National drug shortages worsen during COVID-19 crisis: Proposal for a comprehensive model to monitor and address critical drug shortages

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The Food and Drug Administration (FDA) defines a drug shortage as an interruption in the total supply of all clinically interchangeable FDA-regulated medications where the supply is inadequate or expected to be insufficient to meet projected demand.[1] The most common reasons for drug shortages include shifting of a company's resources from manufacturing to research, shortage of raw materials, voluntary recalls, natural disasters, and supply issues resulting from demand exceeding production capacity.[2] Despite the United States' position as a global leader in pharmaceutical research and innovation, only 28% of manufacturing facilities making active pharmaceutical ingredients (APIs) to supply the US market were domestically based, with the remainder of being based in China (13%), India (18%), and other countries.[3]

The strain on pharmaceutical manufacturing can be amplified in times of crisis, as rapid changes to either the supply of needed resources (labor and raw materials) or demand for pharmaceuticals may occur. The lack of a robust domestic manufacturing infrastructure in the United States has resulted in frequent drug shortages of essential medical items and medications during crises. For example Hurricane Maria affected Puerto Rico's pharmaceutical manufacturing infrastructure and drastically impacted the supply of intravenous saline bags and parenteral amino acid preparations in 2017.[4] In August 2018, China reported its first case of the African swine fever virus, which resulted in the culling of nearly 50% of pigs used in the production of heparin.[5,6]

The FDA Drug Shortages Task Force has identified lower-priced drugs and sterile injectables as being potential targets of drug shortages.[7] Recommendations for addressing shortages have included taking steps to increase the understanding of reasons for shortages and contracting practices; developing a system for measuring and rating quality management of

pharmaceuticals; and considering new contracting approaches to help ensure reliable supplies.[7] Additional FDA recommendations to prevent or mitigate the impact of future drug shortages include extending expiration dates on certain products, expanding review of new drug applications, promoting generic manufacturing, and creating critical drug lists.[8] FDA has also recommended action steps that other agencies could take to address drug shortages and quality issues, including providing manufacturing incentives; using FDA-provided data on manufacturing quality when making purchasing decisions; developing redundancy, capability, and capacity in manufacturing; and minimizing the import and sale of goods by unauthorized sources.[9] However, despite these recommendations and actions, the first 3 to 4 months of the coronavirus disease 2019 (COVID-19) pandemic resulted in a greater number of shortages in US domestic medications supply than occurred in the previous 2 years. This brief report highlights drug shortages due to the COVID-19 crisis as of April 14, 2020, and provides recommendations for reducing future drug shortages in response to future threats.

Impact of COVID-19 crisis on medications supply. The COVID-19 pandemic has uncovered many issues with the drug supply chain in the United States. As the pandemic has progressed, air and ground traffic have been reduced, exports limited, and factories forced to close. In response to the growing risk of public health crises resulting from the COVID-19 outbreak, many countries around the world have attempted to secure adequate supplies of essential medications by limiting exports. India has restricted exportation of many of its API that are essential in making medications like metronidazole, clindamycin, and hydroxychloroquine.[10] Finland subsequently restricted exports of hydroxychoroquine API.[11] The European Union Commission has responded to member states holding exports of essential

medicines and creating national stockpiles by asking all members to lift export bans.[12] Also, the commission requested that member states increase drug manufacturing and monitor medication supply and demands.[13]

To ease the expected supply-side shortages, many API manufacturers have ramped up production. For example, Sanofi, who produces two-thirds of World Health Organization (WHO)–designated essential medicines, pledged that its manufacturing plants would operate 7 days a week to attempt to keep pace with increased demand.[14] Also, in February 2020 Sanofi announced that it was moving its API manufacturing to Europe, by consolidating 6 manufacturing sites into a single spinoff company, with the goal of shortening the supply chain and increasing the ability to increase production when needed.[15]

Impact of COVID-19 on demand for medications. Because of COVID-19 infections and hospitalizations, demand for a number of medications has increased. Both FDA and the American Society for Health-System Pharmacists (ASHP) have reported that many antibiotics and antiviral medications are currently in short supply. Antibiotics such as vancomycin, cefazolin, and gentamicin and many other intravenous drugs are being used in patients who experience post-COVID-19 pneumonia.[16] China supplies 80% of all antibiotics to the US market.[17] Despite claims that manufacturing plants in China have been operating normally, the United States has experienced a significant shortage of several of these essential medicines.[18] Albuterol (salbutamol) metered dose inhalers are being used to treat hospitalized patients with respiratory problems.[19] Although albuterol is manufactured in several countries, including the United States, China, Spain, Mexico, India, and the United Kingdom, the unexpected increased demand has led to shortages.[20]

Hydroxychloroquine and chloroquine, antimalaria drugs that are also used for lupus and rheumatoid arthritis, showed potentially promising results in treating COVID-19 symptoms in early trials. Despite the lack of high-quality, controlled clinical trials assessing the efficacy of these treatments, WHO identified hydroxychloroquine and chloroquine as promising treatment modalities. FDA approved them for emergency use on March 28, 2020.[21] Promotion of these drugs as potential cures subsequently led to individuals stockpiling these medications, to the detriment of those who depend on the drugs for management of chronic immunological conditions. Adding to the stress on medication supplies, the Indian government blocked the export of hydroxychloroquine and its formulations on April 4, 2020.[22]

In March 2020, the French health minister announced that ibuprofen may worsen outcomes in patients with COVID-19.[23] The resulting increased demand for acetaminophen, coupled with restricted exportation from India, left US pharmacies experiencing intermittent acetaminophen shortages.[24] Furthermore, ASHP reported shortages of metronidazole and clindamycin within weeks of India's export restrictions.[16] Even though limitations on these medications were removed by the Indian government on April 6, 2020, these drugs remained on the ASHP shortage list through April 14, 2020.[16,25] This correlation between restricted exports from other countries and shortages in the United States illustrates how foreign manufacturing of pharmaceuticals and related policies can rapidly affect domestic supplies.

As the pandemic progressed, increased demand and supply chain disruptions resulted in shortages of crucial sedative, anesthetic, and analgesic medications commonly used in mechanical ventilation for COVID-19 pulmonary complications. Examples of critical medications in shortage were dexmedetomidine, etomidate, fentanyl, hydromorphone, ketamine,

lorazepam, midazolam, morphine, and propofol.[1,16] In March 2020, there was a 51% increase in demand for sedatives and anesthetics and a 67% increase in analgesic medication demand.[26] Compounding the problem of increased demand, supply chains have also been impacted by manufacturing issues and shipping delays.[27,28]

Drug shortages as of April 14, 2020. WHO maintains a list of medications considered essential medicines that satisfy the priority healthcare needs of the global population.[28] These medications are those that WHO suggests should be in adequate quantities within a functioning health system at all times. While there may be substitutes or alternatives to medicines on this list, the inability to procure these medications may result in less effective treatment and/or a higher cost of care. Both FDA and ASHP maintain lists of medications in short supply. Between March 2018 and December 2019 (a 22-month period), ASHP reported 200 new drug shortages, whereas between January 2020 and mid-April 2020 (a 3.5-month period), 199 new drug shortages were reported. Among those medications on the ASHP drug shortage list, the 199 new drug shortages reported represented 175 unique drugs. Of these 175 drugs, 46.3% were on the WHO essential medicines list.[29] As a result of these shortages, clinicians may be forced to use suboptimal or more expensive medicines to treat common and/or serious conditions.

Proposed policies and actions to address domestic drug shortages. A number of new proposals, rules, laws, and recommendations have been announced by US government agencies to address drug shortages, including some measures to address shortages due to the COVID-19 pandemic.

Increased production and stockpiles. As of April 7, 2020, FDA had approved an abbreviated new drug application for hydroxychloroquine sulfate, an action that supports

increased production of hydroxychloroquine and chloroquine in response to supply chain disruptions and increased demands.[30,31] FDA also granted hydroxychloroquine and chloroquine emergency use authorization, restricting access to specific FDA-approved indications and COVID-19 treatment.[32] Furthermore, hydroxychloroquine has been listed as a national emergency stockpile medication, leading Sandoz and Bayer Pharmaceuticals to donate supplies of these medications to a national stockpile.

Also on April 7, 2020, the Drug Enforcement Administration (DEA) allowed 2020 aggregate production quotas to be increased by 15%.[33] These quotas affect production of controlled substances in high demand during the COVID-19 pandemic and intermediates used in their production, such as hydromorphone, ephedrine, and fentanyl. Also, DEA approved increased imports of medications used to support mechanical ventilation, including ketamine, midazolam, and ketamine, and issued temporary exceptions to its regulations limiting manufacturer inventories of Schedule II controlled substances.

On April 16, 2020, FDA released a temporary policy allowing the compounding of 13 injectable drugs for hospitalized patients, including medications used for pain and sedation and maintaining blood pressure, as well as an antibiotic to mitigate drug shortages caused by supply chain disruptions.[34] Sterile compounding outsourcing facilities must be registered with FDA under section 503B of the Food, Drug, and Cosmetic (FD&C) Act. The policy relaxes manufacturing rules and expands the list of medications and facilities permitted to manufacture these medications.

Improved communication and reporting. On March 27, 2020, FDA published an update regarding permanent discontinuance or interruptions in manufacturing under section 506C of

the FD&C Act. The guideline addresses the importance of early notifications in drug supply disruptions that can negatively affect the US market in the face of a global pandemic. The document outlines when parties are responsible for sending notification to FDA, what should be included in the notification, and the consequences of failing to notify FDA about any supply disruptions. These regulations allow FDA to effectively overlook the US drug market, respond to increased demands for certain drugs, identify possible supply chain disruptions, and cooperate with manufacturers within and outside the United States to maintain adequate supply.[31]

Proposed legislation addressing US drug shortages. The Affordable Drug Manufacturing Act of 2020 (S 3162),[35] proposed in the US Senate on January 8, 2020, included establishing an Office of Drug Manufacturing within the Department of Health & Human Services (HHS), with the purpose of identifying and regulating the rising cost of medications. Through oversight of drug manufacturing and supply, this office would be tasked with identifying and acquiring manufacturing rights for drugs whose APIs were not readily available from existing suppliers, when manufacturing specific APIs would improve other entities' ability to manufacture a generic medication, or manufacturing the ingredient were necessary for the office to fulfill its duties. This office would also have the ability to prioritize manufacturing of drugs with the greatest impact on increasing competition, lowering drug prices, addressing drug shortages, and reducing prescription costs to federal and state health programs. Within the first year of this bill's enactment, the new office would begin the public manufacturing of insulin, naloxone, and at least 3 specific antibiotics. Passage of this bill and creation of a new Office of Drug Manufacturing could reduce the costs of specific API, thereby potentially lowering costs for manufacturers and potentially improving competition and lowering prices for insurers and

consumers. While funding would be required for this office at the taxpayers' expense, it is likely that the benefits to taxpayers of establishing the office would outweigh the costs, provided some of the reduced prices were passed on to consumers.

The Securing America's Medicine Act of 2020 (S 3432),[36] introduced in the Senate on March 10, 2020, proposed federal support for the development of advanced pharmaceutical manufacturing technologies and the establishment of a program to develop National Centers of Excellence in Advanced Pharmaceutical Manufacturing. Through the proposed Advanced Manufacturing Technologies Program, FDA would be allowed to support new drug manufacturing technologies that prevent or resolve a drug shortage, maintain an adequate supply of critical medications for national emergencies, and promote innovation in drug product design and manufacturing. If the legislation were passed, FDA would be tasked with expediting the development and implementation of the manufacturing technology. Institutions with the National Centers of Excellence in Advanced Pharmaceutical Manufacturing designation would help to develop and research advanced pharmaceutical manufacturing, train a workforce specialized in drug manufacturing, and support federal agencies in creating a secure national pharmaceutical stockpile that could rapidly address drug shortages. Proposed appropriations for this act were $100 million over a 5-year period.

The Commission on America's Medical Security Act (S 3478),[37] introduced in the Senate on March 12, 2020, mandated a report that assesses, evaluates, and addresses the United States' dependence on critical drugs and devices that are sourced from international suppliers. This report, to be produced in collaboration with the National Academies of Sciences, Engineering, and Medicine, would evaluate the supply chain of critical drugs and devices,

determine potential public health or national security risks associated with overreliance on imports, review the potential economic impact of increased domestic manufacturing, and address any supply vulnerabilities through supply chain redundancy and improved domestic manufacturing. The results of this report would address medical supply chain vulnerabilities or potential disruptions.

On May 19, 2020, in an initiative aimed at reducing US dependence on foreign manufacturing, it was announced that HHS, through an executive order from President Trump, had awarded a contract to a new US company to manufacture API and drugs for COVID-19 treatment.[38] Under the $354 million (up to a maximum of $812 million) contract, privately held Phlow Corp, in collaboration with Civica Rx, Virginia Commonwealth University, and Ampac Fine Chemicals, would make more than a dozen generic drugs and their ingredients, including medicines for pain management, sedatives for ventilator support, medicines for maintaining blood pressure, and antibiotics.[38,39]

Collectively, these bills and executive orders illustrate how drug shortages and reliance on foreign drug manufacturing have caught the attention of the federal government. Individually, the proposed bills form a patchwork response to the chronic issues of drug shortages prior to and during the COVID-19 pandemic. While S 3162 and S 3478 advocate for the establishment of a new Office of Drug Manufacturing and National Centers of Excellence to identify and address many of the issues resulting from the foreign manufacture of drugs, the bills appear to have a poor prognosis for passage (4% for S 3162 and 14% for S 3478, according to GovTrack website [Civic Impulse, LLC, Washington, DC]), with few cosponsors as of the time of writing.[40] Should these proposals fail to pass, or even if some should pass, there remains a

critical need for a more comprehensive approach to addressing drug shortages. The awarding of a contract to manufacture certain medications currently in short supply due to the COVID-19 response may provide a test case for the ability to quickly manufacture drugs when shortages in API or finished dosage forms are identified. However, the executive order provides only short-term funding, and questions have been raised regarding the cost and ability of the new startup company to deliver on the sole-source, cost-reimbursement contract, thereby threatening the long-term viability of this contract.[39] Below, we propose a framework for such a comprehensive approach, outlining important short- and long-term considerations for ensuring a stable supply of drugs critical to maintaining the health of the US population.

Framework for addressing shortages of critical medications due to reliance on foreign manufacturers. With the growing concern over increasing reliance on imported pharmaceutical products, it is important to understand the economic reasons for outsourcing manufacturing overseas. In a discussion paper by the World Bank's Human Development Network, foreign manufacturing of drug products was noted to provide important economic advantages over domestic production, including lower labor, infrastructure, transportation, and equipment costs.[41] Compared with a Western API company's average index wage (a ratio of the average hourly wage compared to some standard value) of 100, Indian and Chinese index wages are 10 and 8 (ie, labor costs in those countries were one-tenth and one-twelfth as high, respectively). Coupled with lower energy and water costs, closer proximity to supply chains, and fewer environmental, safety, and product quality regulations, manufacturing costs are dramatically lower in some countries compared with the United States. However, decreased regulation at the point of manufacturing increases the need for regulation and quality oversight to ensure

that drug products meet US standards, with the additional risk of shortages when products do not. In times of crisis, such as natural disasters or war, it is possible for supplies of essential medicines to be completely cut off. Given that measures required to increase the competitiveness of US API manufacturing with those of foreign suppliers would require either huge reductions in labor costs or unpalatable government subsidies, alternative methods must be employed to ensure adequate supplies of critical drugs in the short and long term during crises and shortages.

A comprehensive strategy for monitoring, along with short- and long-term responses to shortages, is needed to minimize the impact of drug shortages. Failure to address even one of these 3 important foci would result in an incomplete response and unnecessary shortages during a crisis. Table 1 presents a list of actions developed by us and others that, if implemented in their entirety, would allow the United States to reduce or eliminate the impacts of serious drug shortages.[8,42] We also recommend that a continuous process improvement approach (identify, plan, execute, and review) be taken in updating this strategy as limitations are identified when responding to drug shortages.

Creation of a critical drug list and monitoring. There is a need for the United States to create a list of critical drugs and potential substitutes so that availability and use of these medications and their API can be monitored and stockpiles and emergency manufacturing capabilities developed. Without a critical drug list, there are too many medications to proactively monitor and respond to shortages with efficiency.

As mentioned above, FDA maintains a public-focused database of drugs that have been voluntarily reported by manufacturers to be in shortage.[43] The FDA database includes

information on the reason for a shortage (reported by manufacturers using a legislated prespecified list of reasons; additional information is nondisclosable without the manufacturer's permission), current product availability, and estimated shortage duration. ASHP maintains a similar list of drug shortages, typically reported by healthcare practitioners and patients for use by healthcare practitioners.[44] This clinician-focused database includes the reason for a shortage (if the manufacturer is willing to disclose it), product availability, estimated resupply dates, safety issues, and alternative agents and management.[45] The ASHP database reports more drug shortages than does the FDA database (due to differing criteria for inclusion).[46] However, these databases are reactive rather than proactive, either relying on manufacturer self-report or clinician or patient reporting of shortages after supplies have been exhausted. A more sensitive and proactive reporting infrastructure is needed to ensure that potential shortages due to supply chain interruptions (ie, API shortages), manufacturing issues, or increased demand for critical medications are identified earlier. This approach would require mandatory reporting of any interruptions in API supply or manufacturing capacity and reporting of increased demand by manufacturers. Since it might be difficult to regulate and fine foreign companies for lack of compliance, such compliance could be incentivized with positive incentives for companies providing complete, transparent, and accurate reporting of drug shortages. Reporting could also be enhanced and made more sensitive by allowing health systems, pharmacies, and patients to report observed shortages at the point of care. Another measure that should be explored is the use of predictive analytics to determine when increased demand for critical drugs might occur due to impending supply chain issues or political crises.

Short-term response to critical drug shortages. We recommend the development of a stockpile of finished drug products and their APIs for critical drugs. Important considerations for storing these medications are rapid availability during times of crisis, a need to ensure sufficient supplies to last until longer-term solutions can be implemented, a need to provide for proper storage conditions, and a need to continuously move and use stockpiles so that they do not expire—all at as low a cost to taxpayers as possible. Maintenance of the stockpile could potentially be administered by a number of different organizations, each with its own strengths and weaknesses in terms of meeting these 5 goals (ie, availability, supply chain, storage, expiration, and cost). For example, a federal stockpile of critical drugs could result in greater efficiency and lower cost, with less unnecessary duplication of supplies, than could be achieved with regional solutions. However, maintaining specialized storage conditions for certain medications and rotating stock could be difficult, as the federal stockpile would not likely be part of the usual supply chain for these drugs. In contrast, contracting with national distributors to maintain a stockpile would potentially solve storage and expiration issues, as distributors could continuously rotate stock. However, it would shift some control for maintaining the stockpile from the government agency responsible for maintaining the stockpile to private corporations. State, regional, or health system–controlled stockpiles, with appropriate incentives, would likely improve response time during a crisis but would also likely lead to significant unnecessary duplication of infrastructure and supplies. API would likely need to be stockpiled at the federal level to ensure that supplies were adequate and available to emergency manufacturing plants and that costs for maintaining the stockpile were equitably distributed among all taxpayers.

Long-term response to critical drug shortages. A long-term strategy for addressing critical drug shortages involves increasing domestic production capacity. This may be accomplished by either incentivizing the domestic production of critical drugs or creating an emergency manufacturing infrastructure that could be activated during drug shortages. For both solutions, it would be necessary to secure a domestic supply of an API to ensure that supply chain disruptions do not affect manufacturing of critical drugs.

Incentivizing domestic production of critical drugs has several benefits, including creating American manufacturing jobs and related tax revenue. However, the high cost of labor relative to that in countries where products are currently manufactured may make domestic manufacturing uncompetitive without significant subsidies. These subsidies and other incentives, such as tax incentives, may prove unpalatable to US taxpayers, making the widespread continuous domestic production of critical drugs difficult to maintain. Creating an emergency manufacturing infrastructure that would produce critical drugs only during a shortage could be a much more efficient approach. In this model, manufacturers of generic products could be contracted, or government, military, or other production facilities developed, to maintain these domestic manufacturing capabilities, despite manufacturing costs being higher than in foreign countries. These emergency manufacturing capabilities would be employed when shortages of critical drugs were anticipated to exceed emergency stockpiles. Such an infrastructure has already begun to develop, with Civica Rx and Provide Gx producing generic drugs when in short supply, and the recent executive orders supporting generic manufacturing by Phlow Corp.[38] These emergency manufacturing capabilities, including manufacturing equipment and a well-trained workforce, would need to be maintained when

critical drugs were not in short supply, with the ability to activation production quickly. Costs for maintaining contracts or keeping facilities in a production-ready state would likely be at the taxpayers' expense.

Evaluate and improve response to critical drug shortages. The ability of critical drug stockpiles and manufacturing to meet medication needs during periods of short supply and crises should be periodically evaluated to determine whether response could be improved and to identify critical and latent failures that occur during shortages. In addition, the efficiency of creating the national stockpile and manufacturing capacity should be evaluated by assessing the cost-effectiveness for each of the drugs on the critical drug list. These analyses should include comparisons of alternative therapeutic approaches, monitoring of drug shortages, and the use of new manufacturing technologies.

Conclusion. COVID-19 has exposed major issues within the US healthcare system. Years of shifting pharmaceutical production overseas and a lack of federal planning illustrate a need to reevaluate pharmaceutical manufacturing and its impact on health systems and patients in the United States. With the COVID-19 crisis response limiting manufacturing of certain products and foreign countries placing restrictions on exports of essential medications and equipment, the United States experienced more drug shortages in a recent 3-month period than during the 2 preceding years. These shortages in drugs and supplies have not only placed patients at risk but also endangered healthcare workers' lives. However, the global pandemic provides an unusual opportunity to identify key problems and develop potential solutions. A comprehensive approach to addressing drug shortages can lead to an effective and efficient response and help safeguard the nation from future critical drug shortages.

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Table 1. Framework for Addressing Critical Drug Shortages, With Potential Advantages and Limitations[a]

Recommendation	Description	Advantages	Limitations/Issues
Monitor foreign API and pharmaceutical products for potency and contaminants	Implement more frequent and systematic monitoring of foreign APIs and pharmaceuticals Ensure foreign products meet US quality and safety standards	Limit and manage the risks of sudden drug shortages caused by unexpected contaminant	Possibility of more frequent shortages Costly Increased monitoring can slow drug product importation Foreign countries may prevent US inspectors
Develop a list of critical drugs, their substitutes, and APIs	Create a national catalog of drugs needed to maintain health of US population and APIs	Identifies a limited list of drugs for which additional measures described below are needed to ensure a constant supply Identifies APIs that are common to critical drugs and their substitutes	Must be continuously reviewed Uncertainty may be present in determining which drugs are considered critical, depending on type of crisis (eg, respiratory illness, gastrointestinal illness, war)
Improve monitoring sensitivity and reporting of critical drug shortages	Mandate and incentivize reporting of critical drug shortages by manufacturers Expand reporting of critical drug shortages to include hospitals, pharmacies, suppliers and/or distributors, and patients	Earlier and more complete detection and reporting of potential drug shortages	May provoke hoarding of medications in short supply, further intensifying a shortage
Develop a national stockpile of critical drugs and API	Create a stockpile of critical drugs and APIs	Addresses short-term shortages Advantages vary depending on who administers the stockpile (ie, federal government, states, contracted distributors, or health systems)	Drugs must be used to prevent expiration Many drugs have special storage conditions

Encourage/incentivize manufacturers to produce critical drugs domestically	Increase domestic production of critical drugs	Limits reliance on foreign manufacturing Allows for better monitoring for contamination and identification of manufacturing issues May create new sources of jobs and additional tax revenues	Tax breaks or similar financial incentives typically involve increased costs to taxpayers Medication prices would likely increase due to higher labor and other costs
Develop emergency domestic manufacturing capabilities	Allows rapid production of Critical drugs in short supply when duration of short supply exceeds stores in national stockpile	Allows for indefinite supply of critical drugs during prolonged or severe shortages May be much less expensive than incentivizing the continuous domestic production of critical drugs	Risk of contracts lapsing or manufacturing plants becoming outdated if long periods of time elapse between crises Vastly different manufacturing approaches may be needed for some drugs, thereby requiring different processes and increasing costs
Evaluate the cost-effectiveness of maintaining the critical drug stockpile and emergency manufacturing	Continually evaluate the processes, costs, and benefits of maintaining specific drugs in the national stockpile and compare with alternative treatments Determine the benefits of new technologies in minimizing costs of a national stockpile	Provides justification for maintaining the critical drug stockpile and emergency manufacturing Identify areas for improving the efficiency and reducing taxpayer burden for maintaining these measures	Additional cost for conducting analyses

Abbreviation: API, active pharmaceutical ingredient.