CONSIDERATIONS FOR THE TECHNOLOGY TRANSFER OF GENE AND CELL THERAPY PRODUCTS.

PART 2

Pitfalls are and how to avoid them in your manufacturing process

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Timing

Biopharmaceutical manufacturing is known for its complexity, but gene and cell therapy manufacturing is an order more complicated. If you address manufacturing requirements too late you may then find that you need to change the process to make it economically or even technically viable and you face a huge risk with regard to comparability of products made by the original and new processes. Changing the process at this stage will incur significant time and cost penalties.

Issues:

- Not thinking about what may be needed in the future
- Not thinking of the end game at the beginning
- Not starting "technology transfer early enough
- Not performing a though risk analysis early enough

Risk Analysis / Manufacturing Assessment

It's important to perform a strategic manufacturing assessment by reviewing the business goals for your product and identifying areas that can be invested in immediately, and areas where investment can be delayed.

For example, perhaps risks can be managed by ensuring that manual processes are changed at an early point to those that can easily be automated at a later date, or raw material risks can be reduced by ensuring that GMP grade materials are used whenever possible to start with minimising the risk of having to repeat development and comparability studies at a later date.

Raw Materials

- Not using GMP grade materials (e.g. contains no material of animal origin). In this instance, raw materials can also include lenticular viruses
- Not considering If the raw materials selected can be supplied in the quantities supplied for commercial manufacture
- Not considering if the selected raw materials can be supplied for the next 20 years
- Not considering the grade / purity of the raw materials – are you absolutely sure that the effect you are seeing is not due to impurities in the raw materials?

Analytics

The analytical processes used in the development of gene and cell therapy products are vitally important. A major challenge is developing suitable analytical assays to define and monitor the consistency of a therapy's functional attributes for product release after manufacture. Appropriate analytics are especially needed for autologous therapies to assess potency and to be used for comparability across batches for a single patient, or across multiple patients. It is essential that these analytical techniques be non-destructive, or at least do not use up too much of the product.

Some of the pitfalls regarding analytical procedures can be associated with:

- Not ensuring that the required analysis methods are available at the right time and available at the CMO. Some CMO's outsource / sub-contract their analytics out.
- Not keeping in mind that the analytics are a GMP process in their own right – and being so if new methodologies have to be developed – who has the IP on the analytical method?

Many analytical strategies depend on the use of assays that are destructive and it can also be a hindrance if material is limited (though less of a problem if patient bio-samples can be banked for later use).

Sampling

Some of the issues around product sampling are:

- Developing an appropriate sample plan so that as the product develops, you don't end up using all the product for stability testing and analytical tests – leaving none for clinical trials.
- Take the right samples at the right point in the process, and test the right parameters
- If possible, think of taking samples prior to concentration phases.
- Don't leave potency and comparability to ph3 – it's very tempting to save circa £200,000 during phase 1 rather than leave to phase 3

Documents

- Make sure your documents are up to date and relevant to the products development history and manufacturing process, many products do not even have a cell history.

Manufacturing

- Not manufacturing according to QbD principles – do you know what your products design space is? If not, can you really claim to understand your products manufacturing process, and are you happy to pay the cost and time for a CMO to do that for you?

Planning For Industrialisation

There are currently no "one-automated-platform-suits-all" approaches for commercial-scale development, and manufacturers are instead dependent on manual, skilled specialists working

in accredited cleanroom facilities – which inevitably makes manufacture prone to human error and processing variability.

There are however automated solutions for some of the unit operations.

Whether the manufacturing process is to be scaled-up or scaled -out the successful commercialisation of a product will depend to a large degree on how well it can be automated. A major late stage problem many companies now face is that they are now looking to automate a labour-intensive process which cannot be automated and they now find that they have to re-develop the process (and suffer the time and cost implications). By thinking ahead and planning for industrialisation, companies may be able to save themselves time (typically TWO years) and money (£/$ millions).