
2020
PHARMA
TRENDS
CLARKSTON
CONSULTING

The 2020 pharmaceutical trends reflect the broad shifts currently impacting the industry as it moves from the blockbuster model that dominated for decades to one more focused and patient-centric. The realities of many of the transformational clinical and technological breakthroughs in the pharmaceutical industry are coming to a head in 2020, forcing drug makers to evaluate, dismantle, and rebuild core aspects of their business. An active geopolitical landscape is simultaneously placing new pressures on organizations to become more agile and efficient in their operations. Businesses in the pharmaceutical industry must be prepared to forge ahead with a mindset of change and adaptability in order to meet these trends with sustainable success.

REGENERATIVE MEDICINES MARKET EXPLOSION'S IMPACT ON MANUFACTURING CAPACITY

In 2019, a little over 1000 clinical trials were being conducted globally on regenerative medicines, specifically gene and cell therapies. In 2019, this market's value was $13B but is expected to reach ~$74B by 2027, a **CAGR of 24%**. This growth is driven by the rise in chronic diseases, genetic disorders, and government investments (Cures Act-2016).

Even though small molecule drugs still dominate the number of New Molecule Entities (NME) that are approved by the FDA each year (71%) and have an abundant number of products in research and development (**approximately 8,000 as of 2018**), its growth is slowing vs, large molecule drug, which the majority regenerative medicines are classified under. As of 2019, 5,000 large molecule drugs are in development.

The FDA is expecting 200+ Investigational New Drugs (IND) per year starting in 2020 with the majority of them being cell and gene therapies. And by 2025, the **FDA is expected to approve** 10-20 cell and gene therapy products a year with a large number of these approvals expected to be expedited via the FDA Expedited Approval Programs (e.g. Fast Track, Breakthrough Therapy, etc.).

With this incredible explosion of regenerative medicines in R&D and clinical trials, both sponsors and their supply chain partners have been investing significant capital in developing, validating, and scaling clinical and commercial manufacturing assets to meet the demand; however, as of late 2019, the demand outstrips the industry's supply.

There are a few main drivers as to why constrained capacity exists:

1. Cell and gene therapies are complicated to manufacture, and equipment is designed and engineered to support only one or a few specific molecules; hence, making the operation difficult to scale for a variety of other regenerative therapeutics.

2. Regenerative medicine manufacturing is a core competence for a drug sponsor. The designed and engineered assets and its processes are protected under Intellectual Property (IP) law, making it difficult for other manufacturers to copy for similar therapeutics.

3. On average, production yields are low and out of specification (OOS) batches are moderately high, leading to constrained capacity.

4. Large investment, lead-time, and risk to design and build a manufacturing facility for a therapeutic in clinical trials that may never be commercialized or meet the projected sales projections.

5. Fragmented CDMO market with the large entities (e.g. Lonza, Catalent, etc) representing only a minority of the capacity.

6. **70% of drug development** is occurring at small biopharmaceutical firms that do not have the financial resources to support manufacturing; therefore, demand for capacity is being pushed to the CDMO market.

As global approvals for regenerative medicines increase and private and public investments in biopharmaceutical research and development remain strong, the incentive for drug sponsors and their supply chain partners to build supply chain capacity will continue to grow.

EUROPE'S CLINICAL TRIAL REGULATION SET FOR GO-LIVE IN 2020

According to the European Medications Agency (EMA), there are 4,000 clinical trials authorized each year in the region, predominately in Western Europe; however, according to the latest data available (2007-2015), the number has remained flat.

One of the primary reasons being attributed to this stagnation is the European Clinical Trials Directive (EU 2001/20/EC), which, even though laudable for attempting to improve the safety and effectiveness of both commercial and non-commercial clinical trials and make Europe a competitive region for drug discovery and development, evidence now concludes that it had a negative effect. Since Directives in the EU are implemented by each Member State and are not harmonized among the different countries, the Clinical Trial Directive caused legislative differences between nations, multiple obstacles to launch and conduct clinical trials, and increased the overall cost to conducting clinical trials.

The EMA responded by passing the Clinical Trial Regulation (CTR) (Regulation (EU) No 536/2014) which will replace the European Clinical Trials Directive (EU 2001/20/EC). There are three main goals of the regulation:

Harmonization:

- The new rule is a regulation which will become law within all member states and will eliminate member state's interpretation of the law
- Harmonized electronic submission, requirements, and assessment processes for clinical trials conducted in multiple member states
- Increase the efficiency of trials and avoid duplication of trials conducted in multiple member states
- Improve information sharing and decision making between and within member states
- Enhance transparency of information on clinical trials

Authorization:

- Clinical trial submissions will be entered via an electronic portal titled CTIS (Clinical Trials Information System) maintained by the EMA
- Enable predictable approval timelines on submissions

Increase Region Attractiveness:

- Trial efficiency and elimination of clinical trial duplication in markets makes Europe an attractive region to invest in life sciences drug discovery, development, and commercialization

The original target date for implementation was December 2015; however, due to technical constraints with the CTIS, the scheduled go-live date is planned for mid-2020 (as mentioned by the EMA in September 2019). This is subject to change based on the progress of its implementation as the regulation will not go into effect until the CTIS has been fully approved via an independent audit. After confirmation of a successful audit, the regulation will become applicable six months afterwards.

Trial sponsors of new or in-progress commercial and non-commercial clinical trials are to be aware that there is a three-year transition period once the regulation comes into effect. Many trials approved under the European Clinical Trials Directive will still be on-going in 2023. The EMA will need to develop guidance documents and work with each sponsor to re-assess each clinical trial that is still in-progress.

DRUG SHORTAGES CONTINUE TO POSE CHALLENGES TO PATIENTS

Drug shortages in the United States are a common occurrence and have continued to increase year-over-year after declining from a peak in 2011. Not only have the number of drugs in short supply been increasing, but their duration has also increased, in some cases more than 8 years. The impact to a population that relies on these drugs cannot be underestimated. Drug shortages cause treatments to be either delayed or cancelled or dosing regimens to be altered. **In a recent study**, 56% of hospitals reported that they had to change patient care or delayed therapy due to shortages and 37% said that non-urgent medical procedures had to be rescheduled.

There are a few main drivers to the recurring theme of drug shortages in the United States:

Lack of incentive for drug manufacturers to produce profitable drugs

Due to intense pricing competition and high investment, there is no motivation for a company to continue to invest resources into commercializing a drug.

Market does not recognize and reward manufacturers for mature quality management systems

For a drug that they purchase, payers have no information that links a drug's quality to the quality management system of the drug manufacturer; therefore, a manufacturer is not incentivized to invest in capacity, facilities, and other resources to supply low cost drugs. A drug manufacturer with a subpar quality and compliance management system would be paid the same price for the drug as one with a more robust one. This is the catalyst that leads to quality problems that trigger supply shortages.

Logistical and regulatory challenges make it difficult for the market to respond to disruption

Supply chains are increasing in complexity and length and stringent regulatory thresholds make it extremely difficult for a new manufacturer to supply products in shortage relatively quickly.

The FDA's Drug Shortage Task Force, created in 2018 by the urging of Congress, has proposed three recommendations to address and hopefully resolve the drug shortage issues:

1. **Shared understanding of drug shortage impact:**

   a. Private or public sector quantification of the comprehensive harms of drug shortages both clinically and financially

   b. Better characterization of drug shortage's frequency, duration, and intensity

   c. Greater studies on current contracting prices by group purchasing organizations (GPO) to support development of contracts designed to promote or incentivize manufacturers

2. **Create a rating system to incentivize drug manufacturers to achieve QMS maturity:**

   a. Introduce transparency in the market and provide pricing incentives for manufacturers to improve their QMS and gain a competitive advantage

3. **Promote sustainable private sector contracts:**

a. Greater understanding of GPO's contracting prices and transparency of a manufacturer's QMS would enable payers, purchasers, and GPOs to consider new contracting approaches that enable reliable supply of drugs.

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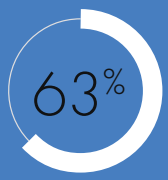
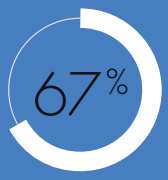
DRUGS WENT INTO SHORTAGE



WERE STERILE INJECTABLES



HAVE A GENERIC VERSION ON THE MARKET

MEDIAN AGE OF DRUGS: 35 YRS.

AVERAGE COST PER DOSE: $8.73

A survey conducted by Vizient found that, on average, hospitals in the United States dedicate

>8.6 MILLION HOURS

OF ADDITIONAL LABOR ANNUALLY TO MANAGE DRUG SHORTAGES,

A FINANCIAL IMPACT WHICH ADDS UP TO JUST UNDER

$360 MILLION

SOURCE

BREXIT'S IMPACT ON PHARMACEUTICAL INDUSTRY

The United Kingdom is set to leave the European Union on January 31, 2020. After this date passes, one of the first agenda items for the UK is to negotiate a trade deal with the EU. The UK wants as much access as possible for its goods and services to the EU and vice versa. Not only will this topic have huge implications for the healthcare sector and all of its stakeholders, but there are other urgent agenda topics that need to be decided relatively quickly in order for research, drug development, and medicine commercialization and distribution to be sustained and eventually grow.

The pharmaceutical industry is one that is most heavily impacted by Brexit and one in which they are championing for consistency and certainty, Under the Brexit Withdrawal Agreement, the legal framework for Brexit, the provisions that provide them the most consistency for continual operation are:

- Transition period from January 31, 2020 to end of 2020, possibly extended to 2022 in which all current EU rules apply including all trade practices and pharmaceutical regulation arrangements
- Rights protection for EU citizens who arrive before the end of the transition period to allow those individuals and their families indefinite protection. This is critical since 1 out of 6 R&D academics are from EU countries.

Topics that still need to be negotiated with the EU include, but are not limited to:

1. Single set of rules and approvals for new medicines used by the EU and UK (Centralized Procedure)
2. Single set of regulatory standards for a drug's lifecycles
3. Market Authorization Holders (MAH) based in UK will still be able to distribute product in the EU and have their quality system sites (e.g. pharmacovigilance) remain in the UK
4. Common system for licensing, clinical trials, and pharmacovigilance
5. Participation of UK regulators in managing Europe-wide standards
6. UK-based R&D in Europe-wide clinical trials

The impact to the healthcare sector in both the UK and the EU cannot be underestimated. **Approximately 75% of the medicines and more than 50% of the devices** that are used by the National Health Service in the UK come from the EU. This could lead to national and localized shortages of some vital products for the treatment and prevention of diseases. **One study** stated that 59 drugs would be difficult or even impossible to access ranging from low dose aspirin to biologics.

To mitigate as much risk to the supply of medicinal products, the UK government has been requesting drug manufacturers in the UK and other markets outside of the EU to stockpile a 6-month supply of generic drugs; however, this is a small contingency plan in the greater context of the situation for which no one, in neither the public nor private sector, is able to predict the outcome.

THE MARRIAGE OF PHARMA AND DIGITAL HEALTH TOOLS

Digital health tools are omnipresent in today's society as lower costs and ease of use have allowed greater access and use for more people. The objectives of these tools range from basic health-related purposes such as heart rate monitoring and exercise tracking to those for specific health conditions and treatments and include disease tracking, diagnostics, and drug regimen compliance. The goal of these digital tools is to achieve high quality, low cost, and greater access through more efficient prevention and management.

The benefits of digital health tools are massive for the health care industry as these tools can be leveraged proactively throughout the lifetime of a patient's condition to diagnose, treat, and monitor without costly doctor or hospital visits and diagnostic tests. The data generated from these tools based on digital biomarkers can help the pharmaceutical industries develop products that prevent, treat, or cure specific diseases. This would lead to better tracking of patient outcomes to determine the long-term value of therapies, which in turn, will make it easier to implement value-based arrangements for drug reimbursements from payers.

Even though the value of digital health tools is massive, there are many barriers to why they are not being implemented across the industry at a faster pace. First, regulations from health agencies across the world cannot keep pace with the rapid technological growth of these tools; therefore, pharmaceutical companies are reluctant to make investments that may be categorized as too risky if health agencies eventually do not approve of their uses.

Second, high quality clinical research studies on digital health, while growing in number, are still lacking. The main driver for this gap is the inability to identify the right patients to be candidates for the use of these devices. Even if they identify the right candidates, it's imperative that device makers use the devices effectively or the data generated will be suspect. Lastly, security of personal data collected and algorithm bias continue to be barriers that need to be overcome before wider spread use of digital health tools.

THE GLOBAL DIGITAL HEALTH MARKET IS PREDICTED TO HAVE A CAGR OF

24%

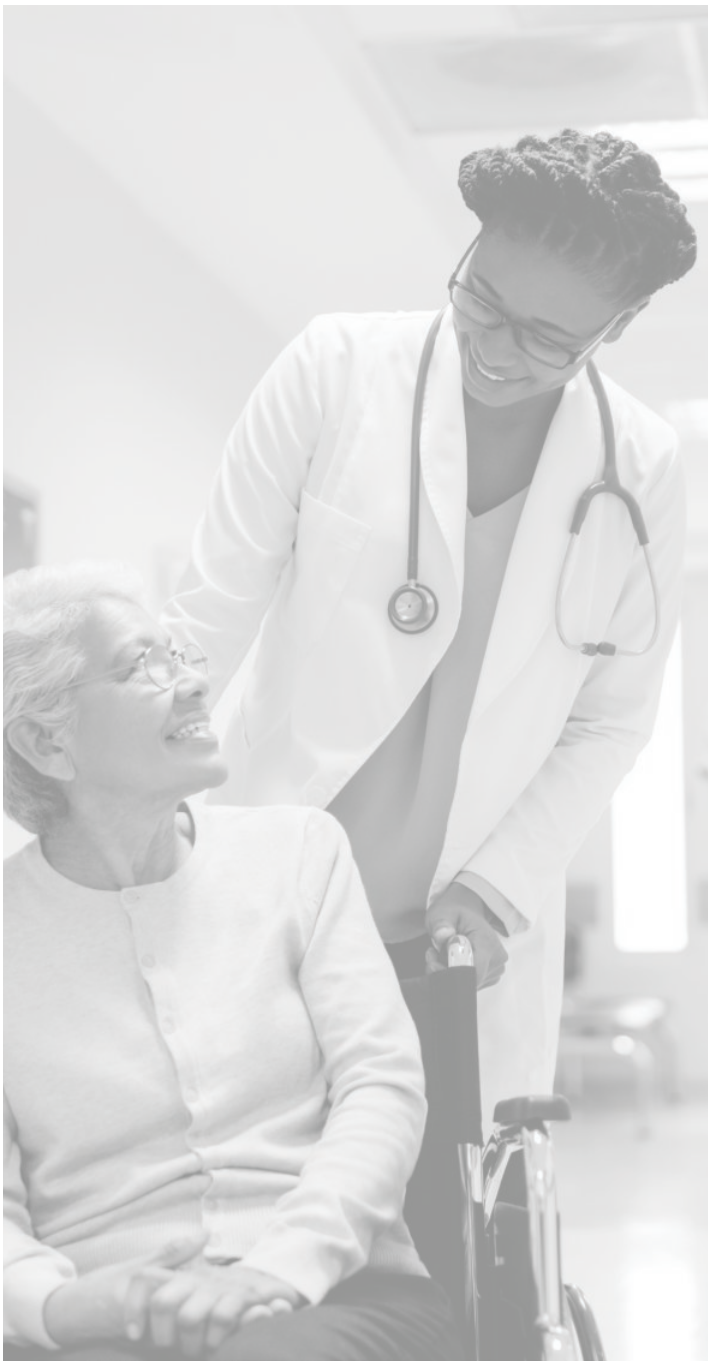
FROM 2018-2026

SOURCE

THE RAPID RISE OF PERSONALIZED MEDICINES

The focus on the investment and development of personalized medicines has been an enormous paradigm shift for the healthcare industry. The traditional path of drug development, which is to identify therapies that can treat an entire population is transitioning to one where medicines will be tailored to the unique molecular or generic mapping of individual patients that causes diseases to occur and progress. Personalized medicines will transform the industry by tailoring care precisely to the individual considering a person's unique characteristics such as ethnicity, local environment exposure, and immunization history. It will leverage all clinical, genetic, and environmental information for a patient to understand and treat diseases in a more holistic manner. The shortcomings in traditional medicines that personalized medicines are looking to address include differences in treatment responses and adverse events for patient populations and lack of a drug's efficacy.

Four critical enablers are driving the rise of personalized medicine while also presenting a host of unique challenges:



The power of the human genome:

Personalized medicine uses genomic information as the foundational element in determining the best care for an individual. A human genome contains an individual's complete set of DNA which includes all genes. Understanding the genome can arm providers with the best knowledge to provide specific, individualized care for a patient. But even with the troves and troves of data at their disposal, scientists and researchers are still unraveling the complex mysteries, variations, and unique characteristics of the human genome.

Big data analytics and machine learning technologies:

Data generated from the genome, clinical history, and the patient with advanced analytical tools is required to transfer huge data pools into insights for care. As always, the quality and integrity of the data remains paramount to its effective use.

Reimbursement methods incentivize health systems to keep patients well:

Personalized medicine will transition the industry from a "fee-for-service" model to a "value-based" purchasing, eliminating unnecessary diagnostic tests and hospital admissions which drive up cost. However, upheaving this cost structure remains difficult for an

industry built around processing reimbursements in the fee-for-service model and requires new technologies and capabilities, a deeper understanding of patient populations, and a more intricate level of collaboration with other stakeholders in the value chain.

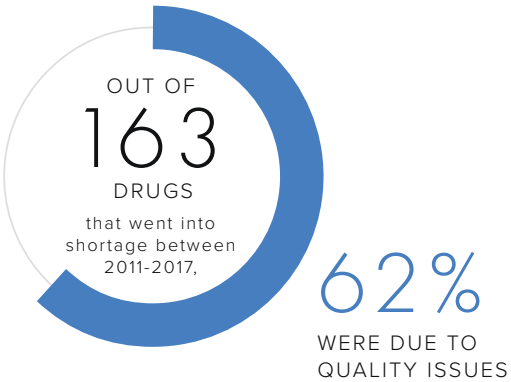
Emerging tools enable more data, more interoperability:

Personalized medicine is reliant on more data and needs methods and mechanisms to access more data and leverage it successfully. While the market of available tools grows daily, selecting and implementing the appropriate solution is challenging. Businesses must also prioritize effective integration, privacy, and security to ensure the safe and effective coordination of the varying technological touchpoints. Moving forward through 2020 and buoyed by impressive scientific breakthroughs in 2019 around gene editing and engineering, organizations will continue to explore personalized medicine in earnest outside therapeutic areas like oncology, where its focus has been heaviest so far.

SOURCE

FDA TASK FORCE RECOMMENDS RATING SYSTEM FOR DRUG MANUFACTURING QUALITY

To promote transparency among drug sponsors and payers and to reward manufacturers for promoting, sustaining, and improving the quality of their products, the FDA in **October 2019** recommended a voluntary ratings program for pharmaceutical companies' manufacturing facilities. The genesis of the recommendation came about through the FDA's Task Force on Drug Shortages, and specifically a report citing quality problems at manufacturing facilities as one of the leading causes of drug shortages in the U.S. To incentivize pharmaceutical companies to go beyond the minimum requirements of quality set forth by the FDA and other health agencies, the rating system could be used as a signal to health care payers that the drugs under purchasing consideration are of higher quality vs. competitors. This could also serve as a competitive advantage for the pharmaceutical company to have leverage to negotiate a higher price for their drugs and grow market share. A higher quality rating can potentially signal to payers that there is low probability that the drugs will be involved in any commercial supply chain disruptions (e.g., recalls) that could lead to drug product shortages.



SOURCE

Although the recommendation for a rating system has beneficial applications, there are multiple concerns at this juncture. One major concern is the development and acceptance of objective criteria to rate the quality management system of manufacturers. The development, monitoring, and reporting approach among industry stakeholders will be contentious, resource-intensive, and lengthy. The next concern is the FDA's current thinking of the program being voluntary vs. obligatory. The voluntary status likely will be insufficient to accomplish the FDA's primary goal for the developing the program in the first place. Lastly, the rating program may be of no interest to payers within healthcare and may not be an incentive for them to pay a premium for drugs that they can source cheaper from another manufacturer.

START-UP BIOTECH FIRMS ARE SOURCE OF FUTURE R&D PIPELINE

For decades, Big Pharma would either invest in their own R&D or look to successful clinical trials sponsored by small biotech firms to generate the next big commercial drug. These large organizations would usually acquire a small biotech firm once the project made it to Phase 2. This paradigm has shifted in recent years and it's the emergence of biotech firms that are responsible for uncovering the newest therapeutics and bringing them to market. Emerging biotech firms are defined as "spending less than $200M annually on R&D and less than $500M in revenue".

1,300

LIFE SCIENCE DEALS WERE CLOSED IN 2018

VALUED AT

$29B

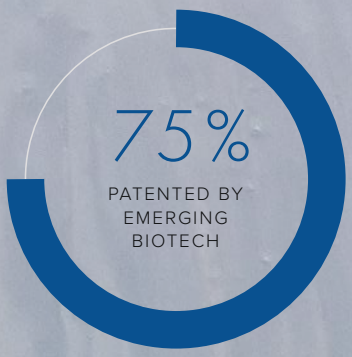
SOURCE

The reasons are not concrete as to why emerging biotech companies are retaining control and going at it alone throughout the pre-commercialization and commercialization phases but there is some evidence to suggest that there are two main drivers.

The first one is venture capital and private equity funding is robust, investing **shy of $29B** in all funding rounds. With a steady supply of capital, smaller biotechs have the support to fund and manage the complete life cycle.

The second driver is the types of therapeutics and the regulatory pathways in which the biotech firms are investing. Smaller companies are being more active in the fast-growing areas of oncology and orphan drugs which lends itself to smaller clinical trials and an increase in regulatory support through the four FDA sponsored expedited approaches (i.e. Priority Review, Breakthrough Therapy, Accelerated Approval, and Fast Track).

NEW DRUGS LAUNCHED IN 2018:



SOURCE

36%
DEVELOPED FROM LARGE PHARMA

64%
DEVELOPED FROM EMERGING BIOPHARMA COMPANIES

SOURCE

EMERGING BIOPHARMA ACCOUNT FOR

72%

OF ALL LATE STAGE PIPELINE ACTIVITY

SOURCE

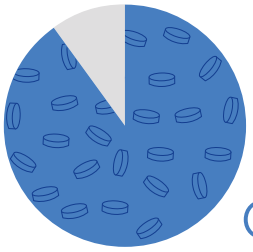
CHINA'S THREAT TO U.S. GLOBAL DRUG SUPPLY CHAINS

In late 2019, the FDA, Congress, and the Pentagon have raised warnings about the risks to the global supply chain for pharmaceuticals due to the dominant position China holds on key production materials.

It's been **reported** that 80% of the active pharmaceutical ingredients (API) used in generic medications, in which 90% of all distributed drugs are classified as, are manufactured in China or by China's manufacturers. These range from common generic drugs that are taken every day by people, including blood pressure medication and antibiotics to over-the-counter (OTC) medications. The reason why China has such a strong presence in the manufacturing of this key drug ingredient stems from years of U.S. and European countries outsourcing internationally to low-cost regions. This is especially true for generics manufacturers, who are under continuous pressure to reduce cost of goods (COGs) in order to compete.

The risks to the supply chain for the U.S. and Europe are two-fold.

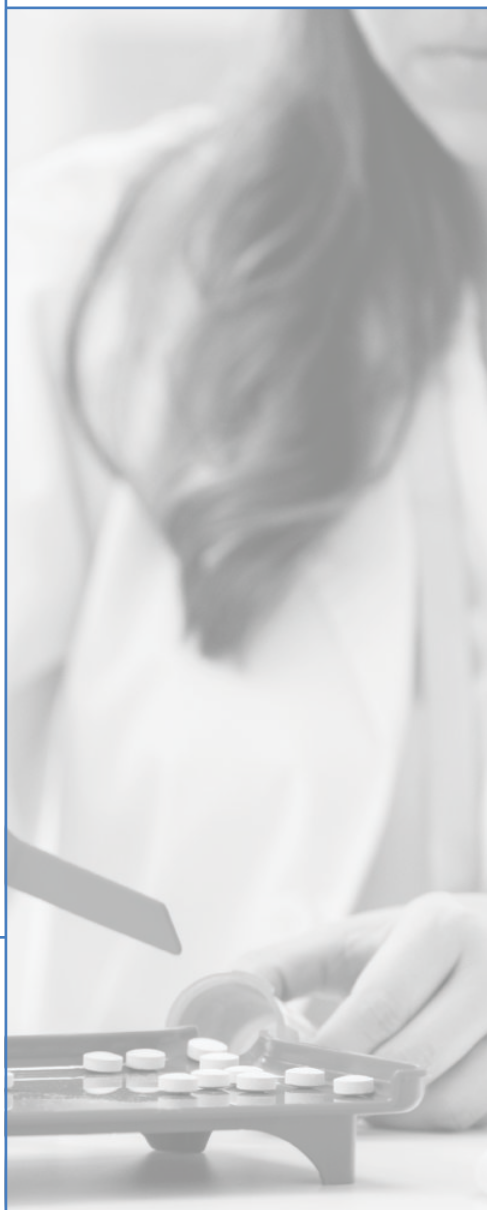
The first risk is directly related to the quality, safety, and efficacy of the API being synthesized at Chinese manufacturing facilities. In 2018, out of **the 75 warning letters** issued to drug manufacturers globally by the FDA, 37 or nearly 50% were against firms in both India and China. The EMA posted 22 compliance notices with 14 or 64% going to those two countries. The number of import blacklists from China into the US jumped from five in 2014 to 22 in 2018. As presented in the statistics, Chinese firms simply do not follow standard manufacturing practices and both the FDA, EMA,



90%

OF ALL MEDICATIONS TAKEN BY AMERICANS ARE GENERICS

SOURCE



80% OF ACTIVE PHARMACEUTICAL INGREDIENTS ARE MANUFACTURED OUTSIDE THE UNITED STATES

SOURCE

and other large global health agencies do not do enough inspections of manufacturer's facilities due to insufficient staff. In 2018, the FDA reported that they have only 22 staff members in China to inspect 700 facilities that supply the US.

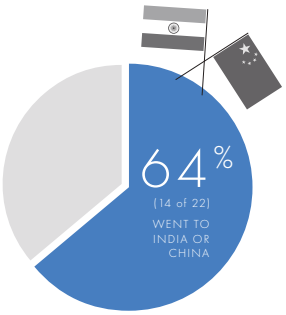
The second risk to supply network is related to U.S. and European national security. Due to rising tensions with China on both trade and military fronts, China could start applying pressure on the U.S. and Europe by brandishing extensive leverage over their control of the supply chain. Chinese firms could manipulate the costs by either raising prices or limiting the supply. The worst-case scenario would be if China just stopped shipping product altogether. It's been reported that if China stopped shipping product to the U.S. immediately, U.S. hospitals and clinics would cease to function within months, maybe days. The risks are so severe that the UK, India, and the Netherlands have already declared a national security issue.

Both the U.S. and other western governments are actively looking for ways to remediate this critical issue. In the U.S., both the public and private sectors need to collaborate and jointly look for ways to diversify away from China and rebuild domestic capacity.

WARNING LETTERS ISSUED BY THE FDA TO DRUG MANUFACTURERS IN 2018

SOURCE

COMPLIANCE NOTES POSTED BY THE EMA



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The 2020 trends will compound the traditional challenges already facing the pharmaceutical industry. In meeting these trends successfully, businesses have the opportunity to create greater efficiencies, unlock innovative capabilities, and enter valuable new markets. To successfully transform for growth, pharmaceutical companies must reexamine how they strategize, operate, and execute their everyday business.

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For more information about how we can help your company with the challenges and opportunities in medical device, please contact us.

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