INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

**ISSCR Members Hold First Scientific Advice Meeting with the U.K.'s Medicines and Healthcare products Regulatory Agency**

The International Society for Stem Cell Research (ISSCR) held its first Broader Scope Scientific Advice meeting with the U.K.'s Medicines and Healthcare products Regulatory Agency (MHRA) on May 15, 2023. ISSCR's 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. The 1.5-hour virtual meeting included attendees from the ISSCR's Manufacturing, Clinical Translation, and Industry (MCTI) Committee, the MHRA's Biological Products group, the MHRA's National Institute for Biological Standards and Control, and representatives from the organizer of the meeting, the U.K.'s Cell and Gene Therapy (CGT) Catapult. After a brief introduction of the ISSCR and a review of its regulatory advocacy, the ISSCR delivered recommendations on two topics: 1) the Manufacture and Testing of induced pluripotent stem cell (iPSC) Banks and Derived Products, and 2) Genomic Heterogeneity in Pluripotent Stem Cell Therapeutics.

**Overview of ISSCR's Regulatory Advocacy**
**Presenter: Tyler Lamb, JD, ISSCR**

Tyler Lamb introduced the ISSCR to the MHRA and provided background on the society and its recent activities in the regulatory affairs space. He shared information on the ISSCR Guidelines for Stem Cell Research and Clinical Translation and the forthcoming Standards for Basic and Preclinical Research. The Standards address basic characterization standards, standards for identifying undifferentiated stem cells and assaying pluripotency, genomic characterization standards, and standards for stem cell-based model systems. He also shared that a phase 2 Standards project is already under way. Phase 2 of the Standards will address clinical translation and will build upon the same principles as the basic research standards to provide precise recommendations to streamline and facilitate regulatory review, manufacturing, and scale up/out of PSC-based cellular therapies. These documents will underpin the ISSCR's policy activities going forward.

Since 2019, the ISSCR's MCTI committee has held annual meetings with the U.S.'s Food and Drug Administration (FDA) on advancements in the field and challenges to commercialization. This meeting represents ISSCR's first outreach to regulators in the U.K. as the society seeks to initiate some of these conversations here and in Europe.

**Manufacture of iPSC Banks and Testing of iPSC Banks and Derived Products**
**Presenters: Jacqueline Barry, PhD, CGT Catapult**
**Melissa Carpenter, PhD, ElevateBio**
**Jane Lebkowski, PhD, Regenerative Patch Technologies**

ISSCR's first presentation addressed the manufacture of induced pluripotent stem cell (iPSC) banks and the testing of iPSC banks and derived products. Dr. Carpenter reviewed the iPSC manufacturing process, describing reprogramming of somatic cells to iPSCs with non-integrating technologies, expansion and cryopreservation of Seed Banks and Master Cell Banks (MCBs) and differentiation of the iPSCs to Drug Substance and Drug Product. A number of iPSC-derived products are being developed in which the iPSCs are genome edited at the Seed Bank stage. Strategies should be developed to assess and mitigate the risks associated with reagents and processes used in iPSC-derived product manufacturing. Non-

GMP reagents can be suitable for Seed Bank manufacturing provided appropriate risk mitigation and laboratory controls are in place. Investigators developing iPSC-derived products should ensure traceability of all reagents.

In addition, Dr. Carpenter discussed the manufacture of iPSC Seed Banks in a research environment in which appropriate traceability, documentation and controls are in place. These unedited or edited iPSC Seed Banks can be used as the starting material for manufacture of MCBs, Drug Substance and Drug Product should be performed in a GMP environment.

Dr. Carpenter additionally commented that there are currently 80-90 clinical trials globally testing iPSC derived products to date.

**ISSCR recommendations for IPSC banks:**

- Characterized, non-GMP reagents can be suitable for seed bank manufacturing provided appropriate sourcing risk mitigation and laboratory controls are in place.
- Processes and documentation should be incorporated to assure the traceability of iPSC lines from donor tissue to creation of master cell banks.

**Topics for Discussion:**

1. **Is risk-based qualification of materials sufficient for qualifying native and edited iPSCs as starting material for clinical development including registration and ultimately commercialization?**
2. **Does the MHRA agree that a risk-based approach to manufacture and testing appropriate to trial phase and patient numbers is acceptable?**

MHRA shared that the risk-based approach (RBA) / qualification of materials is written into the Advanced Therapy Medicinal Products (ATMP) legislation and RBA guideline. The MHRA are willing to accept the RBA approach at Marketing Authorization Application (MAA) and Clinical Trial (CT) stages of development. There are no specific guidelines in Europe to support this for PSC specifically; the recommendation is to consult the European Medicine Agency's (EMA) Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells. The MHRA team will also consult the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines and the European Pharmacopeia (Ph. Eur.) entries associated with cell bank testing. The agency acknowledged a reference in the presentation to the European Union's (EU) regulations on blood, tissues, and cells and confirmed that the requirements of this legislation are considered within the context of the decisions made. Further, the MHRA appreciates that many cell lines were derived in the late 90s and that the referenced guidelines weren't in place at that time, therefore the MHRA takes a pragmatic approach (which is supported by the GMP for ATMP guideline, EudraLex Vol. 4, Part IV), which requires Sponsors to justify use of the chosen starting material.

Members of the MHRA also added that Good Manufacturing Practice (GMP) is a Quality Management System (QMS) and viewed as such in the UK. However, it should be noted that not all EU countries have the same position. For example, Austria refers to GMP taking place in a certain environment. The agency confirmed that GMP applies to the manufacture of medicine, not to reagents. It is recommended to use fit for purpose qualified reagents as early as possible in development.

For assessing the risk/benefit to the patient when making decisions of product assessment, assessors will look to the available information on the cell line. For existing cell lines, risk should be assessed and mitigated to the extent possible, and then judgement will be on an individual product basis and potentially acceptable if the risk/benefit is positive to the patient. When generating new cell lines, the expectation is that developers will engineer the cell line in accordance with existing guidelines.

- Substituting human for xeno reagents is not always preferential—it depends on the risk associated with the materials selected.
- Testing listed in Ph. Eur guidance and ICH guidelines are by default the requirements. However, if the developer demonstrates alternative tests are better, the developer can make an argument for using these alternative tests. The MHRA have examples of accepting tests not described in Ph. Eur/ICH guidelines.
- The MHRA confirmed the above comments apply to both edited and non-edited MCB.

3. **Are iPSCs generated with a non-integrating construct excluded from Gene Therapy Guidelines?**

The agency shared that the MHRA wouldn't classify an iPSC cell line as a gene therapy, regardless of whether the constructs used for development of the cell line were integrated or not (this is because the definition of "gene therapy" requires the effect of the therapy to be directly related to the nucleic acid sequence introduced and this is not the case for PSCs). Further, iPSCs are not directly injected into the patients—they are not the final product. The developer would still be required to address the potential issue of recombinant material (if relevant). The MHRA assessment will be the same irrespective of the classification.

It was also clarified that if PSCs are then further gene modified during downstream manufacturing to generate the drug product (and the nucleic acid sequence introduced was associated with the therapeutic effect), then these would be considered gene therapy. Note: the PSC product can be genetically modified but not be a gene therapy product (based on definition of "gene therapy" and on account that the introduced material has to be recombinant).

In summary, the MHRA confirmed that the MCB will be seen as a cellular starting material and unless genetically modified in accordance with ATMP Regulation 1394/2007 and the genetic material exerting a therapeutic effect, then the drug product will most likely be viewed as a somatic cell therapy.

4. **Is the MHRA considering the introduction of a Drug Master File (DMF) for PSC banks?**

The MHRA asked if this question is in relation to a Qualified Person (QP) sign-off, as developers of PSC banks are often reluctant to share all info with a therapy developer/QP inhibiting the ability to gain all correct information.

The MHRA think it unlikely that they will introduce a Masterfile system. A DMF approach would support a paradigm where the manufacturer is not aware of everything relating to the product's development yet is responsible for safety and quality of product. However, the MHRA are aware of the commercial implications and can accept information from companies (PSC bank developers) directly, but this is not the preferred way of working as it introduces an added layer of complexity. Ideally, developers would find a way to address this from a legal perspective with suppliers, as ultimately the developer should know everything about their product.

- The MHRA has not considered whether it would review (in a rolling review style) a DMF for a PSC bank produced in the U.S., to provide developers with assistance of the appropriateness of the bank.
- From the perspective of International Reliance access and recognition (e.g., if the FDA have approved a product for a PSC bank with DMF), then MHRA would take this into account in their assessment, and a decision on a case-by-case basis would need to be made on whether to accept this.

## Genomic Heterogeneity in Pluripotent Stem Cell Therapeutics

**Presenter: Chuck Murray, MD, PhD, University of Washington Institute for Stem Cell and Regenerative Medicine**

ISSCR's second presentation addressed genomic heterogeneity in pluripotent stem cell therapeutics. Dr. Murry provided an overview of cancer genetics, tools used for genomic analysis, and sources of genomic heterogeneity. It is a priority to mitigate risk at the genome level in translating stem cell applications to clinical therapies. As described, there are 6 orders of magnitude available for use in multiscale genome assessments, and, while this presentation primarily focused on cancer genetics, these techniques can be applied to different areas of genomic risk. Varying sources of genomic heterogeneity including iPSC mutations and dominant clones in PSC cultures pose significant challenges to personalized cancer medicine.

Dr. Murry outlined a recent case study of BCOR mutations in human iPSCs and provided two examples of analytical genomics during stem cell manufacturing, including an analytical workflow were provided. Dr. Murry described the challenge of evaluating genomic heterogeneity as inevitable and that while our ability to detect and quantify mutations is growing rapidly our ability to discern functional consequences is not keeping pace. There is a need to establish which mutations are of concern and what level of allelic frequency is acceptable.

**ISSCR recommendations for genomic heterogeneity:**

- Gain of function mutations in oncogenes and chromosome-level aneuploidies should be avoided. Smaller scale copy number variations should be decided case-by-case.
- Only a few tumor suppressor genes are currently understood well enough to disqualify a line if mutated, e.g., TP53. Investigators/sponsors should interrogate the genome to identify variants of concern, drawing from clinical testing, as well as clinical and research databases.
- These variants should be used to select donors and prioritize clones.

- Mosaicism/heterogeneity is inevitable within any cell population. The frequency of undesired variants should be assessed and minimized during process development.
- The threshold between a safe and an unsafe frequency for an undesirable variant is not known. Sponsors should track this and correlate with toxicology studies and clinical outcomes.
- For the community: Lessons from preclinical and clinical outcomes should be shared with the therapeutic community to enhance patient safety and increase probability of success for the whole field.

**Topics for discussion:**

1. **Are there other critical mutations beyond TP53 of concern to the Agency, e.g., in BCOR or others?**

The agency confirmed that any mutations having implications in oncogenesis are going to prompt concern, so if a developer shows a PSC line has mutations this will prompt discussion and a risk assessment will need to be undertaken. Whether to accept the PSC line with the mutation will depend on level of variation and potential risk of becoming tumorigenesis (e.g., is product administered with intention of life-time integration into patient, versus product administered with intention of serving a short duration in vivo), plus the nature of the clinical indication. The MHRA's list of mutations is not comprehensive, and it is important for developers to look at their product. P21, RB and D-type cyclins are potentially other ones to consider.

Dr. Murry asked if it is useful for developers to introduce data on mutations into a dossier? The MHRA responded that it depends on the purpose. Regulators can't or won't analyze the data, but high-level summaries of the data and associated risk assessments for the mutations would be useful. MHRA said in response specifically to the BCOR mutation, the question remains is it upregulated in response to how cells are derived, or whether mutations are being generated or selected for in the differentiation process? This is tricky to get a handle on and thus understand the implications.

Dr. Pellegrini asked if all testing performed on the PSC derived product (in-vitro and in-vivo) shows no negative impacts, then is it okay to assume the mutation is not a problem? Dr. Glassford responded that if you haven't seen the risk of a mutation, it doesn't mean it isn't a risk. The focus of this discussion is about oncogenesis/tumor formation, but there are also mutations outside of these that can impact safety and efficacy.

The MHRA reminded ISSCR that the MHRA will be pragmatic, however, its position is subject to review by the U.K.'s Commission on Human Medicines.

2. **Does the Agency have any guidance on approaches to establishing thresholds for variant alleles?**

The agency noted that there is no written guidance on variant alleles, but the FDA has published some guidance. This guidance is associated with the design, development, and validation for next gen sequencing in relation to in-vitro diagnostics (IVDs), however, the key themes pertaining to documenting and justifying each step, what samples were used (are they comparable and relevant to medicinal product), and what reference sets were used, are all relevant.

MHRA reminded the group that when there is a paucity of current guidance the recommendation is to go for scientific advice and not to rely solely on guidance.

3. **Are there special analytical genomic considerations for genome-edited cells?**

To support framing of this question, Dr. Murry asked the MHRA to consider a developer who found no off target effects of proposed editing—would the developer need to do Whole Genome Sequencing (WGS) before and after to show this? What is the right level of interrogation to perform?

The agency responded that consideration should be given to the sensitivity of the software being used. If there are no hits, is this because of the method's sensitivity? And is this the standard method employed? In terms of WGS, the MHRA would look at what it felt was reasonable in the context of the risk. For instance, a PSC bank treating hundreds or thousands of patients would carry greater risk versus an autologous therapy.

MHRA said there is the potential for use of in-silico analysis to help better target your experimental approach, which allows or justifies switching from WGS to less intensive methods.

4. **Beyond small animal toxicology and analytical genomics, are there technologies that would provide complementary assessments of safety for a cell product?**

MHRA said that assessors will begin by asking the question "why does the company think this should work?" Next, and assessor will review how critical the evidence is that this might be beneficial and whether there are technologies to support this. Assessors also consider whether the developer has considered similar products used before where information is in the public domain (e.g., same cell type, dose, route of administration). MHRA cautioned that regulators and assessors are often not the people most up to date about technological advances. Therefore, assessment is often a judgement on whether what is being proposed makes sense.

The MHRA are also content with small animal testing on most occasions. Primates are not typically necessary, though larger animal models may be required depending on the indication (e.g., if weight bearing is required). But generally, MHRA is expecting mice and rats for these studies.

**ISSCR Attendees**:
Melissa Carpenter, PhD - Chief Scientific Officer of Regenerative Medicine, ElevateBio
Jane Lebkowski, PhD - President, Regenerative Patch Technologies
Tyler Lamb, JD - Director of Policy, ISSCR
Tenneille Ludwig, PhD - Director, WiCell Stem Cell Bank
Charles Murry, MD, PhD - Director, Institute for Stem Cell and Regenerative Medicine, University of Washington
Graziella Pellegrini, PhD - Director, Cell Therapy Programme, Centre for Regenerative Medicine "Stefano Ferrari" University of Modena and Reggio Emilia
Jack Mosher, PhD - Scientific Advisor, ISSCR

**CGT Catapult:**
Jacqueline Barry, PhD - Chief Clinical Officer
Ryan McCoy, EngD - Senior Regulatory Affairs Lead
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**MHRA:**
Dr. Alison Niewiarowska - Head of Biological Products
Graham McNaughton - Pharmaceutical Assessor (written comments)
Dr. Janet Glassford - Pharmaceutical Assessor
Dr. Louise Bisset - Pharmaceutical Assessor
Dr. Veronika Ganeva - Pharmaceutical Assessor
Dr. Karin Boon - Pharmaceutical Assessor
Francis Galaway - Pharmaceutical Assessor
Dr. James McBlane - Non-Clinical Assessor
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