10 April 2024
EMA/174922/2024
European Medicines Agency

Academia Briefing Meeting report

International Society for Stem Cell Research

Briefing meeting held virtually with the European Medicines Agency (EMA) on 10/04/2024.

The objective of the briefing meetings with academia is to provide a venue for early discussion and exchange on regulatory science in the aim of fostering the regulatory advancement of medicinal products and methodologies from the Academic Sector as well as the understanding of new medical and pharmaceutical technologies and the needs of our academic stakeholders.

Name/identifier:	ISSCR
Product / technology / method / methodology description:	N/A
Intended use:	N/A

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Participants

Applicant:

First Name	Surname	Role
Ricardo	Baptista	Chief Technology Officer SmartCella Holding, and Head of Business, Procella Therapeutics
Jacqueline	Barry	Chief Clinical Officer Cell and Gene Therapy Catapult
Nissim	Benvenisty	Director The Azrieli Center for Stem Cells and Genetic Research, The Hebrew University
Melissa	Carpenter	President Carpenter Consulting Corporation
Denise	de Villa	Manager of Policy International Society for Stem Cell Research
Agnete	Kirkeby	Associate Professor University of Copenhagen and Lund University
Tyler	Lamb	Director of Policy International Society for Stem Cell Research
Jane	Lebkowski	President of Research and Development Regenerative Patch Technologies
Tenielle	Ludwig	Director WiCell Stem Cell Bank
Jack	Mosher	Scientific Advisor International Society for Stem Cell Research
Philippa	Rice	Regulatory Affairs Specialist Cell and Gene Therapy Catapult

Total: 11

EMA experts:

First name	Surname	Organisational entity
Maribel	Rico-Salas	Regulatory Science and Academia (TRS-ACD)
Ralf	Herold	Regulatory Science and Academia (TRS-ACD)
Lucia	Caporuscio	Regulatory Science and Academia (TRS-ACD)
Patrick	Celis	Advanced therapies and haematological diseases (H-TA-ATH)
Caroline	Pothet	Advanced therapies and haematological diseases (H-TA-ATH)

Disclaimer presented at beginning of meeting

The views expressed in this document are the opinion of the participating members. Therefore, the answers provided should not be interpreted as regulatory guidance or review recommendations for an application, but as a preliminary set of scientific considerations of the information presented.

Should aspects of the subject matter discussed herein become part of a formal data submission, application, or supplement, it is at the full discretion of the appropriate working party, evaluation team or scientific committee to completely and independently assess the product(s)/technology(ies) in question.

Data protection notice

By following this process, you are providing your consent to the processing of your personal data (e.g. name, email address), which will be processed by EMA in accordance with Regulation (EU) 2018/1725. You can access EMA's privacy statement for the organisation of meetings and events here: https://www.ema.europa.eu/en/documents/other/european-medicines-agencys-privacy-statement-organisation-meetings-events_en.pdf

1. Background

The International Society for Stem Cell Research's (ISSCR) regulatory advocacy aims to give its members a voice to help educate policymakers about scientific findings and considerations that will help regulators make scientifically informed policy decisions and facilitate the development of advanced stem cell-based therapies and applications.

Since 2019, the ISSCR's Manufacturing, Clinical Translation, and Regulatory (MCTR) committee has held annual meetings with the U.S.'s Food and Drug Administration (FDA) on advancements in the field and challenges to commercialization. They have also participated in a Broader Scope Scientific Advice Meeting with the MHRA to discuss 1) the Manufacture and Testing of induced pluripotent stem cell (iPSC) Banks and Derived Products, and 2) Genomic Heterogeneity in Pluripotent Stem Cell Therapeutics.

2. Topics Discussed

ISSCR were welcomed to the meeting by the EMA. Patrick Celis disclosed that the type of questions asked by ISSCR have not yet been seen in Europe at the Marketing Authorization (MA) stage and has been seen only infrequently at the Scientific Advice Meeting (SA) stage.

Jacqueline Barry introduced the ISSCR to the EMA and provided background on the society and its recent communications and meetings with regulatory agencies. She shared information on the ISSCR publications that underpin the society's policy work, including the Guidelines for Stem Cell Research and Clinical Translation, the recently published Standards for Human Stem Cell Use in Research, and the forthcoming Best Practices for the Development of Pluripotent Stem Cells (PSC)-Derived Cellular Therapies. The Best Practices document will provide recommendations to facilitate and streamline the development of PSC-based cellular therapies regardless of regulatory jurisdiction. It will also provide detailed guidance at key product development pain points.

Topic 1: Recommendations for the manufacture of PSC banks as starting materials for allogeneic PSC-based therapies
Presenter: Ricardo Baptista, Eng Ph.D., SmartCella Holding, and Procella Therapeutics

> **Question 1a.** Does the agency agree that the PSC Seed Banks produced in non-GMP (Good Manufacturing Practice) laboratories according to principles of GMP can be used as starting materials to produce a Master Cell Bank (MCB) and Working Cell Bank (WCB) of PSCs in GMP?
> **Question 1b.** Likewise, assuming all the necessary controls and associated documentation are in place, does the Agency agree that gene editing of material prior to the establishment of the MCB can be performed in a non-GMP laboratory?
> **Question 2.** Is this risk-based qualification of materials and manufacturing processes sufficient for qualifying non-edited and edited PSCs as starting material for clinical development including registration and ultimate commercialization?
> **Question 3.** Assuming there is no further genetic manipulation, are iPSCs generated with non-integrating constructs excluded from Gene Therapy Guidelines?

Applicants Position:

The first presentation by ISSCR focused on the production of PSC Seed Banks (both edited and non-edited) and the quality assurance processes involved in their testing. The iPSC manufacturing procedure was outlined, highlighting the steps of reprogramming, expanding and cryopreserving Seed Banks and Master Cell Banks (MCBs), as well as the differentiation of iPSCs into Drug Substances and Drug Products. Notably, some iPSC-derived products undergo genome editing at the Seed Bank stage, necessitating the development of risk assessment strategies for the reagents and processes involved.

It was emphasized that while non-GMP reagents may suffice for Seed Bank manufacturing, stringent risk mitigation measures and laboratory controls must be implemented. Investigators are urged to ensure the traceability of all reagents throughout the manufacturing process and enforce thorough in-

process testing of the Seed Banks. It is also critical that during the production of iPSC Seed Banks within research settings that emphasis is put on traceability, documentation, and controls.

These unaltered or edited iPSC Seed Banks will aim to serve as the foundational material for the subsequent manufacturing stages of MCBs, Drug Substance, and Drug Product, which should adhere to GMP standards. The question was also raised whether iPSCs generated with a non-integrating construct can be excluded from gene therapy guidelines.

In light of the information provided and the discussion held, the following key points were outlined by the experts:

- For non-edited Seed Banks, the EMA is aligned with the ISSCR's proposed strategy for Seed Bank generation, and their use as a starting material. Characterized, non-GMP reagents can be suitable for Seed Bank manufacturing provided appropriate sourcing risk mitigation and laboratory controls are in place.
- The EMA acknowledged for historical banks that manufacture in a non-GMP environment, to the principles of GMP may be acceptable for use as starting material for ATMP. However, they emphasised that a higher quality standard would be expected for contemporary banks.
- Regulatory precedence has not yet been set as to whether a gene-edited iPSC bank can also be considered as a starting material, as typically the gene-editing step is considered a manufacturing step of the active substance. This impacts where full GMP compliance should be implemented (either before or after the gene-editing step). Jacqueline and Ricardo communicated that the ISSCR sees the gene editing step as a tool to create an effective starting material, rather than a manufacturing step for an active substance. In addition, they stressed the complexity of gene editing and the challenges of completing this step under full GMP conditions, which was acknowledged by the EMA.
- The EMA stated that sponsors should raise this question during a SA procedure for a specific product. Risk should be assessed and mitigated to the extent possible, and then judgment will be on an individual product basis.

EMA confirmed that iPSC-derived products are not considered gene therapies in Europe. The EMA stated regardless of this, they recommend developers to still consider gene therapy guidelines, in particular the Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells.

Topic 2: Recommendations for assessing the genetic characterization of human pluripotent stem cells
Presenter: Nissim Benvenisty, M.D., Ph.D., The Azrieli Center for Stem Cells and Genetic Research, The Hebrew University

Question 4: We believe cell banks should be genetically tested and cells should be euploid and negative for P53 mutation, and we also recommend analysis using cancer-related gene arrays.

- Does the Agency agree?
- Are there any other mutations of concern to the Agency?
- Does the Agency have any guidance on approaches to establishing thresholds for variant alleles?

Applicants Position:

ISSCR's second presentation addressed genomic heterogeneity in pluripotent stem cell therapeutics. This involved an overview of the types of chromosomal aberrations, Copy Number Variations (CNV), particular hot spots for genetic mutations, and the associated consequences of these and some detection methodologies. It is a priority to mitigate risk at the genome level in translating stem cell applications to clinical therapies.

The key message was that most aberrations are found in chromosomes 1, 12, and 17, which are not detected at low passage but are detected at higher passage numbers, often found in ~20-30% of the

PSC lines. The main consequences of these aberrations are profound enhancement of proliferation and tumorigenicity of the PSC cells.

The P53 point mutation is of the most concern to developers; it is the most prevalent and has profound consequences. 20-30% of PSC lines can express this type of mutation, both in differentiated and undifferentiated cells. The ISSCR discussed some proposed, mandatory, and recommended methodologies for detecting chromosomal aberrations and P53 mutations.

In light of the information provided and the discussion held the following key points were outlined by the experts:

- The EMA confirmed that any mutations having implications in oncogenesis, including P53, are going to prompt concern. Screening for such mutations at the chromosome level should be considered standard practice.
- Recommendation to increase testing, thinking prospectively to 5/10 years to pre-empt the safety profile regulatory requirements for a cell bank used as a starting material. Testing during the manufacturing of Active Pharmaceutical Ingredients (API) is also crucial to determine the safety profile.
  The EMA strongly recommends that the developer arrange for one or more SAs when using the cell line so that the risk can be assessed for the specific product at that time.

Additional Questions Not Discussed:

The meeting overran and there was not the opportunity to discuss the last two questions. The EMA kindly said they would feedback on these following questions outside of the meeting:

Question 5: Implementation of Next Generation Sequencing (NGS) technologies for adventitious agent testing as per ICH Q5A(R2) is expected to be highly beneficial for streamlining the quality control of hPSC-based cell products.

— Does the agency foresee challenges or concerns with these new approaches? Are there any considerations we should inform the community about?

Post-meeting note: In line with the recently adopted ICH Q5A (R2), which encourages NGS for multiple uses, we do not expect their should be regulatory issues to implement NGS for adventitious agent testing. Cross-validation against the existing methods is expected; in case of specific technical challenges, the scientific advice working party is the right forum to seek input from.

Question 6: Considering GMP requirements for ATMPs should cover the safety and quality requirements for sterile products, GMP certificate for cell therapy may be sufficient for the production of solvents for reconstitution and diluents to be used for ATMPs. Does the EMA find that it is in adherence with the ATMP GMP guidelines to perform manufacturing of solvents and diluents under a GMP/MIA license for cell therapy (1.3.1.3) and not under a GMP/MIA license for liquid sterile products (1.1.1.4)?

Post-meeting note: Solvents/diluents for reconstitution of an ATMP are seen as finished product. If the solvent is water for injection (WFI) we normally expect to have (in the MIA) small volume liquids terminally sterilised (1.1.2.3).

General discussion points arising during the meeting.

There was a general discussion on the activities ISSCR are undertaking to aid developers in this field in which they explained that they have started the process of the development of guidance for PSC banking and products derived from these for clinical use. The EMA recommended sending in drafts of

the relevant pieces of text from this guidance for review. They emphasised their ability to review is constrained and as such ISSCR should only select key sections where they believe EMA contributions are required.

Regulators also welcome invitations to meetings with developers/companies to engage in more frequent dialogue.

Concluding remarks

- The ISSCR is encouraged to look at the services available from EMA regarding opportunities for engagement, as well as other incentives, and to promote these to their community.
- The EMA confirmed that they will look at specific recommendations and provide guidance if the ISSCR wishes to provide them, but empahsised there is limited resources for review so ISSCR should consider this when sending information on
- The EMA welcomes invitations to meetings that the ISSCR hosts to provide guidance.
- Both parties confirmed that it would be preferable to have regular meetings as part of a collaboration, thus ensuring a bi-directional sharing of knowledge can be maintained between ISSCR and EMA.
- ISSCR will share further information with the EMA regarding their aims, and structure of the organization/working groups.