

EXPERT INSIGHT

Impact of raw & starting materials on the manufacture and regulation of gene & cell therapies

Understanding the definition of raw and starting materials and the impact this has on the regulation and commercialization of your gene and cell therapies is essential. To help shed light on this critical topic, *Cell and Gene Therapy Insights* spoke with members of the CMC team (Richard Dennett, Valérie Pimpaneau and François Gianelli) at Voisin Consulting Life Sciences who partner with Biotech, Pharma and Medtech manufacturers to develop, register and launch innovative products in North American and European markets.

Q What are raw, starting and ancillary materials in the context of cell and gene therapy?

This is a good question for which today the response is in fact not necessarily straightforward and may vary depending on whether we consider the EU or US. From an EU perspective, the definition of “raw materials” and “starting materials” applicable to Advanced Therapy is provided for in Part IV of the Annex to Directive 2001/83/EC on the Community code relating to medicinal products for human use (Directive 2009/120/EC).

Materials used during the manufacture of the active substance (e.g., culture media, growth factors, etc) and that are not intended to form part of the active substance shall be considered as raw materials.

Material forming an integral part of the active substances part shall be considered as starting materials.

The positioning of starting material will vary depending on the nature of the product.

Due to the various challenges of testing the quality of cell and gene therapy products compared to other biologics particular attention is placed on the quality of raw materials. In Europe, the EDQM published a General Chapter dedicated to quality expectations (European Pharmacopeia 5.2.12 ‘raw materials of biological origin for the production of cell based and gene therapy medicinal products’)

In the US, Raw materials are defined in USP <1046> as ALL materials used in the manufacture of cell and gene therapy products (cells, tissues, matrices, media, buffers, etc). Ancillary materials are a subset of raw materials that come in contact with the cell or tissue product but are not intended to be part of the final product and equate to raw materials definition in Europe.

Whilst these definitions certainly help in delineating between a raw and a starting material, it's not entirely black and white when it comes to a specific cell and/or gene therapy. We tend to approach this issue on a case by case basis for each therapy as the boundary of starting and raw materials can vary to a degree depending on the type of cell and gene therapy you are manufacturing. We therefore aim to demarcate starting and raw materials very early on in development.

Q Can you expand upon what impact the type of gene therapy has on the positioning of materials?

With regard to gene therapy, we need to understand what type of gene therapy we're working with i.e., *ex vivo* or *in vivo* for example. The following examples can provide us with an interpretation only for the purpose of this interview and shouldn't be viewed as being definite since raw and starting materials is defined very much case by case.

For an *in vivo* gene therapy consisting of viral vectors, the starting materials are the components from which the viral vector is obtained, i.e., the master virus seed or the plasmids used to transfect the packaging cells and the master cell bank (MCB) of the packaging cell line.

As an example, for an adeno-associated viral (AAV) vector, the vector unit is usually the Drug Substance and clearly forms part of the actual drug product. But now let's look at the plasmids involved in establishing the AAV vector construct: we've got the transfer plasmids which contain our transgene, a helper plasmid, and then an AAV genome plasmid containing the rep and cap genes. Therefore, in this particular example we could describe all of these plasmids as starting materials, since they all contribute and form, via a packaging cell, the final product.

For an *ex vivo* gene therapy product such as genetically modified cells, the starting materials shall be the components used to obtain the genetically modified cells, i.e., the starting materials to produce the vector, the vector and the human or animal cells. If a lentiviral-based system is used as starting material to modify the cell for example, we need to consider that it is constructed from several contributing plasmids. In that case, the plasmids being the starting material for the lentivirus which is itself a starting material could be considered as being raw materials in theory. This being said, the plasmid containing elements that will form the integral part of the

Drug Substance (i.e., the transgene) is to be considered starting material. So positioning each of the components entering in the production of an ATMP is quite important and in some cases not so trivial.

Q So it really is a case-by-case basis whereby you have to dissect a manufacturing process to find clarity?

I think that's very true to say. Positioning each element (starting material, raw material, but also Drug Substance and Drug Product) is a particular and important project step which takes time and a good understanding of the product and process to properly unravel.

Q Why is it so important to have this strict positioning?

This positioning will lead to specific requirements in terms of Quality Control and GMP and different levels of compliance are expected depending on the classification.

It will also guide the organization and level of details to provide in the Module 3 for the application dossier organization, the characterization data to be presented, the testing strategy, and even the comparability plan supporting potential process changes in the course of development.

The key driver is that everything needs to be controlled, consistent and reproducible in terms of the manufacturing processes. If we consider a risk based approach, your starting materials are critical components that will directly feed through to impinging upon the critical quality attributes of your end product, whereas the raw materials support the manufacture of that particular product and would mostly have a less direct impact. That's another distinction between the two.

Ultimately it's a case of applying best logic based on risk.

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Q Another common struggle is regarding the use of GMP and non-GMP material during manufacturing?

If we consider Annex 2 of the GMP guide, concerning the manufacture of biologic active substance and medicinal products for human use, there is an illustrative guide to manufacturing activities which is an incredibly useful table that provides clarity regarding the requirements for current Good Manufacturing Practice (cGMP) and when it comes into play for different product classes.

If we again take the example of an *ex vivo* gene therapy, it's clearly indicated that the donation, procurement and testing of cellular starting

materials can all be carried out as non-cGMP. As soon as we move into the manufacture of the vector, cell purification and processing, creation of master cell banks or viral seed stocks, then from that point onwards we should be controlling all of these aspects under cGMP.

Of note, a new GMP for ATMP guide is currently being proposed and addresses amongst many other topics the need for flexibility on GMP implementation at early stage of development.

Q There's a lot of different things put out there in terms of the 'grade' of media for example full GMP, mid GMP, research grade. Do you feel there is clarity regarding the grade of material required?

We've been lucky enough to be involved in conducting quality audits over the last few years and thereby gaining a good understanding of the various materials used in cell and gene therapy manufacture.

Suppliers often offer "Research Grades" raw materials for early development and "GMP Grade" materials produced under a more stringent quality system. It's important however to understand that, unless a raw material

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is produced as an active substance or drug product (like human serum albumin for example), suppliers will not obtain a formal GMP Certification through inspection by Competent Authorities. Hence the denomination of GMP grade for raw material can be misleading and should be considered with caution. It often means that suppliers have used 'practices and principles' of cGMP for their production at their own discretion but does not necessarily mean GMP certified. More and more often, "clinical grade" vs "research grade" terminology is used.

From a cell and gene therapy manufacturer perspective, you should have a supplier/vendor qualification program in place. Any raw materials you use should be controlled as an integrated aspect of your quality system, which would normally entail a quality audit of the supply company and the particular material you're looking to use within your manufacturing process.

A quality audit will give you a real, and not just a paper insight into the make-up and quality of each of your materials. Say for example you're using a cell culture medium, they are often highly complex with a whole variety of constituent components including growth factors, recombinant sources.

For raw materials it's important to not just take them at face value – even if they are indicated as being GMP, we'd still evaluate them under a quality system to ensure they're actually fit for human clinical use – which is the

level of scrutiny we need to moreover apply in terms of both quality and clinical applicability.

Finally, in certain cases some of the materials being used in your manufacturing process could be something that can't be obtained from anywhere other than a university or research lab for example, which we find happens from time to time with ATMP products. In this situation we would have to quality and risk assess the raw material to ensure it comes from a source that is always going to be obtainable and from a quality perspective that it meets the standards required in terms of purity and impurities and is a consistently produced product. So I think there are very different types of raw materials which all need careful consideration. They're all case by case. And for each one, and certainly if we're using say an *ex vivo* cell in gene therapy, in that respect we have to be extremely careful in terms of the quality and clinical applicability of the products that are being used.

Q One of the biggest issues about when to start using GMP materials is the impact on cost. Could you share your thoughts on the impact raw or starting materials could have on commercial viability?

I think if we are looking at most conventional product manufacturing, one of the key goals is to eventually bring down the cost of goods at the commercial end of the scale and of course one way to approach this is to look at sourcing cheaper materials from different suppliers. In the case of cell and gene therapies in particular, I think we have to be very careful in our attempts to bring down the cost of goods because the source materials are key components of our final products. We have to be extremely careful with the quality of media and raw material used for cell and gene therapy because we can't perform end stage sterilisation, or viral clearance and activation stages.

In addition, starting at the time of first-in-human and clinical development, regulatory authorities will always ask for the highest quality grade/standard available for each material, disregarding the costs. Coming back to the human albumin serum example, since it is available as a Medicinal Product, authorities will not allow the use of research grade human serum albumin for the any clinical batch intended for human use.

Therefore, there's not as much opportunity to drive down your costs of goods at this point in the supply chain. It's more likely that as we move to larger scale production of allogeneic therapies then you can maximize the benefit of economies of scale during the post marketing phase.

Q With the field moving at such a pace do you think the regulatory guidance is keeping up?

Despite this fast pace I do feel the regulatory guidance is keeping up. We're very lucky in the EU in particular in that there's a lot of regulatory guidance out there that we can crucially use for cell and gene therapy

products there's a lot of flexibility afforded by the regulatory agencies who are acutely aware of the challenges involved.

The implementation of the risk-based approach also allows adapting the development of cell and gene therapy based on your product characteristic and proposes a path forward based on risk and risk mitigation. We have to really examine everything we're using – from the raw materials, the genetic construction, and the actual gene therapy itself, to evaluate at the risk-benefit ratios and how we control that - all the way through the manufacturing process.

What's great is that the regulatory agencies have a reasonable open door policy whereby you can consult with them at certain stages throughout the development of your product, via Scientific Advice meetings. There is also a Certification Procedure unique to cell and gene product allowing to present early quality and non-clinical data to the EMA and obtain a first assessment of data generated to date and a certification.

If we look at the guides in place for cGMP, then as an example the European Commission put out a 'stakeholder consultation on the development of cGMP for ATMPs' in 2015 and propose a new GMP Guide to try to address an issue that's quite specific to the cell and gene therapy sector – the fact is that in reality most developers are very much small scale, or possibly even operating out of universities or hospitals. Therefore it's very difficult for them to put in place and operate cGMP to the 'nth degree' as they just don't have the bandwidth, and we also need to consider the initial crossover of non-cGMP manipulations of biological material where this occurs - often under the same roof.

This consultation is in essence saying "we're still going to follow cGMP, but we're going to make it a level of cGMP that's more accessible for ATMPs at early development stage, so as to ensure that hospitals, universities and smaller-scale facilities with less resource and infrastructure can readily accommodate this and initiate ATMP development." Of course there are two 'views' discussed – those who are hard-line cGMP, 'why create another quality layer?' and then a number of companies who of course would like to see a more accessible approach to cGMP, whilst maintaining standards. I think this is a great example of where the regulatory bodies are keenly aware of the difficulties in commercializing cell and gene therapy products in the real world and are looking at workable opportunities to overcome these.

Q You mentioned the EU and FDA – are there big regulatory differences between the two territories?

I think there are some differences between the US and the EU in particular up to Phase 1 stage where we generally see more flexibility from the FDA. In the EU the fully blown cGMP is required close to the outset, whereas in the US they are a bit more 'relaxed about the transition to cGMP and when it needs to occur.

Ultimately, moving into Phase 1 and subsequent phases through to commercialization, the EU and US are pretty much aligned in terms of cGMP requirements, quality, safety, testing etc. and we see that the overall time for development up to commercialization is the same. In fact recently, the EU and US signed Mutual Recognition Agreement on GMP inspections in February 2017, which enters into force on 1 November 2017.

In terms of clinical development and Marketing Authorization, the FDA is responsible to approve INDs as well as the BLA. In Europe however, Marketing Authorization are approved by EMA but Clinical Trial Applications are handled at a National level by each Member State which often translates into more complexity, specific country requirements and in some cases lack of harmonization between Member States.

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