Medicines & Healthcare products Regulatory Agency

Public Board Meeting

16 September 2019

CHIEF EXECUTIVE'S REPORT FOR THE MONTHS OF JULY AND AUGUST 2019

1. HEADLINES for July and August 2019

Brexit: Work on No Deal preparation has ramped up considerably over recent weeks. We have started to see a confluence of No Deal, Deal and Trade discussions. However, it is clear that work is still required on prioritisation and managing any possible conflicts that arise between these different streams.

The Human Medicines and Medical Devices (Amendment etc) (EU Exit) Regulations 2019 – The Agency updated our GOV.UK page and sent an email to stakeholders about the laying in Parliament of The Human Medicines and Medical Devices (Amendment etc) (EU Exit) Regulations 2019. This instrument makes a number of changes to the Human Medicines (Amendment etc.) (EU Exit) Regulations 2019 and the Medical Devices (Amendment etc.) (EU Exit) Regulations 2019 to ensure that the UK legislation accurately reflects technical updates at EU level since April 2019. It also corrects drafting errors and omissions to reflect published policy in the event of a No Deal Brexit. The legislation will be subject to parliamentary scrutiny and approval which we anticipate later in the Autumn.

We have updated all our No Deal guidance on GOV.UK to make all Brexit content as concise and user-friendly as possible, and in line with preferred Government terminology. As the current focus is preparedness for No Deal, our guidance on this is regularly being audited with minor rewrites and webpage restructuring to make it as easy for audiences to understand as possible. We are working with the subject matter experts across the Agency to make these changes.

As part of our 'Shaping our Future' internal communications campaign, we held a Brexit 'open door' session for staff. This was attended by 43 colleagues in person and 10 via Zoom.

The Annual Report and Accounts – The Agency's Annual Report and Accounts were printed and laid in Parliament and published on GOV.UK on 18th July. We emailed a link to the report to the Patient Group Consultative Forum (PGCF).

Calea UK Limited – On 24-26 June 2019 the Inspectorate performed a routine inspection of Calea UK at its registered site in Runcorn. The site manufactures infant and adult TPN for named patient supply to home care patients and bags are also manufactured for stock for hospital supply. During the inspection, problems were identified with the design of the manufacturing process for total parenteral nutrition (TPN) bags that did not meet the requirements of guidance published by MHRA in 2015.

From a sample taken by Calea on 25 June as part of Calea's routine monitoring designed to detect microbial contamination in the production area and on production personnel, bacteria of the type Bacillus cereus / thuringiensis / mycoides were recovered. The equipment used for identification is not sufficiently sensitive to identify the exact type of bacteria, so in these

situations we expect the facility to address the worst-case organism, which would be Bacillus cereus. These bacteria are known human pathogens, which is of particular concern for the many vulnerable patients receiving parenteral nutrition. This contamination, in combination with our inspectors identifying that production processes were not in compliance with MHRA guidelines dating from 2015 presented a potential risk to patients and caused us to take immediate action to instruct the company to implement important changes.

Even though this contamination was found in the production area, it is important to add that we found no evidence to indicate that the products manufactured and supplied to patients during this period were contaminated. When the problems were identified we requested that Calea take immediate action to change their manufacturing process to ensure compliance with the MHRA's published standards. This has led to a reduction in output while they consider longer term changes to their processes.

MHRA Inspection Action Group (IAG) is working closely with DHSC with regard to the supply situation and an Incident Management Team (IMT) has been set up internally to manage the situation. Inspectors continue to monitor the changes at Calea through weekly inspections.

This situation has now been declared as an Emergency Preparedness, Resilience and Response (EPRR) incident, and is being managed by NHSE-I EPRR. An Incident Management Team (IMT) has been set up with Aidan Fowler, National Director of Patient Safety at NHSE-I as the Incident Director. This IMT includes senior members from NHSE-I, DHSC Medicine Supply team and MHRA. The Clinical expert team comprising of national PN experts is continuing to support the IMT management response.

The IMT continues to monitor patient supplies, ensuring patient plans are in place for all patients affected. To ensure patients receive up to date information, the IMT has also co-ordinated a number of letters to patients and healthcare professionals (HCPs) to provide ongoing updates with the supply situation and advice for HCPs. MHRA continues to respond to enquiries from patients, healthcare professionals and journalists and have held a number of telephone calls with both concerned patients and clinicians.

2. PRODUCT RELATED ISSUES

Medicines issues

Valproate and risks in pregnancy – In July VRMM attended the first meeting of the Scottish Government Sodium Valproate Advisory Group in Edinburgh. The Group has been convened to consider what additional Scotland-specific work is required to implement the current regulatory measures and/or increase patient and professional awareness of the risks. There was consideration of the latest data on the uptake of the valproate Pregnancy Prevention Programme (PPP) at the public meeting of the Agency Board in July. The Board noted that MHRA will work with NHS England and NHS Improvement and the devolved administrations to deliver a coordinated response to the advice of the Commission on Human Medicines (CHM) to explore direct recall of women on valproate and a move to closer specialist supervision. The Agency Board supported the proposed next steps. The Agency also met SUDEP Action to discuss the charity's work regarding 'Sudden Deaths in Epilepsy' and its potential contribution to the Valproate Stakeholders Network via its support for the implementation of the regulatory measures.

Isotretinoin and psychiatric reactions and persistent sexual dysfunction – Following concerns raised at the public meeting of the Agency Board, VRMM met with patients groups concerned with depression and suicidal behaviour associated with isotretinoin, and also with persistent sexual dysfunction. There are warnings in the Summary of Product Characteristics (SPC) and Patient Information Leaflet (PIL) for isotretinoin about the risk of psychiatric

reactions, suicidal behaviour and sexual dysfunction, however concerns have been raised that patients are not being fully informed before making decisions about their treatment and that isotretinoin is being prescribed to people who do not have the most severe form of acne and for whom the risks of treatment are not outweighed by the benefits.

Hormone Replacement Therapy (HRT) and breast cancer – On 27 August the Lancet held a press conference to announce publication on 29 August of new data on HRT and invasive breast cancer showing that some increased risk of breast cancer persists for more than a decade after stopping HRT. In accordance with advice from the Medicines for Women's Health Expert Advisory Group (MWHEAG) and from the CHM, VRMM sent a letter to prescribers plus an information sheet for women via the Central Alerting System (CAS) and worked with Communications Division on a press release supported by social media posts and an article will be included in the September edition of the Drug Safety Update bulletin. Media coverage has been relatively balanced to date.

SSRIs and risk of suicide in adults – In 2016 the EU conducted a review based on a publication from the Cochrane group looking at Clinical Trial data on risk of SSRIs and suicidal behaviour. The review concluded no action was required in relation to product information. In March this year a re-analysis of the FDA database was published (Hengartner, 2019) which found evidence that the rate of attempted suicide was about 2.5 times higher in antidepressant arms relative to placebo. VRMM will now review the new evidence to see if there are any implications for product information regarding the risk of suicide in adults who use SSRIs.

Medical Devices issues

Urogynaecological surgical mesh (for the treatment of stress urinary incontinence and prolapse) – We have drafted specific guidance for patients and clinicians. In doing so, we aim to make a wide range of information easily accessible to women to support informed choice regarding their treatment. A draft has been sent to patient groups and organisations in the healthcare system. We are keen to ensure this information reflects, as far as possible, what people would find most useful and will be published on our website later this year. Healthcare Canada has taken action to remove transvaginal mesh for prolapse of the rectum from the Canadian market. It placed restrictions on use of transvaginal mesh for prolapse of the bladder and uterus. Only the former action is in line with other (non-EU) regulators who have taken action. No other mesh product is affected and the manufacturers affected do not supply to the UK. These types of mesh are already subject to restriction in use through the Cumberlege Review (IMMDSR) pause and relevant interventional procedure guidance by the National Institute for Health and Care Excellence (NICE).

Surgical mesh for the treatment of hernias (including inguinal) – We have discussed hernia mesh with other regulators. Hernia mesh (inguinal) is well established as a treatment pathway and is subject to guidance from NICE. It is excluded from the IMMDSR pause and NHS high vigilance restriction programme. We continue to monitor the evidence.

Breast Implants –

- **Patient Engagement –** Comms & Devices worked together to respond to an email from the PIP Action Campaign and participated in a meeting with a breast implant campaigner and a reporter from the Dispatches TV programme.
- **Media Engagement –** Comms arranged and supported an interview with Nigel Mercer, Chair of the Plastic, Reconstructive and Aesthetic Surgery Expert Advisory Group (PRASEAG) and the BBC Health Team on breast implants.
- **Allergan –** MHRA updated the webpage following the global recall of Biocell coated devices (These implants have not been available in the UK since Dec 2018). A link to the US Food and Drug Administration's (FDA) announcement of Allergan's recall was

included in the webpage update. Comms and the Devices Division sent an email to stakeholders on the FDA's decision to remove Allergan's Biocell breast implants and tissue expanders from the US market and Allergan's global recall of these implants, to reassure them that the devices are not currently on the UK market, and that there is no recommendation to explant devices in the absence of symptoms.

- **Breast Implant webpage –** Devices are working with Comms and our experts on a draft .GOV page on breast implants.

Medical Device Alerts

There were three alerts in July 2019

Number	Title
MDA/2019/025	IntelliVue MX40 patient-worn monitors – increased power consumption and no visual or audible alarms when batteries are low.
MDA/2019/026	Professional use capillary blood specimen collection: BD Microtainer® tubes – risk of blood leakage and/or incorrect test results due to defective tubes.
MDA/2019/027	Automated external defibrillators: All Telefunken HR1 & FA1 – no valid CE certificate.

There was one alert in August 2019

Number	Title
MDA/2019/028	Microneedling pens: Dermapen 3 and Dermapen Cryo Sterile single use needle cartridge tips for: Dermapen 3 – risk of injury or infection.

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

- Drager heated breathing circuits – cracks appearing in the breathing tube during ventilation of patients.
- Incorrect expiry dates on Teleflex Arrow central venous catheters.
- Maquet surgical lights – possible breakage of light head shaft.
- Teleflex endotracheal tube for laser surgery – partial detachment of the laser guard foil.
- Change Healthcare cardiac output (blood flow) patient monitors – failure to notify user of medication discrepancies during procedure.

There were no Targeted Letters in August.

3. REGULATION POLICY AND OTHER SCIENTIFIC TOPICS

European/International Highlights

International Coalition of Medicines Regulatory Authorities (ICMRA) – On 16 July an Executive Committee (EC) teleconference took place. The Committee endorsed ICMRA statements on anti-microbial resistance and biosimilars for publication. Subsequently, another next EC teleconference took place on 2 September. Arrangements are in hand for the secretariat to transfer from the MHRA to the EMA at the end of September. The Agency led a telecon with the ICMRA Comms Group, and agenda items included feedback from ICMRA on San Diego event in June. We also discussed proposed ICMRA meetings/events in 2020, a communications plan on antimicrobial resistance, update on ICMRA website, and a proposal to develop a common communications plan on vaccine hesitancy. We also discussed a

proposal to hand over the Communications Group Chair to EMA at the same time as the Chair of ICMRA moves to the EMA at the end of September.

Memorandums of Understanding (MoUs) – On 2 September a MOU was signed with Iceland. There is a meeting arranged for the end of September with Guernsey to discuss updating our current MoU with them.

CHM Annual Report – We assisted the printing and laying of the Commission of Human Medicines Annual Report and its publication on GOV.UK.

UK TOPICS

NIBSC agreements – NIBSC signed and are implementing a partnership agreement with the Coalition for Epidemic Preparedness (CEPI) which means that NIBSC does not need to respond to their calls for proposals individually, but rather have been recognised as the 'go-to' Institution to help develop assays and produce working standards for their emerging viruses portfolio. This includes Lassa Fever, Middle East Respiratory Syndrome (MERS), and Nipah Viruses currently. NIBSC also signed an agreement with FIND for a 5-year contract to help produce Nucleic Acid Amplification Testing (NAT) standards for emerging viruses and will fund our filling and freeze-drying costs to produce these materials that will lead to WHO International Standards. This agreement with FIND also results in NIBSC receiving £350k for the Lassa component of the work and further funding will be provided on a project specific basis.

The Innovation Office – The Innovation Office continues to act as a valuable point of contact for free, consolidated advice and 30 new enquiries were received in July. As well as responding to written enquiries, four face-to-face or teleconference meetings were held in July. We are now starting to record the numbers of Innovation Office enquiries that lead to subsequent requests for national scientific advice. The hope is that by offering an accessible service for researchers that they will feel motivated to seek MHRA advice throughout the later stages of their development programme. Since the launch of the Innovation Office on 11th March 2013 there have been 852 relevant queries.

Partnership – We continue to build effective working relationships with relevant bodies across Government, the health sector and industry. Work continues to develop new MoUs. The MoUs with Health Inspectorate Wales and Health Improvement Scotland have been reviewed and updated and will shortly be ready to be re-signed. We are planning for the next regular meetings with the Medicines Industry Group on 23 September, and the six-monthly bilateral with the Care Quality Commission on 24 September. In August, Policy also had a number of constructive EU Exit meetings with NICE to discuss and ensure the joining up of processes.

Falsified Medicines Directive (FMD) – Following a ministerial steer to commence with informal stakeholder engagement over the Summer to inform a provisional position on FMD in the event of No Deal, we had one external stakeholder workshop on 22 August and a second one will be held on 19 September.

4. MINISTERIAL AND PARLIAMENTARY PRIORITIES

FOI Response Time Compliance – The table below shows FOI activity and compliance for requests received at 30 June. 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're unable to calculate compliance accurately.

Rolling FOI KPI total

June 2019

as at 30/062018	FOI Requests Received 2019/2020			
	Apr	**May**	**Jun**	**Total**
Received	48	39	50	**137**
Replies sent on time	48	38	50	**136**
Replies not yet due	0	0	0	**0**
Breaches	0	1	0	**1**
Compliance %	**100.0%**	**97%**	**100.00%**	**99.3%**

July 2019

As at 31/07/2019	FOI Requests Received 2019/2020		
	Q1	**July**	**Total**
Received	137	61	**198**
Replies sent on time	136	61	**197**
Replies not yet due	0	0	**0**
Breaches	1	0	**1**
Compliance %	**99.3%**	**100.0%**	**99.5%**

5. COMMUNICATION

Patient, Public and Stakeholder Engagement (PPE) – Comms colleagues launched a 12-week public consultation on how the Agency engages/involves patients in its work. We promoted the consultation widely through stakeholder networks/comms channels, created a graphic for social media and worked with Devolved Administration contacts to schedule patient engagement events in Wales (3 September), Scotland (12 September) and Northern Ireland (8 October) to support the consultation. We also published an INsite article explaining the consultation and asking staff to share with their contacts/networks. A total of 520 responses had been received by 29 August 2019. We progressed arrangements with the Devolved Administrations to hold and promote patient engagement events in Wales, (03 Sept), Scotland (12 Sept) and Northern Ireland (08 Oct), plus London (30 Sept and 03 Oct), to support the consultation. Comms attended divisional meetings with Devices, VRMM and CPRD and met VRMM Paediatrics Unit Manager to discuss how to engage and involve younger people, paediatrics and parents in our PPE work and the consultation. Comms met ABPI to discuss its input to the PPE consultation and areas of mutual interest for involving patients, and held a telecon with NHS England and NHS Improvement to discuss the consultation, and potential for closer working on PPE, including staff training opportunities. Comms also launched a parallel internal consultation, seeking the views of MHRA staff on developing our patient and public engagement, to run from 29 August to 20 September.

FakeMeds Campaign – Colleagues engaged with Brook, the Sexual Health Charity, and SH24, a provider of free and confidential sexual health services, to discuss how they can support the next phase of the #FakeMeds campaign focusing on STI kits. We also researched relevant influencers and universities engaged in sexual health topics to inform our approach. We followed up with the Terence Higgins Trust who have requested our social media assets and any messaging to share.

Yellow Card Campaign – We published social media content for World Disability Day to promote reporting of safety issues with assistive technologies to the Yellow Card Scheme. The addition of 'Call to Actions' recently published in the Drug Safety Update (DSU) bulletins has led to higher rates of audience engagement and click-throughs than any other content in mid-June to mid-July. We created a new DSU graphic for social media and another version for Wilmington Healthcare, our external partner. We also updated the links used to make it them easier to track. We also successfully resolved an issue with NHS users not receiving previous DSU emails, working with VRMM, NHS Digital and Granicus. We sent a 'catch-up' email to NHS users only who may have missed out on DSUs from previous months. We continued to liaise and provide reactive lines to the BBC's 'Victoria Derbyshire Show' in relation to adverse reactions to antibiotics and whether more needs to be done to promote awareness of potential risks of fluoroquinolones to patients.

British Pharmacopoeia – We supported the ongoing promotion of the Analytical Quality by Design (AQbD) consultation by selling in the story to trade media, promoting to audiences on social media and developing a video that featured an interview with the Principal Pharmacopoeial Scientist to further encourage feedback. We also created a new video guide to demonstrate enhancements to the 'timeline' feature on the British Pharmacopoeia (BP) website. This will be posted on the BP website and shared with their users.

International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE) – CPRD exhibited and presented oral and poster presentations at the 35th International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE) in Philadelphia, from 26-28 August. The CPRD summer user group took place in Philadelphia before the start of the conference programme. Communications materials included an updated postcard about CPRD data and services and iPads with a new QuickTap survey.

GP practices signed up to CPRD – there is ongoing work to increase the number of GP practices contributing de-identified data to CPRD. This included a PACC amendment to agree budget spend for exhibiting at the Management in Practice event taking place in London on 26 September. There are now more than 1,600 UK practices contributing to CPRD.

Operation Pena – we issued a press release and social media following sentencing of Leonard Cosgrove in relation to Operation Pena which generated significant local and national coverage and led to follow up interview requests with The Telegraph and Sun on Sunday.

Unlicensed erectile dysfunction medicines – An IE&S colleague was interviewed by the Telegraph on unlicensed erectile dysfunction medicines for a health feature on Viagra. Information on when the feature goes live will be circulated once the publication date is confirmed.

Correction in the Liverpool Echo – We sent a correction to the Liverpool Echo following an article they published about a shortage because of a reduction in gallium production by a Liverpool Hospital Trust. They incorrectly stated that MHRA asked them to suspend production.

In July:

The Director's NIBSC-authored Paper of the Month for July 2019 (from those published/indexed on Pubmed in June) was a paper referred to last month entitled:
Applying the science of measurement to biology: Why bother?

Coxon CH, Longstaff C, Burns C.
PLoS Biol. 2019 Jun 20;17(6):e3000338. doi: 10.1371/journal.pbio.3000338
It was selected due to it being a good perspective piece about the important work of NIBSC.

Summary: An excellent Perspective article explaining why the science of measurement matters in biology and how it can support experimental reproducibility.

This was selected from the following original research papers authored by NIBSC in July:
NIBSC-authored Papers July 2019
Original Research Papers

1. The safety and immunogenicity of two novel live attenuated monovalent (serotype 2) oral poliovirus vaccines in healthy adults: a double-blind, single-centre phase 1 study.
Van Damme P, De Coster I, Bandyopadhyay AS, Revets H, Withanage K, De Smedt P, Suykens L, Oberste MS, Weldon WC, Costa-Clemens SA, Clemens R, Modlin J, Weiner AJ, Macadam AJ, Andino R, Kew OM, Konopka-Anstadt JL, Burns CC, Konz J, Wahid R, Gast C.
Lancet. 2019 Jun 4. pii: S0140-6736(19)31279-6. doi: 10.1016/S0140-6736(19)31279-6.

2. Segment 2 from influenza A(H1N1) 2009 pandemic viruses confers temperature-sensitive haemagglutinin yield on candidate vaccine virus growth in eggs that can be epistatically complemented by PB2 701D.
Hussain S, Turnbull ML, Pinto RM, McCauley JW, Engelhardt OG, Digard P.
J Gen Virol. 2019 Jun 6. doi: 10.1099/jgv.0.001279.

3. Variable Baseline Papio cynocephalus Endogenous Retrovirus (PcEV) Expression Is Upregulated in Acutely SIV-Infected Macaques and Correlated to STAT1 Expression in the Spleen.
Maze EA, Ham C, Kelly J, Ussher L, Almond N, Towers GJ, Berry N, Belshaw R.
Front Immunol. 2019 May 15;10:901. doi: 10.3389/fimmu.2019.00901. eCollection 2019.

4. Evaluation of the monocyte activation test for the safety testing of meningococcal B vaccine Bexsero: A collaborative study.
Studholme L, Sutherland J, Desai T, Hockley J, Care R, Nordgren IK, Vipond C; Collaborative Study Group.
Vaccine. 2019 Jun 27;37(29):3761-3769. doi: 10.1016/j.vaccine.2018.05.073. Epub 2018 Dec 10.

5. Multiomics Analyses of HNF4α Protein Domain Function during Human Pluripotent Stem Cell Differentiation.
Wang Y, Tatham MH, Schmidt-Heck W, Swann C, Singh-Dolt K, Meseguer-Ripolles J, Lucendo-Villarin B, Kunath T, Rudd TR, Smith AJH, Hengstler JG, Godoy P, Hay RT, Hay DC.
iScience. 2019 May 24;16:206-217. doi: 10.1016/j.isci.2019.05.028.

6. Antibody-mediated protection against MERS-CoV in the murine model.
New RRC, Moore BD, Butcher W, Mahood R, Lever MS, Smither S, O'Brien L, Weller SA, Bayliss M, Gibson LCD, Macleod C, Bogus M, Harvey R, Almond N, Williamson ED.
Vaccine. 2019 Jun 6. pii: S0264-410X(19)30711-X. doi: 10.1016/j.vaccine.2019.05.074.

7. Rapid and iterative genome editing in the malaria parasite Plasmodium knowlesi provides new tools for P. vivax research.
Mohring F, Hart MN, Rawlinson TA, Henrici R, Charleston JA, Diez Benavente E, Patel A, Hall J, Almond N, Campino S, Clark TG, Sutherland CJ, Baker DA, Draper SJ, Moon RW.
Elife. 2019 Jun 17;8. pii: e45829. doi: 10.7554/eLife.45829.

8. Use of Heterologous Vesiculovirus G Proteins Circumvents the Humoral Anti-envelope Immunity in Lentivector-Based In Vivo Gene Delivery.
Munis AM, Mattiuzzo G, Bentley EM, Collins MK, Eyles JE, Takeuchi Y.
Mol Ther Nucleic Acids. 2019 May 28;17:126-137. doi: 10.1016/j.omtn.2019.05.010.

9. Measuring the Specific Surface Area (SSA) of Freeze-Dried Biologics using Inverse Gas Chromatography.
Duralliu A, Matejtschuk P, Williams DR.
Eur J Pharm Biopharm. 2019 Jun 21. pii: S0939-6411(19)30384-4. doi: 10.1016/j.ejpb.2019.06.026.

In August:

The Director's NIBSC-authored Paper of the Month for August 2019 (from those published/indexed on Pubmed in July) was:

1. Measuring the Specific Surface Area (SSA) of Freeze-Dried Biologics using Inverse Gas Chromatography.

Duralliu A, Matejtschuk P, Williams DR.

Eur J Pharm Biopharm. 2019 Jun 21. pii: S0939-6411(19)30384-4. doi: 10.1016/j.ejpb.2019.06.026.

It was selected particularly for being widely applicable and core to NIBSC's freeze drying capabilities.

Summary: The specific surface area (SSA) of freeze-dried biologics (FD) is usually measured via a Brunauer-Emmett-Teller (BET) analysis of volumetric nitrogen/krypton adsorption isotherms. Inverse gas chromatography (IGC) is chromatographic characterization technique which can be used as an alternative to the BET test. Here the authors compare the two for determining the SSA's of a range of freeze dried biological materials and show that IGC had comparable SSA values to N_2 BET method with better reproducibility. They conclude that IGC is a suitable alternative method for determining the SSA surface of freeze-dried biological materials whose SSA's are generally strongly dependent on their moisture content.

The paper was selected from the following Original Research Papers.

2. The influence of the closure format on the storage stability and moisture content of freeze-dried influenza antigen.

Duralliu A, Matejtschuk P, Dubey S, Koroma H, Gubinelli F, Williams DR.

Vaccine. 2019 Jul 2. pii: S0264-410X(19)30847-3. doi: 10.1016/j.vaccine.2019.06.070.

Kempster SL, Dougall T, Morris C, Gonzalez-Escobar G, **Almond N, Anderson R.**

Biologicals. 2019 Jul 2. pii: S1045-1056(19)30055-7. doi: 10.1016/j.biologicals.2019.06.007.

3. BCG Therapy of Bladder Cancer Stimulates a Prolonged Release of the Chemoattractant CXCL10 (IP10) in Patient Urine.

Ashiru O, Esteso G, García-Cuesta EM, Castellano E, Samba C, Escudero-López E, López-Cobo S, Álvarez-Maestro M, Linares A, Ho MM, Leibar A, Martínez-Piñeiro L, Valés-Gómez M.

Cancers (Basel). 2019 Jul 4;11(7). pii: E940. doi: 10.3390/cancers11070940.

4. Continued provision of WHO International Standards for total and free PSA: Content and commutability of replacement preparations.

Ferguson J, Patel D**, Atkinson E, Rigsby P, Burns C.**

Clin Biochem. 2019 Jul 8. pii: S0009-9120(19)30296-6. doi: 10.1016/j.clinbiochem.2019.07.007.

5. The third international standard for anti-D immunoglobulin: international collaborative study to evaluate candidate preparations.

Fox B, Sharp G, Atkinson E, Roberts G, Rigsby P, Studholme L.

Vox Sang. 2019 Jul 19. doi: 10.1111/vox.12822.

6. Interleukin-1 reduces food intake and body weight in rat by acting in the arcuate hypothalamus.

Chaskiel L, **Bristow AD**, Bluthé RM, Dantzer R, Blomqvist A, Konsman JP.

Brain Behav Immun. 2019 Jul 13. pii: S0889-1591(18)31215-7. doi: 10.1016/j.bbi.2019.07.017.

Reviews/other publications

1. Assays for Determining Pertussis Toxin Activity in Acellular Pertussis Vaccines.

Markey K, **Asokanathan C, Feavers I.**

Toxins (Basel). 2019 Jul 17;11(7). pii: E417. doi: 10.3390/toxins11070417.

Review

2. WHO International Standards and reference preparations for cytokines and growth factors.

Proudfoot A, **Wadhwa M**.

Cytokine. 2019 Aug 8;123:154797. doi: 10.1016/j.cyto.2019.154797.

Letter

6. ORGANISATIONAL TOPICS

Transformation Division Update - Capacity and Capability: The TD Operating Model project has launched with strand leads appointed, and a new HR Business Partner funded by the Division now started. Prioritisation of recruitment is now underway.

Human Resources Update – In August, CET approved a People Transition Support Framework, following consultation on the framework with our trade unions and SMTs. The Framework outlines how the management and movement of staff will take place arising from larger organisational change programmes. Above all, the Framework will ensure that the

Agency fully supports its staff through a period of changes, where it means a change of role through redeployment, change or reporting line, duties or role focus, or leaving the Agency.
CET also approved a new Recruiting Temporary (contingent) Workers Procedure to ensure recruitment of temp staff is controlled through the recognised crown commercial frameworks, and that for the first time we have sound management information on our contingent worker cohort.

NIBSC Carbon Tax – In July the Environment and Energy Manager for MHRA has reported that NIBSC saved £11k on Carbon Tax this year. It is mandatory for NIBSC to comply with the Governments Carbon Reduction Commitment (CRC) Scheme, as the site is a high energy user due to the nature of the work carried out. This is essentially an additional tax directly related to the amount of energy used each financial year; and is typically in the region of £100k per annum. This reporting period however NIBSC has been able to reduce this payment and saved over £11k by differences in the site's energy use. This has been due to a slight reduction in electricity consumption and a more significant reduction of 7% in gas usage over the year, compared to the previous year. This has also been boosted by a bumper year for the Solar PV System, installed over seven roofs across the site and which has produced 18% more energy this reporting period. This has therefore not only helped to reduce reliance on mains grid electricity, but also reduce our Carbon Tax and save money. NIBSC has again, for the tenth year running, managed to reduce its Display Energy Certificate (DEC) score.
DECs are reviewed annually by external assessors on behalf of the Government. They look purely at actual energy consumption in electricity, gas and fuel oil, as well as building use. NIBSC has successfully reduced its score each year; from the original DEC score in 2008 of 544 to this year's score of 239.

Improvements have been seen, for example, from increased onsite solar production, which reduces our peak grid electricity demands, and also decreases in the gas usage. NIBSC received commendation from the external assessor saying, "the overall trend moving forward is a reduction, due to the ongoing hard work undertaken by the Energy Manager, staff engagement and the onsite energy generation." The assessor also commented on the NIBSC Christmas Switch Off campaign; "the energy data demonstrates the ongoing success of the holiday shutdown energy saving campaigns, with the base load stabilising. This is a massive achievement given the nature of the business for the site". The NIBSC Senior Management Team has been thanked for their support with this initiative in what has now become an official site switch off period, as well as all the staff who take responsibility for the equipment they use. The aim of these shutdowns is to collectively reduce energy consumption and the corresponding utility costs, which we have shown works for us.

NHS England and NIBSC – On 28 August, NIBSC hosted a very positive visit by NHS England deputy Chief Scientific Officer (CSO), Angela Douglas, accompanied by Catherine Ross, Clinical Leadership Lead, from the CSO Office. The visit which was arranged and coordinated by the Head of Infectious Disease Diagnostics Division, included a tour of the site and poster presentations on topics such as Clinical Chemistry, Flow Cytometry, Infectious Disease, Molecular Run controls for Hepatitis Viruses, Serological Run Controls, Point of Care testing, Cancer Diagnostics and Standardisation, and Influenza. The tour included an insight into the Analytical Science Facilities such as Mass Spectrometry, Next Generation Sequencing and Nuclear Magnetic Resonance, and finally a visit to see the work of standards production in the Centre for Biological Reference Materials.

There were interesting discussions on ways to work more closely with other organisations. Discussions around all these opportunities will continue and an action plan of work be developed to take forward where appropriate and updates on progress will be provided.

Licensing staff presented at 4 external meetings during July:

Name of Event & Location	Title of Presentation
MSc module on nanotechnology (Oxford)	MSc module on nanotechnology
PSI One Day Scientific Meeting on PROs (Welwyn Garden City)	Regulatory Guidance on PROs
Overcoming Policy Roadblocks to the Application of 3D Printed Drug Innovation (Nottingham)	Novel Pharmaceutical Manufacturing Technologies, a Licensing perspective'. This was a joint venture between Licensing and IE&S
How to do research on therapeutic interventions: protocol preparation (Summertown)	Regulatory Assessment of Clinical Trial Protocols

Licensing staff presented at 2 external meetings during August:

2nd international conference on bioequvalence and bioavailability (Spain)	Licensing of Medicines
PREDiCT 3D Models (Boston)	MHRA insights into the 3D models landscape

CEO meetings in July and August – on 1 July the CEO met with the Health Research Authority and following this held a meeting of the European Medicines Group. On 4 July the first meeting of the Patient Access to Medicines Partnership was held, which is a sub-board of the Life Sciences Council, chaired by Baroness Blackwood and Paul Hudson and was established to provide a forum for strategic, high-level, cross-departmental discussions on all aspects pharmaceutical and medicines access policy. On 16 July the CEO chaired an ICMRA Executive Committee teleconference. On 17 July the Chief Executive and the Chairman met with Baroness Blackwood for the monthly Brexit meeting. A meeting was also held with the Government Internal Audit Agency. On 22 July the Life Sciences EU Relationship Group meeting was held which the CEO and Chairman both attended. On 24 July the CEO attended a Genetic Alliance UK industry meeting to give a presentation on "Next steps for policy and the role of MHRA moving forward". On 31 July the CEO attended a Health and Care Leaders Senior Talent Board meeting, followed by a meeting with the new Prime Minister Boris Johnson at the PM's Top 200 civil servants meeting.

OPERATIONAL PERFORMANCE

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

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

New UK Marketing Authorisations - Existing Active Substances

Procedure	MAA Assessed July 2019	MAA Assessed 2018/19 Average per month
National, UK-only	49	35
Decentralised, UK=RMS	0	9
Decentralised and MR, UK=CMS	15	36
Total	**64**	**80**
Procedure	**MAA Determined July 2019**	**MAA Determined 2018/19 Average per month**
National, UK-only	49	27
Decentralised, UK=RMS	0	28
Decentralised and MR, UK=CMS	15	52
Total	**64**	**107**

Procedure	MAA Assessed August 2019	MAA Assessed 2018/19 Average per month
National, UK-only	59	35
Decentralised, UK=RMS	0	9
Decentralised and MR, UK=CMS	30	36
Total	89	80
Procedure	**MAA Determined August 2019**	**MAA Determined 2018/19 Average per month**
National, UK-only	51	27
Decentralised, UK=RMS	1	28
Decentralised and MR, UK=CMS	10	52
Total	**62**	**107**

Regulatory Information Service – In July, 963 enquiries were received (768 e-mails, 195 phone calls). 23 grouping requests were processed and 12 requests for expedited review were also made to LD in the month of July 2019.The number of complex/technical enquiries forwarded on to assessment teams in July was 4, equating to 0.52% of emails received by the RIS, with an average PLAT response timeframe of 1.3 days. In August, 1585 enquiries were received (1438 e-mails, 147 phone calls). 24 grouping requests were processed and 13 requests for expedited review were also made to LD in the month of August 2019. The number of complex/technical enquiries forwarded on to assessment teams in August was 2, equating to 0.14% of emails received by the RIS, with an average PLAT response 6.5 days

Parallel imports (PLPIs) – In July, 67 PLPI initial submissions were received, 42 were assessed and 48 were determined (52, 40 and 55 respectively in June).Median time from submission to grant was 3.3 months (3.3 months in June).634 PLPI variation applications were received, 541 were assessed and 532 were determined (800, 497 and 494 respectively in June).Average time from submission to grant was 2.5 months (2.2 months in June).

Public Assessment Reports (PARs) – 100% of UK Public Assessment Reports and Lay Summaries (22/22) completed in July 2019 were published within the 60-day high-level target time from grant of the marketing authorisation. There was 1 PAR updated with a non-safety variation of clinical importance (Type II medical) completed in July 2019, all completed on time.100% of UK Public Assessment Reports and Lay Summaries (17/17) completed in August 2019 were published within the 60-day high-level target time from grant of the

marketing authorisation. There were no PARs updated with a non-safety variation of clinical importance (Type II medical) completed in August 2019.

Clinical Trial Authorisations (CTAs) applications: In July, a total of **93** applications were assessed. For the financial year-to-date, **23** fewer applications have been assessed compared with the same period last year (**312** for 2018 compared to **289** for 2019). There were **7** first in UK and **10** first in human (FIH) studies assessed in July. **Nine** applications were discussed at the Clinical Trial Unit (CTU) multidisciplinary meeting. In July, CTU received **1** initial application for a novel trial design (Platform), and **4** novel amendment submissions (all Umbrella). Clinical Trial Helpline: **500** calls and **158** emails were recorded. The response time for emails was an average of **4.9 days** (target is average of 14 days). In August, a total of **64** applications were assessed. For the financial year-to-date, **35** fewer applications have been assessed compared with the same period last year (**388** for 2018 compared to **353** for 2019). There were **10** first in UK and **7** first in human (FIH) studies assessed in August. **Seven** applications were discussed at the Clinical Trial Unit (CTU) multidisciplinary meeting. In August, CTU received **4** initial applications for a novel trial design (1 Umbrella, 1 Platform, 1 Adaptive, 1 Seamless phases), and **2** novel amendment submissions (Platform). Clinical Trial Helpline: **366** calls and **139** emails were recorded. The response time for emails was an average of **3.1 days** (target is average of 14 days).

Pharmacovigilance Adverse Drug Reactions (ADRs) – A total of 3786 UK ADR reports were received in July 2019, of which 755 were received from patients, parents and carers. Results against key performance measures for fatal and serious reports were both 100%. 43.5% of UK spontaneous serious ADRs were sent to EMA within the target of 11 days, 55.6% of reports in 12-15 days and less than 1% of reports were sent over the 15-day legislative target. Work on Brexit preparations has greatly impacted the team's ability to meet ADR targets however compared to previous months this has improved greatly. The reports that were sent over the 15-day target have been investigated and feedback has been provided to the team regarding the importance of meeting legislative targets. Of 114 general enquiries received, 92% were answered within 7 working days and 100% within 10 working days.
A total of 3517 UK ADR reports were received in August 2019, of which 693 were received from patients, parents and carers. Results against key performance measures for fatal and serious reports were both 100%. 68.5% of UK spontaneous serious ADRs were sent to EMA within the internal target of 11 days and 100% within the legislative timeline of 15 days. Of 120 general enquiries received, 96% were answered within 7 working days and 100% within 10 working days.

Devices adverse incidents – In July there were 2,241 Adverse Incident reports received (which compares with 1,552 for the same month last year), an increase of 44.4%. The cumulative total for this year is 12,669, which compares with 11,592 for 2018, an increase of 9.3%.In August there were 1,898 Adverse Incident reports received (which compares with 1,890 for the same month last year), an increase of 0.4%. The cumulative total for this year is 14,567, which compares with 13,482 for 2018, an increase of 8.1%.

Devices clinical investigations – In July, 100% of clinical investigations have been completed within 60 days and the average review time for the year to date is 56 days. 7 clinical investigations were completed.In August 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.

Biologics batch release – Levels of test release certificates issued remained at a similar level this month, with 48 vaccines and blood product batches issued in July compared to 43 batches issued in June. The target for timeliness of product testing was achieved in July. There

were 18 plasma pool releases in July. There were 3 supplementary certificates issued due to manufacturer errors.

Levels of test release certificates issued slightly increased in August, with 62 vaccines and blood product batches issued in August compared to 48 batches issued in July. The target for timeliness of product testing was achieved in August. There were 15 plasma pool releases in August compared to 18 the previous month. There was one supplementary certificate issued due to manufacturer errors.

7. OTHER INTERNATIONAL TOPICS

A member of the NIBSC the Biotherapeutics Division, presented on the use of WHO international reference materials in the context of post-approval changes at the WHO Implementation Workshop on Guidelines on Procedures and Data Requirements for Changes to Approved Biotherapeutic Products (25-26 June 2019) in Seoul, Korea. She participated as a member of the drafting group for the guideline (established by the WHO Expert Committee for Biological Standardisation ECBS in Oct 2017) and also served as a rapporteur for the meeting.

Colleagues from Istituto Superiore di Sanità (ISS), the Italian Official Medicines Control Laboratory and scientific body of the Italian agency, AIFA visited NIBSC on 8 and 9 July 2019. Coordinated by the Biotherapeutics Division, their visit included meetings with the Head of Biotherapeutics, section heads and senior scientists from within the division and other divisions such as analytical and biological sciences, and standards processing where colleagues gave a discussion and tour of reference material development and production. Consequently, through presentations and discussions on specific topics e.g., hormones, cytokines and growth factors, monoclonal antibodies, production of reference standards, they gained information and insight on our analytical capabilities and equipment, bioassays/bioassay development, statistical analysis, WHO international standards and our current activities.

GDP Inspectorate supported the World Health Organisation in-country workshop (22 – 26 July 2019, Bangkok, Thailand) on Good Distribution Practices using the risk-based approach. Inspectors and other regulators from nine of the eleven WHO South East Asia Regional (SEAR) countries attended an intensive and highly interactive five-day workshop developed as part of the WHO programme to improve quality of medicine supply to the SEAR. MHRA GDP Inspectorate was invited in order to share experience gained in applying and inspecting against medicine regulations at what is seen world-wide as a very strong standard. In return, greater knowledge was gained by GDP Inspectorate of challenges faced exporting medicines to this region.

Dr Ian Hudson
Chief Executive