The Pharmaceutical and Healthcare Sciences Society (PHSS) GMP Update May 2020

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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 Australian, EU, USA and UK regulatory authorities.
[This month we in particular note a number of Risk Based decisions pertinent to the coronavirus (COVID-19) outbreak. MBH]
The topics covered in this edition of the "Update" include:

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- **New measures to support availability of medicines used in the COVID-19 pandemic**
- **Guidance for medicine developers and companies on COVID-19**
- **Updates to GMP and GDP with respect to COVID-19**
- **Update to Advanced Therapy Medicinal Products (ATMP): Overview**
- **Q&A on regulatory expectations for medicinal products for human use during the COVID-19 pandemic.**
- **Compilation of Quality Review of Documentation (QRD) decisions on stylistic matters in product information**
- **Reflection paper on GMP and Marketing Authorisation Holders**
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- **Approval of GxP documents when working from home during the coronavirus (COVID-19) outbreak**
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- **Exemption and Exclusion from Certain Requirements of the Drug Supply Chain Security Act During the COVID-19 Public Health Emergency**
- **Temporary Policy Regarding Non-Standard PPE Practices for Sterile Compounding by Pharmacy Compounders not Registered as Outsourcing Facilities During the COVID-19 Public Health Emergency**
- **Policy for the Temporary Use of Portable Cryogenic Containers Not in Compliance With 21 CFR 211.94(e)(1) For Oxygen and Nitrogen During the COVID-19 Public Health Emergency.**
- **Temporary Policy for Compounding of Certain Drugs for Hospitalized Patients by Outsourcing Facilities During the COVID-19 Public Health Emergency**
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- **Reuse of face masks and gowns during the COVID-19 pandemic**
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- **EMA review of Picato concludes medicine's risks outweigh its benefits**

RECENT DEVELOPMENTS IN GMP AND REGULATORY REQUIREMENTS

Europe
EMA
COVID-19: What's new
The latest updates on the COVID-19 pandemic from the EMA, including all news and press releases, are available from :-***COVID-19 what's new*** more detail on certain topics is given below.
New measures to support availability of medicines used in the COVID-19 pandemic
Some EU Member States have indicated that they are starting to see shortages of certain medicines used for patients with COVID-19 or are expecting such shortages to occur very soon. These include medicines used in intensive care units such as certain anaesthetics, antibiotics and muscle relaxants as well as medicines used off-label for COVID-19. EU authorities are therefore putting in place additional measures to mitigate the impact of the pandemic on the supply chain of medicines in a coordinated manner. To help mitigate supply disruptions, the EU Executive Steering Group on Shortages of medicines caused by major

events, which provides strategic leadership for urgent and coordinated action on shortages within the EU in this pandemic, is currently setting up, with the pharmaceutical industry, a system, the i-SPOC (industry single point of contact) system, to fast-track interaction on shortages between industry and the EU Executive Steering Group. With this system, each pharmaceutical company will report directly to EMA, both for centrally authorised and nationally authorised medicines, anticipated shortages or current shortages of critical medicines used in the context of COVID-19. In the context of the pandemic, EMA and the EU network are considering mitigation measures such as regulatory actions to support increased manufacturing capacities, e.g. through speeding up the approval of a new manufacturing line or site. Discussions are also ongoing with the pharmaceutical industry to increase production capacity for all medicines used in the context of COVID-19, and in particular for medicines potentially at risk of supply shortages. The Agency has been, for example, proactively gathering information from Member States to monitor or anticipate EU-level shortages in hospital settings. It has also liaised with Member States regarding how the export ban on 14 active substances (APIs) issued by the Indian authorities impacts the availability of certain medicines in Member States. Together with its partners in the regulatory network, EMA is monitoring the situation very closely.

See:-***availability of medicines*** See also the subsequent EMA news item ***availability of medicinal products during the Covid -19 pandemic***

Guidance for medicine developers and companies on COVID-19

EMA is providing guidance for medicine developers and pharmaceutical companies to help speed up medicine and vaccine development and approval for COVID-19, and on how they should address the regulatory challenges arising from the COVID-19 pandemic. Topics covered are:-

- Early support for medicine and vaccine developers
- Advice for sponsors of clinical trials for COVID-19 treatments and vaccines
- Advice for sponsors of clinical trials affected by the pandemic
- Guidance on regulatory expectations and flexibility

See:-***guidance for medicine developers***

Updates to GMP and GDP with respect to COVID-19

The EMA has updated its GMP page to include a section on Regulatory expectations during COVID-19 pandemic

See:-***updated GMP document*** **&** ***updated GDP document***

Update to Advanced therapy medicinal products: Overview

The EMA has updated its GMP page to include a section on advice to patients and the general public to beware of unproven cell-based therapies. This followed the appearance of advertisements for cell therapies as cures for serious conditions across the EU in early 2020.

See:-***ATMPs overview***

Q&A on regulatory expectations for medicinal products for human use during the COVID-19 pandemic.

The European Commission, EMA and the European medicines regulatory network have developed this document which provides guidance to marketing authorisation holders of medicinal products for human use ("MAH") on regulatory expectations and flexibility during the COVID-19 pandemic. The document will be updated to address new questions and to adjust the content thereof to the evolution of the pandemic. For queries related to specific products that are not specifically addressed in this document, MAHs are invited to address the EMA (for centrally authorised products) or the relevant national competent authorities (for nationally authorised products). This document remains valid until further notice.

See:-***Q&A***

The guidance will be continuously updated. Marketing authorisation holders are therefore advised to regularly check ***this page*** for any new information in this area.

Compilation of Quality Review of Documentation (QRD) decisions on stylistic matters in product information

See:- ***guideline*** for an update on this useful Regulatory and Procedural guideline.

[Remember small errors in detail within printed material can lead to all sorts of problems. Adherence to this guideline could avoid issues of interpretation and subsequent risk to patient and / or recalls MBH]

Reflection paper on GMP and Marketing Authorisation Holders

This Reflection Paper is focussed on the GMP-related responsibilities that apply to Marketing Authorisation Holder (MAH) companies. While it is recognised that many MAH companies are not directly engaged in the manufacture of medicinal products themselves, the current European Commission (EC) guide to GMP (hereafter referred to as the 'GMP guide') refers, in several places, to MAHs and their responsibilities in relation to GMP. In general, these responsibilities relate to outsourcing and technical agreements, that require the MAH to perform certain specific tasks (e.g. evaluating the results of product quality reviews, agreeing irradiation cycles with manufacturers, etc.). These responsibilities are spread over the various chapters and annexes of the GMP guide, and are quite numerous. This Reflection Paper seeks to provide clarity as to what the various responsibilities are and what they mean for MAHs at a practical level. In addition to the MAH responsibilities in the GMP guide, this paper also addresses the various legislative provisions (i.e. in European Directives) and in other guidelines which relate to GMP and which concern MAHs. Some of the responsibilities stated in the legislation (e.g. in Directives 2001/83/EC and 2001/82/EC) and in applicable guidelines are written in a way that they apply to marketing authorisation applicants, and they are included in this Reflection Paper because those provisions also convey responsibilities upon

marketing authorisation holders in the post-authorisation phase.
See:-***relection paper for comment***
Comment is due by July 17 2020

Frequently asked questions about parallel distribution

This document applies to human and veterinary medicines and lists Q&As about parallel distribution. The European Medicines Agency (EMA) revises it as necessary.
See:-***parallel distribution Q&A***

Information note (Q&A) on the format and validity features of electronic certificates for medicines issued by the EMA.

EMA has implemented a new system to issue electronically signed and authenticated certificates for human and veterinary medicines The aim of this´Questions and Answers´ document is to provide guidance on the format of the electronic certificates issued by EMA, the safety features supporting their authenticity and integrity as well as the Agency´s measures to support the regulatory authorities of importing countries for confirming their validity, in case of any doubt.
See:-***information note/Q&A***

Pharmacovigilance inspection procedures

EU pharmacovigilance inspectors have developed Union procedures and guidance on pharmacovigilance inspections of marketing-authorisation holders of human and veterinary medicines.
National Competent Authorities of all Member States are expected to take account of the Union procedures and use them as the basis for standard operating procedures on the quality systems established within the inspectorates themselves.
See:-***pharmacovigilance inspection procedures***

MHRA

Approval of GxP documents when working from home during the coronavirus (COVID-19) outbreak.

Due to the COVID-19 pandemic, remote working has increased. Some organisations have advised that their processes for approving paper documents with wet ink signatures are no longer achievable.
This guidance is to enable organisations to consider alternative methods whilst maintaining basic control of documents.
The guidance is for organisations involved in the pharmaceutical lifecycle (GMP, GDP, GLP, GCP & GPvP) or GLP studies regulated by the MHRA.
The guidance covers:-

- Existing electronic systems
- Paper documents that were approved with wet ink signature
- Alternative methods

Some examples of issues with remote approval are included. In these examples, had the distribution and approval process been clearly defined and assessed, it is unlikely that such issues would have occurred.
See:-***remote approval guidance***

Process Licensing Update

The purpose of this post is to give an update on a change to how MHRA is issuing licences and certificates due to the coronavirus pandemic; and also, to act as a reminder to keep contact details up to date.
See:-***process licensing blog***

Pharmacovigilance Inspection Metrics Report April 2018 –March 2019

MHRA has now released this report. It is interesting to note that one of the critical findings reported relates to "The MAH had failed to ensure that patient information leaflets (PILs) containing updated safety information were being introduced to packaging in accordance with the guidance published by the MHRA. MHRA guidance states that once an MAH has received approval from the Agency, changes to labels, leaflets and packaging must be introduced within three to six months. The data reviewed during the inspection indicated that a large number of batches had been QP certified with PILs which had been superseded by versions approved more than nine months prior, with many of these missing new warnings in section 2 What you need to know before you take...or serious adverse reactions in section 4 Possible side effects. The delays in providing patients with up-to-date information on known product risks was considered to adversely affect the rights, safety or well-being of patients and posed a potential risk to public health.
See:-***2018-2019 report*** & ***reports 2009-present***

United States of America

The US Food and Drug Administration (USFDA)

Exemption and Exclusion from Certain Requirements of the Drug Supply Chain Security Act During the COVID-19 Public Health Emergency

FDA has been monitoring requests related to provisions of the Drug Supply Chain Security Act (DSCSA) because the provisions may affect the prescription drug supply chain during the COVID-19 outbreak. FDA is issuing this guidance to clarify the scope of the public health emergency exemption and exclusion under the DSCSA for the duration of the public health emergency declared by the Secretary of Health and Human Services (HHS) on January 31, 2020, effective January 27, 2020, and renewed for 90 days on April 21, 2020, effective April 26, 2020, to help ensure adequate distribution of finished prescription drug products throughout the supply chain to combat COVID-19. In addition, this guidance announces FDA's policy regarding the exercise of its discretion in the enforcement of authorized trading partner requirements under section 582(b)(3), (c)(3), (d)(3), and (e)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for certain distributions during the COVID-19 public health emergency involving other trading partners that may not be authorized trading partners.
See:-***final guidance***

Temporary Policy Regarding Non-Standard PPE Practices for Sterile Compounding by Pharmacy Compounders not Registered as Outsourcing Facilities During the COVID-19 Public Health Emergency

Due to the COVID-19 pandemic, FDA has received a number of queries from

compounders related to the impact of supply interruptions of face masks, gowns, gloves, and other garb, which we refer to collectively in this document as personal protective equipment (PPE).
FDA is issuing this guidance to communicate its temporary policy related to PPE use during human drug compounding at State-licensed pharmacies or Federal facilities that are not registered with FDA as outsourcing facilities. This policy is intended to remain in effect only for the duration of the public health emergency related to COVID-19
compounders - temporary PPE policy

Policy for the Temporary Use of Portable Cryogenic Containers Not in Compliance With 21 CFR 211.94(e)(1) For Oxygen and Nitrogen During the COVID-19 Public Health Emergency.

As demand for oxygen and nitrogen intended for medical use increases due to the COVID-19 pandemic, FDA has become aware of concerns regarding a low supply of portable cryogenic medical gas containers and has received inquiries regarding the use of gas containers that do not meet certain regulatory requirements for portable cryogenic medical gas containers (e.g., industrial gas containers).
FDA is issuing this guidance to communicate its policy for the temporary use of certain gas containers for oxygen and nitrogen intended for medical use for the duration of the public health emergency declared by the Secretary of Health and Human Services (HHS) on January 31, 2020.
See:-***oxygen and nitrogen containers***

Temporary Policy for Compounding of Certain Drugs for Hospitalized Patients by Outsourcing Facilities During the COVID-19 Public Health Emergency

FDA is issuing this guidance to communicate its temporary policy for the compounding of certain human drug products for hospitalized patients by outsourcing facilities that have registered with FDA under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353b). This policy is intended to remain in effect only for the duration of the public health emergency related to COVID-19 declared by the HHS, including any renewals made by the HHS Secretary in accordance with section 319(a)(2) of the Public Health Service Act (42 U.S.C. 247d(a)(2)). The drugs that are the subject of this policy may change during the emergency.
See:-***temporary policy***

Temporary Policy for Compounding of Certain Drugs for Hospitalized Patients by Pharmacy Compounders not Registered as Outsourcing Facilities During the COVID-19 Public Health Emergency

A similar policy to that for outsourcing facilities that have registered with FDA under section 503B of the FD&C Act has been published for Pharmacy compounders not registered as outsourcing facilities.
See:-***temporary policy - not registered outsourcing facilities***

Temporary Policy on Repackaging or Combining Propofol Drug Products During the COVID-19 Public Health Emergency

During the COVID-19 public health emergency, FDA has received several inquiries from health care professionals concerning the unavailability of propofol drug products used in the treatment and management of patients with complications related to COVID-19. FDA is issuing this guidance to communicate its temporary policy regarding the repackaging or combining of propofol drug products by a licensed pharmacist in a State licensed pharmacy, a Federal facility, or an outsourcing facility registered pursuant to section 503B of the FD&C Act (21 U.S.C. 353b) as outlined in this guidance for the duration of the public health emergency declared by the Secretary of HHS on January 31, 2020, or for such shorter time as FDA may announce through updated guidance.
See:- ***propofol drug products***

International

Australia

Reuse of face masks and gowns during the COVID-19 pandemic

The Therapeutic Goods Administration (TGA) has received several enquiries from organisations wishing to *reuse* medical face masks and gowns amid shortages of these products during the COVID-19 pandemic.
In order to make single use products suitable for reuse, they must be *reprocessed* and, while the TGA understands the critical need to consider all available options to address shortages, it is important to note that reprocessing single use medical devices to enable their reuse could expose patients and medical staff to unnecessary risks.
Individuals or organisations contemplating reprocessing single-use face masks and gowns for reuse need to check the manufacturer's instructions for use (IFU) and their website. Many products are not suitable for reuse.
The following information aims to ensure organisations clearly understand and minimise the risks of reprocessing single-use medical devices for reuse.

Note

If you are reprocessing medical devices for reuse, you will meet the legislative definition of a manufacturer. You will therefore need to meet all the responsibilities of a manufacturer under the therapeutic goods legislation and regulations.
should the device fail to perform as intended.
See:-***reuse of facemasks & gowns*** See also ***regulation of PPE & COVID-19*** & ***advice on surgical masks and gowns during COVID-19***
[I have included this item principally because of its topicality in the current situation. Readers should note that ***it relates to Australia only, however it gives a very clear interpretation of what TGA requires along with warnings of potential impacts.*** *It could therefore make useful reading for readers in different countries faced with this scenario. MBH]*

Domestic GMP inspections during the COVID-19 pandemic

The TGA has developed a process to enable inspectors to undertake remote and/or hybrid GMP domestic inspections where suitable, in place of on-site inspections. The TGA will only use this process during the COVID-19 pandemic. Routine on-site inspections will

recommence at an appropriate time when the pandemic restrictions are lifted. The TGA will continue to provide essential on-site inspections linked to the Australian Government's COVID-19 response plans and any other potential serious threat to public health, where these sites cannot be assessed remotely.
See:-***domestic GMP inspections***

Additional safety protections relating to COVID-19 for faecal microbiota transplant (FMT) products

TGA) is providing advice on safety protections to faecal microbiota transplant (FMT) providers since there is the potential to transmit the SARS-CoV-2 virus via FMT through shedding in stool.
This advice follows a ***recent safety alert from the US FDA*** that highlighted the additional safety precautions that should be in place for COVID-19 disease screening of potential stool donors for FMT products in order to prevent the spread of the SARS-CoV-2 virus.
Providers of FMT products are also expected to regularly monitor the TGA website for safety advice updates relating to the use of FMT during the COVID-19 pandemic.
See:-***additional safety precautions***
Products

EMA provides recommendations on compassionate use of remdesivir for COVID-19

During an extraordinary virtual meeting held on 2 April 2020, EMA's human medicines committee (CHMP) gave recommendations on how the investigational antiviral medicine remdesivir should be used for treating coronavirus disease (COVID-19) in compassionate use programmes in the European Union.
Compassionate use programmes programmes, which are set up at the level of individual EU Member States, are intended to give patients with a life-threatening, long-lasting or seriously disabling disease and no available treatment options, access to treatments that are still under development and that have not yet received a marketing authorisation.
In this case Estonia, Greece, the Netherlands and Romania requested an opinion from the CHMP on the conditions under which early access to remdesivir through compassionate use programmes could be given to patients with COVID-19.
See:-***remdesivir compassionate use***

EMA review of Picato concludes medicine's risks outweigh its benefits

EMA's safety committee (PRAC) has confirmed that Picato (ingenol mebutate), a gel for treating the skin condition actinic keratosis, may increase the risk of skin cancer and concluded that the risks of the medicine outweigh its benefits.
Picato is no longer authorised in the EU. In January 2020, Picato was suspended as a precaution while the review was underway. On 11 February 2020, the marketing authorisation was withdrawn at the request of LEO Laboratories Ltd, the company that marketed the medicine.
Patients who have been treated with Picato should look out for unusual skin changes or growths, which may occur from weeks to months after use, and seek medical advice if any occur.
See:-***Picato***
[A reminder that medicines are not without risk and of the importance of pharmacovigilance throughout the life of a medicine .MBH]

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