INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

ISSCR Holds Second Meeting with UK Regulators on Artificial Intelligence in Stem Cell Therapy

The International Society for Stem Cell Research (ISSCR) held its second Broader Scope Scientific Advice meeting with the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) on October 29, 2025, focusing on the use of artificial intelligence (AI) in developing stem cell therapies.

The session explored key topics including the current state and challenges of AI, machine learning, and digitalization systems for automation in cell and gene therapy; applications of AI in autologous iPSC-derived RPE cell therapy; and AI-based image analysis for in-process characterization and decision-making during iPSC generation.

Representatives from the MHRA included experts in quality assessment, standards and compliance, and stem cell banking. In addition to the presenters, representatives from ISSCR included members of the Board of Directors, the Manufacturing, Clinical Translation, and Regulatory Committee (MCTR), and ISSCR members with expertise in integrating AI into the development of stem cell therapies

Overview of ISSCR's Regulatory Advocacy
Presenter: Jacqueline Barry, PhD

Jacqueline Barry opened the meeting with an overview of the agenda and the background behind the proposed discussion points. She also introduced the ISSCR, highlighting several ISSCR initiatives, including the Best Practices for the Development of Pluripotent Stem Cell (PSC)-Derived Cellular Therapies and the newly launched ISSCR Stem Cell-Based Models for Drug Discovery & Development Consortium. This meeting marks the Manufacturing, Clinical Translation, and Regulatory (MCTR) committee's second meeting with the MHRA.

The MHRA team noted that they are not currently utilizing AI in their routine activities and expressed interest in learning more about the technologies currently in development.

Current State and Challenges in Artificial Intelligence, Machine Learning, and Digitalization Systems for Automation in Cell and Gene Therapy
Presenter: Dalip Sethi, PhD, MBA, MS

The presentation highlighted the rapid growth of AI/ML publications in cell therapy space. It covered foundational concepts such as AI, ML, predictive analytics, digital twins, and metadata, and showcased case studies where AI and ML have been used to optimize manufacturing workflows, predict stem cell donor availability, and potentially improve CAR-T cell therapy outcomes.[1]

The presentation also emphasized several critical challenges that must be addressed for AI/ML to reach their full potential in the cell and gene therapy space. These include the lack of published studies and standardized datasets, limited collaboration due to proprietary models, and issues with data quality, integration, and validation. The need for greater

[1] Artificial intelligence, machine learning, and digitalization systems in the cell and gene therapy sector: a guidance document from the ISCT industry committees - Cytotherapy

acceptance and trust in AI systems was also highlighted. Solutions to overcoming these barriers include robust data ecosystems, harmonized standards, and transparent validation frameworks. Ultimately, the integration of AI and ML promises to transform cell and gene therapy field, but success will require coordinated efforts across technology, data, and regulatory domains.

Applications of AI in Autologous iPSC-Derived RPE Cell Therapy

This presentation highlighted how AI-driven analytics are being integrated into stem cell–based retinal pigment epithelium (RPE) product development for treating age-related macular degeneration (AMD), a condition affecting more than 30 million people worldwide.

The talk outlined the iPSC-to-RPE manufacturing process and demonstrated how deep neural networks (DNNs) are used to assess RPE cell maturity, functionality, and quality. Using more than 10,000 training images, AI models accurately predict transepithelial resistance (TER), a key functional metric, and quantify hexagonality—an essential morphological feature of healthy RPE. Additional AI tools, including donor-specific convolutional neural networks, verify cell identity and monitor cellular shape changes that correlate with functional decline.

The presentation concluded with discussion of a Phase I/IIa clinical trial and the establishment of AI-enhanced product characterization methods that strengthen the reliability and reproducibility of stem cell–derived RPE therapies.

MHRA expressed interest in this methodology and discussed potential advantages of using AI versus manual analysis of RPE samples and the use of this technology to determine cell therapy product safety vs efficacy.

AI-Based Image Analysis for In-Process Characterization and Decision Making During iPSC Generation
Presenter: Marinna Madrid, PhD

The presentation described Cellino’s optical bioprocess for iPSC generation. The optical bioprocess comprised automated imaging, AI-based image analysis of cells in-process, algorithm-based in-process decision making, and laser-based cell removal.

The talk described three AI-based image analysis models in detail: a model to detect live cells, a model to distinguish between pluripotent and spontaneously differentiating cells, and a model to estimate local cell density. The talk also included a description of Cellino's ability to quantify static and dynamic cell/ colony features, and a proof-of-concept demonstrating how those features can be used to predict karyotype status.

Finally, the talk demonstrated how the AI-driven optical bioprocess significantly increases throughput of iPSC manufacturing.

Questions and Discussion

1. Aligning on reporting requirements for AI-based algorithms

The presenters emphasized the value in establishing a harmonized framework for reporting the use of AI-based algorithms in cell therapy development and manufacturing. As an example, the presenters shared a figure from USFDA's draft guidance for the use of AI.[2] The figure summarizes key information the presenters consider necessary to support transparency, traceability, and regulatory confidence in AI implementation during advanced therapy development and manufacturing.

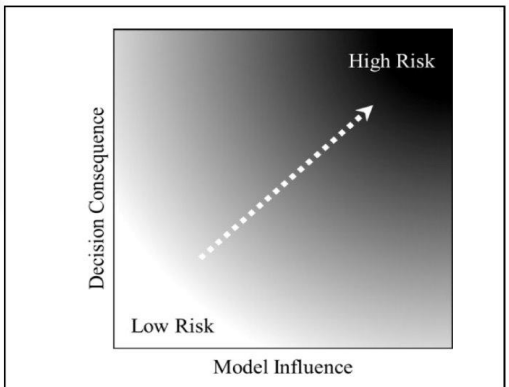

Figure 1. Model risk matrix. The model risk moves from low to high as decision consequence or model influence increases. The ratings for decision consequence and model influence are independently determined.

- Does the Agency agree such a framework would be appropriate and useful for the field?

There was broad agreement that reporting expectations for AI models used in advanced therapy development should be aligned across agencies and industry groups. Regulators noted that existing documents, such as EudraLex Annex 22, which recently underwent public consultation and generated substantial feedback, remain high-level and although may not yet provide the level of detail needed for consistent implementation, is a resource that should be highlighted to developers.

- Is the Agency looking to produce such guidance? If not, is this something the Agency would be keen to collaborate on?

The Annex 22 initiative is led by the EMA, with MHRA participating through PIC/S. Consensus is still formulating and it was acknowledged that there is a need to clearly differentiate between regulatory requirements and industry-led development. The MHRA

[2] Considerations for the Use of Artificial Intelligence To Support Regulatory Decision-Making for Drug and Biological Products | FDA

expressed they are happy to continue conversations with developers on the use of AI in development and manufacture.

- Can the Agency advise on any additional elements or considerations that should be included to ensure adequacy for regulatory evaluation?

MHRA stated that it is important to assess how the proposed framework might specifically affect AI applications, without duplicating broader AI processes that will apply across multiple product types. For stem-cell–derived products, it is necessary to define relevant inputs and outputs and highlight specific risks, such as karyotype integrity. Industry and academic SMEs are knowledgeable but may have biases, and with no licensed pluripotent stem cell products, real-world experience is limited. Guidance was that developers should focus on aligning input–output risks, addressing potential model biases, and ensuring patient confidentiality.

2. Classification of Risk of AI-Based Algorithms

- Under a risk-based approach, informed by the USFDA guidance on AI/ML-based medical technologies, risk is assessed by considering both *model influence* and *decision consequence*. In Cellino's case, the image-based AI system applied to support in-process manufacturing decisions is characterized as low risk, due to human-in-the-loop oversight and the performance of standard cell characterization at the conclusion of the manufacturing process.

  Does the Agency find this risk-based assessment framework appropriate for this use case, and does it agree with the classification as low risk? If not, what alternative frameworks or considerations would the Agency recommend?

MHRA agrees that the principles appear sound but emphasized that, in medicines regulation, risk is assessed in relation to patient impact. For example, in cases of high unmet medical need or life-threatening conditions, a higher level of risk may be acceptable. It is important to validate algorithms through scientific assessment, and the evaluation should consider not only performance metrics, but also the nature of potential failures.

3. Framework for validating changes to AI-based algorithms

- Cellino's AI-based algorithms operate under strict version control, with fixed training datasets and unaltered input-output relationships for any given version. Processing additional patient samples and collecting more imaging data, training datasets can be substantially enhanced, leading to improved performance of the algorithms.

  Does the agency have guidelines or expectations regarding when it is necessary to "lock down" an AI-based algorithm? If not, would there be opportunities to establish a change management framework in which algorithms could be updated throughout the product lifecycle (e.g. during clinical development, post-approval), provided there is a pre-defined testing process with agreed-upon acceptance criteria and reporting requirements? And how will the agency manage these – substantial amendment/variations?

The MHRA advised that during clinical development, any modifications to an AI-based algorithm require demonstration of comparability to ensure consistent results. This may include reprocessing data through the original algorithm. Changes are expected to be managed similarly to license variations or clinical trial amendments, with appropriate oversight. For release criteria, algorithms must be validated and "locked down" early, as tests cannot be altered once established. The acceptability of data for regulatory purposes depends on the specific claims being supported.

ISSCR Participants

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