Comparability for Regen-Med Products
When is comparability required

Minimally processed products. Eg: Bone-marrow transplants

Autologous processed products- Eg: ADSC

Allogenic Minimally processed products- eg: Cord Blood, Adult stem cell

Allogeneic large scale-
   replacement of MCB
   site to site manufacture
   lot to lot manufacture
   major change in manufacturing process
Change in cell line used
Historically FDA has addressed this by asking to demonstrate comparability

- Actual clinical studies - eg Bone Marrow
- In vivo preclinical studies. Eg: AAstrom
- Historical data eg; Cord blood
- In vitro data
  - Comparability of MCB
  - Matching release criteria
What we are asking is for clarity and proposed comparability criteria
Current Model of therapy using iPSC as an example
<table>
<thead>
<tr>
<th>iPSC Therapy models</th>
<th>One to One</th>
<th>One to Many</th>
<th>Many to Many</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Donor</td>
<td>Self</td>
<td>Healthy</td>
<td>Healthy</td>
</tr>
<tr>
<td>No of lines</td>
<td>1-3 clones</td>
<td>5-10 lines</td>
<td>&gt;100 lines</td>
</tr>
<tr>
<td>Regulated as BLA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Multiple products</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Fewer tests and tracking issues</td>
<td>Yes</td>
<td>More</td>
<td>Even More</td>
</tr>
<tr>
<td>Longer time to therapeutic product</td>
<td>Yes</td>
<td>Much shorter</td>
<td>Shorter</td>
</tr>
<tr>
<td>May be GLP</td>
<td>Possibly</td>
<td>Unlikely</td>
<td>Unlikely</td>
</tr>
<tr>
<td>HE exemption</td>
<td>Possible</td>
<td>Unlikely</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Consent straightforward</td>
<td>Yes</td>
<td>Burdensome</td>
<td>Burdensome</td>
</tr>
<tr>
<td>Immune suppression</td>
<td>Unnecessary</td>
<td>High per patient</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Cost</td>
<td>High/patient</td>
<td>Lowest</td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mahendra Rao LLC</td>
</tr>
</tbody>
</table>
One Line many products

- iPSC line
  - NSC
    - NSC
      - NSC as a therapeutic product
        - Dopaminergic Neuron
          - Astrocyte
            - GRP/OPC
              - Retinal Progenitor
                - RPE
                  - Retinal cells
          - Retinal Progenitor
            - RPE
              - Retinal cells
        - GRP/OPC
          - Retinal Progenitor
            - RPE
              - Retinal cells
      - Retinal Progenitor
        - RPE
          - Retinal cells
    - iPSC derived MSC
      - iPSC derived MSC
Our suggestion for the FDA to consider

Use the cell bank for biological product manufacture as a model

Cells are an important input material that should have a defined process for replacement at the MCB stage

New MCB should meet same specs as the old and the final product should meet the same release criteria

This should be released as a white paper or guidance for the industry

• This should allow the current models of therapy to be implemented with clarity and would integrate well with previously approved products.

• It would be of particular important to adult stem cells and allogenic small scale manufacture where intermediate working banks are made
Summary

- It's possible
- It is worthwhile
- Problems are solvable
- But it will take coordination