Regulatory Round-up

April 2023

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EUROPE

European Directorate for the Quality of Medicines (EDQM)

MIRCA: An EDQM tool to enhance safe use of substances of human origin

The EDQM recently released the Microbiological Risk of Contamination Assessment tool (MiRCA), which aims to help users identify and classify potential risks for introducing microbiological contamination during the procurement or processing of tissues and cells, and supports decision making to mitigate such risks. MiRCA complements the Guide to the quality and safety of tissues and cells for human application. The tool generates a summary report, detailing any risks identified, grading risk severity, and prompts users to record the rationale for their decisions and any evidence used to support them. MiRCA can be accessed here and a supporting how-to webinar is available here.

New Certification of suitability to the European Pharmacopoeia monographs to be called "CEP 2.0"

Following a number of public consultations in 2020, EDQM have proposed extensive updates to the Certification of suitability to the European Pharmacopoeia monographs (CEP), also know as a certificate of suitability. CEPs are issued to manufacturers of a material to certify it complies with the relevant pharmacopeial monograph. The new version, CEP 2.0, is intended to better meet the needs of stakeholders by enhancing user-friendliness and improving transparency of the information conveyed, without increasing the regulatory burden on CEP holders for revisions. The implementation is expected to take place in 2023. Information on the sections that will be impacted can be found here.

European Medicines Agency (EMA)

New indication licensed for Breyanzi in the EU

On 30 March 2023, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of the marketing authorisation for the medicinal product Breyanzi. The marketing authorisation holder for this medicinal product is Bristol-Myers Squibb Pharma EEIG. The CHMP adopted a new indication, high grade B cell lymphoma (HGBCL), for patients who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy. Further information can be found here.

ACT EU multi-stakeholder platform kick-off workshop

Accelerating Clinical Trials in the EU (ACT EU) Priority Action 3 aims to create a platform where all stakeholders involved in designing, regulating, performing and participating in clinical trials can identify relevant scientific, methodological and technological advances to develop the clinical trials environment in the EU.

The 2 day event will take place from the 22nd to 23rd of June 2023. Please find further details including how to register here.

New features further strengthen Priority Medicines scheme (PRIME)

The European Medicines Agency (EMA) is introducing a number of new features to the PRIority Medicines (PRIME) following a review of the first five years' experience with the scheme. The review highlighted opportunities for further strengthening the scheme. In order to optimise the early scientific and regulatory support provided to promising medicines, a roadmap for each PRIME development as well as a product development tracker will be established. Starting as a 12-month pilot, accelerated scientific advice can now be provided specifically for PRIME developments in case of issues with a specific development programme that has already received comprehensive initial advice. This setting for scientific advice will allow to address queries from PRIME applicants in a shorter timeframe. Please find further details here.

Reflection paper on establishing efficacy based on single arm trials submitted as pivotal evidence in a marketing authorisation

In a relevant proportion of marketing authorisation applications, the pivotal clinical data stems from single-arm trials (SATs), rather than randomised controlled trials, which are the standard for providing confirmatory evidence on the efficacy of a new treatment. The reflection paper outlines the current thinking of EMA's Committee for Medicinal Products for Human Use (CHMP) in relation to the design, planning, conduct, analysis and interpretation of results derived from SATs, and is applicable across different therapeutic areas, including for rare diseases. The draft document is available for review here, and comments may be submitted to RP-SATs@ema.europa.eu.

United Kingdom

Medicines and Healthcare products Regulatory Agency (MHRA)

MHRA to streamline clinical trial approvals in biggest overhaul of trial regulation in 20 years

Following a public consultation which received over 2000 responses, a series of new measures will be introduced by the MHRA to improve the approval process to run clinical trials in the UK. These changes are intended to help make the UK a desirable location in which to conduct clinical research, through creating a proportionate and

flexible regulatory environment that is streamlined, agile and responsive to innovation. The framework will also introduce a legal mandate to register the trial in a World Health Organisation (WHO) public register, to publish a summary of results within 12 months of the end of the trial, and to sharing trial findings with participants in a timely manner.

Manufacture of IMPs - When is it Reconstitution?

According to the MHRAs blog on the manufacture and supply of Investigational Medicinal Products (IMPs) post-Brexit, the most frequently asked question relates to deciding if an activity should be considered manufacturing or reconstitution. EU GMP Annex 13 states that reconstitution should be undertaken "*as soon as practicable before administration*". The MHRA´s interpretation of this is ideally at the bedside, however the blog states that "*it may be acceptable for the activities to be performed in the clinic's pharmacy* ". Full details can be found in the updated blog post.

USA

Food and Drug Administration (FDA)

FDA Approves Cell Therapy for Patients with Blood Cancers to Reduce Risk of Infection Following Stem Cell Transplantation

The FDA has approved Omisirge (omidubicel-onlv) from Gamida Cell Ltd. Omisirge is a substantially modified allogeneic cord blood-based stem cell therapy, administered as a single intravenous dose and indicated for the treatment of hematological malignancies. It is intended for use in adults and pediatric patients over 12 years old who require stem cell transplant to treat their cancers and has shown accelerated neutrophil recovery and improved infection outcomes following the standard myeloablative conditioning regimen priot stem cell transplant. The application received Priority Review, Breakthrough Therapy and Orphan designations, reflecting the umet need for additional donor sources for stem cell transplant.

FDA outlines risk-based approach to monitoring clinical trials

The Food and Drug Administration (FDA) has issued a final guidance to assist drug and medical device makers in developing risk-based monitoring strategies for clinical investigations involving drugs, biologics and medical devices. This guidance provides recommendations on planning a monitoring approach, developing the content of a monitoring plan, and addressing and communicating monitoring results.

Research Involving Children as Subjects and Not Otherwise Approvable by an Institutional Review Board: Process for Referrals to Food and Drug Administration and Office for Human Research Protections

The FDA has issued a draft guidance to provide information to institutional review boards (IRBs), institutions, investigators, and sponsors on the processes used for review of research involving children as subjects that is not otherwise approvable by

an IRB and has been referred to the FDA under 21 CFR 50.54, the Office for Human Research Protections (OHRP) under 45 CFR 46.407, or both, for review. The deadline for submitting comments is 30 May 2023. Please find further details here.

INTERNATIONAL

International Conference on Harmonisation (ICH)

ICH adopts M7(R2) guideline on mutagenic impurities to limit carcinogenic risk

The ICH has announced the adoption of its M7(R2) guideline that aims to harmonize the framework for assessing and controlling DNA mutagenic impurities in pharmaceuticals as well as an addendum listing the 21 impurities that should be tested along with their daily permissible limits (PDEs).

ICH adopts Q9(R1) guideline on Quality Risk Management

Following the adoption of ICH Q9(R1) Guideline on Quality Risk Management in January 2023, an Introductory Training Presentation has been developed by the Q9(R1) Expert Working Group (EWG) to explain and facilitate the implementation and application of the proposed revisions using examples. ICH Q9(R1) provides guidance on the principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. The four areas for improvement identified with the application of QRM were:

- High levels of subjectivity in risk assessments and in QRM outputs
- Failing to adequately manage supply and product availability risks
- Lack of understanding as to what constitutes formality in QRM work
- Lack of clarity on risk-based decision-making

ICH adopts S12 guideline on Nonclinical Biodistribution Considerations for Gene Therapy Products

The ICH S12 guideline has been now been adopted. It provides considerations for the design, timing and conduct of preclinical biodistribution studies, in the development of gene therapy (GT) products that mediate their effect by the expression (transcription or translation) of transferred genetic materials. Recommendations are offered on the animal species or model to be used, the group size and sex of study animals, route of administration and dose selection, as well as sample collection, in accordance with the 3Rs (reduce/refine/replace) principles.

Public consultations

European Directorate for the Quality of Medicines (EDQM)

	Title	Consultation Period	Category
1.	*Phage therapy active substances and medicinal products for human and veterinary use (5.31)*	*End Date: June 2023*	*Public consultation*
2.	*Reflection paper on establishing efficacy based on single arm trials submitted as pivotal evidence in a marketing authorisation*	*End date: 30 Sept 2023*	*Reflection paper*

Food and Drug Administration (FDA)

	Title	Consultation Period	Category
1.	*Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations: Questions and Answers*	*End date: 15 May 2023*	*Draft guidance*
2.	*Recommendations for Evaluating Donor Eligibility Using Individual Risk-Based Questions to Reduce the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products*	*End date: Open*	*Draft guidance*
3.	*Neovascular Age-Related Macular Degeneration: Developing Drugs for Treatment*	*End date: 30 May 2023*	*Draft guidance*
4.	*Research Involving Children as Subjects and Not Otherwise Approvable by an IRB: Process for Referrals to FDA and OHRP Guidance for Institutional Review Boards, Institutions, Investigators, and Sponsors*	*End date: 30 May 2023*	*Draft guidance*

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