

The Pharmaceutical and Healthcare Sciences Society (PHSS) GMP Update December 2018



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BUT YOU MUST BE CONNECTED TO THE INTERNET FOR IT TO WORK!

INTRODUCTION

During the last 4 weeks there have been several developments in the regulation of the pharmaceutical industry. This month reported issues have come from the Australian, EU, US and PIC/s regulatory authorities.

Once again, we report on a USA compounding pharmacy making and releasing products where there is a lack of sterility assurance. The company also is said to have ignored FDA advice on more than one occasion.

The topics covered in this edition of the "Update" include:

Europe

- **Report of Industry Stakeholder meeting on Brexit and operation of the centralised procedure for human medicinal products**
- **Ph. Eur. seeks feedback on general chapter covering depyrogenation in parenteral preparations**
- **Dose Escalation – is it GCP compliant?**
- **Relevant training for GCP laboratory staff**

USA

- **USA / EU MRA update**
- **FDA Proposes Critical First Steps to Harmonize the Global Scientific and Technical Standards for Generic Drugs**
- **Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products**
- **FDA alerts health care professionals and patients not to use sterile drug products from Pharm D Solutions**
- **Measles vaccine-Option to lower lot release specification for required measles antibody potency testing**

International

Australia

- **Inclusion of Active Pharmaceutical Ingredient in Australia-Canada Mutual Recognition Agreement.**

PIC/S

- **Revised draft PIC/s guidance on good practices for data management and integrity in regulated GMP/GDP environments**

RECENT DEVELOPMENTS IN GMP AND REGULATORY REQUIREMENTS

Europe

EMA

Report of Industry Stakeholder meeting on Brexit and operation of the centralised procedure for human medicinal products

EMA has now published the report on this meeting held 24 Sept 2018.

It should be noted in particular that: -

- The draft text of the Withdrawal agreement, the purpose of which is to wind down EU membership, has been published on the Commission's website. Large parts have been agreed at negotiators' level, however, there are some critical points that are still open. The Withdrawal agreement needs to be ratified by both sides.
- The transition period, until 31 December 2020 (inclusive), forms part of the draft agreement. As part of a transition period the full Acquis will apply to the UK. However, there will be no UK participation in EU institutions or EU bodies, nor will it have a role as leading authority, meaning UK will not have a role as rapporteur or reference Member State. UK will remain subject to obligations of international agreements concluded by the EU.
- Industry should not rely on the transition period as there is currently no certainty that it will apply.
- The EC urges all industry stakeholders to prepare now for the consequences of the UK becoming a 'third country' on 30 March 2019.
- Industry stakeholders are encouraged to submit all Brexit related variations prior to Q1 2019 to ensure compliance in due time.
- The next meeting was tentatively scheduled for 22 November 2018 but has been cancelled.

See:-[report](#)

EDQM

Ph. Eur. seeks feedback on general chapter covering depyrogenation in parenteral preparations

The European Pharmacopoeia (Ph. Eur.) has launched a public consultation on its new general chapter 5.1.12 on depyrogenation of items used in the production of parenteral preparations. While depyrogenation is not a new topic for the Ph. Eur., this is the first time that a dedicated chapter covers specifically the inactivation of pyrogens and related endotoxin indicators.

See:-[press release](#)

MHRA

Dose Escalation – is it GCP compliant?

Dose escalation practices should be the same regardless of whether a clinical trial involves healthy volunteers or patients. Good quality data and sound procedures are vital to ensure the safety of all trial subjects.

First in Human (FIH) trials have had an excellent safety record, with two recent well-publicised exceptions: the dosing of TGN1412 in London in March 2006 where 6 volunteers became extremely ill, and more recently, in January 2016, the dosing of BIA10-2474 in France, where one volunteer died and four others became seriously ill.

Sponsors, clinical research organisations (CROs) and regulators have a continuing duty to ensure that risks are minimised for all types of FIH trials, including patient trials, and that GCP procedures to minimise and mitigate those risks are followed.

Dose escalation is a major safety decision in a trial so good quality data is vital to ensure the safety of the subjects.

See: [blog - dose escalation](#) (An excellent blog. A good example of the combined use of common sense / Risk management and Quality by Design. Well worth a read for those involved in CT and by those outside the CT arena as the principles can in my opinion be applied across a much wider spectrum of pharma operations. [mh])

Relevant training for GCP laboratory staff

MHRA often receives questions about GCP training for laboratory staff.

Training is an essential activity to ensure that all members of laboratory staff are aware of the requirements of the applicable legislation, guidance, analytical techniques and trial protocol relevant to their role. It is important that the level of training can be justified, whilst ensuring that the training given is appropriate and proportionate based on the individual's role in the analysis of clinical trial samples, and that this is clearly documented. Ultimately the rights and safety of trial participants are paramount, as is the integrity of the data being generated, and without appropriate knowledge and training it is easy to jeopardise the outcome of the trial.

See: [GCP lab staff training](#)

United States of America

The US Food and Drug Administration (USFDA)

USA / EU MRA update

Four additional EU Member States, Belgium, Denmark, Finland and Latvia have been approved by FDA. This means that the FDA can now rely on a total of 19 of the 28 EU Member States to replace their own inspections

The Mutual Recognition Agreement (MRA) between FDA and European Union allows drug inspectors to rely upon information from drug inspections conducted within each other's borders. Under the FDA Safety and Innovation Act, FDA has the authority to enter into agreements to recognize drug inspections conducted by foreign regulatory authorities if the FDA determined those authorities are capable of conducting inspections that met U.S. requirements. FDA and the EU have collaborated since May 2014 to evaluate the way they each inspect drug manufacturers and assess the risk and benefits of mutual recognition of drug inspections.

See: [US EU MRA](#) for a full listing of Member States so far determined to be equivalent

FDA Proposes Critical First Steps to Harmonize the Global Scientific and Technical Standards for Generic Drugs

FDA has submitted a proposal to ICH recommending the development of internationally harmonized guidelines on scientific and technical standards for generic drugs. ICH is the global venue for harmonization of standards for pharmaceutical products, including both new drugs and generic drugs. Although many existing ICH guidelines are applicable to generic drugs, historically ICH has focused on standards for new drugs. As a result, there are areas specific to generic drugs where harmonized guidance is lacking. It is anticipated that ICH will review FDA's proposal and that the ICH Assembly will be invited to endorse the proposal at its next meeting in November 2018. FDA envisages that harmonization of scientific and technical standards can potentially bring important benefits. These include: -

- Allowing developers to use data they develop in support of a generic drug in one region to support approval in other regions. This can streamline generic development, making it more cost-effective. For example, harmonization can reduce the number of studies (e.g., bioequivalence studies) that are required to meet the approval standards across markets, by allowing the same studies to meet the standards of multiple regulatory authorities;
- Increasing consistency in the quality of generic medicines globally by implementing common standards that simultaneously meet the requirements of multiple regulatory authorities;
- Increasing the effectiveness of regulatory oversight (and reducing costs) by providing regulators more opportunities for information sharing with counterparts in sister agencies; and,
- Increasing the size of global markets for generic medicines and attracting more competition from different generic drug developers; thereby lowering the fixed costs of generic drug development and expanding patient access by increasing the number of market entrants.

See: [generic standards - Commissioners statement](#)

Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products

This draft document provides guidance to applicants submitting investigational new drug applications (INDs), new drug applications (NDAs), biologics license applications (BLAs), or supplemental applications on the use of meta-analyses of randomized controlled clinical trials (RCTs) to evaluate the safety of human drugs or biological products within the framework of regulatory decision-making. This guidance is also intended for FDA reviewers and for third-party entities that prepare or evaluate meta-analyses assessing the safety of drug products.

Specifically, this guidance describes the factors FDA intends to consider when evaluating the strength of evidence provided by a meta-analysis studying the safety of drugs.

See:-[draft guidance meta analysis](#)

FDA alerts health care professionals and patients not to use sterile drug products from Pharm D Solutions

U.S. FDA is alerting health care professionals and patients not to use drug products intended to be sterile that are produced and distributed by Pharm D Solutions LLC, Houston, Texas, due to lack of sterility assurance. On September 10, 2018, following FDA's recommendation, Pharm D recalled all unexpired drug products intended to be sterile and agreed to cease sterile operations until it makes adequate corrections at its facility. However, Pharm D resumed sterile operations on October 8, 2018, and distributed purportedly sterile products without making adequate corrections at the facility. Pharm D agreed to cease sterile operations again on November 9, 2018 but has not agreed to FDA's recommendation to recall all unexpired drug products intended to be sterile.

See:-[alert](#)

(Yet another sterility assurance incident at a compounding facility plus ignoring FDA advice to recall. - Incredible !!!!! mh)

Measles vaccine-Option to lower lot release specification for required measles antibody potency testing

Under 21 CFR 640.104(b)(2), the Center for Biologics Evaluation and Research (CBER) sets the minimum specification for measles neutralizing antibody levels in Immune Globulin products. At present, the minimum level is 0.48 x CBER Standard lot 176, as adjusted to correct the difference in concentration of lot 176 (16.5%) compared with the subject product. In response to declining titers of measles antibodies in plasma donors, FDA is reducing the minimum measles antibody potency specification for IG products. This letter is to inform manufacturers of an IG (Human) product, that they may submit a request to lower this specification to 0.36 x CBER Standard lot 176, adjusted to correct the difference in concentration of lot 176 (16.5%) compared to that of the subject product. In parallel, manufacturers should add labeling to the Prescribing Information that contains corresponding recommendations for dosing of patients with Primary Humoral

Immunodeficiency (PI) who have been exposed, or are likely to be exposed, to measles.

See:-[letter to IG manufacturers](#)

[International](#)

Australia

Inclusion of Active Pharmaceutical Ingredient in Australia-Canada Mutual Recognition Agreement.

As of November 1, 2018, Health Canada and the Therapeutic Goods Administration (TGA) of Australia concluded an agreement to include APIs under the scope of the MRA on conformity assessment in relation to medicines good manufacturing practice inspection and certification between the government of Canada and the government of Australia. As a result, the TGA will accept GMP Certificates of Compliance (or equivalent) issued by Health Canada under this MRA, for APIs manufactured in Canada, in support of a GMP Clearance application.

See:-[MRA update](#)

PIC/S

Revised draft PIC/s guidance on good practices for data management and integrity in regulated GMP/GDP environments

A revised Draft PIC/S Guidance on Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments (PI 041-1 (Draft 3) has been prepared by the PIC/S Working Group on Data Integrity, co-led by Australia TGA and UK MHRA. The document is subject to a focused stakeholder consultation seeking substantive comments from trade and professional associations on specific questions relating to the proportionality, clarity and implementation of the guidance requirements. In parallel to this stakeholder consultation, the new draft will be applied by PIC/S Participating Authorities on a trial basis for a new implementation trial period. The consultation period will last 3 months and run from 30 November 2018 to 28 February 2019.

See:-[news](#) & [revised draft v3](#)

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/ra/guidelines/intro.htm>

European Medicines Agency Inspections Sector:

<http://www.ema.europa.eu/Inspections/index.html>

European Chemical Industry Council – Active Pharmaceutical Ingredients Sector (CEFIC/APIIC):

<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.ghrf.org/>

International Conference on Harmonisation (ICH):

http://www.ich.org/UrlGrpServer.jsr?@_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-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