The Pharmaceutical and Healthcare Sciences Society (PHSS) GMP Update May 2019

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INTRODUCTION
During the last 4 weeks there have been a number of developments in the regulation of the pharmaceutical industry. This month reported issues have come from the EU Australian and USA regulatory authorities.
The topics covered in this edition of the "Update" include:

Europe
- **The role of regulators in establishing added benefit of novel therapies**
- **MHRA - GDP Office Based Evaluation and Risk Assessment programme (OBERA)**

USA
- **Application of statutory factors in determining when a REMS is necessary**
- **Bispecific antibody development programs**
- **CBER FY 2018 Report**
- **FDA updates on angiotensin II receptor blocker (ARB) recalls including valsartan, losartan and irbesartan**
- **Special 301 Report on Intellectual Property Protection and Review of Notorious Markets for Piracy and Counterfeiting**

International
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- **Guidance for TGO 101 – (Standard for tablets, capsules and pills**
- **Standard for Disinfectants and Sterilants (TGO 54 / TGO 104). - Outcomes from consultation**

Products
- **Extending Expiration Dates of Doxycycline Tablets and Capsules in Strategic USA Stockpiles**

RECENT DEVELOPMENTS IN GMP AND REGULATORY REQUIREMENTS

Europe
EMA
The role of regulators in establishing added benefit of novel therapies
The main conclusions of an article entitled Added therapeutic benefit and drug licensing (which is available through open access in Nature Reviews Drug Discovery) are that regulators have a role to play in ensuring that there is a solid evidence base to support the assessment of added therapeutic benefit of novel treatments compared with existing and potentially cheaper therapies. To help health technology assessment bodies, payers, clinicians and patients to separate merely new from truly better medicines, the regulators, firstly, should provide explicit reasoning on a medicine's added benefit compared to other treatments at the time of approval. Secondly, they should insist on 'evidence by design'. This means they must make companies aware of the need to plan the development programmes of medicines upfront, so that they are suitable to address the evidence needs of all relevant healthcare decisions-makers.
See ***news item***

MHRA
GDP Office Based Evaluation and Risk Assessment programme (OBERA)
The GDP Inspectorate is embarking on a pilot of a new inspection approach that will impact holders of a Wholesale Dealer's Licence (WDA(H)) whose main activities operate from a head office supplied from several 'satellite' facilities. For the companies selected, their satellite sites will be assessed remotely using information provided by the company in a standardised format.
Who will be affected?
- The Office Based Evaluation and Risk Assessment (OBERA) is targeted at companies that operate from a single head office location, where the majority of the wholesale activity takes place, with a number of satellite sites which perform a very limited range of GDP activity.
- Inclusion in the programme will be dependent upon the head office of the company passing an on-site 'Gateway Inspection'.
- For the purposes of the pilot, companies with over 100 sites on their Wholesale Dealer's Licence will be allocated a Gateway Inspection first. These companies will be contacted shortly, with the Gateway Inspections scheduled to commence during spring 2019.

Once the OBERA process has been proven through the pilot, it is anticipated that it will be applied to other companies operating applicable business models. MHRA will publish a follow-up blog post towards the end of 2019 on the findings from this pilot phase.
See:-***OBERA blog***

United States of America
The US Food and Drug Administration (USFDA)
Application of statutory factors in determining when a REMS is necessary
This final guidance is intended to clarify how the FDA applies the factors set forth in section 505-1 of the FD&C Act (21 U.S.C. 355-1) in determining whether a risk evaluation and mitigation strategy (REMS) is necessary to ensure that the benefits of a drug outweigh its risks.2 This guidance fulfils one of the performance goals that FDA agreed to satisfy in

the reauthorization of the Prescription Drug User Fee Act (PDUFA) V.
If FDA determines that a REMS is necessary, the Agency may require one or more REMS elements, which could include a Medication Guide, a patient package insert, and/or a communication plan. FDA may also require elements to assure safe use (ETASU) as part of a REMS. ETASU may be required if the drug has been shown to be effective, but is associated with a specific serious risk and can be approved only if, or would be withdrawn unless, such elements are required as part of a strategy to mitigate a specific serious risk(s) listed in the labeling of the drug. ETASU may be required for approved drug products that were initially approved without ETASU when other elements are not sufficient to mitigate a serious risk.
See:-***REMS guidance***

Bispecific antibody development programs

This draft guidance provides recommendations to assist industry and other parties involved in the development of bispecific antibodies. Discussion includes general considerations and recommendations for bispecific antibody development programs, as well as regulatory, quality, nonclinical, and clinical considerations in the context of bispecific antibody development programs. This guidance does not discuss development considerations for other multitarget therapies that are combinations of monoclonal antibodies or are antibody cocktails or polyclonal antibodies. Although this guidance is specific to bispecific antibodies, the principles discussed in this guidance may also be applicable to the development of other types of bispecific protein products.
Since the first therapeutic monoclonal antibody was commercialized in 1986, monoclonal antibodies have become a vital component of therapy for various diseases and conditions including, but not limited to, cancer, autoimmune and infectious diseases, and inflammatory conditions. The regulatory pathway for evaluation of monoclonal antibodies is well established, but additional guidance is needed regarding antibody-based products that target more than one antigen. Advances in technology and an interest in novel therapies that combine targets have led to the development of bispecific antibodies, which are genetically engineered, recombinant antibodies that consist of two distinct binding domains capable of binding two different antigens or two different epitopes of the same antigen
There is often a strong scientific rationale for engaging two targets in the therapeutic strategy for a specific disease. Bispecific antibodies can target multiple disease-modifying molecules with one drug, with possible advantages over combination therapy or the use of antibody mixtures. The possibility of immune cell retargeting through the delivery of an effector or effector cell to a specific target or the possibility of synergistic efficacy through engagement of multiple targets gives bispecific antibodies the potential to advance the development of antibody-based therapies. There are a number of challenges in developing bispecific antibodies, one of which may be significant immunogenicity caused by novel epitopes. This guidance addresses these considerations and provides recommendations regarding the type of data necessary to support the approval of bispecific antibodies.
This guidance focuses on general regulatory and scientific considerations for bispecific antibodies, not on development of a particular bispecific antibody. Industry and other stakeholders are encouraged to engage FDA to discuss their individual bispecific antibody development program.
See:-***bispecific antibody development***

CBER FY 2018 Report

One of the highlights of FY 2018 was the approval of two gene therapies: Luxturna, the first directly administered gene therapy for a specific genetic disorder, an inherited retinal disease, and Yescarta, a cell-based gene therapy for certain types of adult, large B-cell lymphoma. CBER also approved Heplisav-B, a Hepatitis B vaccine to prevent infection caused by all known subtypes of hepatitis B virus in adults 18 - 70 years of age, Shingrix, a vaccine for the prevention of shingles in adults 50 years of age and older, and Fluarix Quadrivalent, to prevent influenza disease in children as young as 6 months of age. In addition, CBER/FDA granted an emergency use authorization to the Department of Defense to enable the use of Freeze-Dried Plasma to treat haemorrhage or coagulopathy of U.S. military personnel injured during military combat when plasma is not available, or its use is not practical.
FDA's ongoing contributions to controlling Zika virus included CBER's approval of the cobas Zika test and the procleix Zika virus assay (Nucleic Acid Tests), the first donor screening tests for the direct detection of Zika Virus RNA in human plasma from individual donors.
The report highlights these and other CBER accomplishments that reflect its responses to new and ongoing scientific and regulatory challenges, such as those posed by advanced therapies, emerging infectious diseases, and threats to the blood supply.
See:-***CBER FY 2018 director's report***

FDA updates on angiotensin II receptor blocker (ARB) recalls including valsartan, losartan and irbesartan

As well as updating the list of products recalled FDA has posted new testing methods which can help manufacturers and international regulators detect and identify multiple nitrosamine impurities. FDA and international regulators have identified N-Nitrosodimethylamine (NDMA), N-Nitrosodiethylamine (NDEA) and NMBA in ARBs.

- A ***direct injection GC-MS method*** that is able to detect NDMA, NDEA, N-Nitrosodiisopropylamine (NDIPA), N-Nitrosoethylisopropylamine (NEIPA), and N-nitrosodibutylamine (NDBA)
- A ***headspace GC-MS method*** that is able to detect NDMA, NDEA, NDIPA, and NEIPA

These methods should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

See:-***recall/safety update***

Special 301 Report on Intellectual Property Protection and Review of Notorious Markets for Piracy and Counterfeiting

The Office of the United States Trade Representative has released its annual Special 301 Report on the adequacy and effectiveness of trading partners' protection of intellectual property rights and the findings of its Notorious Markets List, which highlights online and physical markets that reportedly engage in and facilitate substantial copyright piracy and trademark counterfeiting.

The Special 301 Report identifies trading partners that do not adequately or effectively protect and enforce intellectual property (IP) rights or otherwise deny market access to U.S. innovators and creators that rely on protection of their IP rights.

Trading partners that currently present the most significant concerns regarding IP rights are placed on the Priority Watch List or Watch List. USTR identified 36 countries for these lists in the Special 301 Report:

- Algeria, Argentina, Chile, China, India, Indonesia, Kuwait, Russia, Saudi Arabia, Ukraine and Venezuela are on the Priority Watch List.
- Barbados, Bolivia, Brazil, Canada, Colombia, Costa Rica, Dominican Republic, Ecuador, Egypt, Greece, Guatemala, Jamaica, Lebanon, Mexico, Pakistan, Paraguay, Peru, Romania, Switzerland, Thailand, Turkey, Turkmenistan, the United Arab Emirates, Uzbekistan and Vietnam are on the Watch List.

These trading partners will be the subject of increased bilateral engagement with USTR to address IP concerns. Specifically, over the coming weeks, USTR will review the developments against the benchmarks established in the Special 301 action plans for countries that have been on the Priority Watch List for multiple years. For such countries that fail to address U.S. concerns, USTR will take appropriate actions, such as enforcement actions under Section 301 of the Trade Act or pursuant to World Trade Organization or other trade agreement dispute settlement procedures, necessary to combat unfair trade practices and to ensure that trading partners follow through with their international commitments.

See:-***special 301 report*** *(A little surprising to see some EU Member States and countries such a Switzerland and Canada on the Watch List [MH])*

International

Australia

Guidance for TGO 101 –(Standard for tablets, capsules and pills

This guidance is to help sponsors and manufacturers of medicines understand the role of the Therapeutic Goods Order No. 101 - Standard for tablets, capsules and pills (TGO 101, the Order) in ensuring that these types of therapeutic goods are of appropriate quality.

The requirements that applied to tablets and capsules under Therapeutic Goods Order No. 78 Standard for tablets and capsules (TGO 78) have been adopted into TGO 101. This means that, generally, a transition period is not needed for these medicines. Sponsors can elect to move to alternative testing requirements, where this is permitted under the Order, at any time. Details on how to request this type of change are provided later in this document.

The TGO 101 requirements that apply to pills commence on 31 March 2021. Pills were not subject to TGO 78. The delayed commencement allows sponsors two years to update their manufacturing documentation and ensure that their goods will comply with the new requirements by the end of March 2021.

A two-year transition period has also been specified in relation to section 16 of the Order. This allows sponsors time to review the manufacturing documentation for their medicines and update them in line with the requirements for elemental impurities and residual solvents in tablets and capsules.

All tablets, capsules and pills subject to the Order and released for supply after 30 March 2021 must comply with TGO 101.

See:-***news TG101*** and ***Guidance for TG101***

Standard for Disinfectants and Sterilants (TGO 54 / TGO 104) - Outcomes from consultation

The TGA has made the new TGO104 to replace the previous TGO 54 which sunset on 1 April 2019.

The TGA has incorporated stakeholder feedback from consultation, about the proposed new TGO and its associated Guidance documents for Listed and Exempt disinfectants. TGO 104 incorporates:

- Updated sections of the previous TGO 54 and clarifies the requirements for hard surface disinfectants;
- The labelling requirements of the previous TGO and TGO 37 'general requirements for labels for therapeutic devices' (which sunset on 1 October 2018); and
- Standards and requirements within the guidelines for the evaluation of disinfectants.

As a result, these regulatory requirements are now contained within one TGO.

TGO 54

Products

Extending Expiration Dates of Doxycycline Tablets and Capsules in Strategic USA Stockpiles

A number of US government public health and emergency response stakeholders maintain stockpiles of doxycycline tablets or capsules for post-exposure prophylaxis (PEP) or treatment of inhalational anthrax in the event of an anthrax emergency. States have asked FDA what would be necessary to provide confidence that stockpiled doxycycline tablets and capsules have retained their original quality (i.e., purity and potency) beyond the manufacturer's labeled expiration date so the replacement of stockpiled product could be deferred.

This final guidance document provides guidance to government stakeholders on testing to extend the expiration date—under section 564A(b) of the Federal Food, Drug, and Cosmetic (FD&C) Act of stockpiled doxycycline tablets and

capsules for public health emergency preparedness and response purposes for an anthrax emergency.
See:***doxycycline expiry extension***

And finally…
We hope that our readers find our reviews to be both informative and helpful in keeping up to date with pharmaceutical legislation and regulatory guidance.
GMP Update is compiled by Malcolm Holmes an independent GMP Consultant

Useful website addresses / Links

Warning – some of the addresses include underscored spaces, which may be difficult to see as they appear in "Word" documents. You will also need to use Adobe Acrobat Reader, which can be downloaded from: http://www.adobe.com/products/acrobat/readstep2.html

British Pharmacopoeia (BP): http://www.pharmacopoeia.gov.uk/

Health Canada Compliance: http://www.hc-sc.gc.ca/dhp-mps/compli-conform/index-eng.php

The European Commission DG Enterprise – Pharmaceuticals: http://ec.europa.eu/enterprise/sectors/pharmaceuticals/index_en.htm

European Commission DG Enterprise – Medical Devices Sector http://ec.europa.eu/enterprise/medical_devices/index_en.htm

European Medicines Agency (EMA): http://www.ema.europa.eu/

European Medicines Agency Regulatory and Procedural Guidance: http://www.ema.europa.eu/htms/human/raguidelines/intro.htm

European Medicines Agency Inspections Sector: http://www.ema.europa.eu/Inspections/index.html

European Chemical Industry Council – Active Pharmaceutical Ingredients Sector (CEFIC/APIC): http://apic.cefic.org/

European Guide to GMP: http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-4/index_en.htm

European Compilation of Procedures for GMP Inspections: http://www.ema.europa.eu/Inspections/GMPCompproc.html

European Federation of Pharmaceutical Industries and Federations (EFPIA): http://www.efpia.org/

European Guidelines on Quality, Safety, and Efficacy for Human Use Products: http://www.ema.europa.eu/htms/human/humanguidelines/background.htm

European Guidelines on Quality, Safety, and Efficacy for Veterinary Products: http://www.ema.europa.eu/htms/vet/vetguidelines/background.htm

European Pharmacopoeia (Ph Eur): http://www.pheur.org/

FDA Home Page:http://www.fda.gov/default.htm

FDA GMP Regulations (CFR21): http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr211_01.html

FDA Inspections Operation Manual: http://www.fda.gov/ICECI/Inspections/IOM/default.htm

FDA Inspection Guides: http://www.fda.gov/ora/inspect_ref/igs/iglist.html

FDA CBER Guidance / Guidelines / Points to Consider: http://www.fda.gov/cber/guidelines.htm

FDA Guidance on Drugs: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

Global Harmonization Task Force (GHTF): http://www.ghtf.org/

International Conference on Harmonisation (ICH): http://www.ich.org/UrlGrpServer.jser?@_ID=276&@_TEMPLATE=254

International Society of Pharmaceutical Engineers (ISPE): http://www.ispe.org/

International Pharmaceutical Federation (FIP): http://www.fip.nl/www/

International Pharmaceutical Excipients Council (IPEC): http://www.ipec.org/

Japanese Ministry of Health, Labor and Welfare (MHW): http://www.mhlw.go.jp/english/

Mutual Recognition Agreements (MRAs): http://www.emea.europa.eu/Inspections/MRA.html

Pharmaceutical Inspection Co-operation Scheme (PIC/S) -GMP Guide and basic standards: http://www.picscheme.org/

Pharmaceutical and Research Manufacturers of America (PhRMA): http://www.phrma.org/

Risk-Based Approach to Pharmaceutical Current Good Manufacturing Practices (cGMP) for the 21st Century – Table of contents: http://www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm

The Irish Medicines Board: http://www.imb.ie/

The Pharmaceutical Quality Group (PQG): http://www.pqg.org/

The UK Medicines and Health Care Products Regulatory Agency (MHRA): http://www.mhra.gov.uk/

The MHRA Pharmaceutical Industry Pages: http://www.mhra.gov.uk/Pharmaceuticalindustry/index.htm

UK GMP (Orange) Guide: https://web110.secure-secure.co.uk/phss.co.uk/?cart=yes&do=item&cid=142

UK Official Documents including Medicines Legislation: http://www.tso.co.uk/bookshop/bookstore.asp

United States Pharmacopoeia (USP): http://www.usp.org/

World Health Organisation GMP Information (WHO): http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/index.html