ISSUE. 10 OCTOBER 2021

ESPL REGULATORY CONSULTING

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Welcome to the 10th Issue of our regulatory newsletter. We have collated some of the important recent updates to EU/UK, USA, and Worldwide guidances to help you keep up to date. This time of the year is always a busy one for new emerging guidelines from regulatory agencies. Please feel free to contact smt@espl-regulatory.com if you have any questions on the information provided below.

EUROPEAN news

EU CONSULTATION ON THE MEDICINES REGULATORY FRAMEWORK

As part of the EU pharmaceuticals strategy, and drawing lessons from the COVID-19 pandemic, the Commission plans to **evaluate** and **revise** the EU's general **legislation on medicines for human use** to ensure a future-proof and crisis-resistant medicines regulatory system.
https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Revision-of-the-EU-general-pharmaceuticals-legislation_en
The revision will aim to:

- Ensure access to affordable medicines,
- Foster innovation, including in areas of unmet medical need,
- Improve security of supply,
- Adapt to new scientific and technological developments,
- Reduce red tape.

The consultation period ends at midnight (CEST time) on 21st December 2021

MAJOR NEW GUIDANCES FOR DRUG DEVICE COMBINATION PRODUCTS AND MEDICAL DEVICES

DRUG DEVICE COMBINATION PRODUCTS (DDCs): a new EU guideline on quality documentation for medicinal products when used with a medical device is available: See https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-documentation-medicinal-products-when-used-medical-device-first-version_en.pdf
Final EMA Guideline: Quality Requirements for Combination Products
https://www.gmp-compliance.org/gmp-news/final-ema-guideline-quality-requirements-for-combination-products

Other new guidances for **MEDICAL DEVICES**:
New Guidance on classification of medical devices – October 2021:
https://ec.europa.eu/health/sites/default/files/md_sector/docs/mdcg_2021-24_en.pdf
Information on the Helsinki protocol – posted on MDCG September 2021:
https://ec.europa.eu/health/sites/default/files/md_sector/docs/md_border-class_helsinki-proc-mdr-ivdr_en.pdf
Q&A on Requirements Relating to Notified Bodies – October 2021:
https://ec.europa.eu/health/sites/default/files/md_sector/docs/md_mdcg_qa_requirements_notified_bodies_en.pdf
New guidances continue to be issued by the Medical Device Coordination Group (MDCG), which are routinely posted on: https://ec.europa.eu/health/md_sector/new_regulations/guidance_en

EU CLINICAL TRIALS INFORMATION SYSTEM (CTIS) UPDATED GUIDANCES

The new Clinical Trials Regulation (No 536/2014) will become effective on 31st January 2022. The Regulation will harmonise the assessment and supervision processes for clinical trials throughout the EU, via a **Clinical Trials Information System (CTIS).** The six-month countdown to the CTIS has therefore begun. For further details see: https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-regulation

Lots of guidance is now being published on the operation of the CTIS, including the **CTIS newsletter.** For further details see: https://www.ema.europa.eu/documents/newsletter/clinical-trials-information-system-ctis-highlights-august-2021_en.pdf

EMA UPDATE OF THE Q&AS ON HERBAL MEDICINAL PRODUCTS

The updated EMA document contains several **revised Q&As on herbal medicinal products** including the Q&As regarding the requirements for the simplified registration procedure and is available at:
https://www.gmp-compliance.org/gmp-news/ema-update-of-the-q-as-on-herbal-medicinal-products

EXTENSION OF GMP AND GDP CERTIFICATES AND TIME-LINKED AUTHORISATIONS.

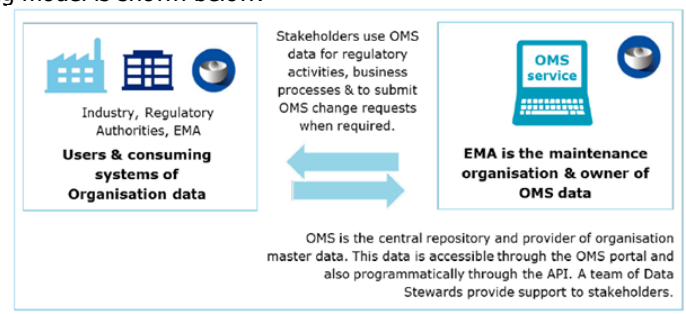
On 30 September 2021 the EMA announced that it had updated its '**Guidance for medicine developers and other stakeholders on COVID-19**' to the effect that the European medicines regulatory network had extended until the end of 2022 the validity of good manufacturing practice (GMP) and good distribution practice (GDP) certificates, and time-limited manufacturing, import and wholesale authorisations. The guidance is available at:
https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/guidance-medicine-developers-other-stakeholders-covid-19

EMA AND FDA UPDATE PRINCIPLES FOR PARALLEL SCIENTIFIC ADVICE (PSA) IN THE MARKETING AUTHORIZATION PROCESS

The purpose of the PSA procedure is to harmonise the different regulatory requirements of the EU and US to enhance the development process of the drug in question. The basic principles of this procedure have now been renegotiated and can be found via the link below.
https://www.gmp-compliance.org/gmp-news/ema-and-fda-update-principles-for-parallel-scientific-advice-in-the-marketing-authorization-process

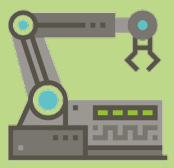
VETERINARY MEDICINES - GMDP DATABASE CHANGES

The EMA has announced an important change that will impact all manufacturers, importers and distributors of both human and veterinary medicines into the EU/EEA whose information is recorded in EUDRAGMDP database.
The new regulatory framework for veterinary medicines (**Regulations 2019/6 and 2021/16, Article 9(h))** require changes to the EudraGMDP database which will come into effect from 28 January 2022. This change will affect manufacturers/importers/distributors of both human and veterinary medicines whose information is recorded in EUDRAGMDP database.
The main change will be the integration of **EudraGMDP with EMA's Organisation Management Service (OMS)**. This is an important change for manufacturers/importers/distributors to be aware of and to ensure that their sites are registered in OMS. As of 28 January 2022, before applying for a new/updated manufacturing or wholesale distribution authorisation with national competent authorities, please check whether your organisation is correctly registered in OMS.
What is the OMS?
The EMA first launched the launched the Organisation Management Service (OMS) in 2016 to support regulatory activities throughout the EU. The OMS provides a single source of validated organisation data that can be used as a reference to support EU regulatory activities and business processes. It stores master data comprising organisation name and location address for organisations such as marketing authorisation holders, sponsors, regulatory authorities and manufacturers.
When launched the EMA said that the use of OMS would become mandatory over time and the integration with the GMDP database will make it mandatory for many organisations.
The OMS operating model is shown below:



More information can be found via:
https://www.salute.gov.it/imgs/C_17_notizie_5652_0_file.pdf

SCIENTIFIC ADVICE, STRATEGY & SPECIALIST APPLICATION



MEDICAL DEVICE SUBMISSIONS

PUBLISHING

EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES AND HEALTHCARE (EDQM)

eCTD CEP APPLICATIONS UPDATED GUIDANCES

Revised guidance **for electronic submissions for CEP applications** is available at https://www.edqm.eu/en/news/revised-guidance-electronic-submissions-cep-applications (01 September 2021). One important update relates to switching to the eCTD format from another format. It is now mandatory to include any information already assessed and approved in a "baseline" dossier to facilitate the lifecycle management. This must implemented by January 2022.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA)

MHRA CONSULTATION ON MEDICAL DEVICE REGULATION

The MHRA are inviting members of the public to provide their views on possible **proposed changes to the regulatory framework for medical devices in the UK**. The aim is to develop a future regime for medical devices that enables:

- Improved patient and public safety;
- Greater transparency of regulatory decision making and medical device information;
- Close alignment with international best practice, and;
- More flexible, responsive and proportionate regulation of medical devices.

More information is available at: https://www.gov.uk/government/consultations/consultation-on-the-future-regulation-of-medical-devices-in-the-united-kingdom
The consultation closes at 11:45pm on 25th November 2021.

GUIDE TO DEFECTIVE MEDICINAL PRODUCTS UPDATED

In August 2021 the MHRA published an updated version of their **guide to defective medicinal products**, which was first published in 2005. The guidance is available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1007537/DMRC_Guide-to-Defective-Medicinal_Products-Aug2021.pdf

NEW UK GMDP DATABASE

As part of the MHRA's online services, it is now possible to access a database of information issued by the MHRA relating to manufacturing and wholesale authorisations and certificates. https://cms.mhra.gov.uk/mhra

UK-US GMP MUTUAL RECOGNITION AGREEMENT EXTENDED TO INCLUDE VETERINARY PHARMACEUTICALS

On 27 September 2021 it was announced that the UK VMD and the US FDA had agreed to extend the scope of the **UK-US GMP MRA** to include inspections of **veterinary medicines.** This means that the scope of the UK-US MRA is now wider than that of the US-EU MRA, which still has not yet been extended to include veterinary medicines. See: https://www.gmp-compliance.org/gmp-news/ema-update-of-the-q-as-on-herbal-medicinal-products

WHO

WORLD HEALTH ORGANISATION

DRAFT GUIDANCE ON GMP FOR INVESTIGATIONAL MEDICINAL PRODUCTS (IMPS) AND GOOD PRACTICE (GP) FOR R&D FACILITIES

The consultation period for the WHO draft guidances shown below completed on 31st August 2021, and feedback received is to be considered by the WHO prior to presentation of revised versions to their Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) this month (October 2021).

QAS/20.863 GMP for Investigational Products
(https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/current-projects/qas20-863-gmp-for-investigational-products.pdf?sfvrsn=3993da76_7)

QAS/20.865 Good Practices for Research and Development Facilities
(https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/current-projects/qas20_865_rev1_gxp_for_rd_facilities_of_pharm_products.pdf?sfvrsn=1a1385fb_5)
Comments on these two draft documents were due to be submitted by 31 August 2021.

PIC/S

GOOD PRACTICES FOR DATA MANAGEMENT AND INTEGRITY IN GMP/GDP ENVIRONMENTS

On 1 July 2021 PIC/S issued the final version of a new guideline for inspectors on "**Good Practices for Data Management and Integrity in GMP/GDP environments**". This is a large 63-page document which can be accessed at https://picscheme.org/docview/4234

ICH

Q13 CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES AND DRUG PRODUCTS

The draft of Q13 gained step 2b approval and was issued for public comment, step 3 of the ICH process, on 27 July 2021.
The file is available at: https://www.ema.europa.eu/documents/scientific-guideline/draft-ich-guideline-q13-continuous-manufacturing-drug-substances-drug-products-step-2b_en.pdf

In Europe the deadline for comments on the new guideline is 20 December 2021. The following template should be used: https://www.ema.europa.eu/documents/template-form/form-submission-comments-ich-guidelines_en.doc
and sent to ich@ema.europa.eu

M7(R2) DRAFT GUIDELINE AND ADDENDUM ON ASSESSMENT AND CONTROL OF DNA REACTIVE (MUTAGENIC) IMPURITIES REACHES STEP 2:

The ICH M7(R2) draft Guideline and Addendum on **Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk** reached Step 2 on 6 October 2021 and now enters the public consultation period.

The ICH M7 (R2) Addendum provides useful information regarding the acceptable limits of known mutagenic impurities/carcinogenic and supporting monographs. seven new compounds have been added in this revision: **Acetaldehyde, Dibromoethane, Epichlorohydrin, Ethyl Bromide, Formaldehyde, Styrene,** and **Vinyl Acetate**. Further information can be found on the ICH M7(R2) webpage.

E8(R1) GENERAL CONSIDERATIONS FOR CLINICAL STUDIES REACHES STEP 4:

The ICH E8(R1) Guideline on General considerations for Clinical Studies reached Step 4 of the ICH Process on 6 October 2021.

Clinical studies of medicinal products are conducted to provide information that can ultimately improve access to safe and effective products with meaningful impact on patients, while protecting those participating in the studies. ICH E8(R1) provides guidance on the clinical development lifecycle, including designing quality into clinical studies, considering the broad range of clinical study designs and data sources used.

This modernisation of ICH E8 is the first step towards the Renovation of Good Clinical Practice initiated in 2017. The revision incorporates the most current concepts achieving fit-for-purpose data quality as one of the essential considerations for all clinical trials.

https://www.espl-regulatory.com/

https://www.linkedin.com/company/espl-regulatory-consulting/

tel:+441806242852

smt@espl-regulatory.com

US FDA

STUDY DATA TECHNICAL CONFORMANCE GUIDE TECHNICAL SPECIFICATIONS DOCUMENT UPDATE

On September 15, 2021, the Food & Drug Administration (FDA) started rejecting submissions subject to section 745A(a) of the Federal Food, Drug and Cosmetic Act (the FD&C Act) (ANDAs, NDAs, certain BLAs, and certain INDs) that fail to pass high validation errors included in the "**Technical Rejection Criteria for Study Data**" (TRC), which are used to determine compliance with the requirement to submit electronic standardized study data. These requirements are summarized in FDA's "**Specifications for eCTD Validation Criteria**" and the TRC documentation and communicated in the technical specifications document "Study Data Technical Conformance Guide." Compliance with these standards established under section 745A(a) of the FD&C Act is necessary to ensure the consistent organization of data to facilitate submission review. On August 16, 2021, FDA updated the technical specifications document "**Study Data Technical Conformance Guide**." This update addresses pilot and failed studies submitted to ANDAs, which the Agency does not expect to comply with FDA's standardized study data requirements as of September 15, 2021, in order to facilitate the submission of these specific studies to ANDAs. However, in order for these studies to pass FDA's TRC which came into effect on September 15, 2021, submission of these studies may require the sponsor or applicant to include a simplified ts.xpt file within the study. For further information see:
https://www.fda.gov/media/152175/download

USA FDA ISSUES DRAFT GUIDANCE ABOUT THE ELECTRONIC SUBMISSION TEMPLATE FOR MEDICAL DEVICES 510(K) SUBMISSIONS

On September 29th, 2021, the U.S. Food and Drug Administration (FDA) issued the draft guidance: **Electronic Submission Template for Medical Device 510(k) Submissions**. This draft guidance builds on the guidance **Providing Regulatory Submissions for Medical Devices in Electronic Format** – Submissions Under Section 745A(b) of the Federal Food, Drug, and Cosmetic Act that specified which medical device submissions will be required to be submitted only in electronic format and which submissions are exempt from electronic format requirements. Read the guidance at:
https://www.fda.gov/media/152429/download

USA FDA ANNOUNCES DRAFT GUIDANCE - MICROBIOLOGICAL QUALITY CONSIDERATIONS IN NON-STERILE DRUG MANUFACTURING

In September, the Food and Drug Administration (FDA) announced the availability of a draft guidance for industry entitled, "**Microbiological Quality Considerations in Non-sterile Drug Manufacturing."** This guidance is intended to assist non-sterile drug (NSD) manufacturers in assuring the microbiological quality of their drugs. This guidance discusses product development considerations, risk assessments, and certain current good manufacturing practice (CGMP) requirements that are particularly relevant to microbiological control in a NSD manufacturing operation. See the link below for more information:
https://www.fda.gov/media/152527/download

USA FDA POSTS ANNUAL FORECAST FOR PLANNED MONOGRAPH ACTIVITIES

The US Food and Drug Administration posted the **first Annual Forecast for Planned Monograph Activities** on the 1st October 2021. The Annual Forecast is a nonbinding list, issued each year, of planned monograph activities that FDA intends to address over the upcoming three years. Topics include:

- Risks associated with codeine-containing cough medicine
- Pediatric acetaminophen dosing
- Risks associated with propylhexedrine abuse and misuse
- Nonsteroidal anti-inflammatory drugs and oligohydramnios
- Oral healthcare in infants and children
- Serious skin reactions associated with acetaminophen
- Anticaries test methods

For more information about OTC Monograph Reform, visit the FDA webpage on Over-the-Counter (OTC) Drug Review | OTC Monograph Reform in the CARES Act:

https://www.fda.gov/drugs/over-counter-otc-nonprescription-drugs/over-counter-otc-drug-review-otc-monograph-reform-cares-act
see the annual forecast at: https://www.fda.gov/media/152546/download