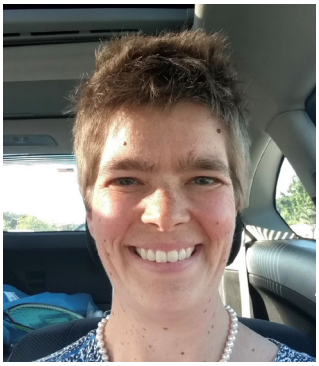
EXPERT ROUNDTABLE

Getting a gene therapy product to market: pitfalls and how to prevent them

HETAL BRAHMBHATT
Principal Investigator - Science and Technology Team, Pharma Services, Viral Vector Services, Thermo Fisher Scientific

Dr Hetal Brahmbhatt is a Principal Investigator in the Science and Technology Team, Pharma Services, Viral Vector Services at Thermo Fisher Scientific. She has a PhD in Biochemistry and Biomedical Sciences from McMaster University where she characterized small molecule modulators of apoptotic proteins. In her present role, she contributes to the development of platform processes and technologies for the manufacturing of viral gene transfer vectors.



ELIZABETH SIMMONS
Associate DirectorQC Analytics,Homology Medicines Inc

Beth has a Master's degree from Lehigh University in Analytical Chemistry and Regulatory Affairs with 13 years of industry experience. She has managed small and large Quality Control laboratories including method transfer, qualification and validation teams in both small pharma and CMO settings. During that time Beth has supported 2 facility start ups (Commercial and Clinical) and managed technical teams focusing on small molecule, oligonucleotides, and now gene therapy.

THOMAS GUARINONI
Manager, Downstream Process team, Viralgen

Thomas Guarinoni, MSc was recruited in January 2017 as manager of the Downstream Process team at Viralgen. He was successful in transferring the entire purification process from Askbio to Viiralgen in record time. Thomas Guarinoni obtained his MSc in 2011 at ENSTBB (National Superior College of Biotechnology) in Bordeaux, France.

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Q How important is early stage process development in supporting success in late stage clinical development and commercialization of a gene therapy? What impact can the choices made early on in a product's development have as it moves towards the clinic?

ES: The greatest inefficiencies we have found stem from relying on external vendors to execute your development and manufacturing. We invested early in our internal capabilities and by keeping bioprocess development, analytics, and manufacturing in-house, we continue to learn and optimize our process throughout therapeutic development, whilst being able to scale-up our capacity and control our own schedule.

With internal capabilities we can collect data quickly, drive decisions, and make appropriate changes as needed. This means that our GMP process is essentially the same as our commercial process, which helps us to expedite that whole system.

"Considering what that final process should look like will dictate how your process development should unfold, both upstream and downstream."

- Hetal Brahmbhatt

TG: As a CMO, we of course share the development we are doing with customers. We also benefit from a technology transfer from AskBio.

One of the most important things for achieving success in your development and commercialization is plasmid design and cell line development. If you already have a good toolbox that is well designed and well selected, and a good small-scale model able to generate a great product with a robust process and robust production, half of the job is done. It is also beneficial if you are able to start working as soon as possible on Quality Control (QC) and validated assays. The more knowledge we gain on the process from an early stage, the better commercialization is likely to go.

HB: To really understand how process development supports late clinical stage development, the first question we like to ask people is: what does the process look like at the end?

Sometimes you have clients who want something 'quick and dirty', so their early process is designed in a certain way. But as you start moving towards the clinical phase, the client may realize that the yields are not sufficient, or the process is not completely scalable. They may need to change the manufacturing platform or to consider multiple batches in order to get to those desired yields. So while they may have originally been seeking a quick and easy, 'good to go' process, they suddenly find they need to establish another process and then do the comparability studies afterwards.

The alternative is to take an approach where you know what the late stage will look like, allowing you to develop the process upfront and avoid the need for additional studies later. A lot of the pitfalls that we see are around planning ahead. Considering what that final process should look like will dictate how your process development should unfold, both upstream and downstream.

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Q If you could go back to the early stages of process development for a product when working with a client, what would you do differently, or what would you advise them to do differently? What would you consider to be the most critical considerations for the effective transition to commercial scale manufacture?

TG: Having something that is scalable and already efficient, and not something 'quick and dirty' as Hetal just described, is often a great help for taking your product to the market more quickly. As she mentioned, if you generate a process for phase 1 or 2 that brings you quickly onto the market, but later on you find you are unable to scale-up, or you have to do bridging studies for comparability in between your toxicology batch, your phase 1/2, and your phase 3, then that presents a big issue.

I would definitely try to find a process that is as robust as possible but also as scalable as possible in an easy way. Also, start QC development and validation as early as possible, in order to avoid losing time in reaching the market. That would be my advice for early stage process development.

ES: We primarily focus on rare genetic disorders, so we have a high likelihood that we are going to expedite fairly quickly from early stage straight through to commercialization. To manage this, we focus on development and on a robust analytical platform early on.

We have developed nearly 40 analytical assays to help quantify and evaluate the quality of our products throughout development. By collecting reliable data, we are able to quickly identify opportunities for process improvements and this also helps us gain process characterization information very early on.

Ultimately, this allows us to help with any necessary process changes and making decisions around that, as well as getting ready for process validation at the end. Focusing on our analytics panel early on helps to expedite the whole system.

HB: From our perspective, we see the need to understand the product- or process-related impurities, and how they affect the critical quality attributes (CQAs).

Using adeno-associated viral (AAV) vectors as an example, you could employ a certain purification process but then as you try to enrich for full capsids, a lot of the understanding of how this affects the potency is unknown. It is good to have that information upfront to improve process design.

Q How important are technology choices during the early stages of process development, and how difficult is it to make changes as you approach commercialization?

ES: We focused early in the process on developing a robust platform and we utilize a fully chromatography-based downstream process. This enables us to have easy scalability and prevents us from needing to make major changes through the development process. Instead, we can just focus on small variations that may be implemented quickly.

The greatest benefit of leveraging a platform-based process is that you can utilize previous learnings to expedite the development of new pipeline programs. We have found that for subsequent programs, we can decrease analytical development time by nearly 90%, and process development time by nearly 50%, for each subsequent platform program.

TG: The platform approach is primarily used in the AAV world and for monoclonal antibodies (mAbs) so far, where affinity chromatography, full/empty separation with chromatography, polishing steps, and tangential flow filtration (TFF) are all used frequently.

If you apply this platform to various serotypes you can save a lot of time in terms of analytical mitigation or analytical assay checks. You already know what to expect, so you don't need to start from scratch. The drawback is that you may have a platform working for various serotypes, but some synthetic capsids may have a different reaction to your platform, so you will need to adapt. Overall, though, we've found you always gain knowledge and save time using this approach.

HB: An important consideration in technology choices is once again, what does the process look like at a commercial scale? Is your choice going to be a single-use system, or a hard pipe system? Are you making sure that your process development design fits the needs of the equipment that you have at scale? Are you accounting for any potential interaction of the molecule with the different surfaces involved? If you are using a hard pipe system, are you going to be sanitizing the system in between runs? Do you have sufficient data collected around the cleaning, the validation? You may choose to reuse the column – is that sufficiently built into your process? Technology choices are very important, and knowing the platform upfront is important.

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> - **Elizabeth Simmons**

Another constraint we see is in considering not just what equipment you are using, but what steps are involved. Take TFF, for example. In a small-scale study where you are working with very small volumes, you may not have the requirement to mix the retentate. However, in a commercial process, you may need to incorporate a mixing step to improve the buffer exchange process. The choice of having a mixer, and having studies done to support that mixing, become really important.

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Q A critical part of a scalable manufacturing strategy is to ensure product quality and safety. How do you develop that scalable analytical strategy for gene therapy?

ES: Analytics always takes longer than you think it will. I can never stress this enough: start before you think you need to!

Regulators are now expecting validation for all dosing methods to help ensure that your dosing strategy is consistent from toxicology straight through to commercialization. Obviously, this front-loads a lot of that analytics work on the dosing method, but by having a robust dosing method you can get critical information about your process performance through all phases of development. It helps both aspects - analytics and process.

The other critical aspect for all gene therapy and gene editing companies is potency, which can be extremely challenging. I always recommend starting potency development as early as possible. Sometimes this might even be before you have a final candidate selected. Here, we try to couple our analytical development folk with our research people, so that they can start working on the biological indicators very early on in order to get a jumpstart on analytical development.

As gene therapy is fairly new, the regulatory guidance changes regularly, so it is key to be flexible with your analytical strategy. Each time a new guidance comes out, it is important to read through it and turn to your regulatory and quality assurance teams to figure out how you are going to navigate any new expectations.

TG: We firstly evaluate the risk to patient safety and the clinical study that the customer will perform. As Beth mentioned, one of the most important considerations is determining the dose you will inject. That has been quite an issue in the past year.

Essentially, the approach is to focus on risk assessment of the QC, and to try to validate as much as possible. You will not be able to validate all of the QC you use in phase 1/2, so you need to focus on what you think is essential.

The dose study, and the dose finding, presents the need to validate the assay for concentration determination, and so on. Regulators have been more and more challenging in this area, and we are seeing quicker acceptance on validation protocols that are much more stringent than in the past.

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- Thomas Guarinoni

HB: When we talk about analytics, starting from process development, it is of course always nice to incorporate assays that are high throughput or have quick turnaround times.

One thing that we have seen come up again and again is that it is helpful to try to use any analytical methods that are partially quantified in the matrices that your product is going to be in, and this is applicable throughout the purification process as well as at the end. The reason for that is you want to make sure that whatever data you have is still going to hold true and is going to be reproducible to hit your target CQAs.

Q We have touched upon the concept of risk mitigation quite a lot. What is your overall approach to risk mitigation?

TG: Clearly the risk assessments of your process, of the definition of your quality target profile, of QC, and so on must all be done based on the patient. Here, we aim to develop, qualify, and validate all the assays that we think are important, particularly in relation to patient safety.

ES: We utilize a phase appropriate approach to risk mitigation and leverage a strong risk management program to ensure that each process decision we make is evaluated before we actually execute it. We ensure everyone is in agreement about the risk before we move forward.

We are a very data-driven organization: all of our decisions are very much focused on the data we have going into them, as well as the data coming out after we have implemented that change. Therefore, we primarily focus on our robust analytics, both during the manufacturing process and for a drug substance, to make sure we are clearing all potential contamination.

As we gain greater process understanding and have a better understanding of contamination clearance throughout the process, we update our testing panel to adjust accordingly, and focus on areas that require additional information. For example, there may be a new process step that we want to evaluate a little more closely.

As part of this approach, for each process change that we implement, we try to put in an appropriate testing panel that assesses that specific process change. That could be yield before and after or, if we are aiming to clear a certain contaminant, we can test before and after to ensure that after we have implemented the change, the desired affect was achieved. There is always a feedback loop and campaign summary to make sure that our data is telling us what we are hoping to find - if not, then we readjust our strategy.

HB: I would echo a lot of what Beth says. It is very important for a risk mitigation strategy to ensure that you have a very well-defined process characterization in place, so that you know the process you have is robust and reproducible.

Another consideration that we have seen is ensuring you are using raw materials that are suitable for the manufacturing phase you are in. Often, we see raw materials that are not GMP grade being used at a point when they should be, for instance. There are certain raw material testing requirements based on the phase you are in, and it is important to conduct the appropriate studies around this, and to be prepared to do all the raw material testing for either a phase 1 or late stage process in-house.

Additionally, try to avoid any supply chain issues. If there is an alternative product available, ensure you have done the studies ahead of time so that when you actually hit your late stage process, you don't run into supply chain issues, or have material that is not suitable for GMP.

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Q As gene therapies for larger therapeutic indications start to move towards the clinic, what developments or innovations would be on your wish list to enable commercial-scale manufacturing?

ES: My background is predominantly in analytics, so I am very much focused on that space for this question. I would like to see more rapid analytical options to help facilitate real-time process performance, whether this is in-line analytics that you see in some other industries, or better analytical column choices. Anything to give you more diverse options for the analytical test panel.

On the process end, we have been able to achieve a 2,000 liter scale for AAV manufacture. It would really be helpful to see that scale-up for starting materials, as supply is getting increasingly competitive, especially during the Covid pandemic. It's becoming increasingly important to evaluate your starting materials and raw materials early, and to be able to purchase them early enough, too.

TG: If I had to write a wish list for AAV, I would say it would be interesting for the field to share knowledge, as we are trying to do now, with proper case studies. We know that for mAbs or vaccines, there have been some publications around chemistry, manufacturing and controls (CMC), with big pharma sharing their knowledge, approaches, and validations. I think the gene therapy field would benefit from more of this at the CMC level, and from trying to get more standards in place.

It would be beneficial for all the players to try to share and focus upon a standard AAV - from ATCC, for example – in order to evaluate the difference versus the CMO or dose study. This is because assay results do tend to vary from one location to another.

In the field of manufacturing, things are improving in terms of bioreactors, columns, TFF, and so on. I don't see any issue of scalability. I also do not expect that the AAV field gene therapy field will have the same production needs as the mAb world. I wonder how big scale really needs to be in order to provide enough material for treating all the patients with a particular disease, at least as long as the field remains predominantly focused on rare diseases. Perhaps this is a shortsighted point of view, but as long as you treat, say, 10,000 patients in the first year, and then you only need to treat the newborn cases of the disease thereafter, you do not need to have the capability of expanding to a 50,000 liter bioreactor, for example.

This leads me to wonder if the scalability of the gene therapy world will be expanded continuously, or will be limited to expanding process capabilities just enough to be able to cover all of the patients who need a particular treatment. It may be a different story with viral vectors used in cell therapy manufacture, but even there, I believe improvements in infectivity, for instance, will make a difference moving forward.

"It's becoming increasingly important to evaluate your starting materials and raw materials early, and to be able to purchase them early enough, too."

- **Elizabeth Simmons**

ES: There is certainly still a big focus on rare diseases and in that area, I would agree with Thomas that perhaps this degree of scalability is not necessary.

However, when considering starting materials and related business continuity, we are seeing increasingly long lead times to procure them. If you could increase those scales so you are not relying on such frequent purchasing of critical starting materials, then you can hold the generous supply needed to facilitate all of your programs. I would agree, however, that for the actual drug substance itself, I don't think we are going to be in that 20,000-50,000 liter scale.

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>
> - **Hetal Brahmbhatt**

HB: In terms of what development I would like to see, I am going to answer from a downstream perspective.

As you move towards commercial manufacturing, automation is a required aspect that you have to build into your processes. A lot of the challenges we see with AAV purification are in the enrichment of full vector particles. There are different approaches to do this – you can do it by chromatography, and you can also do it by ultracentrifugation methods.

Both have their pros and cons; ultracentrifugation works really well, but scalability becomes a concern. Chromatography is the alternative controlled approach, but it may or may not give you the same level of enrichment and is often dependent on the starting feed stream.

What I would like to see would be either a technology that enables you to have better chromatographic separation, or an ultracentrifuge that could be automated, is scalable, and that you would be able to use for multiple purification cycles whilst still achieving the yield and the CQAs that you desire.

Q Finally, with commercial-scale production comes higher supply needs. What challenges can arise when trying to ensure consistent security of supply of quality materials for commercial-scale manufacture? What advice would you give on how to address them?

ES: Right now, we are in unprecedented times and the challenge is much more dramatic than it ever has been before. Covid is impacting the entire industry across the globe.

To remedy this, I think it is a matter of beginning to evaluate your material needs, and of purchasing those materials that are high risk and have long lead times early and in bulk. Having some stability data for those starting materials and raw materials will enable you to do this, and allow you to purchase in larger quantities so that you can keep this material for an extended period of time.

For us, the biggest risk mitigation factor is first leveraging our internal capabilities as

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much as possible, and then supplementing them with multiple different vendors where needed. This enables us to control our own supply, thus enabling us to maintain our development timelines across all of our platform programs, even in these unprecedented times.

TG: It is becoming more and more complicated to ensure your supply chain is working correctly when you scale-up a process. Obviously, dual sourcing is one of the options that we should always try to evaluate, although it is not possible when we are talking about things like cell culture media or transfection reagents. Even with chromatography, it may be quite tricky to assume you can use two different resins without encountering issues.

As Beth said, try to buy early and extend lifetime as much as possible for your important products. For example, if I have a product with a one year lifetime, I might be able to perform an internal study, assess the quality attributes of this raw material, and possibly extend it to two years, making my supply a little more secure.

It is a constant collaboration with your supplier - or, depending on your point of view, a constant fight with your supplier! But generally, the collaboration you see is good. Work as closely as possible with your supplier, try to extend the standard shelf-life of the products that are really important to you, and try to dual source whatever and wherever you can.

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