

Ensuring that intellectual property rights aren't a barrier to scaling-up: the remarkable example of penicillin production in the United States during World War II.

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Introduction.

Faced with the urgent problem of ensuring that intellectual property rights aren't a barrier to scaling-up Covid-19 vaccine production, especially as regards access to manufacturing know-how, it is helpful to consider the remarkable example of scaling-up penicillin production in the United States during World War II.

Scaling up penicillin production during World War II.

Penicillin is an antibiotic, naturally produced by some species of the *Penicillium* genus of fungi (moulds). Although its antibiotic properties were discovered in 1928 by Sir Alexander Fleming at St Mary's hospital, in London, it was a team including Sir Howard Florey, Ernst Chain and Norman Heatley at Oxford University, working between 1936 and 1941, which first isolated penicillin and established its 'miraculous' clinical effectiveness. Given the obvious potential importance of penicillin in treating wounded soldiers if much larger quantities could be produced, Florey and Heatley tried to interest both the British and American governments in massively scaling up its production. To that end, they travelled to the United States in 1941 with the intention of sharing their *Penicillium* moulds and their associated scientific and technical knowledge. Their mission was a tremendous success and penicillin production was indeed massively scaled-up in the United States during the war. By D-Day, in June 1944, American pharmaceutical firms were producing some 100 billion units of penicillin per month and just a year later, in June 1945, had increased this to some 650 billion units per month.

As, for example, Neushul (1993) ("Science, Government, and the Mass Production of Penicillin") and Quinn (2013) ("Rethinking Antibiotic Research and Development: World War II and the Penicillin Collaborative") explain, the key to the organisation of the scaling-up was a remarkable collaboration between the American government and American pharmaceutical firms. Although pharmaceutical firms initially thought that a synthetic chemical pathway to produce penicillin directly could be found, this would not happen until after the war. The scaling-up instead drew on scientific and technological R&D undertaken by, for example, the Northern Regional Research Laboratory (Department of Agriculture) to improve the yield of penicillin produced by *Penicillium* moulds in fermentation units. As to the pharmaceutical firms, the War Production Board (WPB) narrowed a field of 175 potential

producers of penicillin down to just twenty (“Criteria for selection included: experience with penicillin, knowledge of chemical production by fermentation, general experience with biological products, the availability of trained technical staff and facilities.”) The selected partners were also supported through, for example, the supply of necessary equipment (via the Army Service Forces) and the solving of production ‘bottlenecks’ (via the Office of Production Research and Development (OPRD)).

Penicillin production and patents during World War II.

Oxford University chose not to seek domestic or international patent protection for penicillin, either in terms of protecting penicillin in a broad ‘product’ sense (i.e. irrespective of how it was made) or in a narrower ‘process’ sense (i.e. made according to a particular manufacturing process). As Bud (2008) explains (“Upheaval in the moral economy of science? Patenting, teamwork and the World War II experience of penicillin.”), this apparently ethically motivated decision took place against the background of British shock at finding that an American scientist had patented a method of enriching vitamin D in foodstuffs, which built on scientific work on vitamin D undertaken in the United Kingdom and which had important public health consequences. One British civil servant pithily complained that: “It seems intolerable that we are debarred from freely using vitamin D, which is known to be an essential food factor, except on payment of a tribute to a foreigner whose contribution to the isolation and identification of the substance has been relatively small.” (Bud 2008). We would not perhaps choose to express our sentiments in quite the same way today but the feeling is unfortunately one still readily recognisable: the patent system rewards an inventor for their invention and makes no demands on them regarding the mountain of publicly undertaken scientific work on which it may rest. To the extent that patents were sought for the improved fermentation techniques developed by the American government, the prevailing policy reportedly required non-exclusive royalty-free licences to be granted to any interested parties. It appears that no patent barriers existed to hamper partners in the public / private collaboration in the United States either manufacturing penicillin or developing improved processes to do so.

Patent problems were foreseen, however, by both the British and American governments should any of their pharmaceutical firms develop and patent a commercially viable synthetic pathway for penicillin production. The risk that one firm might have a monopoly over such an important new medical asset was a risk too great to ignore. The British ambassador to the United States explained to the British government that: “Any one of these patentees may be able to block some important step in production or levy extortionate tribute on a drug of benefit of humanity.” (Bud 2008). Two mechanisms appear to have been suggested to avoid having to resort to ad hoc compulsory licensing. One was a “...national holding trust to which all penicillin-related patents would be assigned, irrespective of their origin.” (Bud 2008). The other, which was the mechanism chosen, involved the British and American governments negotiating a complex synthetic penicillin patent licensing agreement. This agreement featured a tiered approach: non-exclusive royalty free licences to all relevant patents for all purposes were to be provided to both governments and to just one pharmaceutical firm, Merck, whereas other pharmaceutical firms judged to have made a lesser contribution were to be provided with, for example, non-exclusive royalty free

licences only to publicly held patents and for more limited purposes. Ironically, due to the failure to find such a commercially viable synthetic pathway in time, this complex agreement was never used.

Penicillin production and know-how during World War II.

In addition to not being hampered by patents, perhaps the key feature of the collaboration from an intellectual property perspective was that the WPB not only freely passed on any valuable know-how resulting from the government R&D to all its partners but also asked those partners to freely share with each other any valuable scientific information or manufacturing know-how they had developed. The penicillin project 'czar', Albert Elder, said that: "...attaining maximum production today depends upon the efficient harnessing of the 'know-how' recently developed." (Quinn 2013). He further indicated that: "...it is entirely possible that some one producer may make such a drastic improvement in the process that total needs for penicillin could be met very quickly by applying this information to all of the production facilities." (Neushul 1993). Although the larger pharmaceutical firms such as Merck, Pfizer and Squibb were reportedly reluctant to share everything, since the stakes were so high "...the techniques and productive Penicillium strains were made available to all corporations..." (Neushul 1993), making a huge contribution to "...ensuring an industry-wide adoption of the most valuable wartime developments in penicillin production." (Quinn 2013).

Public vs private penicillin production after World War II.

This lack of patents and free sharing of manufacturing know-how did not survive the war and American (and other) pharmaceutical companies thereafter began to amass commercially focussed intellectual property portfolios relating to penicillin production which helped to propel them to become the 'big pharma' firms we know today. The ultimate source of these huge commercial rewards has not been forgotten by Oxford University and in the context of the recent discussions between Oxford University and big pharma firms over the Jenner Institute's Covid-19 vaccine, Prof. Louise Richardson, the Vice-Chancellor of Oxford University, explicitly noted that it would "...not repeat the mistake of the early 40s when Oxford academics discovered penicillin but handed all rights off to American companies." (Richardson 2020).

Public vs private penicillin production in newly independent India.

An interesting 'second act' of this penicillin production story, especially again as regards know-how, played out afterwards in India. The government of Jawaharlal Nehru decided that it was important to create domestic penicillin production capacity in India. As Tyabji (2004) explains ("Gaining Technical Know-How in an Unequal World: Penicillin Manufacture in Nehru's India"), two options were presented. The WHO and UNICEF together strongly encouraged India to create a publicly owned antibiotic research, training and production facility. The WHO and UNICEF committed to supporting such a facility with funding and equipment and, moreover, gave "...assurances that WHO could provide all the needed technical know-how and assistance." (Tyabji 2004). The facility would be required to freely

exchange newly developed manufacturing know-how with other publicly-owned facilities in an international network that the WHO and UNICEF were trying to establish. Alternatively, Merck offered to assist India in setting up a penicillin production plant on commercial terms, licensing what was now its own know-how, which would require "...royalty payments for fifteen years and continued financial obligations even after that." (Tyabji 2004). Following what was evidently a heated struggle between opposing policy camps, including detailed discussions of patent and know-how issues, the Indian government chose to go with the WHO and UNICEF. Penicillin production at scale began at a newly created and publicly owned facility in 1955.

Conclusions.

It is clear, even on the basis of this brief outline, that the way in which penicillin production was successfully urgently scaled-up in the United States during World War II (and afterwards in India) holds some important lessons for urgently scaling-up the production of Covid-19 vaccines today. The relevance of this remarkable example has unsurprisingly therefore often recently been flagged (see, for example, "What the development of penicillin tells us about developing a coronavirus vaccine", D. Drollette, Bulletin of the Atomic Scientists, May 18, 2020) but it seems likely that it could be used even more forcefully yet, and it certainly deserves to be brought to as wide an audience as possible. It also seems likely that, building on, for example, Neushul (1993), Bud (2008) and Quinn (2013), a deeper dive into the specific intellectual property issues as they bear on scaling-up Covid-19 vaccine production is warranted.

Of course, it will be more challenging to ensure that the necessary intellectual property is adequately shared on a global rather than national basis, not least in terms of the lack of commensurate 'executive' powers, but this example strongly suggests the importance of doing so if optimal scaling-up of Covid-19 vaccine production is to occur at as many sites as possible.

Pharmaceutical firms should therefore be encouraged (or, should it be necessary, compelled) to share their patents, their manufacturing know-how and other relevant intellectual property rights as widely as could possibly make a useful contribution, whether via their own consortium-based voluntary licensing programs and / or via publicly-mediated technology transfer and scaling-up programs. The Medicines Patent Pool (MPP) is already fully operational but other sharing mechanisms such as the WHO Covid-19 Technology Access Pool (C-TAP), or indeed any other equivalent mechanisms, should be brought to ready operational status to support these initiatives as quickly as possible.

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