INTERVIEW

Tackling the plasmid supply bottleneck

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Q The supply of plasmid to the burgeoning gene therapy sector has become a significant bottleneck – can you firstly frame for us the background to and scale of this issue?

MF: The recent and current tremendous increase in demand for plasmid is very much linked to the cell and gene therapy as a whole – and gene therapy in particular – finally achieving really consistent growth. Obviously, gene therapy in its various different forms generally has a viral vector as one of its main components, and viral vector production relies on plasmids.

It is a true bottleneck that we are currently witnessing. Perhaps the growth of the gene therapy field could have been predicted, but then again, with highly dynamic industries such as ours, it's always the case that some things occur differently to what was expected. It was probably natural in years gone by for us to think 'OK, let's take it step by step and not rush into an increase in production capacity'. But suddenly, everyone is asking for this particular kind of technology to be readily available on demand.

The resultant backlog in production and long waiting lists are certainly generating a lot of difficulties for the industries we serve – and it is a situation that is likely to become more severe as demand only increases for starting materials, the intermediates of production and the final means of transduction or transfection.

I would say that the major risk we face today as a sector is an inability to serve the industry properly and at the right time with specific compounds like plasmids. This could result in a slowing of progress in R&D pipelines worldwide, and it can negatively affect the expectations both of the market and more importantly, of the patients who are waiting for new products and solutions for their specific needs.

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SB: While we've recently seen several players investing in new facilities, new capacity, plasmid was neglected for a number of years. This may have been the case because in a sense, it is not part of the cell and gene therapy industry - it's more similar to a standard biological in many respects. Everyone was looking into the cells, looking into the viral vectors, but plasmid was not something that people in this space really thought about too much.

For many years, there were just a couple of providers that could offer true GMP quality plasmid, plus many others supporting laboratory and early clinical demand. Today, the industry is shifting towards the commercial

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sphere very quickly, and I think there are many companies deciding to invest in commercial-quality production even at the earliest stages of R&D. Hence, there is this gap between need for high quality plasmid and what the supply side can support. We regularly hear from suppliers of 6-to-12-month backlogs, which is an issue.

We are a relatively new player on the plasmid side. We're coming with a lot of background in biologics, and we're now trying to leverage this knowledge in the plasmid space, recognizing these key needs related chiefly to time and quality.

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Q Tell us about some of the key considerations in plasmid DNA production today

SB: The first thing to bear in mind is an IP issue, really, relating to how the plasmid is created. There are several components that come from different sequences that were identified (and patented) separately in years gone by, which have been pulled together to form the backbone of what has become the packaging plasmid to make lentiviral vector, or the different serotypes of AAV, or the many other viral vectors that are used.

Plasmid production begins with R&D aimed at creating a plasmid that is optimal for a specific use. In the past, plasmids were mainly created for internal academic approaches, whereas today, there are companies that specialize in making their own plasmid and then selling it to a third party.

The next stage is process development: identifying the best manufacturing strategy for the given plasmid. Again, there's a lot of knowledge applied here that comes from the wider biologics world, but equally, every product has its own unique characteristics and that is something to account for.

Finding a process that is fully closed and automated is of course highly desirable and important for meeting quality requirements, which are stringent - for example, there is the 'triple c', which is a standard of quality for the plasmid. Obviously, it's important at the end of the process to have a plasmid that can be considered fit for purpose.

R&D is really the foundation on which to build the production strategy, with ease of transfer to production a further key responsibility of the process developer. With production, I think it's important to stress that currently, manufacturing capabilities are not equivalent to those in the biologics realm. For example, whilst biologics fermentation is measured in the thousands of liters, with plasmids, you would be looking at hundreds of liters for a big production run. So the scales of production are different but just because you're making less of the plasmid, it doesn't necessarily mean the process is any easier.

Q Where specifically can/should further improvements and development be sought in this area?

SB: From my perspective, the area that needs the greatest attention is the regulatory aspect, in the sense that plasmid is yet to be properly accommodated within the regulatory framework.

There's always this vague reference to 'high quality', but there are still no real guidelines that explain exactly what 'high quality' should look like. I think the picture here is complicated to a degree by a sense of expectation that plasmid should tie in somehow with the same quality progression that occurs with the drug product, as it proceeds through R&D and towards full GMP. But of course, we're not talking about the drug product - we're talking about a raw material that will contribute to the generation of the final product, but that will not be a part of it by any means.

In our opinion, we need a clear statement from regulators on how the plasmid should be assessed by everyone, creating a level for all to work to. It would provide much-needed clarification and simplification relating to the lingering question of what GMP actually means in the context of plasmid produced for viral vector manufacture.

On the technological side, I think there's room of improvement to specific steps that were originally designed for other purposes. The technology does already exist - it's more a question of working together with a supplier in order to maximize the use of existing technologies – so I would say the technological aspect is perhaps less of an issue. Again, what remains the area of greatest concern is how to properly frame the plasmid used for viral vector manufacture in regulatory terms.

Q What are the keys to maintaining high quality and consistency of plasmid DNA production?

SB: The keys to maintaining high quality are really the quality assays.

We as a company decided to apply all of the GMP standards that would be applied to final drug product to our plasmid production. In other words, we have in place a quality system that is exactly the same as it would be if we were manufacturing a drug. That has allowed us to work with batch records, operate a system to notify clients if something goes wrong with a batch, etc. It's really raising the bar in terms of the quality framework within a company doing plasmid manufacturing, and of course, the analytics are absolutely key to achieving this.

The other important aspect is selecting the proper analytical panel. Again, there's no 'right' panel or standard way of doing things at the moment. However, there are some guidelines in the pharmacopeia relating to plasmid where the plasmid is the actual drug product, so if you're going to physically inject the plasmid into a human being, you know what you have to do. One exercise we did was to review that guidance, selecting the different analyses that are required in the context of a drug product. We then put them in the right context for plasmid that is not going to be a drug product, but that will be a building block in the manufacture of something else.

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We also decided to internalize all analytical development, meaning we gained both in terms of time but even more importantly, in terms of control of the analytical side. We believe that's a plus not just for us as a plasmid provider, but for the eventual end user, too.

So to summarize, the keys from my perspective are to create the proper quality framework - to create the proper quality panel for both the master cell bank used to produce the plasmid, and also the plasmid itself - and to maintain full control of the analytical side. Whether you're looking at release criteria or in process controls, you really have to know what you're doing and be able to do it properly.

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MF: I would just emphasize Stefano's comment on the importance of being in control of the process not just from the plasmid provider's viewpoint, but from the customer's, too.

This leads me back to the topic of current regulatory uncertainty. A customer expecting a certain grade of production, but there being no clear guidance on how the quality aspect will be interpreted on the regulatory side, can lead that customer to be misled in terms of understanding exactly what is happening in the facility where the plasmid is being produced – what is actually being done by the provider to ensure the desired grade is being reliably achieved. Having the capability to be very clear and transparent in this regard is in our view a major plus.

So it's really, really important to be capable of maintaining this level of control. That doesn't mean being capable of controlling everything, but it does mean being able to answer specific requests that come to us, and to provide rationale and viable solutions to end users.

Q It is notable how significant a role Italian organizations play in gene therapy manufacture on a global scale – can you share your thoughts on why this is the case, and what benefits this phenomenon brings to Anemocyte in particular?

MF: I think this role that the Italian cell and gene therapy community has created for itself is fundamentally related to the resilience demonstrated during the past 20-30 years of strong activity in the field. I believe it is a resilience that is quite unparalleled worldwide. It's very much testament to the efforts and belief of the many researchers and other stakeholders who always strongly believed in the opportunities that lay beyond the scientific and technical complexity of cell and gene therapy, and who kept investing in it year after year.

This resilience and willingness to continuing investing throughout difficult and uncertain periods like the '90s led directly to the creation of today's world-leading Italian facilities and pool of expertise. And I think that we as a country and community kind of deserve to take

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a leading role in cell and gene therapy today - or perhaps a better was to put it is we insist upon it - because we truly contributed to its creation. But of course, it's not enough to say we have been true believers and innovators in this field: we now have to demonstrate that we are able to master the knowledge and expertise that we developed in order to maintain and potentially increase our contribution to cell and gene therapy moving forward.

Anemocyte benefits in the main through the ecosystem that exists in Italy today, which is very lively and competent. It comprises excellent research centers, leading hospitals on the clinical application side, ambitious start-ups, and also competent authorities. All of these together create and foster an environment geared to accelerate the growth of our sectors. This ecosystem is key for Anemocyte as it facilitates exposure to innovation and knowledge, helping nurture talents and competencies that are core for us. Of course, it also creates a favorable environment for investment, which is such an important part of the story for each and every actor in this field.

So in my opinion, I think Italy did a great job!

Q What are your expectations for the growth of demand for plasmid moving forward?

SB: As we mentioned earlier, the cell and gene therapy industry is growing, and not just in terms of early clinical trials, but there are and will be more and more products in phase 3 and on the market. Furthermore, we've recently started to see more and more products jumping directly from first safety assessments in man to pivotal trials, simply because they are aimed at rare diseases where the unmet medical need is high. That means that you have to very quickly address all these GMP-related question marks around the plasmid you're using. All of this speaks to a growing recognition of the importance of securing a robust, high quality plasmid supply from the earliest stages of product development. So we obviously expect demand from the maturing gene therapy industry to continue growing substantially, and the onus is on plasmid suppliers such as Anemocyte to find ways to increase both the number and size of the batches we produce while maintaining the highest quality standards.

However, I think it is important to also stress the fact that plasmid demand is not restricted solely to viral vector production. In parallel, you have tools like transposons and gene editing

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platforms that in some cases require plasmid as well. So we also expect to see considerable growth in demand from other fields, and different uses of plasmids continuing to emerge.

Q How is Anemocyte mobilizing to meet this demand?

SB: For the past 12 months or so we've been really digging into reports, but perhaps more importantly, we've also been asking questions directly of the players that have reached commercialization.

The aim of these interviews was really to understand what challenges they face from a plasmid supplier perspective. These boil down to time and quality, basically - those were the two key points there were mentioned.

So we've aimed to build a facility that addresses these particular aspects. For example, we've created spaces where we can easily manufacture multiple batches in parallel, without creating specific bottlenecks. That was the first phase of the solution that we identified

We were also able to build a footprint that was very scalable so that if we realize that the existing facility is forming a bottleneck, it's relatively easy to 'copy and paste' what we have designed into another manufacturing unit. And each unit is designed to include everything needed for plasmid production, making them very self-sufficient. This combination of features allows us to meet current demand, whilst also affording us the flexibility to quickly replicate our footprint next door - or if necessary, elsewhere in the world – in order to cater for a growing market.

We've also started a collaboration with a player that has knowhow on specific areas relating to plasmid manufacturing, such as having IP around a specific plasmid. That's an area where it's really much easier for us to collaborate with third parties that have already established this knowledge and their position as a supplier of plasmid as starting material. We are also in other collaborative discussions – for example, with a transposon provider – so that if there is a need to enter into other emerging spaces, we have access to possible solutions.

I think the interviewing process and these collaborative interactions have combined to provide a really good foundation for us to create the right sort of flexible, scalable manufacturing environment.

Q EXELLULA is a particularly exciting initiative – can you go into more depth on that and what it will bring to the cell and gene therapy space?

MF: EXELLULA is an extremely exciting and fascinating project. It was built from a strong base, which began with the very challenge we've been talking about - how to meet rapidly increasing demand in the field of cell and gene therapy.

As we've discussed, quality, innovation and capacity are all key considerations. The basic idea behind EXELLULA is to bring all of them together, and importantly, to do so at just the right time for the industry.

EXELLULA is a modular project, the first step of which was the creation of the new plasmid unit that Stefano mentioned earlier - our key move in the plasmid space. It is an initiative specifically aimed at answering a real need with a state-of-the-art solution. So we're delivering a solution to something that was and is a genuine pain point for the industry, which of course is the bottleneck in the production of plasmids. We are offering something that is real and tangible. It's not just a dream or a marketing tool; it has walls, people working in it, technology that is actually available in order to provide services. And it's something that was conceived of purely with the immediate and future needs of industry in mind.

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