Medicines for All
REVOLUTIONIZING THE GLOBAL SUPPLY CHAIN

By Eric Peters

“Discovery is seeing what everybody else has seen, and thinking what nobody else has thought.”

Albert Szent-Györgyi, Nobel-Prize winning co-founder of the National Foundation for Cancer Research
According to the FDA, more than 100 drugs are in short supply in the U.S. alone right now. These are prescription drugs that are lifesaving, life-sustaining or used in the prevention or treatment of debilitating diseases and conditions. Furthermore, approximately 80% of all medications consumed in the U.S. are produced in India or China, which drastically reduces our ability to control drug supplies and causes considerable supply chain risks.

The World Health Organization and others have said this is not just a U.S. problem, but a global one, and the need for drugs is growing. More than 37 million people are infected with HIV, 219 million malaria cases and 10 million tuberculosis cases worldwide.

These issues — domestic and international drug shortages and hundreds of millions facing life-threatening diseases — are enormous and complex. Staring down one, let alone all of them, is daunting to say the least.

But the mantra of a lab in Richmond at Virginia Commonwealth University perfectly summarizes the way its students, faculty and staff have begun to approach these global challenges.

**Medicines for All: Nevirapine Results**

Changes to nevirapine production processes that Medicines for All has identified and implemented have improved:

**Nevirapine Isolated Yield**

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The isolated yield, or the amount of product obtained from the chemical reaction after purification, improved from 56% to 94%. This means that the efficiency of the process has drastically improved, and manufacturers can produce more product.

**Nevirapine Process Mass Intensity (PMI)**

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The PMI, or total mass of all materials used to produce 1 kilogram of final product, improved from 56 kilograms to 4 kilograms. This drastic reduction in the amount of materials it takes to produce the final product has reduced costs and environmental impact.
The substantial cost savings that Medicines for All has created have enabled global relief agencies to procure and distribute more HIV medications to people who need them in order to lead healthier lives or to prevent HIV transmission from mothers to their children, which is the way 90% of new HIV infections are transmitted to children.

Their creed, “Discovery is seeing what everybody else has seen, and thinking what nobody else has thought,” is an Albert Szent-Györgyi quote often shared by Frank Gupton, Ph.D., the Floyd D. Gottwald Professor and Chair of the Department of Chemical and Life Science Engineering in the VCU College of Engineering.

Dr. Gupton, a former pharmaceutical industry executive, leads VCU’s Medicines for All Institute. The institute examines commercial drug manufacturing processes to find ways to substitute lower-cost raw materials, simplify operations and increase yields. It then transfers its findings to manufacturers and suppliers that can reduce consumer prices and establish production closer to patients, where it previously wasn’t economical to do so.

This approach, and the promising findings it has produced, have caught the eye of the Bill and Melinda Gates Foundation, earning Medicine’s for All nearly $40 million in funding since 2014.

One of the institute’s first projects examined nevirapine, a widely prescribed treatment for HIV that is on the World Health Organization List of Essential Medicines. Medicines for All pinpointed inefficient chemical conditions and production processes related to the drug, then streamlined routes to the materials that come together to create its active pharmaceutical ingredient (API).

The team’s changes to nevirapine’s production improved isolated yield, or the amount of product obtained from the chemical reaction after purification, from 56% to 94%. The changes also improved the process mass intensity (PMI) value, or the total mass of all materials used to produce 1 kilogram of final product, from 56 kilograms to 4 kilograms.

Medicine’s for All researchers shared the details of their streamlined nevirapine process with the Clinton Health Access Initiative (CHAI), which quickly integrated the new process into its supply chain network in 2015. So far, savings on the cost of goods used to produce the drug have been close to 40%. This substantial cost savings enables agencies that procure and distribute HIV drugs, such as USAID, Unitaid and the South African government, to purchase more medication for the same amount of money. The extra medication then reaches people who need it in order to lead healthier lives or to prevent HIV transmission from mothers to their children, which is the way 90% of new HIV infections are transmitted to children.
healthier lives or prevent HIV transmission from mothers to their children, which is the way 90% of new HIV infections are transmitted to children globally. CHAI’s Prevention of Mother-to-Child Transmission program, for example, supports HIV-positive mothers from pregnancy and delivery through breastfeeding and into long-term care.

Anita Deshpande, who previously worked for CHAI, is the director of market engagement at the Medicines for All Institute. “I have spent time in HIV clinics across Africa, in India and in the Caribbean,” she said. “It has been clear in all of these places that securing the supply chain for these lifesaving medications will enhance the lives of all patients, including mothers, young men and adolescents. These are the drugs that allow patients to live fairly normal lives. Making sure everybody has access to them gives people an opportunity to raise their children and see those children live HIV-free lives.”

Dr. Gupton and his team have only published their nevirapine results, but they are working through manuscripts on five other medicines. In all the cases, they’re finding what Dr. Gupton calls “low-hanging fruit,” similar to what they found in the nevirapine process that is allowing them to reduce both cost and the amount of materials needed for production. These changes will lead to an estimated consumer price reduction of approximately 10% on each therapy, bringing the potential savings across several HIV regimens around the globe to almost $90 million annually.

“The medications that Medicines for All is working on are the most used HIV drugs in the world,” Deshpande said. “Securing their supply chain and improving their affordability will ensure more patients have access to these World Health Organization-preferred treatments.”

IDENTIFYING OPPORTUNITIES FOR CHANGE
How did this “low-hanging fruit” grow, and why has no one come along to pluck it from the branch until now?

Synthetic processes to develop new APIs often evolve with limited regard for commercial viability and efficiency. In many cases, these early processes help define the final commercial production processes of drugs because that is the fastest route to market. In the eventual drug price for consumers, APIs represent only about 10% of the cost, while research and development represent about 75%. Therefore, in the 20 years that follow, pharmaceutical companies put their resources into research and development of new drugs rather than fine-tuning the processes for their existing APIs.

Then, after a couple of decades, those API processes are frequently carried forward into the production of generic versions of drugs without ever being questioned. It is here that the major opportunities and “low-hanging fruit” lie, because the economics completely flip in the generic marketplace. The APIs in generic drugs now represent 50% to 70% of the selling price, so if a group could reevaluate the decades-old processes that are being used to produce the APIs, it could dramatically reduce the selling price.

“That’s exactly what we do here,” Dr. Gupton said. “We go in and look at drugs with a new set of eyes and some new chemistry tools, and we make them cheaper and more accessible.”

Another way inefficient drug production has perpetuated is through a generally accepted method known as batch production. Batch production involves making drugs in single clusters, which is a practice Dr. Gupton’s team is working on moving away from in favor of continuous manufacturing, or flow chemistry. They first completed...
their nevirapine work using a batch process, but were able to translate that drug’s process, and the processes of others, into a continuous format.

Dr. Gupton uses a metaphor about spaghetti to explain the importance of a continuous method over a batch method. The sauce is made in a batch — everything goes into the pot, cooks and then is taken out. Not only is there a beginning and an end to this process, which slows it down, it also means that each batch is going to be slightly different from the previous one. Pasta, on the other hand, can be continuous in that ingredients are going in one end of the pasta maker and coming out the other, uninterrupted. Each noodle is the same.

“Continuous processing technology is not anything new, it’s just new to the pharmaceutical industry,” Dr. Gupton said. “The FDA is really interested in implementing this for the simple reason that it creates a process that consistently produces materials that meet specifications.”

The continuous format also creates a tremendous advantage from a manufacturing perspective, which is leading to opportunities to improve domestic drug supplies. “Right now, nearly all of our drugs are being produced in India and China,” Dr. Gupton said. “One of the reasons people go to China is because of their labor costs. If you were to be able to do these processes continuously, that is, in an automated fashion, the labor requirement would go down and make it more competitive to bring these processes back to the United States.”

In bringing these processes back to the U.S., supply chains — not just for HIV drugs, but for many others that are currently produced outside of the U.S. — can be established and strengthened domestically for the foreseeable future.

**ENVIRONMENTAL IMPACT**

In addition to lowering costs and access to drugs, the fresh perspective that Medicines for All is applying is reducing the environmental impact of drug making.

Traditional commercial API processes produce between 50 and 200 kilograms of waste per single kilogram of final product.

Through its previous production processes, nevirapine produced about 60 kilograms of waste per kilogram of final product, but Dr. Gupton’s team cut that waste to just 4 kilograms. “That is unheard of in a pharmaceutical product,” Dr. Gupton said. “And since we hit that number with nevirapine, it’s the benchmark for every new process we develop moving forward.”

This dramatic reduction in waste generation was a key success factor in getting these new processes implemented at existing manufacturing facilities. China, for example, has been aggressively pursuing waste reduction related to the pharmaceutical industry and has shut down facilities that generate significant quantities. By reducing the amount of waste generated in these processes, the Medicines for All approach has enabled companies to adhere to the new regulations in the country and helped to get the new process for nevirapine implemented more quickly around the world.

Several industry groups have recognized the impact Medicines for All is making on the environment, and in 2018 the American Chemical Society presented Dr. Gupton and his colleague Tyler McQuade, Ph.D., professor of chemical engineering at VCU, with the Award for Affordable Green Chemistry and the Green Chemistry Challenge Award, which recognizes corporations and institutions for developing new chemical processes or products that reduce waste and hazardous chemicals. The team was cited for
MASSEY CANCER CENTER
The NCI-designated VCU Massey Cancer Center is in the top 4% of cancer centers nationally. It produces groundbreaking research, training and the best possible care. One barrier to the center moving into an even more elite designation is its access, for research purposes, to the absolute newest drugs that are still in early trial phases.

“The pharmaceutical companies that are developing these drugs want to control the use of them in both preclinical research and clinical trials, which is understandable,” Dr. Gupton said. “But when Massey mentioned this challenge to me, I said, ‘They publish the structures of the compounds, so there’s no reason why we can’t make them for you.’”

The Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Amendments, allows organizations to produce a drug that is under patent if that organization isn’t planning to sell it. “So, we set up a lab here, and we’ve been making the drugs for Massey for a little less than a year,” Dr. Gupton said.

“The partnership with Dr. Gupton’s Molecules for Medicine program opened a whole new avenue for Massey Cancer Center investigators to move laboratory discoveries forward to clinical trials,” said Gordon Ginder, M.D., former director of VCU Massey Cancer Center and Lipman Chair in Oncology. “We believe that growing this partnership will accelerate translational research, and with it, our ability to bring innovative new treatments to patients with cancer.”

SCHOOL OF PHARMACY
In 2019, the State Council of Higher Education for Virginia approved the nation’s first Ph.D. program in pharmaceutical engineering. The doctoral program, a collaboration between VCU’s School of Pharmacy and College of Engineering, will focus on research and training students in areas of drug product development, such as continuous manufacturing and drug-containing nanomaterials.

“We have a lot of people from the pharmaceutical industry working in the space with Medicines for All, and other researchers throughout the College of Engineering who are working with various drugs and therapies, so we can coalesce all of that activity with the School of Pharmacy to create something meaningful and unique,” Dr. Gupton said. “People have been compartmentalized in their skill sets in this industry. You have organic chemists who are focused on the synthesis and drug discovery part. Then someone must formulate the product. What if you had somebody who understood what those requirements were downstream who could interface between drug discovery and drug development? That’s where we think the sweet spot is for this degree.”

“VCU has always prepared professionals and scientists for the healthcare needs of the future, and this new collaborative Ph.D. program supports that mission,” said Joseph T. DiPiro, Pharm.D., dean of the VCU School of Pharmacy and the Archie O. McCalley Chair. “It will bring together students and researchers from the two disciplines to solve problems that will have visible and important effects on health.”

It is through this partnership that the university is teaching students, hopefully a new generation of pharmaceutical industry experts, to take Dr. Gupton’s adopted mantra about looking at familiar things with a fresh perspective into the rest of the pharmaceutical and global health world.

Barbara D. Boyan, Ph.D., the Alice T. and William H. Goodwin Jr. Dean of the College of Engineering, said, “With the creation of the pharmaceutical engineering Ph.D. program, VCU will be a national leader in the education of the pharmaceutical workforce of today and innovators leading future developments. The program will address the growing need for a new generation of researchers trained in cross-disciplinary and interdisciplinary science who recognize the need for a team-based approach to solving challenges related to the design and manufacturing of pharmaceutical products.”

“Our charter here is to train students to think differently — to use common sense,” Dr. Gupton said. “The question is how do we change the industry culture to achieve those objectives both in the training of our academicians here and when they go into the world to start implementing these key principles in the marketplace.”
outstanding success in developing a sustainable and efficient synthesis of nevirapine, resulting in reduced costs and improved access to HIV treatment.

WHAT’S NEXT?
Next year, Dr. Gupton and his team will begin working on tuberculosis and malaria drugs. “It made perfect sense to do it this way,” Dr. Gupton said. “We started with these high-volume HIV drugs. If you have a good return on investment with them, that allows you to baseload your cost here at the institute so you can now work on TB and malaria. The research on HIV drugs basically paid startup costs for moving into the new diseases. We are extremely well-equipped. The Gates Foundation has enabled us to build up this infrastructure, allowing us to look at these other drugs much more cost effectively.”

If you would like to help strengthen Dr. Gupton’s partnerships across the MCV Campus, please consider reaching out to gift officers who can help you begin the process. To learn more about the School of Pharmacy, contact Louie Correa, senior director of development, at 804-828-3016 or lacorrea@vcu.edu. To learn more about Massey Cancer Center, contact Martha Quinn, executive director of development, at 804-827-0652 or mquinn3@vcu.edu.