Summary from the ISCBI/ISCI meeting, Broad CIRM Center in Los Angeles, 30th June 2019

1) Introduction and ISCBI update. Glyn Stacey ISCBI Coordinator

Glyn Stacey (ISCBI Coordinator) reported the recruitment of Jenny Nelder (JNAE, Cambridge, UK) as ISCBI administrator and initiation of ISCBI news-bulletins with 'focus articles' intended to give perspectives on current status of stem cell research and networks. The first article in June 2019 focused on key Indian research institutions was contributed by Prof Maneesha Inamdar, JNCASR, Bangalore). Glyn also reported that the Melbourne 2018 meeting summary was on the ISCBI website and that the usual 'round-the -world' update sessions would be virtual (i.e., circulated as PDFs by email web-links) for 2019 meetings and would be available via the website to ISCBI members. This latter change was necessary to allow sufficient time for workshop discussion sessions.
Future meetings in Korea 24th September (Local symposium and workshop organisers were respectively Prof Jihwan Song of CHA University and Dr Jung-Hyun Kim of KNIH, Osong (see www.iscbi.org for details). Upcoming meetings in 2020 were reported for a whole day workshop hosted by Laurence Daheron at Harvard Stem Cell Institute on 28th June and a longer meeting in Beijing hosted by Prof Qi Zhou and Prof Fanyi Zeng at the Institute of Zoology-Chinese Academy of Sciences.

2) ISCI genetic stability project, Chaired by Martin Pera, ISCI Coordinator

Martin Pera (Jackson Labs, USA) reviewed the key issues of genetic stability in hPSCs and the importance of knowing what you are working with. He outlined the overall goals of the ISCi genetic stability group to establish a database of recurring hPSC genetic variants which could provide researchers and regulators with a useful source of information regarding the relationship between growth conditions and genetic stability and facilitate the development of robust and sensitive assays that could be used on a regular basis. Specific objectives of the project were to collect a number of data sets including changes affecting specific loci, interrogate the influence of genetic background and collate and analyse the emergence of genetic variants during culture and differentiation.

Peter Andrews (University of Sheffield, UK) summarised the latest data on the development of genetic variation following recloning and expansion of hESC lines and the impact of culture conditions. His report included the observation that Rock inhibitor does not alter rates of mutation whilst low oxygen tension culture decreased mutation frequency (1). The utility of the database would be not just to map changes, but to provide interpretation on what their implications might be for research and clinical development.

Erik McIntire (WiCell, USA) reviewed karyological data from analyses of 15,000 hPSC samples tested by WiCell. Erik reported that approximately 16% of cell lines submitted for karyotype analysis harbor a recurrently acquired abnormality. Similarly, the WiCell Stem Cell Bank has found that fully one-third of deposited cell lines fail to meet WiCell's basic quality standards upon testing, and the primary reason for failure is recurrently acquired abnormality. His talk focused on an observed shift in the common genetic variants detected in karyotypes produced between 2009 and 2016 (2), whereby there had been a significant increase in gains of chromosomes 1 and 20 and decreasing frequency of chromosome 12 gains for both hESC and hiPSC lines. He ventured that this change in incidence of particular genetic variants arose due to changes in culture conditions, however it has not at this point been linked to a particular medium or culture parameter. Erik also noted that some genetic variants were very complex and referenced a computational tool developed by Zach Abrams at The Ohio State University (OSU) to manage karyological data. Investigators from WiCell and OSU are working collaboratively to use this tool to identify previously unrecognized recurrently acquired abnormalities in hPSC culture (publication in preparation). It is hoped that these data could be employed to develop targeted assays to inform future control experiments and improve testing for genetic stability.

Nissim Benvenisty (Hebrew University of Jerusalem, Israel) reported on studies of point mutations and RNAseq in hPSCs (3). He reported that 60% of samples failed to show genetic variants and whilst single mutations in cancer related genes occurring in approximately 30% of samples, only 3% of samples showed more than ten mutations in these cancer related sequences. Also, established mutations were found to persist in differentiated cells. He also reflected on the potentially significant role of epigenetic aberrations which would require further attention in future research.

Yoji Sato (JNIHS, Japan) presented a regulators perspective on genetic stability in hPSCs. He reflected on the fact that the human body is a natural mosaic of variant genomes. He summarised work to fund studies of different assays for tumorigenicity in cell lines that would be used to revise Japanese regulatory advice on safety testing of hPSCs. Yoji also reviewed the consensus list of cancer related genes used in Japan to analyse genetic stability and raised the need for a mechanism to regularly update this list. However, he also warded caution in interpretation of genetic data as different types of software for data analysis appeared to reveal different results and some cell lines showing cancer related genetic changes failed to produce positive results when tested by *in vivo* tumorigenicity assays. Finally, he emphasised the need for continued research to help develop informative assays for tumorigenicity.

Selected discussion points:

The convener (Martin Pera) asked if the group felt that the trends observed in karyotype abnormalities were influenced by cell culture conditions. The responses led by Tenneille Ludwig (WiCell) indicated that to date, data had been collected retrospectively and a key issue was that the full history of cell culture conditions may not be clear at the point when genetic status is assessed. It was suggested that more data would need to be collated before clear conclusions could be drawn. The discussion went on to consider the current state of international dissemination and coordination on genetic stability of hPSCs. It was concluded that whilst ISSCR had instigated a number of related efforts in standards and manufacturing, there was an important role to be fulfilled by ISCI to develop the proposed database and consider what guidance would be helpful in this rapidly moving area of hPSC science. In a straw poll of all delegates it was clear that many were using *in situ* hybridisation, whole genome sequencing and SNP/CNV analysis. In ongoing discussion it was emphasised that it was important for hPSC-workers to publish genetic analysis. It was also considered important to consider the mutations arising in the germline as well as in cell line derivation and culture, but also to keep such discussions in perspective as a number of studies had now shown the emergence of cell culture variants which appear to occur in the majority of hPSCs analysed.

References.

1. Thompson O, von Meyenn F, Hewitt Z, Alexander J, Wood A, Weightman R, Gregory S, Krueger S, Andrews S, Barbaric I, Gokhale PJ, Moore HD, Reik W, Milo M, Nik-Zainal S, Yusa K, Andrews PW. 2020 Low rates of acquisition of de novo mutations in human pluripotent stem cells under different culture conditions. Nat Commun 11, 1528. *https://doi.org/10.1038/s41467-020-15271-3*.
2. McIntire E, Taapken S, Leonhard K, Nisler B, Larson AL, Velazquez G, and Montgomery K. "Relative Frequencies of Recurrent Acquired Karyotypic Abnormalities in Human Pluripotent Stem Cells from 2009 to 2016." Poster presented at International Society for Stem Cell Research (ISSCR) Annual Meeting; June 2017; Boston, Massachusetts.
3. Avior Y, Eggan K, Benvenisty N (2019) Cancer-related mutataions identified jn primed and naïve human pluripotent stem cells. Cell Stem Cell. 25 (4), 456-461. DOI: 10.1016/j.stem.2019.09.001

3) **ISCBI workshop presentations on qualification of raw materials, Chaired by Glyn Stacey, ISCBI.**

The chair explained that speakers had been selected by the ISCBI Steering Group to represent a range of approaches used to qualify reagents and equipment for development and manufacture of hPSC-derived cell therapies.

Quality aspects of MACS cell culture reagents. Thorsten Decker, Regenerative Medicine and Cell Culture, Miltenyi Biotec GmbH, Bergisch Gladbach, Germany.

Thorsten Decker summarised the Miltenyi Biotech involvement in CAR T cell trials and in particular obtaining manufacturing authorisation for CAR T cells and lentiviral vectors which had involved regular interactions with the German regulatory authority (Paul Ehrlich Institute) the European Medicines Agency (EMA) and the US Food and Drugs Administration (USFDA). The Miltenyi Biotec projects used closed processing in a class C (EU) air grade manufacturing environment. Thorsten identified three important elements in reagent, equipment and product delivery which were:

1) A suitable and robust quality management system which in the case of Miltenyi Biotech included a) research products manufactured under ISO9001 accreditation, b) the MACS GMP™ products manufactured and tested as 'ancillary materials' under an ISO13485-certified quality management system and designed to meet the requirements of cell therapy manufacture, and c) production of lentiviral vectors as APIs and CAR T cell products within their individual manufacturing authorisations.
2) Thorsten also identified key documentation relating to qualified manufacture included certificates of analysis (CoA), certificates of origin (COO), a description of the production procedure and statements on TSE risk, as part of a final Product Information File. He also explained that Miltenyi Biotec are willing to provide opportunities for audit of their manufacturing systems.
3) Design criteria for quality elements, including raw material qualification and functional performance. This had been enhanced by early consideration of chemically defined reagents to replace ingredients of biological origin, development of automated solutions for scale-up and adoption of relevant pharmacopeial standards and GMP requirements. Experience at Miltenyi Biotec has demonstrated that it was also important for cell product developers to be prepared for the complex and time-consuming process required to develop and implement a GMP-compliant manufacturing system.
4) In house production: Miltenyi saw benefits in manufacturing their own basal media, recombinant cytokines and growth factors as ancillary materials as this had facilitated rational "animal component-free" media design tailored towards specific product cell types, better control using bespoke biological assays and more consistent production processes leading to greater reproducibility of the final product.

Thorsten concluded by summarising the decade long process to establish the Miltenyi manufacturing processes and emphasised the importance of early engagement with regulators.

In discussion with delegates Thorsten Decker emphasised the value Miltenyi had found in their in-house raw material and equipment development as it had made the inevitable process changes during GMP-development much easier to implement than if all such inputs had been out-sourced. He was also asked about the stage of development of a GMP mRNA-based reprogramming kit. Thorsten reported that this was in development for GMP-compliance as part of a product development project. When asked about the common issues such as cell-aggregation that can arise in some automated devices, Thorsten reported that with the current raw materials they were using this had not been a serious issue.

Stem cell growth media validation at STEMCELL Technologies, Roy Musil, VP Quality, STEM CELL Technologies Inc., Vancouver, Canada.

Roy Musil began by emphasising that in the routine operation of a GMP process it was necessary but not sufficient to know what you had done as GMP compliance required the manufacturer to also be able to provide documented evidence for exactly what had been done for each production run. Roy also considered the definition of both raw and ancillary materials which he described as any key components that come into direct contact with the therapeutic product during its manufacture, that will not be present in the final product. In support of this he also guided interested delegates to a seminar on raw material qualification on the STEMCELL Technologies website. He also indicated a range of useful standards and best practice documents for cell and gene therapies including USP 1043 (Ancillary materials for cell, gene and tissue engineered products)(1), Pharmeuropa 5.2.12 (Raw materials of biological origin for production of cell-based and gene therapy medicinal products for human use) (2), a newly developing ISO standard on ancillary materials (ISO/TS 20399 1:2018 see ref. 3) but emphasised that these were not necessarily adopted in national regulation. Roy also alerted delegates to be aware of the difference between the commonly used terms "animal-component-free" and "not of animal origin" as a raw material not of animal origin may be exposed to materials of animal origin during its preparation.

Roy explained that no raw material was risk-free and encouraged a risk-based approach to raw material evaluation as part of employing the principle of safety by design. He illustrated the level of detail that this may require with a worked example. He identified adventitious agents as a critical element but also emphasised that manufacturers need to be aware of how risks are viewed and assessed by any different organisations and regulators involved in the development of a manufacturing process.

Roy pointed to a 30 year history of development of monoclonal antibody therapeutics which had provided a valuable paradigm for the development of effective assurance of patient safety. This was based on the three pillars: Prevention through effective sourcing of materials, Removal by effective processing and Detection through effective testing regimes. However, Roy also explained that implementation of these three pillars for processing and testing of advanced therapies was not a linear process. In conclusion, he emphasised the importance of supplier support in enabling the manufacturer to establish appropriate Service Level Agreements and to obtain suitable documentation including high quality certificates of origin (COO) and certificates of analysis (CoA).

Discussion with delegates following Roy's presentation focused on adventitious agents and in particular, viral safety testing and viral clearance during processing. It was pointed out that some useful information on this topic could be found in cell substrate guidance established for biological products since the 1990s e.g., ICHQ5D (4), CBER 1997 (5), WHO 2010 (6), IABS (7). The issue of adventitious agents was clearly critical to demonstrating safety of biologicals in general, but was often not fully addressed by current cell therapy developers. It was concluded that that the Internationally accepted guidance on this topic in in ICH Q7 (8) was relevant for hPSC manufacturers.

References and weblinks.

1. https://www.drugfuture.com/Pharmacopoeia/USP32/pub/data/v32270/usp32nf27s0_c1043.html (Accessed 12 April 2020)
2. www.edqm.eu/ (Accessed 12 April 2020)
3. https://www.iso.org/standard/67897.html) (Accessed 12 April 2020)
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6. https://www.who.int/biologicals/Cell_Substrates_clean_version_18_April.pdf (Accessed 12 April 2020)

7. Petricciani J, Hayakawa T, Stacey GN, Trouvin J-H, Knezevic I (2017) Scientific Considerations for the Regulatory Evaluation of Cell Therapy Products. Biologicals, 50; 20-26. PMID: 28888427 DOI: 10.1016/j.biologicals.2017.08.011
8. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q7/Step4/Q7_Guideline.pdf (Accessed 12 April 2020)

NIH iPSC RPE trial, Shekhar Jha, CMC Manager, NIH, Washington DC, USA.

Shekhar Jha described approaches to sourcing raw materials for an 80 days autologous hiPSC manufacturing process with 2 cryopreservation stages for which an Investigational New Drug (IND) application had recently been submitted to the US FDA. The exposure to raw materials was significant as the early manufacturing stages took 80 days with two cryopreservation steps and a further 77 days for differentiation of patient derived iPSCs into retinal pigmented epithelial cells (RPEs) with in-process QC at day 25, day 40 in addition to final product QC. This protocol, which included cell seeding of a PLGA scaffold, had been trialled with 34 hiPSCs and reported by Sharma et al., 2019 (1).

Jha reviewed the critical materials included in the final product based on experience gleaned from a number of IND-enabling studies completed at National Eye Institute (NEI) and which included testing for sterility, stability, efficacy and toxicity. He reported that safety of donor starting materials were safety assured by donor screening by immunological assays for hepatitis B, hepatitis C, syphilis (T. pallidum), M. Tuberculosis, T. cruzi and West Nile Virus. Pharmacopeia grade chemicals such as water for injection, niacinamide, ascorbic acid and taurine were used where feasible, but Jha also listed more than 20 reagents for cell culture, differentiation and cryopreservation for which there was no Pharmacopeial standard. More than 20 raw materials used were of biological origin for which sources of non-animal origin had been established except for the use of fetal calf serum. In order to address potential safety issues from such reagents IND applications had included a table of raw materials giving quantities and concentrations of raw materials and validation of removal of fetal bovine serum amino acids and a number of other cell culture supplements from the product cells after up to four washes. For each reagent a Certificate of Analysis was included in the IND along-with Certificate of Origin for the reagents of non-animal origin. Jha warned developers to be cautious with so-called “GMP” reagents as this term may be used to “advertise” products as meeting quality system standards but does not necessarily include key safety tests. He gave a specific example where a bFGF2 reagent claimed to be GMP had not been tested for endotoxin.

Discussion with delegates following Shekhar’s presentation revolved around the various terms which inferred that products were made according to “GMP”. It was explained that the term Good Manufacturing Practice in the regulatory sense, only applied to the manufacture of a specific licensed therapeutic product and was not generally applicable to raw materials (including cell lines) as they themselves were not licensed products. However, GMP guidance and facilities established to meet GMP requirements could be used to make raw materials and Shekhar Jha emphasised that robust documentation to record all elements of raw materials sourcing and manufacturing was key to demonstrating quality and safety to regulators. Delegates noted that product developers considering international operation also needed to recognise that there may be differences in the specific requirements for GMP manufacturing in different regions.

Reference.

1. Sharma, Ruchi, et al. "Clinical-grade stem cell–derived retinal pigment epithelium patch rescues retinal degeneration in rodents and pigs." *Science translational medicine* 11.475 (2019): eaat5580.

Ajinomoto media qualification experiences with the StemFit culture medium in Japan, Akira Chiba, Associate General Manager, Ajinomoto, Japan.

Akira Chiba described the strategy of collaboration to create an prototype animal human material free iPSC growth medium, StemFit AK01, through a collaboration between Ajinomoto with their biotechnology expertise in cell nutrition, medium powder technology and analytical tools and CiRA (Kyoto) experience in iPSC culture, characterisation and preservation (1). This medium was refined to provide a culture medium StemFit AK03N, for use in regenerative medicine which was free of any materials outlined in chapters 3 & 4 of the Japanese Standards for Biological Materials (2, 3). This medium was approved for the growth of iPSCs form clinical use by the Pharmaceuticals and Medical Devices Agency in 2014 and made available to many Japanese academic and industry collaborators developing hPSC-based regenerative medicines in Japan and some international programmes. Akira also reported the process of independent validation of StemFit AK03N by the Cell and Gene Therapy Catapult in the UK where a stability study had demonstrated stable gene expression and karyology for the clinical grade iPSC RCiB10.
Akira went on to describe Ajinomoto's current development of an animal origin free differentiation medium supplement AS400 used with different differentiation factors to drive two phase ectodermal (using bFGF, AB301, LDN1931899), mesodermal (bFGF, CHIR99031, LDN193189, Activin A, SB431542) and endodermal (CHIR99031, Activin A, PI-103 LDN-193189) differentiation (postscript: the description of some growth factors has been further modified and the current product name is 'StemFit For Differentiation').
In Q&A Akira was asked wether the authorisation process was being developed for the US, and the speaker said this had yet to be addressed although the media were available in the US, EU and Asia.

References.

1. Nakagawa M, Taniguchi Y, Senda S, Takizawa N, Ichisaka T, Asano K, Morizane A, Doi D, Takahashi J, Nishizawa M, Yoshida Y, Toyoda T, Osafune K, Sekiguchi K, Yamanaka S (2014) A novel efficient feeder-free culture system for the derivation of human induced pluripotent stem cells. Sci Reports, 4, 3594. PMID: 24399248, PMCID: PMC3884228, DOI: 10.1038/srep03594
2. http://www.jpma.or.jp/english/parj/pdf/2019e_ch03.pdf
3. http://www.jpma.or.jp/english/parj/pdf/2019e_ch04.pdf

Cellartis experience in development and qualification of tools for banking clinical grade hESCs, Anders Aspegren, Cellartis/Takara, Goteborg, Sweden.

Anders Aspegren summarized Takara Bio's progress in developing an hPSC manufacturing capability, bridging from the establishment of a facility purpose built to meet the requirements of GMP in Japan in 2014 (later expended to over 14000m^2) to a GMP facility in Sweden focused on hPSC manufacturing, which became operational in 2019. The Swedish production work started in 2001 and went through several key stages of cell banking (2001), creation of the first "xeno-free" line (2005), media development (2008-2014), establishment of animal origin-free manufacture (2014) and granted a Tissue Establishment license (2017) and manufacturing license (2018). The current hPSC manufacturing process uses animal origin free growth media manufactured at Takara Bio in Japan. For qualification and validation Anders described the use of the EU GMP guidelines (Eudralex volume 4) (1) and in particular Annex 1, Manufacture of Sterile Medicinal Products, Annex 15 (Qualification and Validation) and performance of Quality Risk Management according to International Council for Harmonization ICH Q9 (see Part 3 EU GMP). He also pointed to new guidance (Specific EU GMP for Advanced Therapy Medical Product) (EudraLex Volume 4, Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products') that had been in force since May 2018 within EU and was being implemented in Swedish legislation.

Anders went on to identify the key steps and issues experienced by Takara Bio during the cell culture qualification process. It had been important to consider the use of expert guidance from both Japanese and European regulatory environments and Anders also reflected on the different perspectives that may be taken by different national GMP inspection processes, even between different EU countries. In addition, he explained that it had been important to have a constructive two-way interaction between QA and production groups and in support of this to seek quality assurance staff with existing cell therapy experience to cope with the different specialist knowledge required compared to traditional drug production. Furthermore, Takara Bio had found that whilst it was clearly important to recruit scientific staff with cell biology expertise, they also needed careful training in the principles of GMP which can seem very alien to academic researchers. Finally, Anders identified that close coordination with regulators had been a key element in making efficient and effective progress.

Assessment of cell culture component providers had been carried out according to a risk-based approach in which key assessment parameters had been: knowledge of the supplier, the type of material, component or services supplied, vendor questionnaires including site audits of vendors.

Anders Aspegren concluded with a review of the sequence of information and interactions with the regulators in the following sequence: 1) Institutional Review Board permission, 2) evidence of donor consent process, 3) contract with IVF clinic, 4) agreement with the tissue shipment company and the regularly updated import permission, and 5) Tissue Establishment audits (EUTCD) (every 2years) and Manufacturing License audits (every 1-3 years) both carried out by the Swedish Medicinal Products Agency (”Läkemedelsverket”).

In discussion with delegates Anders revealed that hESC lines derived specifically for cell therapy including specific consent for commercial development, would be made available for research and development.

Reference.

1. https://ec.europa.eu/health/documents/eudralex/vol-4_en

4) General workshop discussion session on validation of raw materials, Chairs Tenneille Ludwig (WiCell, USA) and Steve Oh (A-star, Singapore)

Speakers were asked to reflect on the most challenging issues they had encountered which hPSC product developers need to be prepared for. Responses included that:

- it was important not to be too enthusiastic in setting specifications which may turn out to be unrealistic during process development and validation
- product developers should dedicate adequate time to identify safe and reliable sources of raw materials and beware of quality claims which may not be substantiated on later investigation.
- identifying alternative suppliers to assure a robust supply chain can be very time-consuming but is important.
- the development of standards for raw materials continued to be a priority

Discussion focused on the need for careful risk assessment and evaluation of suppliers which should include suppliers willingness to undergo auditing, to assure traceability of reagents, facilitate robust risk assessment and verify claims of operation to certain standards. Delegates recalled experiences with suppliers of reagents that were purported to be “GMP”, “prion-free” and “xeno-free” but on more detailed and time-consuming investigation were proven to be unfounded claims. Some stem cell banks were initiating their own bespoke raw and starting material testing including a programme to screen hESC banks for prion agents (UK Stem Cell Bank).

Delegates discussed the potential problems of differences between regulatory jurisdictions. Experiences were shared from Europe and North America which demonstrated that the interpretation of regulations may vary even within the same regulatory zones and at the level of individual inspectors. Attention was also drawn to the potential for significant variation between donor consent procedures between one institution and another (an area where ISSCR was considering guidance). However, it was generally agreed by delegates that GMP certification applies to the final product, and not to raw materials or the production cell line. It was evident from delegates experiences in the EU that cell line master cell banks were considered to be starting materials (i.e., raw materials intended to form part of the final product). These stem cell banks were prepared under a license for the facility and its operation under the EU Tissues and Cells Directive (1) which prescribed procedures consistent with the principles of GMP. In the USA it was indicated that the cell you start with was the raw or starting material and that typically a cell line equivalent of a "Drug Master File" (DMF) would be required by the FDA for evaluation. A similar dossier called a "Cell Line Master File" had been described in an ISCBI publication (Andrews et al, 2015 (2)) which outlined key content for such a dossier. However, it was also recognised that the requirements for content and completion of a DMF may be specific to particular regulators. Delegates with experience in banking cell lines not derived in the banking centre emphasised the importance of a due diligence process to review all available information including donor consent and regulatory compliance for each individual cell line (for an ISCBI consensus see ref. 2.). It was noted by regulatory representatives that cell lines isolated in research backgrounds without full documentation, traceability and suitable facilities could require a significant amount of costly work to meet their requirements for the manufacture of a cell therapy product.

One of the speakers had indicated some key benefits of in-house manufacture of raw materials, but this was not necessarily feasible in all stem cell banks. Sourcing raw materials where the supplier had already carried out virus testing validation/qualification processes and possibly even viral clearance studies could help to reduce cell banking costs. However, it was important to assure the veracity of suppliers claims regarding suitability of raw materials for manufacturing purposes and it was recommended procedures should include setting clear specifications for individual raw materials, auditing suppliers at some level (depending on risk), quality agreements with suppliers and checking received materials against the specification.

Delegates reported experiences with various commercially-used terms for raw material quality "grades" and concluded that these terms and descriptions could be misleading and concluded that a crucial requirement was that suppliers should provide evidence for the standards indicated and that they are willing to work with users to meet the user specification and needs for supplementary information. Drug master files (DMF) were also in use by suppliers of raw materials (see above for cell lines) but as already discussed regulators may have very specific requirements for the details to be included in a DMF. Delegates also commented that completion of a DMF for all reagents may not be practicable or required by regulators and it was helpful to start with risk assessment for all raw materials and then consider the need for DMFs focussing on those materials which presented issues arising from complexity, stability, microbial contamination and other residual risks such as those where there was a special reliance on final safety testing.

Discussion on the application of definitions for raw materials, ancillary materials and starting materials revealed that clearly there were issues in relation to understanding of what these terms meant and some concern that there was variation in the terminology used in different jurisdictions and in addition, on how standards might be used and implemented by some suppliers. It was concluded that this could be an area for future consideration by ISCBI.

Whilst the responsibility for quality and safety of hPSC-based products would ultimately reside with the manufacturer who needed to have early discussions with regulators to ensure they have access to

all information that may be required in a cell line master file or DMF. However, the suppliers which included stem cell banks providing cells for clinical use, would still be expected to contribute to this information and assure traceability.

Delegates concluded that there could be considerable benefit in having a description of what would be needed to qualify an hPSC for clinical use in different jurisdictions and what consensus there was internationally on this issue. It was proposed by the session chairs that ISCBI should draft a white paper on some of the key regulatory terminology and the requirements for cell line qualification in different jurisdictions to give clarity for the early academic developers of hPSC products and the stem cell banks supplying them. It was also concluded that whilst it is important that the final product must be suitable for its particular clinical application, the whole process of manufacturing is important in assuring product quality and safety. It was also agreed that early engagement with regulators on cell source and raw materials was considered to be crucial to ensure the most secure and efficient path for the development of cell lines suitable for manufacture of cell therapies. This was considered especially important when manufacturers plan to move products across borders as this may require consultation with multiple agencies.

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The ISCBI workshop was followed by panel discussions on hPSC manufacturing coordinated by GAiT in collaboration with CIRM, CTRACS, HESI, ISCBI and ISCT. This is being reported independently.

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