Science

POLICY FORUM

Cite as: W. N. Price *et al.*, *Science* 10.1126/science.abc9588 (2020).

Knowledge transfer for large-scale vaccine manufacturing

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Massive, rapid production will require firms to share know-how not just about what to make but how to make it.

As the world rushes to identify safe and effective vaccines and therapeutics to counter the coronavirus disease 2019 (COVID-19) pandemic, attention is turning to the next step: manufacturing these products at enormous scale. To speed up the process, firms are even establishing manufacturing capacity "at risk," before products receive regulatory approval (*1*). Yet for at least some complex COVID-19 vaccines and biological therapeutics, fast manufacturing, particularly of products originally developed by other firms, will require not only physical capacity but also access to knowledge not contained in patents or in other public disclosures; one reason for the expense and delay historically associated with entry of biosimilars into the market has been the cost and time associated with reverse engineering originator firms' manufacturing processes (*2*). But a change may be coming. A group of six biopharmaceutical firms researching monoclonal antibody (mAb) candidates recently sought [and the U.S. Department of Justice (DOJ) granted] permission under antitrust law to exchange "technical information" on each other's manufacturing processes and platforms (but not information on cost or price) (*3*). A focus on rapid information exchange of the sort recently encouraged by the DOJ will not only be critical for the current crisis but could also create the foundation for fewer siloes, improved standardization, and less secrecy over manufacturing information in the future.

Methods, know-how, and secrecy

Knowledge transfer can facilitate manufacturing scale-up in multiple contexts. Most straightforwardly, other firms may need to manufacture the "winning" vaccine of an originator firm under some form of license that encompasses transfer of know-how. Knowledge of one firm's processes can also facilitate the manufacturing efforts of firms with other vaccines, particularly if the vaccines use the same manufacturing platform. And sometimes, a firm may even need knowledge held by others to make its own product in large quantities. For example, Inovio claimed in a June court filing that its own experimental vaccine is being held "hostage" by a contract manufacturer that refuses to share manufacturing details (*4*).

One might reasonably ask why robust dissemination of manufacturing knowledge for complex biologics is only beginning to emerge, given the longstanding dominance of patenting in biopharmaceutical innovation and the legal requirement that patents disclose how to make the products they cover. Regrettably, for reasons related to the early timing of when patent applications are filed and failure on the part of patent offices to enforce disclosure obligations, patents on biologic products often fail to disclose necessary manufacturing information (*2*).

Reliance on manufacturing secrecy (including secrecy that improperly overlaps with patent protection over the manufactured products) is not specific to the pharmaceutical industry. But secrecy in other industries has generally been more time-limited than it has been with complex biologics. In the latter case, the combination of tight regulatory control over biologic products and complex and sometimes idiosyncratic manufacturing methods has slowed both competition and innovation.

To be sure, product lines differ, and crises can be valuable catalysts. As noted, in the case of mAbs and the COVID-19 crisis, large biopharmaceutical firms are now willing to share—and perhaps ultimately standardize on the basis of—information that they might previously have viewed as providing at least some competitive advantage (*5*). The available evidence suggests, however, that vaccine manufacturing still lacks standardization, even within manufacturing platforms (*6*). And some new vaccine technology platforms, such as mRNA, have never been manufactured at scale. Given this variation, the persistence of secrecy is unsurprising.

But maintaining pervasive secrecy for manufacturing COVID-19 vaccines during the pandemic could cause dramatic failure. Relevant information for quick and effective scale-up must be readily available. Vaccines are being developed in a massively parallel fashion; the World Health Organization (WHO) reports that as of 31 July 2020, there are 26 candidates in clinical evaluation and 139 candidates in preclinical evaluation. Preparations for manufacturing scale-up of vaccines are taking place before a single effective vaccine has been identified, let alone multiple vaccines (*1*). Along the way, firms are developing information about manufacturing, both of the specific product at issue and of vaccine manufacture more generally. This information is added to

existing firm-specific stocks of knowledge about how to make products.

Greater sharing of firm-specific manufacturing knowledge—as well as firm-specific and otherwise secret manufacturing precursors, such as cell lines and production software—help the information ecosystem generally. Especially for more established platforms, knowledge transfer could promote standardized best practices across the industry. Newer technologies could also benefit from greater background or case-specific knowledge. For example, even mRNA vaccines, which should be simpler to make than traditional vaccines (*7*), appear to have involved technology transfer—that is, transfer of both knowledge and material—to other firms (*8*). And nongovernmental organizations (NGOs) such as the Coalition for Epidemic Preparedness (CEPI) appear to build into their funding contracts provisions for technology transfer to additional parties that may be needed to perform manufacturing (*1*). Similarly, an 11 August 2020 Securities and Exchange Commission (SEC) filing by the firm Moderna indicates that at least some U.S. government contracts build in provisions for technology transfer in the event of the firm's decision to terminate production.

Although individual contracts that anticipate technology transfer are important, when the products that will ultimately be made at scale are as-yet unidentified, broader efforts to ensure their eventual scalability should happen as quickly as possible so that all potential manufacturers are prepared once the right candidates are identified. This is particularly true given U.S. government pronouncements that capacity established during the scale-up for potential vaccines will be used regardless of which firm has developed capacity, requiring the ability to retrofit and adapt facilities to products different from their initial design parameters.

As with mAbs, we see signs in the vaccine context that some firms are open to more collaboration and knowledge-sharing than in the ordinary course. Sanofi and GlaxoSmithKline have entered a collaboration for the development of a joint vaccine, which likely requires at least some technology transfer about production of the underlying vaccine elements (*9*). Robust knowledge-sharing across platforms and products should be commonplace during the pandemic response.

Transferring such knowledge may not be trivial. Aside from the competitive concerns, some knowledge may be tacit—that is, more context-specific, based on experience, and more difficult to codify. The tacit knowledge concern may be less acute for biopharmaceutical products than other goods, however, for the simple reason that regulatory approval typically requires the extensive codification of tacit manufacturing knowledge.

Where knowledge is already explicit and codified, whether in regulatory filings or elsewhere, that knowledge should be shared, at least as a club good within the universe of major industry players working to develop COVID-19 vaccines or, ideally, even more broadly. If explicit knowledge is codified in patents, pooling of those patent rights or other licenses should also be pursued, although patents surrounding manufacturing processes generally reveal little information and are therefore particularly unhelpful as a vehicle of knowledge transfer for manufacturing (*2*). And where tacit knowledge has not been codified at all, collaboration should include efforts to explore and share such tacit knowledge.

Incentives, actors, and realpolitik

Several entities might facilitate this type of knowledge transfer, at least if they could provide the right incentives and potentially the administrative infrastructure for such sharing to occur. In determining the best facilitators, international aspects are key because knowledge transfer will necessarily occur across borders.

Existing international organizations are one set of candidates. WHO is currently promoting the idea of a COVID-19 intellectual property (IP) pool (*10*). Although patents seem not to be the key barrier to successful scale-up, the pool as organized does include provisions related to nonpatent knowledge transfer. Under the proposal, any government, pharmaceutical company, or organization developing COVID-19 vaccines or tests could transfer its IP to WHO on a voluntary, uncompensated basis. It is unclear how much uncompensated transfer of know-how this pool will receive, and there appears to be some industry resistance (*11*).

National governments can and should also address issues of knowledge transfer. Although the rhetoric of war on the virus might suggest all-out government coordination along the lines of the U.S. government's mass production of penicillin during World War II (*12*), it is unclear how broadly the current federal government will invoke its more coercive powers. At the moment, the U.S. government, operating primarily through Operation Warp Speed, appears focused on using the lure of very substantial funding to secure future supply of various vaccine candidates. Specifically, the United States has committed billions of dollars to multiple vaccine manufacturers (Astra-Zeneca, J&J, Novavax, Moderna, Pfizer, and Sanofi/GSK), with each contract aiming to secure hundreds of millions of doses and manufacturing platforms ranging from viral vectors (AstraZeneca and J&J) to RNA (Moderna and Pfizer) to protein subunit (Novavax and Sanofi/GSK).

Particularly given the U.S. government's commitment to use all capacity available, regardless of the winner vaccine(s), a government commitment could usefully require transfer of manufacturing know-how across firms with which it has contracted. A contract manufacturing firm to which the U.S. government has given hundreds of millions of dollars, Emergent

Biosolutions, is already committed to manufacturing for J&J, Astra-Zeneca, and Novavax and could therefore serve as a natural locus for such knowledge transfer. Of course, like the exchange of mAb manufacturing information recently approved by DOJ, such transfer would be limited to a few firms. And unlike the DOJ process, any process that may be occurring through Warp Speed is not transparent (*13*), which might be highly problematic from a competition and antitrust law perspective.

Regional organizations could also facilitate knowledge transfer. For example, given the substantial resources that the European Union (EU) has committed to a vaccine and the EU's demonstrated commitment to data sharing and willingness to allow some pharmaceutical sector cooperation under EU competition law, the EU might be well suited to using the lure of funding to nudge firms toward knowledge transfer (*14*). Ideally, this would be done through a transparent process such as the DOJ review letter.

NGOs could also be an option for facilitating knowledge transfer. NGOs such as CEPI are providing funding for some vaccine candidates; they could condition receipt of funds on the contribution of manufacturing knowledge to a central pool of information. Even if NGOs were not able to bargain for such general sharing, if each agreement includes a requirement to provide knowledge transfer to other manufacturers funded by the NGO, such provisions would widen the base of available knowledge. This approach has worked in the past in the semiconductor industry, where the U.S. government–led partnership SEMATECH increased knowledge transfer across the industry (*15*).

Whatever the facilitator, the knowledge transfer could take different forms. One model would provide open access to essential information—including patents, know-how, and critical components—to all comers, without need of licensing. This would maximize access but decrease private sector incentives and strikes us as politically challenging. Another would leave all knowledge transfer to purely private mechanisms (if permitted by antitrust authorities). But history suggests that purely private mechanisms are unlikely to transfer enough knowledge quickly. An intermediate position, which seems more feasible, would leave control with the originator firm but use the lure of funds to require early knowledge transfer and licensing to third parties necessary for adequate scale-up and production—knowledge transfer that occurred even before the product was a clear success.

It is possible, perhaps even likely, that some or all of the ongoing efforts to facilitate product development and manufacturing may already include provisions to foster knowledge transfer, including codification of tacit knowledge and the sharing of otherwise-secret manufacturing process information. Certainly, the recent activity by manufacturers of mAbs suggests a recognition that knowledge transfer is important. However, unlike the business review letter from DOJ, the contracts that have been executed by Warp Speed are not public. Although the NGO Knowledge Ecology International has used Freedom of Information Act requests to secure outlines of a few contracts, almost all key information is redacted as commercially confidential. Ironically, this may include information on knowledge sharing.

Broader implications

Although the issues described here apply most directly to COVID-19 vaccines and therapeutics, a push for information sharing of manufacturing know-how could have broader positive effects across the industry. Where highly complementary skill sets and know-how are brought to the table and more problematic collaborations on costs and prices are excluded, as specified in the recent DOJ letter, this can also have a positive effect on competition in the sector. However, where the know-how of foreign companies is part of the deal, such as in the recent U.S. mAb agreement, the long-term effects on fair global competition and international sensitivities should also be considered very carefully.

In the most transformative scenario, robust sharing of manufacturing information in the current crisis could drive more robust sharing of such information more generally. Rather than relying on secrecy to limit competition in the underlying products, firms could share basic information about manufacturing processes, enabling greater innovation, flexibility, and quality. Outside the COVID-19 context, the current levers for maintaining exclusivity in the underlying products—patents and regulatory market and data exclusivity—could still shape competition rather than manufacturing secrecy, which impedes any transfer of information outside firms. Sharing in the pandemic could catalyze an industry-wide move to a high-information, high-innovation state of manufacturing, overcoming the collective action problem inherent in any one firm disclosing more on its own and confronting the free-rider dilemma directly.

Of course, transformation is easy to call for and difficult to achieve. Even without transformation—that is, in the scenario in which pharmaceutical companies maintain secrecy over manufacturing information that does not relate to COVID-19 vaccines and therapeutics—one-time sharing of knowledge could still advance the field's collective understanding. Such an outcome would be a missed opportunity for long-term broader change but would still carry substantial benefits, even outside those arising from improved manufacturing during the pandemic.

Whatever the long-term effects on industry innovation, the most important goal is to make high-quality vaccines for COVID-19 available as quickly and broadly as possible. To pursue that goal and to promote global solidarity and reciprocity, the policy-makers and companies jointly engaged in

the worldwide race to develop CoVID-19 drugs and vaccines should share information about how to actually make them.

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ACKNOWLEDGMENTS

W.N.P. and T.M. were supported by the Novo Nordisk Foundation (NNF17SA0027784). We thank J. Barnes-Weise of the Global Health Innovation Alliances Accelerator for comments on an earlier draft.

Published online 13 August 2020
10.1126/science.abc9588

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published online August 13, 2020

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