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Perspective

# Can global pharmaceutical supply chains scale up sustainably for the COVID-19 crisis?

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The COVID-19 pandemic has escalated into the largest health crisis of the 21st Century. According to the COVID-19 situation dashboard of the World Health Organization (WHO), the virus has infected more than 900,000 people worldwide to date, and has also killed over 45,000. Epidemiological projections show that the outbreak can overwhelm even well-developed healthcare systems (Ferguson et al., 2020). Many countries have thus imposed pandemic suppressions measures such as lockdowns and community quarantines in an effort to stem the progress of the pandemic. In response to these dire forecasts, research and development on COVID-19 vaccines and antivirals has been intensified. For example, the WHO is undertaking the SOLIDARITY drug trials to determine the efficacy of remdesivir, chloroquine/hydroxychloroquine, ritonavir/lopinavir and ritonavir/lopinavir-interferon-beta for treatment of COVID-19. As these pharmaceutical products are already in the market for treatment of other diseases, SOLIDARITY can potentially deliver solutions to the pandemic much faster than normal, bypassing many regulatory hurdles in the commercialization of novel drugs. However, given the projected global magnitude of the pandemic, the scale up of pharmaceutical supply chains to meet the demand surge in an equitable and sustainable manner will be a major challenge.

Let us consider the case of chloroquine and its hydroxy-derivative hydroxychloroquine, which are originally antimalarial drugs that are seen as promising candidates in the SOLIDARITY trials. Over the years, chloroquine and hydroxychloroquine have also found other uses as treatment for lupus and rheumatoid arthritis, among others. With millions of people suffering from such illnesses, large chloroquine and hydroxychloroquine production facilities were already in place even prior to the COVID-19 pandemic. The synthesis of chloroquine can be done via the reaction of 4,7-dichloroquinoline and 4-diethylamino-1-metylbutylamine; on the other hand, hydroxychloroquine can be obtained via the reaction of 4,7-dichloroquinoline and 4-[*ethyl*(2-*hydroxyethyl*)*amino*] − 1-methylbutylamine (Vardanyan and Hruby, 2006). As shown in Table 1, these immediate precursors are themselves synthesized from other specialty chemicals via supply chains that can ultimately be traced back to feedstocks such as petroleum. At present, most of the production capacity of these drugs and chemical precursors are in the United States, China and India. As the global number of Covid-19 infected persons is still continuously increasing, with projections pointing to millions of active cases at its peak, and with each patient needing similar daily dosages as malaria victims during the span of the treatment period, there is really a need for pharmaceutical firms to step up production. Also, it is noted that the chemical reagents or raw materials are only limited down to the ones that are generally manufactured by the chemical industry. That way, drug manufacturers can effectively be relieved of basic materials sourcing, crude purification and preliminary synthetic procedures.

The case of chloroquine/hydroxychloroquine illustrates many of the potential hurdles in the anticipated scale-up of the supply chains of future COVID-19 drugs. While efforts to ramp up the production of future COVID-19 drugs must be done rapidly in order to keep pace with the surging demand, potential bottlenecks may be encountered either in drug synthesis capacity, or in the upstream supply chain from which specialty chemical precursors are sourced (Rajeev et al., 2019). Planning is further hindered by the lack of solid scientific knowledge about COVID-19, which makes demand projections highly uncertain. Compounding the challenges of rapid scale up are problems caused by the disease itself. Global supply chains have been disrupted due to loss of labor and raw material inputs, creating ripple effects that cross national boundaries (Yu and Aviso, 2020). Shortages may also prompt countries – in the spirit of self-interest – to impose restrictions on the export of these drugs or their chemical precursors. The environmental impacts occurring throughout the life cycles of these pharmaceutical products will also be magnified by the sheer scale at which they are administered as the pandemic progresses. For example, un-metabolized drugs and their metabolites are widely regarded as emerging trace pollutants which are problematic because conventional sewage treatment plants cannot destroy them (Gogoi et al., 2018). The quantity of these trace pollutants in sewage will certainly increase during the pandemic, and

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**Table 1**
Chemical precursors for the synthesis of chloroquine and hydroxychloroquine.

| Immediate precursors | Specialized chemical precursors | Industrial chemical precursors |
|---|---|---|
| • 4,7-dichloroquinoline<br>• 4-diethylamino-1-metylbutylamine<br>• 4-[*ethyl*(2-*hydroxyethyl*)*amino*] − 1-methylbutylamine | • 3-choroaniline<br>• ethyl 3-oxopropanoate<br>• ethyl acetoacetate<br>• 2-diethylaminoethylchloride<br>• 1-chloro-4-pentanone<br>• 2-ethylaminoethanol | • benzene<br>• acetic acid<br>• ethanol<br>• ethylene<br>• ammonia<br>• methanol<br>• sulfuric acid<br>• hydrochloric acid<br>• nitric acid<br>• ferric chloride |

unnecessarily so if the drugs are used indiscriminately. Based on these concerns, five urgent research and development challenges for pharmaceutical supply chains can be identified:

- Decision-making under epistemic and stochastic uncertainty.
- Optimal supply chain planning taking into account agility, resilience and sustainability.
- Game theoretic analysis of conflicts of interest among agents in global value chains.
- Life-cycle sustainability assessment of pharmaceutical product systems.
- Development of drug allocation strategies under resource or supply constraints.

These five priority areas show substantial overlap with many recent topics published in *Resources, Conservation and Recycling* (e.g., Rajeev et al., 2019). The global scientific community has been galvanized into action in a frantic search for a cure for COVID-19. Once effective pharmaceutical treatments are found, there will be the major engineering challenge of ramping up production at a rate that matches the pandemic. It is important to maintain a proper system-wide perspective to ensure that the complex sustainability aspects of rapid production scale-up are anticipated and addressed accordingly.

## Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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