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Pandemic intellectual property dispute deepens as Inovio is countersued, leaving its COVID-19 candidate in limbo

Court cases and FOIA reveal notable details on DNA vaccine production efficiency

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The lawsuit between the COVID-19 vaccine company Inovio and biologics maker VGXI over intellectual property to manufacture DNA vaccines is heating up and has taken on geopolitical tones. The lawsuit has revealed interesting information on making DNA vaccines and on relationships between vaccine companies and the contract manufacturers on which many vaccine companies depend for production capacity.

On 25 June, a Pennsylvania judge denied Inovio's request for an emergency injunction against its former manufacturing partner, Texas-based VGXI, which is owned by the South Korean company GeneOne Life Science. VGXI won't transfer its DNA vaccine manufacturing intellectual property, which both sides agree is more efficient than other processes, to other companies so that they make more of Inovio's candidate COVID-19 vaccine, INO-4800. Inovio says VGXI's refusal violates a contract between the two.

While the judge did not rule on the validity of Inovio's claim, aspects of which he expressed sympathy for, he was insufficiently persuaded by it to impose the injunction on VGXI,[1] setting the stage for further legal wrangling at a future trial.

Inovio's loss came despite its bolstering of its initial claims against VGXI by alleging, in late June, that VGXI is deliberately stymying production of INO-4800 in order to give advantage to Corona-19, another candidate COVID-19 vaccine, also a DNA vaccine, which has been announced by VGXI's parent company GeneOne.

Indeed, Inovio's court filings seem aimed at inviting Trump administration "vaccine nationalism" scrutiny by suggesting that VGXI may be reserving its Texas manufacturing slots to make Corona-19 for use in South Korea, and that GeneOne may have stolen Inovio vaccine design intellectual property to help a planned South Korean stockpile of COVID-19 vaccines – "time will tell whether it misappropriated Inovio's trade secrets, which VGXI has had in its possession for months."[2]

1 Memorandum and Order. Court of Common Pleas of Montgomery County (Pennsylvania). Case 2020-06554 (June 25).
2 Reply in Support of Plaintiff's Petition for a Preliminary Injunction. Case 2020-06554 (June 16).

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With Inovio's allegations against it growing more strident and taking on political tones, VGXI is unsurprisingly hitting back. On 7 July, it countersued Inovio and its new manufacturing partner, Florida-based Ology Bioservices.

In the countersuit, VGXI and GeneOne make striking claims against Inovio. They allege that enrichment is Inovio's motivation to steal VGXI's intellectual property – both its patents and trade secrets. "Inovio got greedy: it saw the opportunity to reap vast riches and keep its stock price soaring" by, VGXI claims, "secretly planning for months to take VGXI's intellectual property and disseminate it to other manufacturers."

Countering Inovio's allegation that VGXI is blocking Inovio in the interest of its South Korean owners, VGXI suggests that Inovio is the party whose actions should stoke US nationalistic fears, accusing it of "a scheme to steal its longtime partner VGXI's proprietary technology and manufacturing process, and disseminate that confidential information to as many as ten other manufacturers around the world, including in China and India."[3]

VGXI directs equally tough allegations at Ology, Inovio's new manufacturing partner and VGXI's direct competitor. VGXI claims that Ology is "fraudulently passing off VGXI's proprietary DNA plasmid manufacturing technology and processes as its own," and that it has conspired with Inovio "to steal VGXI's confidential DNA plasmid purification process and techniques."[4]

Adding to the muddled political overtones, Ology is a company that is closely associated with the US defence ministry, which funded the construction of Ology's facilities and is the source of many of its contracts. Ology's contract to manufacture INO-4800 is to provide vaccine to the US Department of Defense.

Seeking its own injunction against Ology, VGXI argues: "If Ology is allowed to persist with its scheme to use and transfer VGXI's DNA plasmid manufacturing and purification and methods, VGXI will lose control of its intellectual property and suffer grave harm."[5]

Inovio's COVID vaccine candidate, INO-4800, which has received support from the Gates Foundation and the Coalition for Epidemic Preparedness Initiatives (CEPI), is thus presently stuck in legal limbo because of the intellectual property disagreement between the two companies.

The dispute casts light on issues of wider relevance beyond the fate of Inovio's vaccine and VGXI's process. No human DNA vaccine has gained regulatory approval, and there is limited experience and considerable secrecy surrounding manufacturing of them. The same holds true for mRNA vaccines, another novel technological approach being used for COVID-19 vaccines that has little record of large-scale manufacturing. Examples include vaccines from Moderna, Pfizer and Curevac.

And, like Inovio, many vaccine companies rely on contract manufacturers, companies such as Lonza, Catalent, Emergent Biosolutions and others whose processes may be proprietary. Even if a vaccine company is willing to make its intellectual property widely available, that may be insufficient to enable widespread, efficient production, particularly for vaccines with novel technological approaches.

Indeed, in this case, intellectual property has become a COVID-19 vaccine problem for one of the world's most powerful institutions, the US Department of Defense, whose bet on INO-4800 for use on US soldiers – if it passes safety tests – is turning sour due to the intellectual property dispute.

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3 Defendants VGXI Inc. and GeneOne Life Science Inc.'s Answer to Plaintiff Inovio Pharmaceuticals Inc.'s Complaint, with New Matter and Counterclaims. Case 2020-06554 (July 7).

4 Defendants/Counterclaimants VGXI Inc. and GeneOne Life Science Inc.'s Third Party Complaint Against Ology Bioservices, Inc. Case 2020-06554 (July 7).

5 Ibid.

Background

Inovio created a candidate vaccine against COVID-19, but like a number of other companies touting COVID vaccines, it is unable to produce its product in significant quantity and is reliant on outside companies. Because Inovio's vaccine uses technology never before used in a human vaccine, there is limited open source knowledge on how to make it in commercial quantity.

VGXI was Inovio's standing manufacturing partner for 12 years. But VGXI's capacity is less than what is needed to meet Inovio's target of making 1 million doses in 2020, and far less than the 100 million doses Inovio wants to produce in 2021. In part, this is because **none of Inovio's DNA plasmid products has ever been approved for use**.

Frustrated by VGXI's limits, Inovio has sought deals with other manufacturers and believes it can oblige VGXI to give up its secrets, but VGXI believes its process to make Inovio's vaccine is proprietary. After VGXI refused Inovio's demands that it transfer its intellectual property to Ology and others, Inovio sued the Texas company and its South Korean parent on 1 June (see https://twn.my/title2/briefing_papers/twn/Hammond.pdf).

Is Inovio facing a problem with the US Army?

Inovio may be feeling pressure from the US Army, which is expecting Ology and Inovio to produce INO-4800 with US Army funding. Records related to this contract were recently obtained by Knowledge Ecology International (KEI) under the US Freedom of Information Act (FOIA).[6]

The statement of work under the contract says that "The project will include technology transfer of the Inovio plasmid DNA manufacturing process" to the Ology facility. Yet it would appear that much of the "Inovio plasmid DNA manufacturing process" that the contract references may actually belong to VGXI. This statement in the contract may be the source of VGXI's claim that Ology and Inovio have misrepresented the intellectual property situation to the US government.

Indeed, Inovio specifically complains in court filings that VGXI has not transferred to Ology trade secrets related to its cell "lysis coil holder",[7] which echoes a specific obligation under Inovio's arrangements with Ology and the US Army.

The US Army may consider the ongoing difficulty in transferring VGXI's manufacturing process to Ology as being Inovio's fault.

Intellectual property and COVID-19 vaccine production efficiency

Information from the lawsuit can be paired with Inovio's contract with the US Army to provide insight into production of Inovio's vaccine. Few, if any, potential COVID vaccine makers have publicly discussed such details, which are important to achieving an efficient allocation of manufacturing capacity. These insights into the Inovio/VGXI process illuminate the current state of manufacturing of DNA vaccines more generally, as such vaccines have never before been produced at large scale and details about making them are often shrouded in secrecy.

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6 Contract W911QY-20-9-0003 between the US Army and Ology Bioservices, Appendix A-4 – Statement of Work for "Rapid COVID-19 Plasmid Manufacturing for Phase 1 Clinical Programs". Obtained by KEI under FOIA, US Army Communications-Electronics Command Case FP-20-019617/FA-20-15.

7 The court records reveal that the trade secrets that Inovio demands VGXI transfer to other companies include VGXI's process for the assembly and operation of two pieces of equipment – a "sintered air sparger" and a "lysis coil holder" (see: Reply in Support of Plaintiff's Petition for a Preliminary Injunction. Case 2020-06554). The first is a porous rod-shaped device that injects air into the liquid bioreactor mass to stimulate aerobic cell growth. The second is the mounting for a metal coil that cells pass through as they are harvested from the bioreactor and killed, as the process of separating and purifying the DNA plasmid vaccine begins.

Inovio's court filings and the US Army contract both state that Inovio anticipates a vaccine dose of 1 milligram (mg), or a kilogram of bulk vaccine per 1 million individual doses. The output of INO-4800 production runs at VGXI and anticipated runs at Richter Helm, a German manufacturer that has contracted with Inovio and that has access to VGXI's intellectual property, indicates yields of 66-69 milligrams of vaccine per litre of bioreactor capacity (per run).[8]

Thus, at present production efficiencies, in order to produce its target of 100 million doses of INO-4800 in 2021, Inovio will need about 1.5 million litres of total bioreactor output.[9] Using a typical large-scale biologics manufacturing setup,[10] Inovio will need the full-time use of about 60,000 litres of installed bioreactor capacity in 2021 in order to reach its target. (To date, INO-4800 has not been produced in a bioreactor over 400 litres, so it is not firmly established, from a technical standpoint, that production at such a level is possible.)

The scale of production necessary to make 100 million doses of INO-4800 is ambitious, but it may not be a wise allocation of resources, from a societal perspective. Since wealthy countries will pay almost anything for vaccine supplies for themselves, if the market directs capacity, it will not result in the most efficient solutions, especially for those in developing countries, because the most efficient candidates won't necessarily win.

Thus, Inovio's potential demand for bioreactors, and the complicating role of manufacturing trade secrets, exemplifies broader questions about allocating capacity rationally to produce the most vaccine the most quickly, and at the lowest price possible, given the urgent global pandemic needs.[11]

For example, producing enough of Inovio's vaccine for the US in one year – 325 kilograms for its population of 325 million – would, at present efficiencies and anticipated dosing, require the entire annual output of a 200,000-litre biologics plant, roughly the full capacity of one to two bulk biologics facilities of a large multinational manufacturer, such as Samsung, Lonza or Fujifilm. Facilities of such size are typically engaged in simultaneous manufacture of a variety of products that use varied processes, including other important vaccines and cancer drugs.[12]

Viewed from a global perspective, if an equally effective or better vaccine than Inovio's (or another maker's) can be produced in the same bioreactor base at substantially greater efficiency, then making the less efficient product at large scale makes little sense, since the same capacity might be deployed to make enough vaccine not only for the United States but perhaps many more countries in the same amount of time.

By way of comparison, *Science* has reported claims by the top scientist at Johnson & Johnson (J&J) that it can make 300 million doses of its COVID-19 vaccine per year in a single 2,000-litre bioreactor, using its own proprietary manufacturing system.[13] If that is true, then J&J's adenovirus vectored vaccine can be made perhaps 27 times more efficiently than Inovio's DNA vaccine. Put differently, J&J's claims imply that, in the

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8 The 1 mg dose figure is certainly preliminary. By the time vaccine testing ends, if INO-4800 is successful, the number of doses per individual might be more than one, and the final dose may be larger or smaller than 1 mg. Information on bioreactor yield comes from court filings, which state that VGXI's 400-litre bioreactor makes about 27,500 doses per run, while a 1,500-litre bioreactor at Richter Helm (Germany) is anticipated to yield 100,000 doses per run.

9 1.5 million litres x 67.5 milligrams per litre = 100 million doses. 1.5m litres assumes there are no batch failures or other delays.

10 A typical process would utilize 2,000-litre disposable bioreactors with each batch taking about two weeks. At reported efficiencies, each 2,000-litre bioreactor run would yield ~136,000 doses (2,000 x 68 mg). To make 100 million doses, ~735 bioreactor runs are necessary (735 x 136,000 = ~100m). Each bioreactor can run about 26 batches per year; thus, to make the full amount in one year, 29 (28.28) wholly dedicated 2,000-litre bioreactors are necessary. Expressed in terms of facility capacity, this would be the equivalent of a 58,000-litre facility (29 x 2,000), without adding margin to account for unexpected problems.

11 Since much the same bioreactor base that is capable of producing DNA vaccines may also be used to produce monoclonal antibodies, COVID-19 antibody production should also be considered here.

12 And, it should be recalled, the basis of VGXI's claims against Inovio is that its proprietary DNA plasmid manufacturing process is more efficient than that of its competitors, so if Inovio's vaccine were manufactured using a less efficient process, then it would need more bioreactor capacity to produce the same amount.

13 Cohen J 2020. The $1 billion bet: Pharma giant and US government team up in all-out coronavirus vaccine push. *Science*. 31 March. (Interview with Paul Stoffels, Chief Scientific Officer of Johnson & Johnson.)

same-sized factory that would be required to make enough of Inovio's vaccine for the United States (325 million) in a year, more than enough doses for the entire world (8.4 billion) could be made of J&J's vaccine.

It should be noted, however, that experts have cast doubt on J&J's claims. A senior US academic predicted it will prove to be "off by an order of magnitude or more". It should also be noted that, like Inovio, J&J is relying on outside contractors to make some of its vaccine, though in its case apparently using J&J's process.

As human trials advance with COVID-19 vaccine candidates and a smaller number of most promising candidates can be more rationally determined, the vaccines that can be produced most efficiently and most widely should be prioritized, even if that means that vaccine companies and contract manufacturers have to hand over in-house manufacturing secrets. It is worrying, however, that manufacturers are relying on proprietary production techniques that prevent or complicate production by others, potentially thereby making vaccines more expensive and less available, especially for the developing world.

Equally worrying, large commitments of manufacturing capacity in 2021 and 2022 are being sealed up in contracts before a rational selection of processes and allocation of capacity can be made to maximize production and minimize cost. Will factories in the US, Belgium, France, India and other places be producing less vaccine than they might have next year because of such intellectual property and contractual constraints?

Europe, the US and other developed countries are locking down COVID-19 vaccine supplies through big-money contracts that appear to attach little importance to cost and production efficiency. As Europe strays further from its early pandemic rhetoric about the necessity of COVID-19 vaccines being quickly and equally available to all, the issues brought forward by the Inovio-VGXI lawsuit underscore why successful vaccines and the knowledge to make them need to be global public goods, because that is the means by which the widest distribution at lowest cost can be achieved.

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