Regulatory & Pharma News Update
July & August 2018

REGULATORY NEWS

MHRA Publishes 'Annual Review of MHRA GCP Referrals: 2017' document.

On 13 July 2018, the Medicines and Healthcare products Regulatory Agency (MHRA) published their serious breach GCP referrals metrics report covering the period from January to December 2017.

Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Annual Review of MHRA GCP Referrals: 2017

Period covered: January – December 2017

Cumulative Summary:

Total Referrals				
Serious Breach?	**No**	**Yes**	**Pending**	**Grand Total**
Total	47	101	1	149

Type of Notifying Organisation				
Serious Breach?	**No**	**Yes**	**Pending**	**Grand Total**
Sponsor	40	95	1	136
CRO	2	3	0	5
Trust	0	2	0	2
Investigator	0	0	0	0
HRA	1	0	0	1
Whistleblowers	1	0	0	1
Other	3	1	0	4
Grand Total	47	101	1	149

Impact/Reason for Serious Breach				
Serious Breach?	**No**	**Yes**	**Pending**	**Grand Total**
Approval issues	4	9	0	13
IMP	6	15	0	21
Other non-compliances	9	14	0	23
Patient confidentiality	0	6	0	6
Patient safety	8	42	1	51
Scientific value / data credibility	11	14	0	25
N/A	9	1	0	10
Grand Total	47	101	1	149

Outcome/Action				
Serious Breach?	**No**	**Yes**	**Pending**	**Grand Total**
In-house Follow-up	12	57	0	69
None	31	30	0	61
Recommend Routine Inspection	3	11	0	14
Recommend Triggered Inspection	0	1	0	1
Transferred	1	1	0	2
Pending	0	1	1	2
Grand Total	47	101	1	149

https://www.gov.uk/government/statistics/annual-review-of-good-clinical-practice-referrals

UK Government Publishes Guidance on the Effect of a 'No Agreement' Brexit

Guidance is given on how medicines, medical devices and clinical trials would be regulated if there is no 'Brexit deal'; on batch testing medicines; on how to apply for authorization in the UK; and, also, for marketing authorization holders.

If there is no agreement, MHRA would need to take on the functions for medicines on the UK market (currently undertaken by EU) which would require changes to the UK law via the Human Medicines Regulations 2012.

Medical devices approved for the EU market and CE-marked would be recognized in the UK (if this changes then adequate time would be provided to implement changed requirements). The UK would comply with all key elements of the Medical Devices Regulation and the in vitro diagnostic Regulations, which will apply in the EU from May 2020 and 2022 respectively. The new EU Clinical Trials Regulation (CTR) 536/2014 will not be in force in the EU at the time that the UK exits the EU and will not be incorporated into UK law on Exit day, but UK regulations will align where possible with the CTR. This alignment will happen after 29th March 2019.

If there is no agreement the UK would continue accept batch testing of human medicines carried out in countries on a list from the MHRA. A Qualified Person (QP) based in the UK, EU or EEA would be required to certify batch testing.

In the event that there is no agreement, regulatory information relating to human medicines and medical devices would need to be submitted directly to the MHRA.

https://www.gov.uk/government/news/medicines-and-healthcare-products-regulatory-agency-statement-on-the-outcome-of-the-eu-referendum

EMA Announces Temporary Cuts in Activities

The European Medicines Agency (EMA) released news that temporary cuts in activities will be required as the Agency expect to lose more staff than initially anticipated. It was announced by EMA that staff who will not relocate to Amsterdam have already started to leave the Agency and that, overall, EMA expects a staff loss of about 30%. EMA plan to launch the next phase of its business continuity plan on 1st October 2018 at the latest. Following the implementation of phase 1 and 2 of the business continuity plan, in phase 3 additional activities are anticipated to be reduced or suspended through to 2019. Activities initially impacted by phase 3 include: collaboration at international level; development and revision of guidelines; holding of non-product-related working parties; programmes and projects, where activities in relation to project governance will be reduced in line with the reduction/suspension of projects; organisation and attendance at stakeholder meetings.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/08/news_detail_002999.jsp&mid=WC0b01ac058004d5c1

Starting on 1st August 2018 EMA has suspended all new activities related to clinical data publication. EMA will continue to publish clinical data submitted by the end of July 2018 but no new data packages will be processed until further notice.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000555.jsp&mid=WC0b01ac05809f363e

EMA's First Report on Unprecedented Transparency Policy

EMA published the first report on the implementation of policy on the publication of clinical data (Policy 0070) on 16th July 2018. The report covers one year from the launch of EMA's clinical data website on 20th October 2016 and lists the 50 medicines for which clinical data were published, including orphan, paediatric, biosimilar and generic medicines, as well as the corresponding 54 regulatory dossiers. It is highlighted that the EMA is the first medicines regulatory authority worldwide to give open access to the clinical data submitted by pharmaceutical companies in support of marketing authorisation applications. The report states that the first year of implementation of EMA's clinical data publication policy has been productive.

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf

http://www.ema.europa.eu/docs/en_GB/document_library/Report/2018/07/WC500252071.pdf

Draft Questions and Answers on Data Monitoring Committees issues

EMA opened a consultation on 1st August 2018 on a question-and-answer document, the aim of which is to supplement the CHMP Data Monitoring Committee Guideline (Doc Ref. EMEA/CHMP/EWP/5872/03). The deadline for comments is 31st July 2019.

http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500252790&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc

Guidelines for Phase I Clinical Trials 2018 Edition

On 29th May 2018 the Association of the British Pharmaceutical Industry (ABPI) published a new 2018 edition of the guideline, which reflects the current EU legislation for the performance of Phase I clinical research as set down in the EU Clinical Trials Directive. The new edition incorporates the previous ABPI First in Human Studies guidelines with the aim of compiling all the different aspects of conducting Clinical Pharmacology Phase I trials into a single document.

https://www.abpi.org.uk/about-us/resources/publications-library/guidelines-for-phase-i-clinical-trials-2018-edition/
https://www.abpi.org.uk/media/4992/guidelines-for-phase-i-clinical-trials-2018-edition-20180626.pdf

FDA Takes Action Against 21 Websites Marketing Unapproved Opioids

FDA released news on 28th August 2018 that four more online networks operating a total of 21 websites were warned for illegally marketing potentially dangerous, unapproved and misbranded versions of opioid medications, including tramadol. The warning letters issued by the FDA to each of the networks state that they must immediately stop illegally selling these products to American consumers. The publication states that there was a total of 13 warning letters to more than 70 websites issued this summer. The FDA warns that patients who buy prescription medicines, including opioids, from illegal online pharmacies may be putting their health at risk because the products, while being marketed as authentic, may be counterfeit, contaminated, expired, or otherwise unsafe. The networks receiving warning letters include: CoinRX, MedInc.biz, PharmacyAffiliates.org, PharmaMedics.

The FDA takes severe measures against these networks to protect the public health and is working closely with legitimate Internet stakeholders, including leading social media sites, in these public health efforts.

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm618658.htm

FDA Issues Policy to Facilitate the use of Electronic Health Record Data in Clinical Investigations

The Food and Drug Administration (FDA) announced the availability of final guidance for industry entitled "Use of Electronic Health Record Data in Clinical Investigations" on 18th July 2018. This document is intended to assist sponsors, clinical investigators, contract research organisations, institutional review boards (IRBs), and other interested parties on the use of electronic health record data in FDA-regulated clinical investigations.

https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM501068.pdf

FDA Releases Biosimilars Action Plan

The Action Plan gives a summary of main FDA activities to encourage innovation and competition among biologics and the development of biosimilars. The FDA try to maintain the balance between innovation in drug development and facilitating timely market competition. Among other actions this necessitates the creation of incentives for innovation in the form of exclusivity periods; modernisation of regulatory requirements with the purpose to reduce time, uncertainty, and cost of drug development; and support of a competitive marketplace through 'the efficient approval of lower-cost generic and biosimilar alternatives'. The FDA highlights the importance of ensuring that this balance exists across the spectrum of pharmaceutical products – from small molecules to complex products and biologics.

The 'Biologics Price Competition and Innovation Act' (BPCI Act) established an abbreviated pathway for biologics, called biosimilars, in 2010. The BPCI Act aligns with the FDA's longstanding policy of permitting appropriate reliance on what is already known about a drug, thereby saving time and resources and avoiding unnecessary duplication of human or animal testing. At the time of Action Plan issue the FDA had approved 11 products under the BCPI Act including the first biosimilars for the treatment of cancer.

Among other actions, the FDA plan to develop information resources and development tools that can assist biosimilar sponsors in developing high quality biosimilar and interchangeable products.

The FDA emphasises that it will continue to play a critical role in facilitating increased access to biosimilars.

https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm613761.pdf

https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/ucm215089.htm

PHARMA NEWS

Companies Risk Failure to Comply with Falsified Medicines Directive

Around 1,500 pharmaceutical companies are at risk of failure to comply with the Falsified Medicines Directive (FMD) because they have yet to start working with the European Medicines Verification Organisation (EMVO). The EMVO said that just 841 companies have completed the first stage of connection to the EU Hub — the EU-wide database at the centre of the FMD — which is the beginning of a process known as 'on-boarding'[1]. The main purpose of the European Hub is to serve as the principal place for storage of master data and as a gateway for the transmission of manufacturer data to the national and national Blueprint systems. Data reconciliation on repackaging activities, i.e. maintaining a link between original and repackaged product batches, is exclusively performed on the European Hub.[2]

The EU Falsified Medicines Directive (2011/62/EU) was adopted in 2011 and introduced new harmonised measures to ensure that medicines in the European Union (EU) are safe and that trade in medicines is properly controlled. Member States have until 9 February 2019 to implement the final part of the Directive, the 'safety features' Delegated Regulation.[3]

The ESMO letter of announcement dated 06 August 2018 warns that the on-boarding process can take up to 6 months to be fully completed by an On-boarding Partner.[4]

[1]Ref: *The Pharmaceutical Journal*, 10 August 2018, https://www.pharmaceutical-journal.com/news-and-analysis/news/almost-1500-pharma-firms-could-miss-fmd-deadline-warns-body-in-charge/20205306.article

[2]https://emvo-medicines.eu/new/wp-content/uploads/EMVS-URS-Lite.pdf

[3]https://www.gov.uk/government/consultations/implementing-safety-features-under-the-falsified-medicines-directive

[4]https://emvo-medicines.eu/new/wp-content/uploads/EMVO_LoA_0001_20180806_Letter-of-Announcement_EMVO-notice-of-On-boarding-on-time.pdf

EMA's and FDA's Update on Medicines Containing Valsartan

EMA released news on 5th July 2018 that some valsartan medicines were being recalled across the EU. EMA is reviewing medicines containing the active substance valsartan that is supplied by Zhejiang Huahai Pharmaceuticals, a company in Linhai, China. EMA stated that the review was triggered after the company detected an impurity, N-nitrosodimethylamine (NDMA) (which is classified as a probable human carcinogen), in the valsartan active substance which the company supplies to manufacturers in the EU. EMA informed that while the review is underway, national authorities across the EU are recalling medicines containing valsartan supplied by Zhejiang Huahai. In the publication, EMA provides an information for patients and health care professionals and also outlines the procedure for the review of medicines.[1]

EMA published an update on 20 Aug 2018 stating that the company Zhejiang Tianyu is no longer authorised to manufacture the valsartan active substance for EU medicines following the suspension of its CEP (Certificate of Suitability) – a certificate verifying that the quality of its valsartan meets European requirements. EMA's review of valsartan in relation to NDMA is continuing and the EMA is working closely with the European Directorate for the Quality of Medicines and Healthcare, international partners and national authorities in the EU.[2]

FDA announced a recall of certain batches of valsartan tablets on 13 July 2018 because of an impurity (NDMA). The investigation is still ongoing as stated in the FDA portal. FDA publishes regular updates on recalled valsartan-containing product information. FDA states that will update the list of products included in the recall and the list of products not included in the recall as more information becomes available.[3]

[1]http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/07/news_detail_002984.jsp&mid=WC0b01ac058004d5c1

[2]http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/08/news_detail_003008.jsp&mid=WC0b01ac058004d5c1

[3]https://www.fda.gov/Drugs/DrugSafety/ucm613916.htm

Cochrane Intend to Initiate an Urgent Update of HPV Vaccine Review

The Cochrane research concluded in the review published in May 2017 that the vaccines are effective against precancerous changes that lead to cervical cancer and that the risk of side effects is no greater in the vaccinated than in the control groups. However, the review was based on 26 studies involving 73,428 women, but it could have included as many as 46 trials involving more than 120,000 according to researchers from the Nordic Cochrane Centre in Copenhagen and from the Centre for Evidence Based Medicine in Oxford.

David Tovey, editor-in-chief of the Cochrane Library, said: "To date, we also have no reason to believe that the main conclusions of the review relating to benefit and serious adverse effects are unsafe. However, we intend to initiate an urgent update of the review that will incorporate information provided in the *BMJ EBM* study."

"In addition, there is work ongoing on a second review that will tackle matters of comparative benefit and harms from the different forms of HPV vaccine."

Ref: *BMJ* 2018;362:k3472, https://www.bmj.com/content/362/bmj.k3472 (Published 09 August 2018)

Dutch Sildenafil Trial 'Immediately Stopped' due to Baby Deaths

Published on 25-Jul-2018 by Flora Southey. Researchers have halted a clinical trial testing sildenafil citrate – the active ingredient in Pfizer's Viagra – in pregnant women, following reports of baby deaths.

https://www.in-pharmatechnologist.com/Article/2018/07/25/Dutch-sildenafil-trial-immediately-stopped-due-to-baby-deaths

GSK and 23andMe Unveiled an Exclusive Four-year Collaboration

On 25 July 2018 GSK released news that GSK and 23andMe had signed an agreement to leverage genetic insights for the development of novel medicines, using human genetics as the basis for discovery. The goal of the collaboration is outlined to gather insights and discover novel drug targets driving disease progression and develop therapies for serious unmet medical needs based on those discoveries.

https://www.gsk.com/en-gb/media/press-releases/gsk-and-23andme-sign-agreement-to-leverage-genetic-insights-for-the-development-of-novel-medicines/