Generic drug repurposing for COVID-19 and beyond

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Summary: COVID-19 is an all-out attack on our lives and our economy. We need a proportionate all-in response. Government leadership in generic drug repurposing should be part of that response.
Abstract:

The novel disease caused by the SARS-CoV-2 virus (COVID-19) is both a shock to our health and our wealth, with more than 110,000 dead in the U.S., the sharpest reduction in economic activity since the Great Depression, and (thus far) $3 trillion in federal fiscal relief. These massive costs imply that there are enormous social returns to therapeutic development that would either prevent, or treat, COVID infections effectively.

Much of the attention of U.S. policy makers has been focused on scaling up manufacturing capacity for COVID-19 vaccines. There has been less policy attention paid to the development of therapeutics. For novel therapeutics, patent protection allows for innovators to charge monopoly prices far exceeding the costs of new drug discovery, development, and manufacturing, making these markets attractive for private company investment. But the private sector has little incentive to pursue another important avenue: drugs that have already been approved to treat another disease might be repurposed to prevent or treat COVID-19.

Repurposed drugs have been successfully developed to treat a wide range of diseases, including rare genetic disorders, cancer and infections. They can be brought to market quicker and more cheaply than new drugs, because their safety is already established and manufacturing processes are well understood. In comparison to vaccines, repurposed drugs have the advantage of having low liability risk, and they are easily accepted into routine clinical practice. Scientists have already identified over 100 candidates for repurposing drugs that might be used alone or in combination to prevent or treat COVID-19.

However, in many cases repurposed drugs do not appeal to private sector innovators and financiers in the same fashion as new therapeutics, because they often lack the opportunity for the innovator to patent the intellectual property developed thereby limiting profits. Incorporating drug repurposing into the U.S. government’s COVID-19 response would remedy this market failure.

Developing any drug to treat COVID-19 faces another challenge: identifying enough patients to successfully enroll and complete the requisite clinical trial to establish the drug’s safety and effectiveness. Reports are already emerging of shortages in the number of new patients eligible for tests of drugs aimed at treating COVID-19. This is in part because so much attention has been placed on hydroxychloroquine - despite very limited evidence supporting its’ effectiveness in treating COVID-19. These trials have limited coordination among them, using up the limited pool of available patients and therefore limiting our ability to thoughtfully investigate a broader portfolio of promising candidates.

We propose a three-part plan for U.S. leadership. The objective of this plan is to advance a low cost, high impact response to fighting COVID-19 and future pandemics. The plan is built on current public agency infrastructure, employs public-private partnerships with established academic laboratories, clinical development networks and drug manufacturers and will pay prizes to innovators that successfully bring repurposed drugs to market. Public agencies will fund studies aimed at identifying promising drug repurposing targets and coordinate clinical trials of promising candidates alone and in combination with new therapeutics. Government will also contract for the manufacturing of promising candidates, paying costs plus a premium to ensure sufficient capacity for the exploration of new uses without undercutting the adequacy of supply for existing uses. We estimate the total cost per therapeutic successfully developed and produced from this effort would amount to on average $200M.
Background on Therapeutic Paths to Combatting COVID-19

COVID-19 disease follows a predictable progression - from infection of one individual, possible transmission to others, to disease progression, including symptom development in some individuals, and then full recovery, partial recovery, or death. This should be a strong argument for amelioration of disease and more public investment into prophylactic approaches, approaches that will not just prevent death, but also long-term problems such as loss of lung function, need for dialysis, or neurological sequelae. We need to make COVID-19 not only a survivable illness for those that are high risk, but also a disease that doesn’t leave behind a chronically ill population that can no longer contribute to the workforce.

We can divide interventions into three types: (i) intervening prior to the virus taking hold in the body, including the use of vaccinations and antivirals; (ii) intervening after diagnosis, but prior to symptom onset; and (iii) intervening to slow or stop disease progression. The second and third categories include therapeutics that prevent or limit the damage the virus can inflict, by protecting vital organs or properly calibrating immune responses. Examples in the second category include steroids (Figure 1).

Figure 1: Therapeutics aim to reduce COVID19 infection incidence, person to person transmission, disease severity and death.

An Appendix available upon request shows examples of therapeutics to fight COVID-19. Using a variety of public domestic and international sources we identified 267 candidates. This list is not comprehensive but it shows the scope for the search for therapeutics against COVID. We have identified the name of the product, the countries conducting clinical trials when available, the mechanism of action, the stage of trial, the route of administration, whether the drug is on the World Health Organization’s (WHO) list of essential medications - an indicator of the drug’s clinical effectiveness for non-COVID disease and affordability, if the product already has been developed and approved for at least one indication, manufacturer, the date that the drug was approved, and whether the drug is has already lost patent protection and is available as a generic or biosimilar. We have compiled some summary statistics based on this list enumerated in Table 1.
Table 1: Summary of therapeutics in development for COVID-19, last updated June 22, 2020, vaccines, plasma and monoclonal antibody-based therapeutics excluded from this list. See Appendix for sources and details.

Based on this list, we have some observations. First, new products and potential repurposing therapeutics are evenly split in number. Among the latter category, 70% are generics or biosimilars, the remainder are branded drugs already approved and enjoying patent protection for a non-COVID-19 indication. Second, among drugs that might be repurposed, approximately two-thirds are currently in clinical trials. Based on the views of clinical experts and a review of relevant literature, the evidence suggests that there are many more promising generic drugs that might be effective treatments for COVID-19 if investigated. Third, among the repurposing drug candidates in clinical trials, more are in foreign trials overseas (43% foreign vs. 57% domestic) and among these many appear to be funded by foreign governments or the innovators themselves. Novel drugs appear to be more commonly in domestic trials compared to drug repurposing candidates. Fourth, most of the repurposed drug candidates in trials are in the later stages of development (phase 3+) whereas the majority of the novel drugs in trials are in earlier stages of development (< phase 3).
Market Failures in Generic Repurposing

The biopharmaceutical sector has produced many path breaking drugs that save millions of lives annually, while innovators and their investors have been handsomely rewarded. Nevertheless, drug development is a risky, lengthy and expensive business. It takes more than 10 years to bring a drug from pre-clinical testing through to approval. Approval rates rise as therapeutics progress from pre-clinical testing to later stages in development; whereas only 15% of therapeutics in phase 1 testing are expected to gain approval, 50% of therapeutics in phase 3 clinical trials are expected to gain approval.\footnote{Visible successes hide critical market failures that are prominently present in the case of COVID-19. Many drugs that have a large benefit to society that cannot be monetized in a way that provides high returns to investors will not be the focus of research and development by commercial drug companies.}

Repurposing of generic drugs to fight new disease represent an important case in point. Off patent drugs can easily be produced if from public information without fear of violating intellectual property protections. That means that any attempt to charge much above the marginal cost of production and distribution will lead to new firm entry and a return to marginal cost pricing. Such entry is not costless, and generic drug manufacturers can make some profit. Yet, when generic drugs are successfully repurposed, most obtain some type of market exclusivity related to their reformulation or approval for a rare orphan or pediatric disease. There are success stories of therapeutics that have been repurposed for pediatric hematologic and/or oncologic conditions, including chloroquine to treat sideroblastic anemia and gabapentin to treat Opsoclonus-myoclonus.\footnote{\footnote{\footnote{In each of these examples, some patent protection or market exclusivity was awarded to the repurposed product to guarantee sufficient rewards to their innovators.}}}

For each of these successes, there are many more generic drugs that might hold clinical promise but remain unexplored because innovators view the revenue potential as small compared to the development costs and the risks. It will therefore be hard to adequately monetize the benefits to justify a large new investment in trials to demonstrate the efficacy of a repurposed drug. As a result, there is too little activity in this area. Repurposing of any drug as a treatment for COVID-19 faces another key challenge: identifying enough patients to successfully enroll and complete the requisite clinical trial to test therapeutic efficacy. Reports are already emerging pointing to shortages in the number of new patients eligible for trial participation creating competition among potential therapeutic agents being tested to recruit patients. The result can be that all trials in an area come up short of an adequate number of patients for testing efficacy. Given the financial incentives at work in our current system, the limited patient pool tends to be prioritized to trials for novel therapeutics over generic repurposing candidates despite equal promise in treating COVID-19. These challenges are increased when multiple potentially redundant trials testing the same therapeutic are initiated by different investigators.\footnote{This challenge was also a concern when the U.S. and the international community faced other infectious disease threats including Ebola.}

There are also economic incentives that make pursuing novel therapeutics more attractive than repurposing drugs. While academic investigators might be interested in exploring new uses for old drugs, they face pressures from a peer reviewed funding stream that prioritizes new
discoveries and that offer them and their institutions the opportunity to make profits by partnering with innovator pharmaceutical companies.

Finally, those investing in therapeutics to prevent or treat COVID-19 face the threat of a potential winner take all market, where the first vaccine or therapeutic to market may obviate the need for follow on innovation. This is a different market dynamic than that observed in non-infectious chronic disease where multiple therapeutics are frequently approved in sequential order, covered by insurers and compete for market share, guaranteeing some return on investment to innovators. The risk to investors is compounded in infectious disease when the threat itself may resolve over time, as occurred in addressing Zika, and as a result government priorities in supporting therapeutics efforts may wane (see below for more details).\textsuperscript{x}\textsuperscript{i}

The payoff to overcoming these challenges and widening the number of COVID-19 therapeutics available to prevent and to treat COVID-19 is substantial. First, government investment in the repurposing of drugs to prevent and treat COVID-19 will substantially widen the possible “shots on goal” to recover our health and our wealth. As such it represents the pursuit of a portfolio approach to addressing COVID-19 suggested by Athey et al. (2020). Second, the probability of approval for repurposed drugs is more than twice that of novel treatments since repurposed candidates have established safety profiles and thus can go directly into phase 3 clinical trials. The time to approval for repurposed drugs is also likely to be greatly reduced compared to new drugs.

Third, relative to new and repurposed branded drugs, repurposed generic drugs offer the possibility of a much lower price after development, increasing affordability and access particularly among budget constrained payers and patients in U.S., including the public insurers Medicaid and Medicare and their beneficiaries. As a consequence, the development of repurposed generics is not only critical for the U.S., but for the rest of the world as well. Expensive patented drugs are not affordable for developing nations – leading to undertreatment and an inability to fully eradicate the disease. We suspect this is one reason why so many of the repurposed drugs in clinical trials are being pursued by innovators outside the U.S.

Fourth, public leadership in the development of repurposed generics transforms the availability of competing manufacturers from a problem, due to the disincentive for private investment, into an opportunity, where production will be inexpensive after research is complete. Currently, a major disincentive for investment in repurposed generics is that there may be other generics that could easily substitute – undercutting any market power for the first entrant. But if the government’s goal is to simply maximize supply, encouraging private entry by competing generics is a positive, rather than a negative. Public leadership to indicate opportunities for repurposed generics can productively generate follow on investment.

Finally, it is worth noting the cost of inaction in repurposing drugs. First, as a result of the current environment for research and funding, most trials to date for repurposed drugs have focused on hospitalized patients, even though prevention might be more valuable and effective if initiated earlier in disease progression. Second, there has been substantial inefficiency to date in an environment of limited resources and access to patients to participate in trials. According to a recent analysis of clinical trials conducted in the early months of the pandemic, most studies were destined to be uninformative from the start, for reasons ranging from insufficient sample size, lack of a control group, and duplication, despite the fact, had the trials been better designed and coordinated, the overall patient population enrolled in trials would have been large enough to
provide meaningful answers about the efficacy of a variety of potential treatments.\textsuperscript{xii} Instead, most of these questions remain unanswered.

The recent case of hydroxychloroquine in COVID-19 is a leading example of what went wrong. Claims based on very limited evidence about the drug’s effectiveness in treating COVID-19 recently led to a massive rise in demand over a few months, potentially exposing many people to harmful clinical effects and financial demands without any potential for therapeutic benefit. A large number of small, poorly designed trials were started, slowing the path to learning about the lack of efficacy, while exposing clinical trial patients to risk without a corresponding benefit to scientific knowledge. The widespread use of the drug further complicated analyses of other therapeutic strategies, as patients were treated with hydroxychloroquine in unsystematic ways. If the treatment had been effective, the result would have been inequitable distribution of the treatment, while in the absence of benefit, it redistributed the drug away from more vulnerable patients who needed it for other conditions. We expect these challenges may become increasingly reported for many promising therapeutics that entail repurposed products alone or in combination with new drugs that are produced by a limited set of manufacturers supplying global demand. This example also highlights the importance of a rigorous scientific evaluation of candidates for generic repurposing. It also highlights a potential role for the public sector in ensuring adequacy of drug supply to satisfy existing demand, support clinical trials utilizing these products and securing sufficient supply to meet potential increases in demand once news of successful early results becomes public.

**Government Successes – and Challenges**

It is well known that the U.S. government commonly invests in pre-clinical research that may lead to the development of new therapeutics. Less well appreciated is that government also plays a proactive role in the development of vaccines and therapeutics to protect the nation against chemical attacks and pandemics through the Department of Health and Human Services’ Biomedical Advanced Research and Development Authority (BARDA) and in the repurposing of drugs through the National Institutes of Health’s National Center for Advancing Translational Sciences (NCATS) program.\textsuperscript{xiii} Our proposal builds on the experiences of these existing programs.

BARDA was established in 2007 to contribute to national security against threats from chemical, biological, radiological, nuclear threats, and those emanating from pandemics. BARDA’s role is to promote the development of medical countermeasures. These include therapeutic drugs, vaccines, and diagnostic tools. BARDA activities can be seen as involving three somewhat distinct stages: basic discovery, clinical development and manufacturing/scaling. In each case, BARDA plays a crucial “air traffic control” function that the private sector is unable to provide. BARDA funds research and development (R&D), and further provides technical assistance and supports R&D by organizing clinical research. In addition, BARDA creates manufacturing capacity by developing manufacturing networks as well as by directly contracting for capacity that will be available when the need arises – even before that need is evident.

BARDA’s work is exemplified by its efforts to develop therapeutic drugs against the threat of Anthrax. Anthrax therapeutics were among the first projects pursued by BARDA. BARDA contributed to the development and supported the path to manufacturing for three therapeutic products: Anthim (obiltoxaximab), Raxibacumab, and Immune Globulin (which is
also being tested for use in treating COVID-19). In the case of Anthim, basic discovery work had been supported by $22 million in grants from the NIH and the Department of Defense (DOD) to a private firm, Elysis, prior to the establishment of BARDA. BARDA then participated in additional development work with the NIH investing an additional $12 million. Based on that work BARDA entered into a five-year contract for advanced development and manufacturing worth $143 million. The manufacturing work was conducted by a joint venture of Elysis and Lonza, a Swiss manufacturer of the Active Pharmaceutical Ingredient (API). The two other products followed similar paths to developing patented therapeutics. BARDA spent approximately $200 million to ensure GlaxoSmithKline’s development and production of the antitoxin Raxibacumab.

BARDA has also led in the development of vaccines and treatments for Zika and Ebola. For Zika, BARDA awarded $133 million in vaccine award funding, $30 million in diagnostic funding, and $119 million in therapeutic funding. For Ebola, BARDA awarded $208 million in vaccine funding and $192 million in therapeutic funding. The results have once again been very positive, resulting in the world’s first Ebola vaccine.

But one feature marks BARDA’s investments to date: they commonly lead to newly patented medical products. This makes some sense: The existence of patent potential provides a strong “pull” incentive for private developers to use initial BARDA funding to undertake risky ventures. These are also the potential products that manufacturers explore first since that carry the greatest profit potential. The ability of private industry to patent products resulting from BARDA support also reduces the budgetary cost to BARDA of encouraging new therapeutic development. However, this feature also imposes new costs to society since buyers must pay the monopoly prices of the drug developer, and it creates a missed opportunity to explore potentially useful products for treating COVID-19. Pursuing the repurposing of generic drugs would require BARDA to take a more aggressive role, since it may not be able to rely on the patent incentive to encourage potential private sector partners. In essence, public intervention would reduce risks and development costs and increase the revenue potential. We provide a plan for such a role here.

The challenge facing BARDA is a common one for government agencies: the vagary of appropriations. Consider the example of the Zika vaccine. The federal government awarded Sanofi $43 million in 2016 to help develop a Zika vaccine. In August 2017, despite significant progress, BARDA cut back funding because the government had shifted its priorities, and Congress opted not to renew the one-year supplemental appropriation it gave BARDA during the Zika outbreak. Meanwhile, Sanofi had devoted significant resources to vaccine development and delayed other pipeline projects – and preliminary results published after the drop in funding offered very promising results. Despite this, the funding cutback resulted in the end of the project, creating perception that funding commitments associated with outbreaks might not be reliable, thus undermining future investment incentives.

This example suggests the importance of a dedicated and committed funding stream for emerging infectious diseases of pandemic potential, such as COVID, that is safeguarded from politics. Currently, BARDA relies on supplemental funding during public health crises, and not regular appropriations to guarantee ongoing support to those developing new vaccines and treatments. It also suggests that development of COVID-19 therapeutics might be best served by making more regular payments to innovators for reaching specific milestones along the development continuum.
Indeed, recent developments suggest political risks to BARDA’s role in fighting COVID-19. BARDA’s recent announcement that it would no longer support development of therapeutics highlights this issue. This may represent a form of government failure in the sense that funds are not being invested where market failures are significant and potential social benefits are large. For this reason, Congressional action using appropriation legislation to direct the use of funds would be necessary.

And while the U.S. government moves backwards, other nations move forwards. The UK Recovery trial is a large multi-arm trial testing two repurposed generic drugs and one branded combination. This trial has already shown that steroids have efficacy in COVID-19 inpatient treatment – at an all-in budgetary cost of 2 million pounds! This is the type of model on which the U.S. should be leading, not following.
Pursuing an “All in” Strategy: A Plan to Effectively Develop and Repurpose Existing Therapeutics to Fight COVID-19 and other emerging infectious disease

The CARES Act directed $3.5 billion towards development of vaccines and therapeutics related to COVID-19 and the manufacturing capacity to serve the nation with those products. Those funds can be used for the construction and renovation of production facilities that are either publicly or privately owned (Title VIII of CARES). The HEROES Act adds an additional $3.5 billion to BARDA for development of therapeutics and vaccines plus $500 million for manufacturing of products.

We propose a specific dedicated program devoted to pursuing, developing, and manufacturing promising repurposed candidates to fight infectious disease, beginning with COVID but continuing onwards to protect us against evolving risks: the repurposed generic development program (RGDP) (Figure 2). The RGDP could be an independent organization, or it could be housed within existing agencies such as BARDA, the NCATS at NIH, or others. Regardless of the organizational bureaucratic home, the key would be to outsource each step of the process to private sector partners – while playing a key “traffic” coordination role.

**Figure 2:** The Repurposed Generic Development Program (RGDP) functions and organization structure overview

The RGDP would play two key functions: financing and coordination. The financing would come from the dedicated appropriation. The coordination would be in three critical areas of “air traffic control.” The first is in coordinating the selection of pre-trial candidates, and the prioritized platform trials of this set of candidates. The second is solving the problem of allocating patients across trials to ensure that the most promising trials have sufficient patient
population to quickly determine effectiveness. And the third would be in coordinating manufacturing with trials to ensure adequate supply during the development period and a ready, accessible supply once the drug(s) are approved.

In particular, the RGDP goals would be:

1. Funding the initial screening and structural biology of pre-clinical research, including animal studies, for a broad range of promising candidates, as well as retrospective analyses of widely prescribed generics to support the planning and prioritization of clinical trials
2. Organizing a network of organizations to test promising products in clinical trials
3. Prioritizing drugs for study, as is done in Europe and by the WHO.
4. Playing a crucial “air traffic controller” role of ensuring that sufficient numbers of patients are recruited, allocated to the trials of promising therapies and trials are completed in a manner that facilitates regulatory approval and widespread use
5. Contracting and paying for the advanced development and manufacturing of promising treatments and scaling if and when the product demonstrates efficacy
6. Purchasing adequate supply for treatment of disease

To carry out this mission, the RGDP would focus on three separate streams of work – streams that are not distinct from each other but coordinated to ensure effectiveness:

Stream 1: Funding Pre-Trial Work

In the first stage, the RGDP would work from a pre-selected list of promising candidates to fund pre-trial structural biology work. The RGDP would contract with a set of structural biology operations to carry out the screening and other pre-clinical work, both paying for the costs of the work (push) and providing prizes based on both investigating candidates that make it to clinical trial and investigating candidates that successfully makes it through trials (regardless of whether the product is needed or the need subsides). For treatments that are widely prescribed for other conditions, the RGDP would conduct retrospective analyses of patients who have taken these drugs historically in order to assess outcomes for relevant populations and in particular study patients who were taking the drugs at the time of COVID-19 infection.xv

Cost and Time Estimate: Examining recent NIH, DOD and BARDA early stage development of therapeutics for Anthrax and Hydrochloriquine for COVID 19, indicates that spending at the pre-clinical stage ranges from roughly $20 million to $50 million. These estimates are similar for early stage development under BARDA of vaccines for Ebola and Anthrax. For Ebola, the range of pre-clinical spending was $20 million to $50 million. For Anthrax, the corresponding expenditures ranged from $34 million to $57 million.

Previous examples have relied on relatively small “pull” incentives. The range of prizes falls in the range of $50,000 to $200,000.xvi

Stream 2: Funding Clinical Trials

The most important challenge facing the RGDP is prioritizing and coordinating clinical trials. The “all in” strategy for fighting infectious disease suggests taking many shots on goal – but not shots in the dark. The existing lack of coordination across trials can lead to poor comparability – and, more importantly, wasting of volunteers on too many control arms. For this reason, experts such as Janet Woodcock, director of FDA’s Center for Drug Evaluation and
Research, have emphasized the role of “master protocols – trials that examine the safety and efficacy of many agents in parallel rather than the traditional trial that just looks at one drug candidate… which could allow for rapid elimination of less promising agents and the quick selection of more promising ones to move forward into more extensive evaluation.” This is an approach which is being embraced haltingly in the U.S., but much more aggressively in the other nations such as the UK.

In particular, the RGDP should set up and contract with network of research organizations capable of recruiting a sufficient number of patients to the trials and carrying out the completion of the clinical trials. The RGDP will ensure resources are in place to coordinate the network, give the organizations sufficient resources to meet trial recruitment goals, complete planned data analysis, and take responsibility for common administrative tasks associated with the trials. The RGDP would consider societal objectives such as acquiring a patient pool that is sufficiently representative of impacted demographic groups, and considering the most effective and ethical approaches to assess efficacy for vulnerable populations. Other public and private funders of clinical trials can be encouraged to coordinate with the RGDP in order to align incremental funding better with societal need and avoid inefficient duplication, ensuring that trials enrolling patients truly meet the stated objective of advancing knowledge.

The RGDP will act as the facilitator between the institutions and the FDA, working to minimize barriers such as the establishment of a centralized IRB (as has already been established for cancer clinical trials), the pre-approval of adaptive-designed clinical trials by the FDA and associated sample sizes and trial endpoints, expedited review and approval by FDA, and relabeling of original generic drugs. Through discussions with experts, we believe FDA’s pursuit of a highly expedited review and manufacturing approval process may shave 3-6 months off of typical development times.

The RGDP will reimburse all clinical costs and provides a prize for candidates that successfully make it through phase 3. The magnitude of the prize will be tied to both rewarding speed of development and demonstrated efficacy in clinical effect. The RGDP must also ensure sufficient manufacturing capacity is available in Stage 2 to ensure successful trial completion and availability after approval. Ongoing investments in continuous manufacturing can contribute to speed of drug production and national independence in manufacturing.

Cost and Time Estimate: An upper bound on the expected costs of later stage development of promising therapeutics can be gleaned from examining reports on repurposed drugs and from advanced development contracts for promising therapeutics issued by BARDA. The repurposing of a drug to fight sleeping sickness (fexinidazole) cost roughly $55 million in 2009 (Mullard, 2019). Advanced development contracts for Anthrax therapeutics issued by BARDA since 2010 were in the range of $50 to $57 million. This is an upper bound since it includes some manufacturing costs.

Stream 3: Secure and Consistent Manufacturing

In the third stream, the RGDP would establish contracts with manufacturing organizations to produce the final therapeutic formulation. This would mirror past BARDA contracts, but critically it would have to guarantee support to cover the costs of manufacturing all necessary units (so as not to leave manufacturers “hanging” if the threat of COVID wanes). This would alleviate innovator concerns of inconsistent incentives for development.
Contracts would have to be written early in the trial process, similar to that advocated for vaccine development. This is critical for two reasons. First, as noted above, early indications that repurposed generics have promise as a treatment might lead to a run on the products, leaving insufficient supply to carry out trials. Second, should the trials prove successful, speed is of the essence in creating sufficient supply.

These considerations imply that the government should use a low/no risk approach for cost plus contract manufacturing pricing. In such a case, government could restrict costs to paying for the facility & equipment (retaining ownership for future resale if no longer needed) and then having a labor manufacturing contract with 1-year cancellation notice to allow for wind down.

In addition, there would be additional incentives (or penalties) based on speed of production adequate to meet expected demand and assurance of quality manufacturing over time. There have been some notable failures in quality manufacturing of essential generic drugs in the past that should not plague this effort.

One major concern of innovators in the repurposed generic drug space and the patented drug space is the adequacy of supply and its quality of inputs for manufacturing of the therapeutics. Contracting organizations must have a strategy for avoiding supply interruptions, guaranteeing manufacturing quality and contracts should include a penalty for supply interruptions.

Cost and Time Estimate: Recent estimates by Hill and colleagues (2020) examined the costs of manufacturing several existing small molecule drugs to treat COVID-19 (remdesivir, hydrochloriquine, chloriquine, sofosbuvir and pirfenidone). Their estimated manufacturing costs ranged from less than $0.10 to $1.09 per person per day. The ‘all in’ costs of developing anthrax therapeutics, including preclinical work, trials and manufacturing enough supply to stock the SNS stockpile for each therapeutic amounted to approximately $200 Million.

Based on past experience, investing in the development of 5-6 repurposed generic drugs that would be available to 45 million people for a month of treatment each would cost about $1 billion in the first year and considerably less in subsequent years.
ENDNOTES


v https://www.nature.com/articles/nbt.2786

vi https://www.pharmaceutical-technology.com/comment/potential-drug-repurposing-orphan-drug-development/


viii https://www.covidcp.org/

ix https://www.nap.edu/read/24739/chapter/2


xiii https://ncats.nih.gov/preclinical/repurpose


xv such as those described at https://www.ohdsi.org/COVID-19-updates/

