

# News from the EMA

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## EMA finds no evidence linking viral vector in Zynteglo to blood cancer

July 9 and 23, 2021

**Z**ynteglo is a one-time treatment for a blood disorder known as beta thalassaemia in patients 12 years and older who require regular blood transfusions. It is a gene therapy that uses a viral vector (or modified virus) to deliver a working gene into the patient's blood cells. Zynteglo was granted conditional marketing authorisation in May 2019, which means that the company will provide more evidence about the

medicine to EMA for review.

EMA's Pharmacovigilance Risk Assessment Committee (PRAC), has concluded that there is no evidence Zynteglo causes a blood cancer known as acute myeloid leukaemia (AML). The PRAC reviewed two cases of AML in patients treated with another investigational medicine, bb1111, in a clinical trial for sickle cell disease. Although there have been no reports of AML

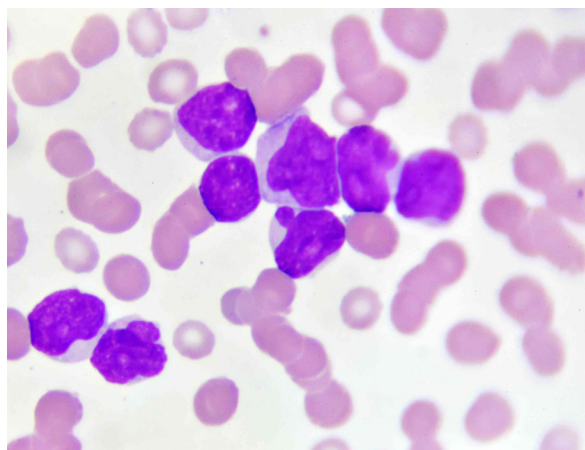
with Zynteglo, both medicines use the same viral vector and there was a concern that the vector may be implicated in the development of the cancer (insertional oncogenesis). The review found that the viral vector was unlikely to be the cause. In one of the patients, the viral vector was not present in the cancer cells, and in the other patient it was present at a site (VAMP4) that does not appear to be involved in cancer development.

After examining all the evidence, the PRAC concluded that more plausible explanations

for the AML cases included the conditioning treatment the patients received to clear out bone marrow cells and the higher risk of blood cancer in people with sickle cell disease. Patients having Zynteglo treatment for beta thalassaemia also need conditioning treatment to clear out their bone marrow cells. Healthcare professionals should therefore explicitly inform patients receiving Zynteglo of the increased risk of blood cancers from medicines used in conditioning treatments.

The Committee for Medicinal Products for Human Use (CHMP) has agreed with PRAC's recommendation that healthcare professionals should check their patients for signs of blood cancers at least once a year for 15 years.

The review of Zynteglo was initiated on February 18, 2021, at the request of the European Commission, under Article 20 of Regulation (EC) No 726/2004. The Committee, which worked closely with experts from the Committee for Advanced Therapies (CAT), concluded that the benefits of Zynteglo continue to outweigh its risks. As for all medicines, the PRAC will monitor any new data on its safety and update advice for patients and healthcare professionals when necessary.



## Artificial intelligence in medicine regulation

August 16, 2021

**T**he International Coalition of Medicines Regulatory Authorities (ICMRA) set out recommendations to help regulators to address the challenges that the use of artificial intelligence (AI) poses for global medicines regulation, in a report published today on ICMRA website.

AI includes various technologies (such as statistical models, diverse algorithms and self-modifying systems) that are increasingly being

applied across all stages of a medicine's lifecycle: from preclinical development, to clinical trial data recording and analysis, to pharmacovigilance and clinical use optimisation. This range of applications brings with it regulatory challenges, including the transparency of algorithms and their meaning, as well as the risks of AI failures and the wider impact these would have on AI uptake in medicine development and patients' health.

The report identifies key issues linked to the regulation of future therapies using AI and makes specific recommendations for regulators and stakeholders involved in medicine development to foster the uptake of AI. Some of the main findings and recommendations include:

- Regulators may need to apply a risk-based approach to assessing and regulating AI, which could be informed through exchange and collaboration in ICMRA;
- Sponsors, developers and pharmaceutical companies should establish strengthened

## Six-month countdown to go-live for the Clinical Trials Information System (CTIS)

August 2, 2021

**T**he European Commission has confirmed that the entry into application of the Clinical Trials Regulation and hence the go-live date for the CTIS will be on January 31, 2022.

As set out in the Clinical Trials Regulation, the entry into application of that regulation is set by the publication of a notice in the Official Journal of the European Union (EU), which confirms that the clinical trial EU Portal and Database, one of the main deliverables of the regulation and the key component of CTIS, has reached full functionality. The application of the regulation and the go-live of CTIS take place six months after the publication of this notice.

The Clinical Trials Regulation aims to harmonise the submission, assessment and supervision processes for clinical trials throughout the EU. CTIS will allow the streamlining of these processes, ensuring the EU remains an attractive region for clinical research.

CTIS will become the single-entry point for clinical trial application submission, authorisation, and supervision in the EU, and in the European Economic Area (EEA) countries Iceland, Liechtenstein and Norway. Currently, sponsors must submit clinical trial applications separately to national competent authorities and ethics committees in each country to gain regulatory approval to run a clinical trial.



With CTIS, sponsors can apply for clinical trial authorisation in up to 30 EEA countries with a single application. The CTIS will also, together with other EMA IT tools, support the coordinated assessment of safety reporting in the context of clinical trials and therefore contribute to the understanding of the benefits and the risks of medicinal products that are planned to enter or are already on the market of the EU.

The system will facilitate recruitment of trial participants by allowing sponsors and researchers to easily expand trials to other EEA countries, and will support collaboration across borders for better results and knowledge sharing. The system will contain a public website with detailed information on and outcomes of all clinical trials conducted in the EU, thus improving transparency and access to information for patients, healthcare workers, and other interested parties.

The Clinical Trials Regulation foresees a *three-year transition period*. Member States will work in CTIS immediately after the system has gone live. For one year, until January 31, 2023, applicants can still choose whether to submit their application to start a clinical trial according to the current system (Clinical Trials Directive) or according to the Clinical Trials Regulation. From January 31, 2023 onward, submission according to the Clinical Trials Regulation becomes mandatory and by January 31, 2025, all ongoing trials

approved under the current Clinical Trials Directive will need to transition to the new regulation and to CTIS.

While the authorisation and oversight of clinical trials is the responsibility of Member States, EMA will maintain the system. EMA has created an extensive training programme to help clinical trial sponsors, national competent authorities, and ethics committees prepare for using CTIS. The training catalogue consists of several modules, covering the full lifecycle of clinical trial submission, authorisation, and supervision. Modules are available for use on the CTIS training programme webpage. The CTIS training programme webpage is progressively updated as more training materials become available. EMA has also published a sponsor handbook to provide clinical trial sponsors with the information they need to get ready for, and use, CTIS.

governance structures to oversee algorithms and AI deployments that are closely linked to the benefit/risk of a medicinal product;

- Regulatory guidelines for AI development, validation and use with medicinal products should be developed in areas such as data provenance, reliability, transparency and understandability, pharmacovigilance, and real-world monitoring of patient functioning.

The report is based on a horizon-scanning exercise in AI, conducted by the ICMRA Informal Network for Innovation working group and led by EMA. The goal of this network is to identify challenging topics for medicine regulators, to explore the suitability of existing regulatory frameworks and to develop recommendations to adapt regulatory systems in order to facilitate safe and timely access to innovative medicines.



Photo: Freepik





Photo: Freepik

## Interoperability of track and trace systems: key to public health protection

August 06, 2021

**E**MA has endorsed recommendations developed by the International Coalition of Medicines Regulatory Authorities (ICMRA) to facilitate the use of track and trace systems at the global level. A paper published today on ICMRA website identifies common technical denominators that allow different systems to exchange and use the available information on medicines and their supply chains in order to protect public health.

Production and distribution of medicines are globalised and rapid exchange of information among regulatory authorities is integral to the protection of supply chain integrity and patient safety. Track and trace systems are considered to be a useful tool to

mitigate the risk of shortages and fight production and marketing of falsified medicines. They provide visibility into the supply chain of medicines at any given time. However, until now, traceability systems have been designed and implemented with a local or regional focus, without taking into consideration whether they can exchange information with other systems at the global level.

In this paper, international regulators emphasise that the interoperability of track and trace systems helps to protect public health by improving information sharing in case of quality defects, reducing shortages, contributing to the fight against falsified medicines and supporting pharmacovigilance activities. A common under-

standing of these potential benefits of interoperability is fundamental to promoting global planning and implementation of interoperable systems for medicines.

The ICMRA paper was open for public consultation from November 2020 to February 2021. The extensive and helpful feedback was carefully analysed and reviewed in order to refine and finalise the recommendations on common technical denominators for track and trace systems. More details on the comments received and the ICMRA analysis of these comments is available on ICMRA website.

ICMRA developed the recommendations in consultation with the World Health Organisation (WHO), representatives from international medicines regulatory authorities and experts from the private sector.

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