England, set up to ensure that staff and patients have the technology they need. On the 28th November Dr Raine chaired a round table meeting on the Valproate Pregnancy Prevention Programme which was attended by a patient group INFACT and representatives from NICE, the CQC, General Medical Council, General Pharmaceutical Council, the Chief Pharmaceutical Officer, NHS England and NHS Improvement.

OPERATIONAL PERFORMANCE

New UK Marketing Authorisations (MAs) – No new active substance applications were assessed in October or November.

New UK Marketing Authorisations (MAs) - Existing Active Substances – The number (volume) of new MA applications assessed in October was higher when compared with the average number of assessments completed in 2018/19. The numbers of new applications determined in October was lower compared with the average monthly figures for 2018/19. (Annex - Table 1)

The number (volume) of new MA applications assessed in November was lower when compared with the average number of assessments completed in 2018/19. The numbers of new applications determined in November was lower compared with the average monthly figures for 2018/19. (Annex - Table 1).

New UK Marketing Authorisations - Existing Active Substances

Procedure	MAA Assessed October 2019	MAA Assessed 2018/19 Average per month
National, UK-only	55	35
Decentralised, UK=RMS	0	9
Decentralised and MR, UK=CMS	31	36
Total	86	80

Procedure	MAA Determined October 2019	MAA Determined 2018/19 Average per month
National, UK-only	39	27
Decentralised, UK=RMS	1	28
Decentralised and MR, UK=CMS	40	52
Total	80	107

Procedure	MAA Assessed November 2019	MAA Assessed 2018/19 Average per month
National, UK-only	24	35
Decentralised, UK=RMS	0	9
Decentralised and MR, UK=CMS	38	36
Total	62	80

Procedure	MAA Determined November 2019	MAA Determined 2018/19 Average per month
National, UK-only	24	27
Decentralised, UK=RMS	20	28
Decentralised and MR, UK=CMS	22	52
Total	66	107

Regulatory Information Service – In October, 973 enquiries were received (769 e-mails, 204 phone calls). 18 grouping requests were processed and 11 requests for expedited review were also made to LD in the month of October 2019. The number of complex/technical enquiries forwarded on to assessment teams in October was 1, equating to 0.13% of emails received by the RIS, with an average PLAT response 5 days. In November 2019 809 enquiries were received (667 e-mails, 142 phone calls). A total of 18 grouping requests were processed and 5 requests for expedited review were also made to LD in the month of November 2019. The number of complex/technical enquiries forwarded on to assessment teams in November was 1, equating to 0.15% of emails received by the RIS, with an average PLAT response in 3 days.

Parallel imports (PLPIs) – In October, 78 PLPI initial submissions were received, 65 were assessed and 61 were determined (58, 87 and 35 respectively in September). Median time from submission to grant was 3.4 months (3.7 months in September). 1033 PLPI variation applications were received, 602 were assessed and 573 were determined (741, 779 and 812 respectively in September). Average time from submission to grant was 2.6 months (2.0 months in September). In November, 55 PLPI initial submissions were received, 63 were assessed and 58 were determined (78, 65 and 61 respectively in October). Median time from submission to grant was 3.4 months (3.4 months in October). A total of 686 PLPI variation applications were received, 680 were assessed and 614 were determined (1033, 602 and 573 respectively in October). Average time from submission to grant was 2.7 months (2.6 months in October).

Public Assessment Reports (PARs) – 100% of UK Public Assessment Reports and Lay Summaries (19/19) completed in October 2019 were published within the 60-day high-level target time from grant of the Marketing Authorisation. 100% of UK Public Assessment Reports and Lay Summaries (14/14) completed in November 2019 were published within the 60-day high-level target time from grant of the Marketing Authorisation. There was one update to a PAR for a Type II variation published in November 2019.

Clinical Trial Authorisations (CTAs) applications: In October, a total of **82** applications were assessed this month. This includes 79 'standard' applications and 3 applications received via the combined ways of working (CWoW) pilot. For the financial year-to-date, **68** fewer 'standard' applications have been assessed compared with the same period last year (**555** for 2018 compared to **487** for 2019). CWoW applications have increased from 21 in 2018 to 51 in 2019. There were **12** first in UK and 11 first in human (FIH) studies assessed in October (including CWoW). In October, the Clinical Trials Unit received **4** novel amendment submissions (2 Platform and 2 Umbrella).
In November a total of **69** applications were assessed this month. This includes 66 'standard' applications and 3 applications received via the combined ways of working (CWoW) pilot. For the financial year-to-date, **87** fewer 'standard' applications have been assessed compared with the same period last year (**640** for 2018 compared to **553** for 2019). CWoW applications have increased from 21 in 2018 to 54 in 2019. There were **10** first in UK and **14** first in human (FIH) studies assessed in November (including CWoW). In November, CTU received **1** novel initial and **1** amendment submissions (1 Platform and 1 Umbrella).

Pharmacovigilance Adverse Drug Reactions (ADRs) – A total of 4133 UK ADR reports were received in October 2019, of which 971 were received from patients, parents and carers. Results against key performance measures for fatal and serious reports were both 100%. 88% of UK spontaneous serious ADRs were sent to EMA within the High-Level Target of 11 days, 11% of reports were sent to the EMA in 12-15 days with 1% (26 reports) being sent after the 15-day legislative target. We are currently looking into our processes to ensure this does not happen moving forwards. Of 150 general enquiries received, 95% were answered within 7 working days and 100% within 10 working days.

In November, a total of 4067 UK ADR reports were received in November 2019, of which 897 were received from patients, parents and carers. Results against key performance measures for fatal and serious reports were both 100%. 91% of UK spontaneous serious ADRs were sent to EMA within the High-Level Target of 11 days, 5% of reports were sent to the EMA in 12-15 days with 4% (26 reports) being sent after the 15-day legislative target. Since we are continuing to process non-serious reports from our ADR backlog, some of these will inevitably become serious upon manual review and therefore given the different legislative timelines for expedition between serious and non-serious reports some will miss targets. Of 155 general enquiries received, 93% were answered within 7 working days and 100% within 10 working days.

Devices adverse incidents – In October, 2,352 Adverse Incident reports were received (which compares with 2,227 for the same month last year), an increase of 5.6%. The cumulative total for this year is 18,659, which compares with 17,279 for 2018, an increase of 8.0%. 2,017 Adverse Incident reports were received in November (which compares with 1,774 for the same month last year), an increase of 13.7%. The cumulative total for this year is 20,676, which compares with 19,053 for 2018, an increase of 8.5%.

Devices clinical investigations - 100% of clinical investigations have been completed within 60 days and the average review time for the year to date is 56 days. 4 clinical investigations were completed in October. 100% of clinical investigations have been completed within 60 days and the average review time for the year to date is 56 days. 6 clinical investigations were completed in November

Biologics batch release – Levels of test release certificates issued again slightly increased this month, with 75 vaccines and blood product batches issued in October compared to 72 batches issued in September. The target for timeliness of product testing was achieved in October. There were 20 plasma pool releases in October compared to 11 the previous month. There were two supplementary certificates issued originating from the manufacturer.

7. OTHER INTERNATIONAL TOPICS

GMP Symposium – The GMP Inspectorate hosted their annual symposium on the 12, 14 and 27 November, alongside the accompanying Good Distribution Practice (GDP) days on the 11, 13 and 26 November. This event was run jointly between the GMP and GDP Inspectorates due to the number of licence holders who operate in both areas, and the requirement for manufacturers to distribute their products in accordance with GDP even if no separate licence is held. This year the GMP event focused on the theme of 'Control Strategies'. Sessions introduced the concept and building blocks of a control strategy, gave examples of where a lack of control had led to safety, quality and regulatory issues, and explored specific applications within cross-contamination and sterile product manufacture. Delegates were then given an opportunity in a workshop setting to develop a control strategy for a case study relevant to their area of work. Question and answer sessions were also held featuring a panel of inspectors. This was the first time the GMP event had travelled to Glasgow, allowing MHRA to reach a larger number of stakeholders as for the past few years the London event has been sold out. Across the three days a total of 826 delegates attended which is an increase of 147 over the 2018 event. We also welcomed several guests from our regulatory partners such as VMD, HTA and European Regulatory Agencies

Serum Institute of India representatives visited NIBSC on 11 October for a follow-up meeting to discuss research and development Projects and collaborations. It was a very positive meeting with good discussion and development of a strong relationship.

A member of the Bacteriology Division, and one of the partners in TBVAC2020 consortium, participated in a workshop on ‘Maintaining European scientific excellence and global leadership in Tuberculosis (TB) Vaccine R&D, EU funded collaborative research and innovation’ on 8 October 2019 in Brussels. This meeting brought together scientists, policy makers, funders and other key stakeholders in TB vaccine research and innovation (R&I). The results and impact of three Horizon 2020-funded TB research projects (TBVAC2020, EMI-TB and STriTuVaD) on the TB vaccine field were presented. Meeting participants also contributed in discussion on recommendations to sustain and strengthen collaborative R&I to maintain European scientific excellence and global leadership in TB vaccine R&I.

The Principal Scientist in Standardisation Science group at NIBSC, was invited to lecture at the Department of Applied Sciences at Politecnico di Torino, in Turin, Italy on 1 October and spent the day networking potentially useful contacts between academics there and NIBSC. He combined this with the Care Coordination Quality Measure for Primary Care (CCQM) workshop on advanced analytical technologies in the life sciences at which Sandrine Vessillier (Biotherapeutics Division) was speaking, and then attended part of the Protein Analysis Working Group at the Italian National Metrology Institute (INRIM).

The Acting Head of Virology at NIBSC, visited the University of Texas Medical Branch (UTMB) at Galveston. She presented a seminar, “Raising the (biological) standards of viral vaccines”, met with faculty and students and had a tour of the high containment facilities. The visit was in support of the MoU NIBSC has with UTMB and developing regulatory science collaborations including the potential for hosting doctoral students at NIBSC.

Dr June Raine
Interim Chief Executive