Table 3: Cell and Gene Products - Control Strategy

Session 1:
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Session 2:
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SCOPE:

While the principles of control strategy for cell and gene therapy products are the same as other parenteral biotherapeutic, there are unique challenges with these newer modalities. Control of raw materials, analytical reference standard, stability testing, and supply chain and making manufacturing changes create unique approaches for the cell therapies. For gene therapy products templated approach to control strategy should be feasible for accelerating development. In this roundtable the phase appropriate controls for production, testing and distribution of cell and gene therapy products will be discussed.

QUESTIONS FOR DISCUSSION:

1. What are the unique aspects of raw materials control for cell and gene therapy products?
2. What are the unique aspects of progression of control strategy for cell and gene therapy products through clinical development?
3. Envisioning a templated approach to manufacturing and testing -what are your thoughts?
4. How would one demonstrate comparability of cell and gene therapy products?
5. What are the challenges with gene and cell therapy products that you are facing?

DISCUSSION NOTES:

Session 1:

While the principles of control strategy for cell and gene therapy products are the same as other parenteral biotherapeutics, there are unique challenges with these newer modalities. Control of raw material, analytical reference standard, stability testing, and supply chain and making manufacturing changes create unique approaches for cell therapies. For gene therapy products templated approach to a control strategy should be feasible for accelerating development. In this round table the phrase appropriate controls for production, testing and distribution of cell and gene therapy products will be discussed.

Raw Material Control

Small batches are a constraint

What are some of the unique aspects?

- Biggest variability is the patient – media, additives, in many cases no qualified scale down model
- Very limited in the materials that you can work with
- May have country specific requirements around donor
- Different between cell therapy and gene therapy – although both are small batch
- Development moves very quickly
- Very limited time to understand your process

Cell Therapy – If you want to move to a different country, you will need to build to CMOs and they may not be able to access the same raw materials – or perhaps the sponsor needs to provide. Need to watch for "supplier equivalents."

For Cell and Gene Therapy – When HSA is used, often regulators will ask if you have used on of the lots that is undergoing recall in your product. Regulators are looking for you have this information available, at the point that you recognize that you have used the material and the batch is long gone – may need to let the clinical program know

Is there a generic cell line? Most are using the "healthy donor" which has its own level of variability; Minimum of 3 healthy donors needed for testing

What are the Unique Aspects of the Progression of the Control Strategies?

- Very short periods of time; cannot test 100s of patients

Close interactions with the FDA are needed – they will give you feedback on if what you are proposing is sufficient.

Compare to therapies that are already approved?

Comparability?

Need some sort of window of your attributes – need to do the work upfront with healthy donors. On Cell Therapies – FDA wants to know what the mix of cells. What is the mix of cells at the beginning and after your process? If you end up with the same fraction of cells before and after could help with comparability. How much have I changed from what came in, rather than what did I end up with? FACS assay? You want to test upfront and have material set aside to do this

Gene Therapy for example – would test of adventitious agents

Cell Therapy Patient Specific for example – how to you make sure that you haven't introduced adventitious agent. You would want to make sure that you didn't introduce something in the vector

Any FDA guidance – Gene Therapy – Yes this is available

Oncolytic Virus is unique from Gene Therapy

What are you seeing for potency assays?

Is gene expression enough, or do you need to see function of the protein expressed. This may depend on if it's a novel protein or not.

Cell Therapy needs a potency assay

Reference Standard is an ongoing issue/concern. "Pooled positive Control" example – to use for a few rounds of the assay

Not uncommon for the read out from the Potency Assay after the patient has received the product – in many cases you are up against a 2-week cycle time.

- Release Criteria
- Cell Viability
- Cell Number

Identity – especially on patient specific to make sure nothing has been mixed up. Typically controlled by labeling and tight procedures

There is typically an "interim" CofA and then a final CofA.

Template Idea – Are we at Platform Stage Yet?

Are we at a stage that we can "create" the mAb case study for "Cell Therapy"

AV Therapies – some efforts to go through a primary cell line which is a start. Downstream – affinity purification, ion exchange.

Formulation – some unique formulations

Analytical Side-

- AV Therapies-
    - AUC methods used as a characterization method currently – typically works for all serotypes, UPenn may be using this as a release assay.
    - SEC has some issues with sero dependent; has issues with some -see monomer but not aggregates; we know they are there but we are not seeing them.
    - DLS – semi quantitative method; as aggregation assay is being used
    - TEM – can use for empty-full but not aggregation

SEC and Ion Ex, and Reverse Phase (Purity)and other methods are being used to put together a "package" Some customers asking for peptide mapping depending on their product

- ID Testing
  Genome confirmation – Next Gen Sequencing
- Capsid – LC /Mass Spec

Purity Ratio and Empty/Full Ratio is expected

Is anyone working on mRNA? How is FDA looking at it? Likely would be looking at it as a Gene Therapy. Or as a vaccine?

- There is a use of live bacteria as a gene therapy – there is a guidance on this.
- Is anyone hearing about gene editing products
- Yes, there are some clinical trials started.
- Is anyone trying to combine multiple DP batches more than one batch into a single patient for gene therapy?
- Not much familiarity here

Cell Therapy: Lenti-virus – is it a raw material, a DS or a starting material? Not clearly defined. Could use a guidance here. Regardless – they are looking for the same information against it and so may not be as important what you call it

- For a long time, people were writing Cell Therapy as a "DP" only – FDA does want a defined DS now
- Juno has a frozen cell therapy, so they are able to use a matrix approach to determine stability
- Allogeneic Cell Therapy Products – yes there are some companies out there

<u>Session 2</u>:

1. What are the unique aspects of the raw material control for cell and gene therapy products?

- Quantity requirement is very small, many materials are single sourced, donor material may not reflect the true model
- Most cell therapy are focused on the patient cells. Comparability needs to be shown between healthy and patient donors.
- Is there enough data available to characterize the healthy donor: head to head experiments are needed?
- Try to qualify the in-coming material, since cells go through chemo and various other treatments.

2. What are the progression of the control strategy (phase appropriate strategy)
   - Control of process needs to be phase appropriate: Process-product coming from academic institution is very different and then needs to be converted into commercial process
   - Industry Assay qualification, process qualification does not exist earlier, now academic places are doing much better job in the qualification of method and process. Data integrity is still concerning
   - Making of MCB must be more stringent. Expectation needs to be very clear for Ph3. There should be a clear path on what are the things can be changed, what are things can wait.

3. Envisioning a templated approach to manufacturing and testing: what are your thoughts?
   - Templating approach can be done for manufacturing and testing. What strategy is needed for clinical and what strategy is for commercial needs to be clarified.
   - There are some vectors that can be used to standardize the process. To some extent it can be platform approached.

4. How could you demonstrate the comparability for cell and gene therapy products?

   - Showing comparability head to head is challenging.
   - Freezing the samples at <-70 C is challenging. Stability: 24-48 hrs stability has been observed. Freezing has been done and product is stable at -70C by one company. Novartis whole supply chain is frozen. You need to show quality attributes are maintained throughout the freezing and thawing.
   - Methods needs to be updated throughout the life cycle of the products. Methods needs to be validated for Ph3 and commercial testing; Ph1 no validation needed only qualification of the methods
   - Stability are being done with the patients' cells. EMA regulations have different expectation
   - RS or controls samples are needed. There is no RS vector can be used. AAV can be done for characterization
   - Sterility: Rapid sterility methods would be nice to consider, currently 2 weeks is the typical timeline for sterility testing. Cell need to be infused in the patients within 3 days of manufacturing. The sterility is done using the In-process testing. Shipping is done under quarantine and after it is released, no problem to frozen products.
   - Comparability for cell and gene therapy: side to side comparability, release assay and characterization assay for viral vector gene therapy: FDA is comfortable with analytical comparability.
   - Clinical comparability is needed for cell therapy products. Cell therapy is living drug, infusing the drug that can grow 1000s-fold. Expansion fold is correlate with real model to predict
   - Variability comes from Vector, MCB, process and methods

- 80% of the variability comes from the patient
- 20% variability comes from the analytical and process variability
    - Depend on the product knowledge adding the animal study needs to be added.

5. What are the challenges with cell and gene therapy that you are facing?
    - Potency assays (predictive and qualitative)
    - Comparability study
    - Finding a good CMO is challenge for next 10 year
    - Limited vendor for raw material