Question & Answers from September 11, 2014 iPSC webinar

1. Q - The main issue with iPSCs at the moment is the embryonic or fetal phenotype. How can we address this to create a model more reflective of the adult phenotype?

Answer: The application of more sophisticated culturing systems has shown that cells begin to express more genes that are shown in vivo- a maturation process/aspect. In some cases, the advances in culturing involve the optimization of extracellular factors, changes in substrate, the extent to which three dimensional physiological niches are created as well as the co-culture of other cell types and in the spatial and numerical relationship in which they exist in vivo. There are also a number of small molecules that can be used to optimize a more mature phenotype. This is all dependent on the purpose and how they are used.

2. Q - What are the current or probable qualitative tests that can be done to determine safety of the iPSCs upon transplantation in humans?

Answer: For ipsc derived tissues (vs ipsc as the question states), the probable safety tests will be determined on a case by case basis. The fundamental concerns are around residual pluripotent cells in the final product causing tumor formation, so typically a longer term study of at least 6 months in an animal model is conducted to assess. Methods of assessing gene transcription (such as lin28) as well as looking at known pluripotency surface markers can be used to characterize the absence of pluripotent cells within the final differentiated product. Other safety concerns are related to the biodistribution, phenotype of the administered cells (e.g., do they change into a different cell population) as well as immunogenicity.

3. Q - What do you think is a realistic timeline for seeing iPSC cellular therapy trials initiated in the United States? (We have recently seen one initiated in Japan for macular degeneration.)

Answer: The answer will be quite dependent on the clinical indication. If the indication is a long lived indication (like diabetes) then the challenges for demonstrating safety will be quite significant. If it is a shorter lived indication (like ALS where there is a huge unmet need) then there might be a greater risk tolerance and a faster move into the clinic. In Japan once they start implementing, there will be some comfort about not testing every single cell.

4. Q - What is the potential for use of small molecule adjuvants for iPSC therapy?

Answer: There are applications for small molecules iPSc therapy. Before cells are administered, there are a number of examples where small molecules are used to increase efficiency as well as mature cells during differentiation. In vivo, depending on the cell therapy, small molecules could be used to improve functionality but the utility will need to be understood on a case by case basis. Clearly, there is a role of small molecule immunosuppressive agents when allogeneic cell therapy is being considered.

5. Q - Does donor screening / testing apply to autologous use of iPSC-derived products?

Answer: Donor testing and screening is not required for the use of autologous cells. If you do not perform donor testing on autologous cells there are labelling requirements that apply.

6. Q - Primary bio materials are manipulated to achieve hPSC and ultimate cell prod = handled by many people. What is the purpose of DONOR TESTING on the primary material when we should test the ultimate cells to ensure patient safety?

Answer: The FDA rules were created to cover a range of products including cell therapy, drugs and tissues for transplant, etc. We include safety testing of donors and testing of master and working cell banks as well as the final products themselves. All of these testing measures ensure the quality and safety of the product.

7. Q - For hESC cell lines that had a brief contact with irradiated mouse feeder cells when the cell lines were initially established, to what extent do the xenotransplantation product requirements will apply?

Answer: These cells are subject to the guidelines for xenotransplantation products because of their exposure to the mouse feeder cells. The answer about how the requirements will apply is dependent on the degree to which you are able to show that you have addressed any infectious disease concerns: What has the manufacturer done to mitigate disease transmission? Was there extensive testing of the cell lines for animal viruses? Etc. This is evaluated on a case by case basis.

8. Q - In the case(s) in which hiPSC-cardiomyocytes have been used to support a regulatory filing: were they used instead of or in addition to hERG screening, and if the latter: were the results the same or different?

Answer: The applications of ipsc-CMs in regulatory filings have been in support of human specific toxicity vs an application related to arrhythmia*. In the future, when ICH7B changes, my expectation (Speaker Kolaja) would be hERG screening would still occur but stem cell derived cardiomyocytes (As well as ion channel screens and in silico modeling) would be used to put the hERG results in a better context of what occurs in humans. The hERG screening will still be an early screening activity that we then set the stage for using more accurate, lower throughput models subsequently. **HER2-targeted liposomal doxorubicin displays enhanced anti-tumorigenic effects without associated cardiotoxicity*, 2012, Toxicology and Applied Pharmacology, Volume 262, Issue 1, 1 July 2012, Pages 1–10, Thomas J. Wickham.

9. Q - Are exemption requests for the use of cell lines prior to the May 2005 final rule made at the time of pre-IND, IND or BLA submission

Answer: If the cell lines were created before May 25, 2005, an exemption under 21 CFR 1271.155 is not required. However, the same scientific questions surrounding safety will still need to be addressed and submitted in the IND or BLA.

If the cells were collected after May 25, 2005, you should submit an exemption request before you start first in human clinical trials. Depending on the situation, FDA may allow use of the cells for the IND which would need to be followed by another request at the time of the BLA.

10. Q - Can you speak to the issue of heterogeneity with respect to hESCs -- is this a concern for FDA?

Answer: FDA is certainly concerned about heterogeneity as it pertains to the safety, identity, purity, and potency of the product. Therefore, characterization and control of heterogeneity is a critical element of quality control.

11. Q - What is the FDA's view with regards to requiring the stem cell industry to adhere to QbD, PAT guidelines (i.e., due the complexity of stem cell manufacture will the FDA ease up on the requirements outlined in the guidelines as it relates to validation lifecycle?

Answer: The use of modern manufacturing principles such as QbD and PAT are encouraged, but are not required.