Medicines & Healthcare products Regulatory Agency

Board Meeting – Public Board

15 April 2019

CHIEF EXECUTIVE'S REPORT FOR THE MONTH OF MARCH 2019

1. HEADLINES for MARCH 2019

Brexit – Overall, we still face great uncertainty. There will be an emergency meeting of the European Council on 10 April, at which the UK is expected to set out its request for a further extension to Article 50, along with a rationale for this. This is subject to the UK Parliament agreeing a path forward on how the UK should leave the EU. Until then we are continuing to prepare for all eventualities, particularly moving into a No Deal or Implementation Period at the point of EU Exit.

The Agency has prepared for the possibility for no-deal and was ready to operate by the end of March:

- Legislation – 3 No Deal Statutory Instruments (SIs) successfully passed through Parliament – at the very start of April these were in the process of being signed by Ministers and being 'made'.
- Operational readiness – we continue implementing the many changes to keep the Agency functioning on day 1, including one-off tasks to enable certain new functions are operable (e.g. grandfathering of Centrally Authorised Products (CAPs) and Parallel Distribution Notices (PDNs)). All 'essential for Day 1' guidance is now published, or going through clearance, with the exception of some of the ESC (European Systems Contingency) guidance, e.g. user guides, due to the final details being dependant on the final ESC product.
- IT systems – delivery of 3 core systems (an e-submission portal, a case management system and a publishing system) is on track. The portal will be ready for Day 1, but the timeline is still very tight for some other elements.
- Contribution to DHSC's Day 1 supply programmes – we continue to provide expert input as required, and also now have provisions for rapid response in the event of urgent issues with a regulatory component; linked in through the various operational readiness centres.

We continue to hold staff briefings and drop-in events on EU exit, as part of our 'Shaping our Future' internal communications campaign. This included an update event with the CEO and the Head of EU, Brexit and International Strategy, updating staff on developments. 125 staff attended in person or remotely via Zoom, and we had over 100 views of the recording on INsite.

Independent Medicines and Medical Devices Safety (IMMDS) Review – MHRA attended a second hearing on 27 February, the Agency is continuing to give the review full support and is providing additional information to supplementary questions from the Review Team.

NIBSC has been awarded a Certificate of Achievement for Warp-It re-use system for achieving £100k worth of savings since it was first used at NIBSC.
Since implementing the resource reuse and management system in 2014 there have been great benefits from being more effective with general consumables, laboratory consumables, furniture, and other resources and assets which has resulted in the high savings, now totaling £177.7k.
Led by NIBSC's Environmental and Energy Manager, 'Warp It champions' in each division have really led the way and encouraged staff to re-use items across NIBSC, and where appropriate the Agency, to reduce wastage costs and avoid unnecessary new purchases.
So far on the system NIBSC has saved:

We will continue to encourage staff to continue with their fantastic efforts to date in using Warp-It.

2. PRODUCT RELATED ISSUES

Medicines issues

Opioids and dependence and addiction – The Expert Working Group (EWG) on Opioids met for a second time on 27 March. A stakeholder network has been developed to support this work. The first meeting of the network was held on the morning of 27 March 2019 and was attended by 28 different stakeholder organisations representing relevant healthcare professionals, health system agencies and regulators, plus patient groups. The stakeholder meeting discussed the need for warnings about addiction on the outer packaging of opioid medicines and the options for education and raising awareness amongst healthcare professionals and patients. Stakeholders at the meeting emphasised the need for better education of healthcare professionals in the management of pain and in the prescribing of opioids and the need for patients to have clear warnings about the risk of addiction. There will be further meetings of the stakeholder network in the coming months.

Hormone pregnancy tests and possible association with congenital abnormalities – In line with a commitment to review any new information in relation to hormone pregnancy tests (HPTs) and a possible association with congenital abnormalities, an EWG of the CHM met on 18 March to consider a re-analysis of studies on HPTs and congenital anomalies by Heneghan et al.

Batch release of malaria vaccine – Mosquirix – Since 2012, scientists (Bacteriology Division) at NIBSC have been engaging with the manufacturer (GSK) for the preparedness of batch release of a new malaria vaccine, Mosquirix. This is an Official Medicines Control Laboratory function undertaken as a member of a network of laboratories across Europe (OCABR Network) and follows the regulatory guidance of Article 58. Agreed with the manufacturer, some of the batch release assays were transferred and established at NIBSC following the process using the analytical method transfer protocols. This method transfer process involved scientists from both Bacteriology and Virology Division and was successfully completed in 2016. Samples for batch release testing were received in 2017. The final component of batch release submission was received in February 2019. The first three final packaging lots of Mosquirix were released in March 2019 to mark the official start of batch release of this new vaccine product.

Defective Medicines Reporting Centre (DMRC) – One Drug Alert and one Company-led Drug Alert were issued in March:

- 20/03/2019 Losartan Containing products, Accord Healthcare Limited. Recall due to the presence of N-nitroso-N-methylamino butyric acid (NMBA) in affected batches. The API was manufactured by Hetero.
- 18/03/2019 Company-led Drug Alert (CLDA) Ozurdex, Allergan Pharmaceuticals, Ireland. This was a follow-up recall to one issued in October 2018 due to the potential for a silicone particle being implanted into the eye during administration of the product. Certain batches where additional testing had not identified the defect but for which it could not be ruled out, were recalled due to sufficient unaffected replacement stock being available.
- The issue discussed in the February monthly report, concerning GSK vaccines, including Infanrix Hexa has now been resolved. The company carried out further studies which showed that the temperatures reached for the relevant times did not result in a lack of potency. The Belgian Rapporteur assessed the stability report and agreed with the conclusions, therefore all batches are now being released.

Fluoroquinolones – we advised Quinolone Toxicity Support UK of the publication of the new UK restrictions on the prescribing of quinolones, including patient sheet for HCPs to use, in Drug Safety Update and CAS alert.

Inspectorate Laboratories Symposium 2019 – The Laboratories team in IE&S ran their annual symposium on 13 March 2019 in London. The event sold out with 300 delegates present to hear presentations relating to Goof Laboratory Practice, Good Clinical Practice and GMPQC topics.
Topics covered in the symposium included:

- Practical Applications of Data Integrity for Laboratories
- Quality Assurance and Quality Control
- Effective CAPA & Justifying Data Decisions
- Method Validation
- Updates and inspection feedback

There was plenty of interaction and questions by the audience and all the presentations were successful. The audience particularly enjoyed interactive role play sessions to highlight good and bad practice that inspectors observe when on inspection. There were also some inspector's surgeries, where delegates could meet face-to-face with inspectors to ask them questions.

Devices issues

Surgical mesh update – We agreed an approach on seeking input from patient representative groups on a draft GOV.UK page on mesh.

IV fluid warmers – An Issue has been identified with IV fluid warmers which have an aluminium warming plate within the fluid pathway. Testing has shown that when infusing a range of common fluids, including balanced electrolytes, blood and lactated Ringers solution, harmful levels of aluminium can leach from the device. The manufacturer has issued a revised FSN (Field Safety Notice) to advise against use of these devices. MHRA is a member of a taskforce to determine whether other products on the market are similarly affected and will establish an EAG (Expert Advisory Group) to consider the extent of the clinical risk to patients. We have issued 2 MDAs relating to this issue.

Paclitaxel coated balloon catheter for treatment of the femoropopliteal artery – This month has seen the review of all the data held by MHRA by the Expert Advisory Group and two teleconferences with the group to gauge progress and initial findings/opinions. A face to face meeting has been scheduled, where EAG members are to set out their

recommendations. A statement was posted on our website outlining the work of the EAG. We may need to take further action depending upon their findings and recommendations. We published a news story on GOV.UK about the Expert Advisory Group.

Ventilators colonised with vancomycin resistant enterococci (VRE) – MHRA became aware of a hospital site which had identified a number of ventilators that had been colonised with vancomycin resistant enterococci (VRE). Once case of infection in a patient has been confirmed and a number of other patients are confirmed to be colonised. More information is being sought from the hospital and the manufacturer (Draeger). PHE made a number of recommendations to the hospital; once the manufacturer has responded MHRA will be able to assess whether an alert is required.

Emollients (fire hazards) – we liaised with the Fire Service for their input on stakeholders to target and to request details of the victims' families for invitation to a stakeholder meeting. We also organised a planning meeting for the first stakeholder group meeting (26 April).

Medical Device Alerts – There were five alerts in March 2019

Number	Title
MDA/2019/013	All T34 ambulatory syringe pumps need a sponge pad fitted to the battery compartment to prevent battery connection issues.
MDA/2019/014	All Bard urogynaecological mesh – voluntary product withdrawal, implanted devices do not need to be removed.
MDA/2019/015	Superseded by MDA/2019/016.
MDA/2019/016	enFlow® IV fluid and blood warmer - risk of unsafe levels of aluminium leaching from the device – updated safety advice from manufacturer.
MDA/2019/017	Pagewriter Cardiographs (TC20/30/50/70) manufactured before 20 November 2018 and Efficia Monitors (CM10/12/100/120/150) manufactured before 25 October 2018 – risk of batteries overheating or igniting.
MDA/2019/018	Fresenius 5008 & 5008S haemodialysis machines – low risk of inadequate fluid removal during treatment.

There were two targeted letters sent in March 2019:

- Drager disposable breathing circuits – risk of incorrect connection of circuit leading to loss of ventilation to patient. Updated instructions for use, showing correct connection of breathing circuit to anaesthetic machines and ventilators.
- Stryker Tritanium PL spinal implant – risk of fracture during insertion and post-operatively. Update of the Surgical Technique Guide to reduce the likelihood of this occurring.

3. REGULATION POLICY AND OTHER SCIENTIFIC TOPICS

European/International Highlights

International Coalition of Medicines Regulatory Authorities (ICMRA) – An all member teleconference was held on 13 March and we are planning for the plenary meeting at the Drug Information Association (DIA) San Diego on 23 June.

Falsified Medicines Directive (FMD) implementation – Compliance is steadily increasing, but we do not expect to reach full compliance across the system (particularly the dispensing end of the supply chain) until an Exit Deal is confirmed. The Agency

continues to make key contributions to resolving EU-wide technical issues and is supporting pragmatic solutions to UK-specific implementation issues, to ensure the supply of medicine remains a priority.

Partnership – We continue to build effective working relationships with relevant bodies across Government, the health sector and industry. We held productive CEO-level bilateral meetings with Healthcare Inspectorate Wales on 26 February and Healthcare Improvement Scotland on 1 March, as well as quarterly working-level meetings with Healthcare Improvement Scotland on 14 March and NICE on 27 March.

Corporate and Business Planning – The Agency's business plan for 2019/20 was signed off by the Board at their 18 March meeting and sent to DHSC for review/agreement.

International Meeting of World Pharmacopoeias (IMWP) – 4/5 March 2019 – The meeting took place at the WHO's headquarters in Geneva and included many pharmacopoeial peer organisations from across the globe including well established and influential peers, such as the European, United States and Japanese Pharmacopoeias and those from key pharmaceutical markets, including the Chinese and Indian Pharmacopoeias. The UK was represented by the British Pharmacopoeia (BP) Secretary and Scientific Director and the BP Editor-in-Chief.
The focus of the meeting was the discussion on a draft white paper on the value of pharmacopoeial standards, including elements such as our role in the assurance of medicine quality and our collaborations with stakeholders and peers. The technical content of the paper was agreed and would be progressed into an editorial review for public release targeted for later in the year. The BP had participated in the drafting group for the paper as well as being a key contributor within the meeting, reinforcing our status as a globally important and recognised pharmacopoeia.
Outside of the meeting, the BP held bilaterals with attending peer organisations. Key outcomes of these meetings included:

- Invitations from the Chinese Pharmacopoeia to participate at CPhI China in Shanghai, an international conference that hosts over 100,000 visitors and the opening of a museum dedicated to pharmacopoeias
- Receiving a report from the Ukrainian Pharmacopoeia which, through our MoU with them, reproduces BP standards within their publication.

UK TOPICS

Central Alerting System (CAS) – We visited NHS National Services Scotland to provide a demonstration of the Central Alerting System to them along with colleagues from Healthcare Improvement Scotland, the Scottish Government and various Health Boards and Local Authorities. Within the Income Generation project of Operational Transformation, we are working on a pricing model for CAS which we will share with Scotland whilst they progress internal discussions about whether they wish to use the platform. In parallel we have also discussed the use of CAS with Northern Ireland and we intend to meet with them in April to discuss next steps.

Representatives from the MHRA presented at a meeting in Oxford, hosted by the Bioescalator, to communicate the work we do and explain how people can interact with us more effectively. The audience included academics engaged in translational research, spin-out companies, clinicians, and grant funders. The event was organised by NIBSC and there were presentations from Horizon Scanning, Licencing, Paediatrics, the Innovation Office, Devices, and NIBSC. Early feedback from attendees suggested they felt much better informed about what the MHRA does, how we work, and how they can interact with us, which was one of the major objectives for this meeting. Future meetings may take place following positive written feedback.

4. MINISTERIAL AND PARLIAMENTARY PRIORITIES

FOI Response Time Compliance: The table above shows FOI activity and compliance for requests received at 28 February. 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. The target for 2018/19 is to ensure that 100% of requests receive responses within statutory limits (20 working days; or exceptionally within 40 days where an extension is required to complete a complex public interest test).

Rolling FOI KPI total as at 28/02/2019	**Freedom of Information Requests Received 2018/2019**					
	Q1	**Q2**	**Q3**	**Jan**	**Feb**	**Total**
Received	192	172	116	59	43	**582**
Replies sent on time	190	172	114	59	42	**527**
Replies not yet due	0	0	0	0	0	**0**
Breaches	2	0	2	0	1	**5**
Compliance %	99.0%	100.0%	98.3%	100.0%	97.7%	**99.1%**

5. COMMUNICATION

All Staff meeting – Feedback shows February All Staff Meeting was a success. This was our first single all-staff meeting, delivered in five locations and via Zoom. Evaluation shows more staff reached, positive feedback for a single event with consistent messaging, access for remote workers, high levels of positive feedback for format and content.

Patient and Public Engagement (PPE) – We presented the PPE delivery plan 2019-21 at CET and the Board and shared it with the new PPE Champions Network which we have established. The overarching aim is to ensure that the views and interests of patients and the public are at the heart of the Agency's decision-making and culture. We are now taking forward work to implement the delivery plan and will be keeping CET and the Board regularly updated on progress.

We delivered a presentation at the Charities Research Involvement Group meeting to 26 research charity representatives to raise awareness of the Agency, update them on the Agency's PPE delivery plan, invite their participation in the Patient Group Consultative Forum and seek input to the development of MHRA's longer term PPE Strategy.

Events programme:

A Pharmacokinetics Masterclass took place on 29 March at 10 SC.

International wheelchair day – Comms colleagues created an animation promoting Yellow Card that was published on social media for international wheelchair day.

GREAT Britain campaign – We arranged a presentation to internationally-based staff in the Department for International Trade on 5 March. This presentation covered the Agency, centres, products and services with a particular focus on innovation. Feedback from Department for International Trade (DIT) colleagues has been very positive and we plan to build on this foundation of knowledge at a future training session so that DIT colleagues remain informed and empowered to promote the Agency to their networks.

Clinical Practice Research Datalink (CPRD) communications – Via CPRD's Twitter account we shared information about recently published studies using CPRD data. We also continued to publicise job vacancies and our attendance at GP meetings.
We have prepared updates for clients and contacts about online access for CPRD Aurum data being available from April.
We met with communications contacts at NIHR Clinical Research Network and NHS England to discuss our continuing partnership work during the next year. We also attended a workshop about transparency and patient data, organised by Understanding Patient Data.

Love Your Lenses campaign – We supported the General Optical Council (GOC) 'Love Your Lenses' campaign to inform contact lens wearers of the steps they need to follow to keep their eyes healthy. We used social media to promote our messages about the Yellow Card Scheme, dangers of buying medical devices online and our GOV.UK page on contact lenses. We also asked the GOC to refer to our messages.

Unlicensed and fake medicines – We worked with celebrity doctor Oscar Duke to promote the dangers of buying unlicensed medicines for a Daily Express feature. We responded to the Daily Express following a misleading headline about 'Fake Medicines flooding Britain'.

British Pharmacopoeia (BP) product insight survey – We promoted the British Pharmacopoeia user survey through social media, Gov Delivery and the BP website. This delivered 260 respondents and the debrief on the product user insight took place on Thursday, 28 March detailing some important 'hygiene' factors that need to be addressed across the portfolio of BP products.

British Pharmacopoeia (BP) How To Guide – A short companion publication has been developed to help users get more out of the BP. A communications plan to support the promotion of this is being developed and delivery will be implemented in partnership with TSO.

Yellow Card – We sent a blog on our Yellow Card scheme to the General Pharmaceutical Council, who will publish it in the next edition of their e-bulletin Regulate.

Economist Reports – The CEO gave an interview to a journalist from The Economist Intelligence Unit, who is producing a report on the intersection between self-care and policy. 9 senior executives and other experts in the field are also being interviewed.

Diet Pills – We liaised with BBC Radio on MHRA's involvement with diet pills and the #FakeMeds campaign. We also engaged with celebrity doctor Ruth Langsford about diet pills on twitter.

Recent CPRD authored publications – CPRD has had a very productive quarter in terms of CPRD-led research publications. Over the last month, 6 CPRD papers authored by staff across the CPRD Observational Research and the Data Tools and Technology teams, have been published or accepted for publication peer-reviewed academic journals. This represents a new publication record for CPRD.
Following on from the highly cited paper Herrett et al 2015 characterising CPRD GOLD data derived from GP practices using Vision GP software systems, a data resource profile describing CPRD Aurum, the new CPRD database containing primary care data extracted from GP practise using EMIS GP software has been published in the *International Journal of Epidemiology* (Wolf et al., 2019). The aim of this paper is to provide researchers with an overview of the CPRD Aurum database including where it is sourced from, population coverage, its representativeness compared to the UK general population, the database structure, content and available linkages. The paper also describes the data quality

assurance undertaken by CPRD to ensure that this database is suitable for research. Since its online publication on the 11 of March 2019, the paper has already been viewed 822 times and downloaded 152 times.

Gallagher et al. (2019) compared the accuracy of death recording in CPRD primary care data to that recorded in the Office of National Statistics (ONS) death registration data (considered to be the gold standard database for death records). The publication in *Pharmacoepidemiology and Drug Safety* demonstrated that most deaths were recorded in UK primary care data with death rates comparable in the two data sources.

The *British Journal of General Practice (BJGP)* has accepted a paper by Booth et al. (*in press*) describing the CPRD-RCGP quality improvement (QI) initiative. The paper focuses on the pilot study and scale-up of the drug safety prescribing pilot reports. The significance of this project is automation of the production of the reports, which are bespoke to each of the 1000 plus CPRD contributing practices. The reports enable benchmarking of practice-level prescribing safety indicators, with individual case finding, within a robust data governance framework.

A study by Strongman et al. (*in press*) assessing the impact of restricting the scope of electronic health record data collection on the ability to conduct research has been accepted for publication in *Pharmacoepidemiology and Drug Safety*. CPRD studies published in high impact journals (e.g. the BMJ) or referenced in clinical guidelines (e.g. NICE) were systematically analysed to assess whether they would have been possible using a database with data collection restrictions in place. Overall, 91% studies were compromised and 56% were unfeasible. The study concluded that national initiatives seeking to collect electronic health records should consider the implications of restricting data collection on the ability to address vital public health questions.

A collaborative CPRD-VRMM review led by Ghosh et al. (*in press*) on the use of CPRD data to support pharmacovigilance has been accepted for publication in *Therapeutic Advances in Drug Safety*. The review discusses how CPRD databases provide representative and comprehensive capture of patient risk factors and outcomes. Examples of where CPRD data have been used for pharmacovigilance and how these have fed into guidelines and policy are presented.

Finally, the first paper from the Regulator's Pioneer Fund MHRA proof-of-concept project to develop and pilot test a synthetic benchmarking dataset for validating machine learning algorithms, has been accepted for publication. The paper by Wang et al, outlines a proposed framework to generate and evaluate synthetic data in a way that preserves both the biological relationships in real patient data and patient privacy. The paper, which will also be presented, is to be published in the highly prestigious conference proceedings of the *IEEE International Symposium on Computer-Based Medical Systems (CBMS).*

NIBSC Publications:

The Director's NIBSC-authored Paper of the Month for March 2019 (from those published/indexed on Pubmed in February) was a paper entitled:

Establishment of an erythropoietin CRS with stable measurable dimer content for SEC system suitability qualification

Matejtschuk P, Duru C, Bristow AF, Burns CJ, Cowper B, Daas A, Costanzo A.

Pharmeur Bio Sci Notes. 2019;2019:11-26.PMID: 30714898

Summary: The European Pharmacopoeia (Ph. Eur.) monograph 1316 'Erythropoietin concentrated solution' prescribes that the dimer content of therapeutic erythropoietin (EPO) preparations must not exceed 2% as determined by Size-Exclusion Chromatography (SEC). This report describes the evaluation of a candidate Chemical Reference Substance (cCRS) to serve as system suitability reference material for the qualification of SEC systems used to assess dimer and oligomer content in EPO solutions. The cCRS was adopted by the Ph. Eur. Commission as Erythropoietin for SEC system suitability CRS batch 1 following consideration of the report.

Further papers that were considered this month are listed below:

Original Research Papers

1. Establishment of the WHO 2nd International Standard Factor V, plasma (16/374): Communication from the SSC of the ISTH.

Hubbard AR, Thelwell C, Rigsby P; subcommittee on factor viii factor ix, rare coagulation disorders.

J Thromb Haemost. 2019 Feb 7. doi: 10.1111/jth.14403.

2. Proteomic analysis reveals temporal changes in protein expression in human induced pluripotent stem cell-derived cardiomyocytes in vitro.

Hellen N, Pinto Ricardo C, Vauchez K, **Whiting G, Wheeler J,** Harding SE.

Stem Cells Dev. 2019 Feb 13. doi: 10.1089/scd.2018.0210.

3. Comparison of Volumetric and Bead-Based Counting of CD34 Cells by Single-Platform Flow Cytometry.

Saraiva L, Wang L, Kammel M, Kummrow A, Atkinson E, Lee JY, Yalcinkaya B, Akgöz M, Höckner J, Ruf A, Engel A, Zhang YZ, O'Shea O, Sassi MP, Divieto C, Lekishvili T, Campbell J, Liu Y, Wang J, Stebbings R, Gaigalas AK, Rigsby P, Neukammer J, **Vessillier S.**

Cytometry B Clin Cytom. 2019 Feb 20. doi: 10.1002/cyto.b.21773.

4. Pertactin-deficient Bordetella pertussis isolates: evidence of increased circulation in Europe, 1998 to 2015.

Barkoff AM, Mertsola J, Pierard D, Dalby T, Hoegh SV, Guillot S, Stefanelli P, van Gent M, Berbers G, Vestrheim D, Greve-Isdahl M, Wehlin L, Ljungman M, Fry NK, **Markey K**, He Q.

Euro Surveill. 2019 Feb;24(7). doi: 10.2807/1560-7917.ES.2019.24.7.1700832.

5. An activated-platelet-sensitive nanocarrier enables targeted delivery of tissue plasminogen activator for effective thrombolytic therapy.

Huang Y, Yu L, Ren J, Gu B, **Longstaff C,** Hughes AD, Thom SA, Xu XY, Chen R.

J Control Release. 2019 Feb 23. pii: S0168-3659(19)30116-6. doi: 10.1016/j.jconrel.2019.02.033.

6. By-Products of Heparin Production Provide a Diverse Source of Heparin-like and Heparan Sulfate Glycosaminoglycans.

Taylor SL, **Hogwood J,** Guo W, Yates EA, Turnbull JE.

Sci Rep. 2019 Feb 25;9(1):2679. doi: 10.1038/s41598-019-39093-6.

6. ORGANISATIONAL TOPICS

Transformation Division (TD) Update - European Systems Contingency Programme delivered 11 systems in time for the 29 March. A major and significant achievement

- The Clinical Trials Programme delivered its major release successfully
- The TD operating Model has been developed and makes a clear case for change and insourcing

- The Annual Senior Information Risk Owner Information Assurance report was produced and welcomed by CET – representing a major step forward in Agency Information Management
- A single summary Portfolio roadmap was produced that was understood and welcomed by senior stakeholders
- Priorities for OT agreed by Operational Transformational Steering Group and CET

Human Resources (HR) Update – During March HR:

- delivered Performance Ratings Training for all line managers
- launched a 'one stop shop' for employee benefits and employee support on INsite, ensuring quick and easy access to a broad range of information and benefits
- relaunched the Special Bonus Guidance
- initiated the annual Conflict of Interest declaration exercise for all staff

In addition, CET approved the People Survey Pan Agency action plan, plus Divisional/Centre plans, for 2019 and these were published on INsite.

CEO MEETINGS – On 11 March the CEO attended a meeting on EU Exit Planning with the Secretary of State. The CEO and Chairman attended the EU Relationship Group Meeting on the 14 March; and following this the CEO attended an Accelerated Detection of Disease challenge stakeholder reference meeting, chaired by Professor Sir John Bell. On the 19 March the CEO and Chairman met with the Chief Medical Officer Professor Dame Sally Davies; and on the 20 March attended the first of the MHRA monthly Brexit meetings with Baroness Blackwood, Lord O'Shaughnessy's successor. A meeting of the Accelerated Access Collaborative meeting was held on the 21 March; and on the 26 March the CEO attended a Summit on Anti-Microbial Resistance.

OPERATIONAL PERFORMANCE

New UK Marketing Authorisations (MAs) – One new active substance was assessed in March.

New UK Marketing Authorisations (MAs) - Existing Active Substances – The number (volume) of new MA applications assessed in March was lower when compared with the average number of assessments completed in 2017/18. The numbers of new applications determined in February was higher compared with the average monthly figures for 2017/18.

New UK Marketing Authorisations - Existing Active Substances

Procedure	MAA Assessed This Month	MAA Assessed 2017/18 Average per month
National, UK-only	44	29
Decentralised, UK=RMS	6	22
Decentralised and MR, UK=CMS	14	46
Total	**64**	**97**

Procedure	MAA Determined This Month	MAA Determined2017/18 Average per month
National, UK-only	34	18
Decentralised, UK=RMS	40	29
Decentralised and MR, UK=CMS	106	48
Total	**180**	**95**

The Innovation Office continues to act as a point of contact for free, consolidated advice and 23 new enquiries were received in March, with five of these being directed to the regulatory advice service for regenerative medicines (RASRM) to provide joint advice from

regulators. It has been a very busy month for the innovation office with not only a high number of enquiries being received but also nine face-to-face meetings and two teleconferences held. Since the launch of the Innovation Office on 11 March 2013 there have been 771 relevant queries.

Regulatory Information Service – 1021 enquiries were received in March 2019 (779 e-mails, 242 phone calls). 34 grouping requests were processed and 5 requests for expedited review were also made to LD in the month of March

Parallel imports (PLPIs) – In March, 32 PLPI initial submissions were received, 47 were assessed and 85 were determined (51, 59 and 75 respectively in February).
Median time from submission to grant was 5.1 months (4.4 months in February).
596 PLPI variation applications were received, 470 were assessed and 468 were determined (496, 420 and 638 respectively in February).
Average time from submission to grant was 1.8 months (2.7 months in February).

Public Assessment Reports (PARs) – 100% of UK Public Assessment Reports and Lay Summaries (43/43) completed in March 2019 were published within the 60-day high-level target time from grant of the marketing authorisation. There were two PARs with a non-safety variation of clinical importance (Type II medical) completed in March 2019, completed on time.

Clinical Trial Authorisations (CTAs) – Clinical Trial Authorisation (CTA) applications: A total of 77 applications were assessed this month. For the financial year-to-date, 75 fewer applications have been assessed compared with the same period last year (1010 for 2018 compared to 935 for 2019).
There were 11 first in UK and 9 first in human (FIH) studies assessed in March. 9 applications were discussed at the Clinical Trial Unit (CTU) multidisciplinary meeting.
In March CTU received no initial or amendment submissions for a novel trial design
Clinical Trial Helpline: 536 calls and 278 emails were recorded. The response time for emails was an average of 2.1 days (target is average of 14 days).

Pharmacovigilance Adverse Drug Reactions (ADRs) – During March, the Division continued to meet all Agency targets related to the capture of ADR reports and signal detection. A total of 3791 UK ADR reports were received in March 2019, of which 644 were received from patients, parents and carers. Results against key performance measures for fatal and serious reports were both 100%. 81% of UK spontaneous serious ADRs were sent to EMA within the High-Level Target of 11 days, 19% were sent to the EMA in 12-15 days and 1 report was sent over the 15-day target. Of 112 general enquiries received, 89% were answered within 7 working days and 100% within 10 working days. 95% of all signals generated for Additional Monitored / Black Triangle and established medicines were initially evaluated in March, meeting the Agency target.

Devices adverse incidents - 1,724 Adverse Incident reports received in March (which compares with 1,806 for the same month last year), a decrease of 4.5%. The cumulative total for this year is 5,077, which compares with 5,068 for 2018, an increase of 0.2%.

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. 2 clinical investigations were completed in March.

Biologics batch release – There was a small decrease in test release certificates issued for vaccines and blood products from 93 product batches in February to 85 batches issued in March. The target for timeliness of product testing was achieved in March. Plasma pool

releases increased to more normal levels with 346 in March compared to 283 in February. There were 5 supplementary certificates issued due to manufacturer errors.

7. OTHER INTERNATIONAL TOPICS

MHRA involvement in the WHO Pilot Prequalification of Similar Biotherapeutic Products - In order to explore options to facilitate access to safe, effective and quality assured biotherapeutic products (BTPs) and their corresponding similar biotherapeutic products (SBPs), WHO has launched a pilot procedure to prequalify selected BTPs and SBPs as a step forward to support national and global efforts to increase access to and the affordability of BTPs and their corresponding SBPs http://www.who.int/medicines/regulation/biotherapeutic_products/en/. Currently the pilot procedure is limited to two biotherapeutic products: rituximab and trastuzumab.
Following a request to the MHRA CEO from the WHO in August 2018 to help establish a pool of assessors with experience in assessing biosimilars (a proposed ICMRA-WHO partnership for enabling access to medicinal products), the MHRA nominated five assessors from the Biologicals Unit to assist with this pilot project.
Three assessors (quality, clinical and non-clinical) were able to attend the initial introductory meeting and interviews regarding this project in Copenhagen on 21 November 2018.
Following this initial meeting, the WHO decided that they needed quality and clinical expertise for the pilot in Copenhagen in March 2019. They invited 2 assessors (one quality and one clinical) from the MHRA to attend a 3-day workshop on the full assessment pathway, including 2 pre-submission meetings with applicants, followed by 2 assessment days working on the abridged pathway.
The assessors received very positive feedback from these meetings in March and thanks from the WHO team on their significant contributions. The WHO also indicated that they are keen for our continued involvement as needed, dependent on the submissions received and progress of the pilot.

The NIBSC Principal Scientist in Infectious Disease Diagnostics Division (IDD) at NIBSC, attended the second **WHO Strategic Advisory Group of Experts for In-vitro Diagnostics (SAGE IVD).** The group was tasked with the development of the second WHO Essential Diagnostics list, aimed at enhancing global healthcare through the accurate and timely diagnosis of illness. They attended in the capacity of a member of the WHO Expert Committee on Biological Standardisation (ECBS) and presented to the group the advances made by the committee in the standardisation of IVD's; the work of NIBSC featured heavily in the presentation. They continue to work with both groups to align work programs and identify synergies for work programs at NIBSC.

The NIBSC Principal Scientist in Analytical and Biological Sciences hosted on 11 March a visit and a lecture on the **application of solid state Nuclear Magnetic Resonance (NMR) in biophysical characterisation** by Eric Munson, Professor of Industrial & Physical Pharmacy at Purdue University USA. Their team has been collaborating with Eric on potential application for some lyophilized preparations since initial discussions at a freeze-drying meeting last year.

The NIBSC Principal Scientist in Analytical and Biological Sciences also attended the **Engineering and Physical Sciences Research Council (EPSRC) Future Manufacturing Hub in Targeted Healthcare working group** on Formulation at University College London (UCL) on 19 March interacting with industrial, academic and research funding bodies on the research being undertaken within the Hub of which NIBSC is a partner.

Dr Ian Hudson
Chief Executive