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The $100,000 problem gene therapy companies would rather not mention

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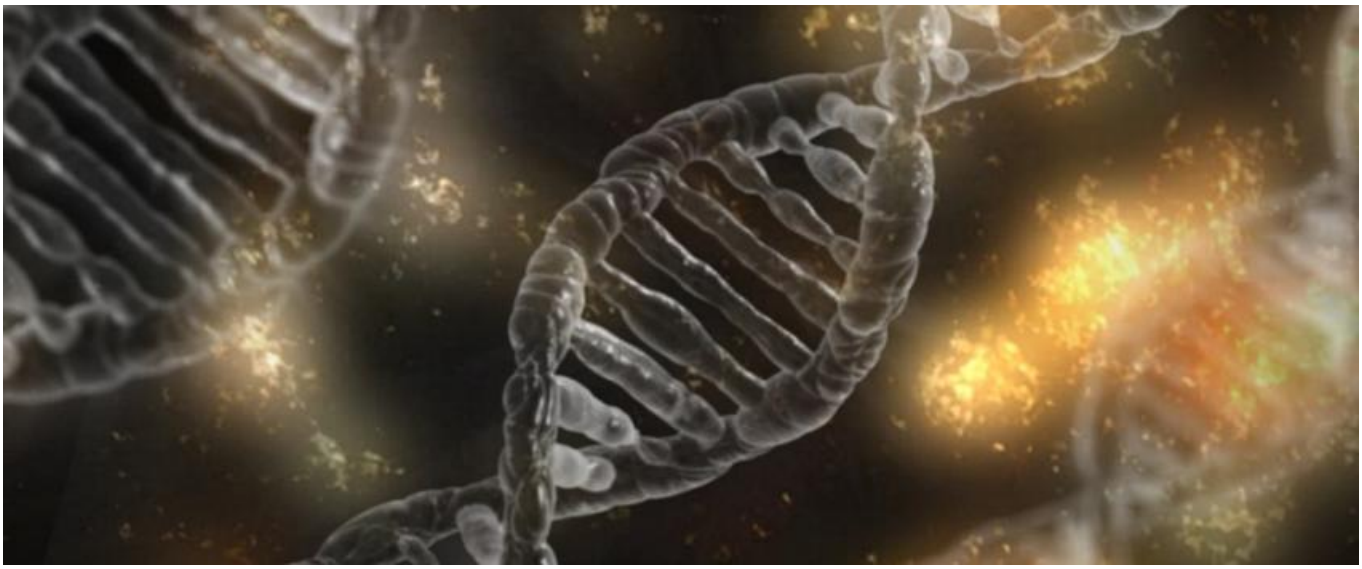

The high doses of recently studied gene therapies threaten manufacturing problems that few have fully considered.

When a scientific breakthrough is made in just a few patients the harsh reality of trying to turn it into a commercial treatment is often outpaced by frothy market expectations. Two excellent examples are Biomarin and Sarepta's gene therapies, both of which dose patients with never-before seen quantities of AAV vector.

Biomanufacturing specialists contacted by *EP Vantage* say this fact poses huge logistical and cost problems not appreciated by many companies, let alone the markets. The figures cited – both for the current per-patient cost of manufacturing such gene therapy doses and the capacity needed to meet demand – are staggering.

At the dose levels cited by Sarepta last week and by Biomarin in December the problem is how even a few hundred patients a year can be treated, reckons Tony Hitchcock, technical director at the contract manufacturer Cobra Biologics. Current capacity can treat just a handful of patients, he states.

400 swimming pools

He has a wake-up call for biopharma. "I've worked out that [necessary capacity] is equivalent to something like a billion litres of cell culture to treat 1,000 patients," he says. A billion litres is roughly equivalent to 400 Olympic-size swimming pools.

Anandita Seth, head of R&D for viral therapy at Lonza Pharma & Biotech, agrees that the problems are significant. "These high doses are definitely a challenge for manufacturing given the current manufacturing platforms," she states.

This is weighty enough in its own right, but it is magnified by the extent to which the market, and even some companies, underappreciate the problem.

"In reality I don't think [biopharma companies] have thought out the long-term investments and challenges that are going to be required," reckons Mr Hitchcock. "There's a risk that these companies have very inflated values, and can't meet the expectations of the market and also of patient groups who desperately want these products."

Such considerations are particularly prescient in the case of Sarepta, which has behind it the support of a hugely influential Duchenne muscular dystrophy patient lobby.

Last week the company wowed the market with the first three case reports of DMD patients given its AAVrh74.MHCK7.micro-dystrophin gene therapy (*Sarepta investors party like it's 2015, June 19, 2018*). This was dosed up to 10^{14}vg/kg, and the trial's dose-escalation plan calls for a highest dose of $2x10^{14}$vg/kg; in a 40kg DMD child this is equivalent to $8x10^{15}$ AAV vector genomes.

Such a level would eclipse even Biomarin's haemophilia A gene therapy valoctocogene roxaparvovec, which has been criticised for being dosed at up to $6x10^{13}$vg/kg – said to be 20-30 times higher than a competing Spark project, SPK-8011. In a 70kg adult Biomarin's dose works out at over $4x10^{15}$ AAV vector genomes, and even with this there have been worries that the effect might wane over time.

Don't mention the commercial reality

Yet the public pronouncements made by Biomarin and Sarepta have focused on the revolutionary nature of such once-and-done treatments, with barely a suggestion of how difficult it is to turn them into a commercial reality – or their likely high cost.

Drug cost has become a live issue in biopharma, and it could be especially tricky for a company like Sarepta, which has benefited from large amounts of US government funding (*Vantage view – Sarepta and biopharma want to take, but how much will they give back?, June 25, 2018*).

Another contract manufacturer speaking to *EP Vantage* anonymously estimates that the costs of making a single dose of $8x10^{15}$ AAV vector genomes are in the region of $100,000, adding that "the goals should be to get them at least tenfold lower".

Mr Hitchcock agrees, estimating that a large batch size might cost half a million dollars but yield just a few treatments. "It's not unrealistic to think that it's going to cost – by the time you've made it, done all the testing, release, filled it – over $100,000 per patient," he states.

The problem is twofold: most processes require virus to be transfected in plasmid DNA into cell lines, from which vector is then recovered. Manufacturing therefore requires not only generation of the AAV vector but also the sourcing of large amounts of plasmid DNA – this is actually one of Cobra's business lines.

"Traditionally people used to make a few grams of plasmid to support clinical trials; when you start looking at what those companies want in terms of commercial manufacturing we start looking at hundreds [of grams] if not kilograms per year of plasmid," Mr Hitchcock says.

"At the moment no companies making commercial amounts are making kilograms per year of plasmid."

Investment needed, fast

So what can be done about the problem? Lonza's Ms Seth: "At Lonza we are investing in facilities and people – we recently opened a new 300,000sq ft facility in the Greater Houston area – as well as in improving efficiency. Our focus is on developing better platforms that are scalable [and] novel vectors that provide higher transduction efficiency."

But change will not happen overnight. The massive improvements needed in product efficiency and capacity are comparable to the need that once had to be met for antibody production; ultimately this was achieved, but not before 30 or 40 years elapsed.

"Have we got the manufacturing tools to do that at the moment? Probably not," accepts Mr Hitchcock. Given enough time scale-up is realistic, but he cautions that right now it is not even clear whether you scale up existing capacity or invest in developing brand new second and third-generation platforms.

"With existing [AAV vector] platforms these demands require multiple large batches. And, depending on the platform used, it might not be scalable at all," says Ms Seth.

The problem is not localised, but rather affects the industry globally, says Mr Hitchcock. Ms Seth argues that there is evidence of an upward trend in industry investment, but accepts that improvements have so far been "incremental".

Antibodies took a long time to become established as a cornerstone of drug treatment – a luxury that genetics might not have, since companies "have patients here and now that require [gene therapy]", says Mr Hitchcock. "They'll only be able to treat, at the moment, a handful of patients."

If there is awareness among at least some groups of the problem, he offers a final clue as to why so few have spoken about it: "The early start-up companies probably … want to show proof of principle, and then expect someone to buy them out and resolve a lot of those issues."

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