



Europe Legal and Regulatory Affairs

Watchdog Update **REGULATORY** WATCHDOG

This European watchdog is providing information relevant to ISCT areas of concern, including: 1) upcoming events (workshops, meetings), 2) recently published regulatory documents, 3) public consultations and guidelines currently opened for comments, and 4) follow-up on previously addressed events.

1) Multi-stakeholder paediatric oncology strategy workshop organised by EMA on 30 & 31 January 2017 (London, UK)

The aim of the EMA and the ACCELERATE platform's workshop is to review unmet therapeutic needs of children with certain types of cancer and opportunities for targeted paediatric development of innovative anti-cancer medicines. Cancers that are addressed include soft tissue, lymphoid, and embryonal neoplasms such as inflammatory myofibroblastic tumour, rhabdomyosarcoma, anaplastic large cell lymphoma and neuroblastoma. Important biological aberrations such as that of the anaplastic lymphoma kinase (ALK) type occur across these diverse cancers, albeit in small numbers of patients, and represent challenges to address the therapeutic needs of affected paediatric patients. The workshop convenes stakeholders from patient organisations, academia, pharmaceutical industry, and regulators, however; participation is by invitation only.

The draft meeting's agenda can be found here:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2017/01/event_detail_001380.jsp&mid=WC0b01ac058004d5c3

SME information day on the new clinical trial regulation (regulation EU no. 536/2014) organised by EMA on 20 March 2017 (London, UK)

This event will provide an overview on the key features and objectives of the new clinical trial regulation. It will also cover the future clinical trial authorisation process, the functionalities of the EU CT portal and database, transparency aspects of the new regulation and safety reporting requirements.

The event is open to companies that have been assigned SME status by the EMA and representatives of stakeholder organisations and a live webcast of will be available. Registration deadline is 24 February 2017.

More information including the draft meeting's agenda can be found here:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2017/01/event_detail_001385.jsp&mid=WC0b01ac058004d5c3



2) EMA - “Set of ideas” to better support development and expand patients’ access to ATMP published by EMA on 3 February 2017

Following the multi-stakeholder expert meeting organised in May 2016 to foster ATMP development and expand patient access in Europe, EMA has released a document providing an overview of the on-going and planned EU initiatives to optimise the current regulatory framework to facilitate ATMP development.

The announcement and the document can be found here:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/02/news_detail_002687.jsp&mid=WC0b01ac058004d5c1

France - Changes in Clinical Trial Application (CTA) to Ethics Committee (EC): Decree No. 2016-1537 of 16 November 2016 on researches involving human beings

From 18 November 2016, the CTA to EC in France is no longer submitted to an EC chosen by a sponsor from the inter-region where the coordinating investigator of the study is located but by an EC designed by a random drawing. In this context, a new commission has been set-up (national commission for researches involving human beings “*commission nationale des recherches impliquant la personne humaine*”) to randomly draw the EC in charge of each new study. This EC will be in charge of the study assessment and follow-up from CTA to end of study including any amendments.

More information can be found here, from article D1123-27 (mainly D1123-34, *in French, this link must be copied/pasted into a browser*):

<https://www.legifrance.gouv.fr/affichCode.do?idArticle=LEGIARTI000033408283&idSectionTA=LEGISCTA000033408224&cidTexte=LEGITEXT000006072665&dateTexte=20170119/>

The content and the format of the CTA dossier to be submitted to the EC is defined here (*Arrêté du 2 décembre 2016 fixant le contenu, le format et les modalités de présentation du dossier de demande d'avis au comité de protection des personnes sur un projet de recherche mentionnée au 1° de l'article L. 1121-1 du code de la santé publique portant sur un médicament à usage humain*):

https://www.legifrance.gouv.fr/affichTexte.do;jsessionid=7C3506AEAF374FA2B817E7AACABF82A2.tpdila07v_1?cidTexte=JORFTEXT000033545400&dateTexte=&oldAction=rechJO&categorieLien=id&idJO=JORFCONT000033545003

3) Public consultation on the Roadmap for the evaluation of the EU blood and tissues and cells legislation until 15 February 2017

The Commission is currently carrying out an evaluation of the EU blood and tissues and cells legislation. This is the first formal evaluation of this legislation since the adoption of the basic Acts in 2002 (blood) and 2004 (tissues and cells). This evaluation aims to assess whether the legislation has achieved its original objectives and whether it is still fit for purpose. The evaluation will consist of several steps starting with a Roadmap and including a study by an external contractor and extensive consultation of stakeholders. The final evaluation report is



expected to be published by the end of 2018. The Roadmap released by EC in January 2017 is a first step in the evaluation process and outlines the purpose, content and scope of the evaluation.

More information can be found here:

https://ec.europa.eu/health/blood_tissues_organs/policy/evaluation_en

Public consultation on ICH Reflection paper on “GCP Renovation”: Modernization of ICH E8 and Subsequent Renovation of ICH E6 until 11 March 2017

The scope of the renovation would include the current E8 General Considerations for Clinical Trials and the E6 Guideline for Good Clinical Practice. The goal is to provide updated guidance that is both appropriate and flexible enough to address the increasing diversity of clinical trial designs and data sources that are being employed to support regulatory and other health policy decisions. The underlying principles of human subject protection and data quality would remain.

The GCP renovation will be conducted according to a step-wise approach and, as a first component of expanded consultation, ICH is seeking stakeholders to comment on the proposed renovations at an early stage, ahead of guideline development efforts.

More information about this consultation can be found here:

<http://www.ich.org/ichnews/newsroom/read/article/ich-reflection-on-gcp-renovation-modernization-of-ich-e8-and-subsequent-renovation-of-ich-e6.html>

In addition, a revised ICH E6 (R2) guideline on Good Clinical Practice will come into effect on 14 June 2017 (EMA/CHMP/ICH/135/1995). It was amended to encourage the implementation of more efficient approaches to clinical trial design and conduct oversight in light of advances in electronic data recording and reporting. The guideline can be found here:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC50002874.pdf

UK - Public consultation on Strategy for pharmacopoeial public quality standards for biological medicines launched by the MHRA until 10 April 2017

Biological medicines are an increasingly important part of healthcare worldwide, including ATMPs. In the UK, documentary standards exist as texts published in the British Pharmacopoeia. The MHRA is developing a strategy for the creation of pharmacopoeial public quality standards for biological medicines. This public consultation seeks input from stakeholders regarding how they are used and can be improved as well as feedback on the Agency's draft strategy.

More information about this consultation can be found here:

<https://www.gov.uk/government/consultations/strategy-for-pharmacopoeial-public-quality-standards-for-biological-medicines>



Draft reflection paper providing an overview of the current regulatory testing requirements for medicinal products for human use and opportunities for implementation of the 3Rs, opened to consultation until 31 May 2017

This reflection paper has been developed by the CHMP as a follow-up to the draft guideline published in October 2014. It provides an overview (in tabular format) of the main animal tests required for the regulatory testing of medicinal products for human use. It includes information on opportunities for limiting animal testing that can already be implemented as well as information on opportunities that may become available in the future. A section is dedicated to ATMPs.

More information about this consultation can be found here:

http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500216428&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc

In addition, the final version of the Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches has been published in December 2016 and can be found here:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500174977.pdf

Guidelines opened for comments:

- *Draft guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products* until 28 February 2017

http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500216158&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc

- *ICH E11 (R1) guideline on clinical investigation of medicinal products in the pediatric population* until 13 April 2017

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/10/WC500214185.pdf

- *Q&A on ICH guideline Q11 on development and manufacture of drug substances (chemical entities and biotechnological / biological entities)* until 15 March 2017

http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500218125&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc

- *Q&A on implementation of risk based prevention of cross contamination in production and 'Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities' (EMA/CHMP/CVMP/SWP/169430/2012)* until 30 April 2017

http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500219500&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc



4) 5th EMA-EBE on optimising the development of advanced therapies to meet patient needs held on 16 December 2016 (London, UK)

Meeting objectives were to discuss initiatives to improve ATMPs access to patients, specific requirements for gene-therapy medicinal products, meeting specific standards for development and commercialisation of ATMPs and listening to the stakeholders of innovative medicines.

The presentations are available here:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2016/10/event_detail_001334.jsp&mid=WC0b01ac058004d5c3

EMA adaptive pathways workshop held on 8 December 2016 (London, UK)

Adaptive pathways are a scientific concept of medicine development and data generation intended for medicines that address patients' unmet medical needs. The EMA organised this workshop in collaboration with the European Commission to gather the views and proposals from stakeholders on the adaptive pathways approach, in light of the practical experience gained during the pilot project EMA ran between March 2014 and August 2016, and to plan the next steps in the exploration of this concept.

The presentations are now available here:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2016/09/event_detail_001324.jsp&mid=WC0b01ac058004d5c3

European network of paediatric research at the European Medicines Agency (Enpr-EMA) awareness webinar held on 1 December 2016

Enpr-EMA was set up to facilitate the conduct of clinical studies in children. It is an umbrella network of 39 national and international networks recognised for their paediatric research experience. It acts as a platform for sharing good practices as well as a pan-European voice to foster high-quality, ethical research on the safety and effectiveness of medicines for children.

The webinar aimed to raise awareness on Enpr-EMA and illustrate the benefits Enpr-EMA and clinical research networks can offer.

The presentations as well as video recording are now available here:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2016/11/event_detail_001364.jsp&mid=WC0b01ac058004d5c3

4th EMA-EuropaBio information day held on 22 November 2016 (London, UK)

Three main topics were discussed during this meeting: innovation and development support, international cooperation with Medicines Agencies, and evidence generation during medicinal life-cycle.

The presentations are available here:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2016/11/event_detail_001360.jsp&mid=WC0b01ac058004d5c3

Feedback on the EMA-CAT workshop on “Scientific and regulatory challenges of genetically modified cell-based cancer immunotherapy products” held on 15 & 16 November 2016 (London, UK)

The CAT organised a two-day workshop to discuss the scientific developments and regulatory requirements for products manufacture and testing, non-clinical studies and clinical development of genetically modified cell-based cancer immunotherapy products.

Christelle Boniface provided the following brief summary of the meeting: *During this workshop, it has been recognised by both developers and regulatory authorities that the development of genetically modified cells is really challenging: many scientific and regulatory challenges are linked to rapid scientific advances and iterative improvements (e.g., CAR-T design, manufacturing, therapeutic management) that may require legislative changes to define a regulatory path allowing for such innovation.*

The major challenges highlighted are:

- *It is not appropriate to follow the small molecule approach for development*
→ Think differently
Manufacturing aspects: complex/multi-step process with high costs and risk of failure, many sources of variability, lack of automation and trained operators, challenge to demonstrate comparability after process or manufacturing sites changes
→ Quality, safety and efficacy are interlinked
- *Non-clinical development:*
 - *In vivo models are often questionable and not always relevant*
→ Low predicted value of clinical effect: keep clinical studies short and uncomplicated
 - *Additional in silico and in vitro tools can be more relevant*
→ Choose the assays based on science and relevance
→ Dose definition and selection is a recognised issue for living/dividing drugs
- *Clinical development: clinical trial design differs from other medicinal products with randomised trials not always feasible (-> single-arm studies) and specific risks linked to the product, benefit/risk is evolving and should always be seen in the context of the target condition*

To overcome these challenges:

- *Developers ask for global harmonisation of the regulatory processes and requirements for market authorisation*
- *Regulators encourage early interactions between scientists, physicians, developers, regulators and are providing different tools to this intent*
→ It is recognised that many open questions remain and that answers will always be a compromise, requiring case-by-case decisions (and so, close interactions are encouraged early on)



The take home messages of this workshop were:

- ***Novel safety aspects need novel strategies to address them***
- ***Scientific aspects = regulatory challenges***
- ***The field is rapidly evolving, it is difficult to foresee the regulatory context after approval of the first products***

The presentations as well as video recording are available here:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2016/08/event_detail_001318.jsp&mid=WC0b01ac058004d5c3

Feedback on the 3rd IABS Conference on Best Practice in Cell Therapy Medicinal Product Manufacturing & Testing held on 2 & 3 November 2016 (London, UK)

The 3rd IABS Cell Therapy conference, co-sponsored by NIBSC, was held on November 2nd & 3rd 2016 at the Wellcome Collection, London, UK. The meeting aimed to bring together representatives from industry, academia, health services and regulatory bodies. The conference objectives were to build on the important discussions from the first two conferences that were held in Japan in 2014 and 2015 to provide core elements useful in establishing international consensus on the requirements for manufacture of cell-based medicines and enable progress towards a potential future WHO guidance.

The programme covered recent developments in regulation, registries and banking of stem cell lines, requirements for raw materials, manufacturing, standardisation, characterisation and (cryo)preservation. The meeting brought together an outstanding and diverse group of speakers from regulatory agencies, industry, and academia, all of whom are at the forefront of the cell therapy field.

Presentations made at the conference are available upon request to Jean-Hugues Trouvin, IABS vice-president (jean-hugues.trouvin@parisdescartes.fr).

Targeted stakeholder consultation on the development of Guidelines on Good Manufacturing Practice for Advanced Therapy Medicinal Products

The European Commission (EC) consulted stakeholders involved in the development, manufacture and/or commercialisation of ATMPs.

After a first round of consultation in 2015, a second consultation was opened from 28 June to 26 September 2016. A summary of the stakeholder responses to this second consultation has been published by the EC in December 2016 and can be found here:

http://ec.europa.eu/health/human-use/advanced-therapies/2016_pc_atmp_en

The final guideline will be a standalone document and should be published Q1 2017.