CELL & GENE THERAPY INSIGHTS

VECTOR CHANNEL:
RAW MATERIALS

PODCAST INTERVIEW

Identifying and mitigating risks in the viral vector supply chain

CLAIRE WARTEL has a PhD in Molecular Pharmacology and Pharmacochemistry from the University of Strasbourg (France, 1999). After several post-docs in different prestigious universities, Claire joined Polyplus-transfection in 2004 as Cell Biology project leader and participated in the development of our flagship product jetPRIME®. Claire has taken Quality responsibility since 2007, and nowadays manages the department of Quality and Regulatory Affairs.

ULISES VILLAVICENCIO attended California State University, Long Beach (CSULB) where he earned a Bachelor's Degree in Anthropology and focused on Archaeometry. Ulises participated in numerous archaeological research projects, domestic and international, and assisted in various analytical projects at CSULB's Institute for Integrative Research in Materials, Environments, and Societies to further analytical research in Archaeometry via chemistry-based applications. Ulises applied his education and experience in Quality test environments where he then expanded into the auditing field in 2015. Since then, Ulises has focused his attention on improving Quality and Compliance programs for the security and assurance of patient safety, where he manages the Supplier Qualification program in his current role.

Cell & Gene Therapy Insights 2019; 5(10), 1339–1346

DOI: 10.18609/cgti.2019.139

Q The commercial scale manufacture of viral vectors presents a number of challenges for cell and gene therapy companies. What do you view as the critical pain points in this transition?

CW: As a key supplier of transfection reagent for the cell and gene therapy market, we are currently facing an increase in demand in terms of volume of supply and also in terms of supplier qualification process and regulatory support.

These aspects are manageable, but in the near future, with more and more companies moving to commercial-scale manufacture it could become a critical pain point. As you can imagine, moving to commercial scale means a higher quantity of raw material for the scale up of the manufacturing process, and a greater level of regulatory support for submission of market authorization.

That's why gene and cell therapy companies need to organize themselves in order to secure their supply chain of raw material.

UV: I believe some of the key components are not just those associated with shortages of key raw materials but also in final yields obtained due to inefficient downstream processes. For example, some of your purification processes, and ultimate potency are currently creating pain points for many cell and gene therapy companies.

Q There's a great deal of discussion around the quality of raw and starting materials that are required at the different stages of product development. What impact can the quality of your starting materials have on vector production?

UV: Throughout the field the quality of starting materials can have a significant impact on the final product. A rather simple example that comes to mind is contamination. Raw and starting material manufacturers typically offer more than one product, therefore understanding their manufacturing and process contamination controls is critical. For example, human interactions with a manufacturing process and how well you change over at the end of each manufacturing run is a key indicator of positive quality output.

So this is one significant impact that's going to have on the process and quality.

> "We launched the very first global GMP transfection reagent for the gene and cell therapy market ... and immediately received a great level of interest from all of our customers."

CW: At Polyplus we have regular discussions with our customers around the quality of raw materials for the different stages of product development.

DOI: 10.18609/cgti.2019.139

We provide a transfection reagent called PEIpro® at three different quality levels: PEIpro®, PEIpro®–HQ and PEIpro®–GMP.

You have to know that each quality grade has its own market from process development going through clinical trials and up to commercialization.

We guarantee the same vector production yield whatever quality of PEIpro® is used, ensuring a smooth transition from the process development through to commercialization.

In fact, the different qualities of the transfection reagents we propose are related to quality control, traceability, quality environment and regulatory support. But definitely our customers have to be assured that they will get the same vector production level when using one or the other quality grade PEIpro® products, otherwise they would have to fine tune the manufacturing process at each step of the product development, and this is definitely not manageable.

Q At what stage do you typically see companies starting to think about using GMP grade materials in their manufacture? Is it early enough in your opinion?

CW: This question is really interesting, and the answer is really customer dependent. The vast majority of our customers request a GMP-grade transfection reagent.

We launched the very first global GMP transfection reagent for the gene and cell therapy market, less than 1 year ago and immediately received a great level of interest from all of our customers, independent of their product development phase.

Regarding the potential reasons that influence a company's decision to move to GMP-grade raw materials, we have observed that when a gene and cell therapy company decides to use a GMP-grade transfection reagent, it's very often linked to a mature risk-based approach on their side. They deeply need to decrease the risk of their raw material supply chain.

Manufacturing GMP-grade raw materials ensures that the manufacturing process has been validated. As such, customers are assured of high lot-to-lot consistency and reproducibility, which greatly limits any impact on their own manufacturing process.

In addition, using GMP-grade raw materials is linked to a stronger relationship between gene and cell therapy manufacturer and the supplier. For example, the qualification process of the supplier, signature of quality and supply agreement, and having a secured supply chain allows the gene and cell therapy manufacturers to reduce risks relating to the sourcing of raw materials such as shortage of supply or any other critical issue.

UV: I second Claire's response for the first portion of that question; however, it's difficult for me to fully address this question without understanding the specific goal of the company. Perhaps it may sound a little cynical, but it's no surprise that some companies seem to bring a product beyond Phase 1 to ultimately become acquired by a larger entity.

With this in mind I believe some companies tend to shift to GMP-grade materials at a later phase. Now that being said a company with a strong focus on scaling up to commercial grade manufacturing will surely seek GMP-grade material much sooner rather than later.

I often receive feedback from manufacturing stakeholders that budgeting seems to be a key factor as to why they may opt for non-GMP grade solutions.

Q What guidance is provided by the regulatory agencies in terms of the quality requirements for your raw materials? Is there any confusion around this issue?

UV: There's certainly plenty of guidance that can be referenced, for example you look at 21CFR 211 and 210.A4, ICHQ10, and the EU Commission directive 2003 94EC.

However, I think we can all agree that when considering the requirement for raw materials, some of the requirements can be rather vague or high level. I strongly believe that the ticket to changing or improving raw material requirements is via risk assessments.

By performing assessments of materials based on risk, a manufacturer is able to soundly and objectively justify the raw material program, and assign criticality. One obvious implication of confusion around requirements can be an inadequate incoming testing and acceptance program and a situation such as this can be detrimental to the final product.

"...the ticket to changing or improving raw material requirements is via risk assessments."

CW: From the European point of view I can highlight the Part 4 of the GMP guidelines specific to advanced therapy medicinal products (ATMPs), adopted by the European Commission in November 2017. Here you can find a many of the current requirements concerning the quality of raw material, for example in sections 7.10 and 7.13, where it is written that the quality of starting and raw material is a key factor to consider in the production of ATMPs.

DOI: 10.18609/cgti.2019.139

It is also written that particular attention should be paid to avoid contamination and to minimize the variability of the starting and raw material. Using GMP-grade raw material will definitely address these two requirements. In the same section of these guidelines it is also clearly stated that while raw materials should be of pharmaceutical grade, it is acknowledged that in some cases only raw materials of research grade are available. And also that the risk of using research grade materials should be understood, including the risk to the continuity of supply when larger amounts of products are manufactured. Meaning that using research-grade raw materials is a risk taken by our customers. As soon as GMP-grade raw material is available on the market they should switch to this.

I think it is critical for the gene and cell therapy manufacturer to comply with this requirement in order to obtain their marketing approval and certainly we see no confusion at all around this topic.

Q The cell and gene therapy supply chain is incredibly complex when compared with traditional biopharma, how can developers mitigate some of their risks across the supply chain?

UV: I think auditing agreements can serve as a strong tool to assist in the mitigation of supply chain risk. While ensuring robust controls in a supply chain process amongst adequate resourcing should consist of strong forecasting, redundancy in suppliers wherever possible of course, accurate cycle counting, material controls, and training, which should also be assisted by a solid inspection program that shall detect potential risks prior to the manufacturing stream.

CW: Sourcing GMP-grade raw material is associated to a deeper interaction and closer cooperation between gene and cell manufacturers and suppliers. We at Polyplus adapt our support according to the needs of each of our customers, as Ulises highlighted, we are used to entering into supplier qualification process, meaning that we are qualified either through paper-based questionnaire or more and more through on-site audits.

We are also used to signing quality agreements but also supply agreement if needed. It is true that more and more customer want to secure the supply chain by sharing annual forecast with us. It really is a good way of mitigating risk.

For us, it is easier to plan manufacturing campaign having this annual forecast in mind. And from a customer point of view they are assured they will be delivered on time, meaning that they will not delay their cell and

gene therapy product manufacturing. While other, less organized customers, will take the queue for the supply of their transfection reagent.

Q How does Polyplus work with clients as they move through to commercialization? And can you share with us any future development plans to further support the growth of this industry?

CW: At Polyplus we build strong relationships with our customers from the very beginning. And it is visible in different departments, scientific and technical support, business, quality assurance, supply chain and logistics.

Usually it starts at the very beginning of their product development, so when they move to commercialization a strong partnership is already in place. They are used to contact our amazing scientific support team in order to get optimization advice for their transfection step for example. They have secured their supply chain by sharing annual forecast with us, quality and supply agreements are in place in order to fulfil regulatory requirements, qualification process of Polyplus as an approved supplier is finalized, etc.

And regarding future development plants, our outstanding R&D team is actively working on new generation transfection reagents in order to increase the vector production yield and decrease the volume of DNA needed, with still high-quality environment. And it is true that we are also developing more and more analytical methods around our transfection reagent in order to address regulatory requirements.

UV: I would like to add that I fully recognise the committment Polyplus has invested into our working relationship - Claire's quality team at Polyplus have been highly transparent and accommodating to ensure Audentes continues to be supported with the supply of quality material. I know from my experience with other vendors that this is not always the case and so working with Polyplus has been a breath of fresh air.

AFFILIATIONS

Claire Wartel
Director of Quality and Compliance,
Polyplus-transfection

Ulises Villavicencio
Quality Auditor,
Audentes Therapeutics
San Francisco, CA, USA

DOI: 10.18609/cgti.2019.139

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

Acknowledgements: *None.*

Disclosure and potential conflicts of interest: *The authors declare that they have no conflicts of interest.*

Funding declaration: *The author received no financial support for the research, authorship and/or publication of this article.*

Article source: Invited.

Interview conducted: Sep 16 2019; Publication date: XXX.

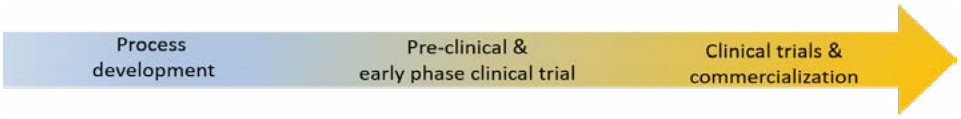
PEIpro® product range

Looking for a scalable transfection reagent to produce viral vectors for Gene & Cell Therapy?

Try PEIpro®!

Seamless transition from process development up to clinical trials and commercialization

- Best-in-class PEI-based transfection reagent for viral vector production
- Highest virus yields in producer cell lines (HEK-293 and derivatives, VERO, others)
- Customized regulatory support to meet compliance requirements
- Chemically defined and animal derived component free



Characteristics	PEIpro®	PEIpro®-HQ	PEIpro®-GMP
Quality Grade	R&D grade	Pre-clinical grade	GMP grade
Composition	Ready to use, chemically defined and animal derived component free		
Packaging	Bottles	Bottles	Bags (closed system)
Fill & finish manufacturing process	Sterile filtration	Sterile filtration	Sterile filtration Validated aseptic process
Quality Controls	Standard QCs	Extended QCs to assess Identity, Potency, Purity and Safety	Validated QCs according to European Pharmacopeia assessing Identity, Potency, Purity and Safety

Range of PEIpro® quality grade reagents for each step of nucleic acid-mediated viral vector-based manufacturing.

Contact us:
Phone: +33 (0)3 90 40 61 80
Email: support@polyplus-transfection.com
Web site: www.polyplus-transfection.com