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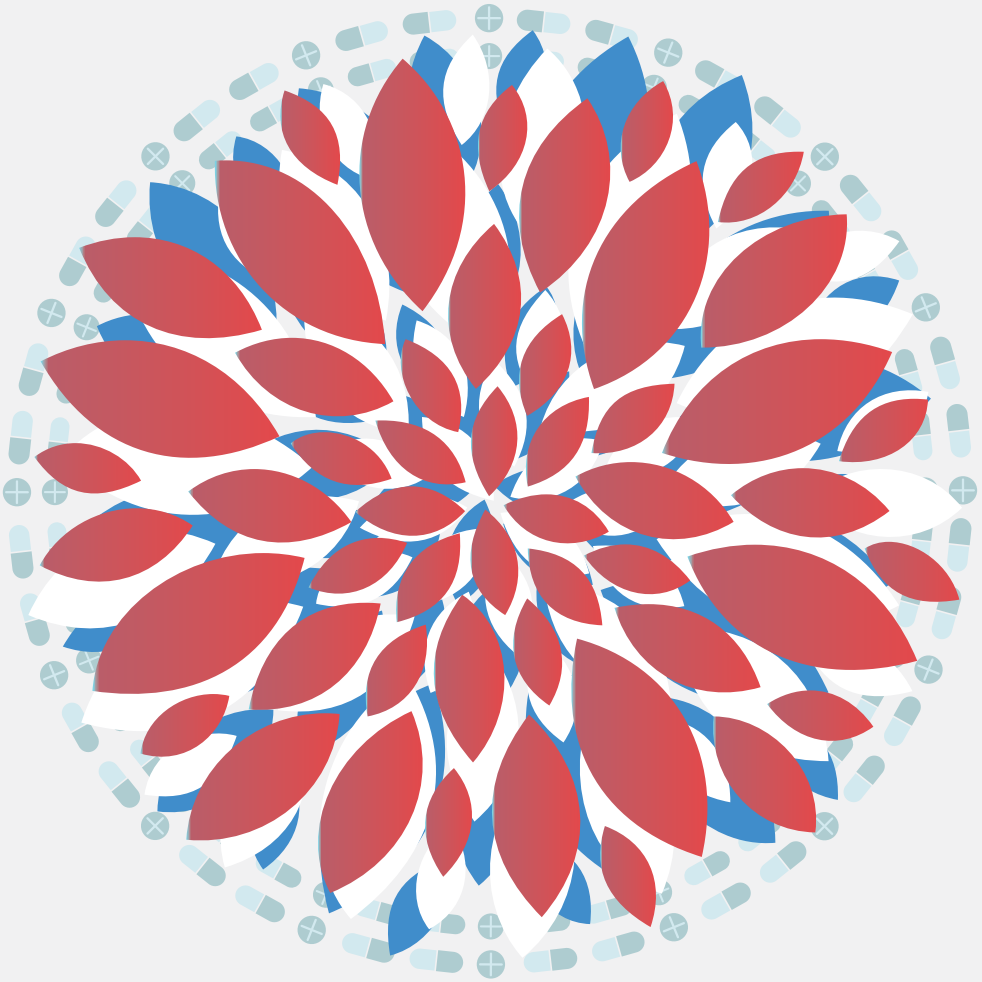


UNITED STATES BIOPHARMACEUTICALS

2017

Innovation – Hubs - Manufacturing
Contract Services – Logistics & Distribution

Navigating the Regulatory Framework

Balancing Regulations, Safeguards and Incentives

The FDA continues to set the gold standard globally, governing the U.S. industry and responsible for approvals for any international company with interests in the U.S. market. Providing the benchmark for quality, its Center for Drug Evaluation and Research (CDER) regulates over-the-counter and prescription drugs, including biological therapeutics and generics, with the aim of enabling availability of safe and effective drugs.

Drug Approvals

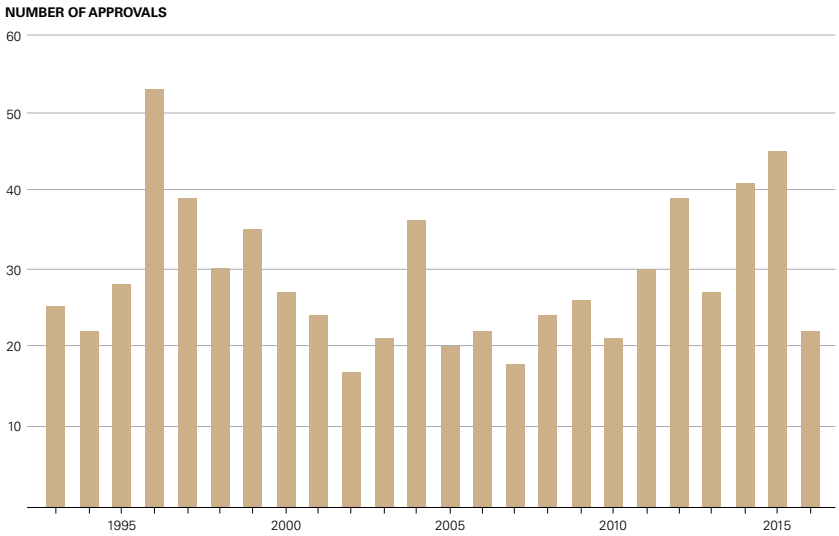
With Rob Califf leaving his FDA position in January, Scott Gottlieb has taken over as the new commissioner. Widely considered a positive choice, Gottlieb is an advocate for faster, more flexible drug approvals. Changes to the drug approval process, especially related to efficiency, are welcomed by the industry. The FDA cleared only 22 new medicines in 2016, a huge step down from 2015's 45 approvals and the lowest number in six years. Generic drug approvals were also down. "As an industry, there has been a drive for the FDA to really streamline and clear up the backlog of ANDAs, of which there are more than 3,000 still unapproved," said Alok Sonig, executive vice president at Dr. Reddy's Laboratories, the Indian generics company. "It is still critical for us to focus on reducing the cost burden by accelerating competitive generic entries vs. slowing them down through tariffs or other forms of blockage. Any disruption can create challenges for the industry's ability to produce new generic high-end equivalents at competitive prices."

Beyond resource challenges within the FDA, increasing hurdles within the approval process and rising development costs disrupting development, another impacting factor has been that a number of applications were turned down due to problems at the prospective manufacturing facilities. 2016 was a record year for complete response letters being issued. "The FDA will not approve a drug if the factory is not in order," explained Ira Loss, executive vice president at Washington Analysis. Instances such as these can be hugely disruptive to drug development and hinder patient access to important new drugs. As proclaimed by Loss: "This is equivalent to showing up to an automobile race with a flat tire. Those are inexcusable reasons for not getting out of the starting box."

Whilst safety is the primary concern, streamlining and accelerating approval processes would be hugely beneficial to the industry. Currently, as the cost of drug development rises, long approval timelines result in limited patent life once commer-

U.S. FDA DRUG APROVALS

Source: U.S. Food and Drug Administration



cialized and greater challenges in return on investment. The industry may be focused on helping patients, but it is also an incredibly high-risk business with a large number of failures and currently limited time to recoup expenses in the market. Investment is, however, hugely important and needs to be incentivized. Operating in a country with one of the highest net corporate income tax rates in the world, rigorous defense of intellectual property and accelerated approval processes are a necessity.

Some companies and R&D groups are looking increasingly into treatments and cures for rare diseases with very specific patient populations, registering under designations such as orphan drug to take advantage of expedited review so the drug can be brought to market faster. Orphan drug designation can grant seven extra years of exclusivity, in addition to the standard five years under Hatch-Waxman. There is also the 505(b)(2) mechanism, which allows companies with re-formulated compounds to forego pre-clinical and Phase 1 trials.

Intellectual Property and Exclusivity: Timelines and Patent Life

The United States is well regarded for its innovation, for which its favorable intellectual property (IP) laws form an essential support. Underpinning discovery of new medicines and development of treatments, innovation must be protected from competition to increase incentives.

Prolonging exclusivity increases incentive by extending timelines for reimbursement and profit before copycat drugs enter the market. According to PhRMA, IP-intensive industries in the United States accounted for 83% of annual R&D spending across all U.S. manufacturing industries between 2000 and 2010, with R&D investment growing by 53% compared to 34% for non-IP-intensive industries. Within the IP-intensive industries, the pharmaceutical manufacturing industry outperformed all others, accounting for 27% of all R&D investment.

The Drug Price Competition and Patent Term Restoration Act, passed in 1984, is a U.S. federal law enabling generic manufacturers to forego a second clinical study program or risk liability for patent infringement. Informally known as the Hatch-Waxman Act after its sponsoring representative and senator, the Act provides a supportive framework to the generics industry and the resultant competition to their brand counterparts. By abbreviating and alleviating some of the financial pressure of the FDA approval process, the generics market has grown to account for nine out of 10 prescriptions dispensed in the United States.

Even within the boundaries of the Hatch-Waxman framework, the industry has seen an increasing trend for post-grant proceedings, such as post-grant review (PGR) and inter partes review (IPR) processes at the patent office. By making minor changes to a product and pursuing new patents, brand companies prohibit their generic-producing competitors from market entry. Taking place outside of the court system, IPRs are an alternative to litigation and, as such, are more efficient. The process allows generic and biosimilar manufacturers to challenge new patents and, if the innovation is deemed too tenuous at the U.S. Patent and Trademark Office (USPTO) to warrant additional patent protection, the patent will be invalidated.

"Specifically, with respect to pharmaceutical IPRs, when it comes to formulation and compound patents, it has been observed that compound patents tend to be invalidated less than formulation patents," commented Vishal Gupta, partner at Steptoe and Johnson, a 600-attorney international law firm specializing across all areas of IP. "Looking forward, in addition to IPRs we will see the PGR area grow in the life science space," he added.

Generic and biosimilar manufacturers take the view that the IPR process expedites patient access to more affordable drugs. According to the Association for Accessible Medicines (AAM), previously the Generic Pharmaceutical Association (GPhA), exempting pharmaceuticals from the IPR process could add around $1.3 billion in increased government spending on medicines. The association claims that the IPR process works in favor of patient access by promoting generic and biosimilar competition.

However, a key challenge is that this opens up the landscape to the entire industry; not just for the two companies involved. Equally, decisions reached in IPR can still be challenged by the original patent holder.

Patrolling Borders

Companies overseas exporting products into the United States will be very familiar with the FDA, which has long monitored all drugs entering the U.S. market tracing back to the 1848 Drug Importation Act. However, as the FDA increasingly crosses over the U.S. border, ramping up inspections of overseas facilities to ensure that the highest quality requirements are met, some companies may find their ties to the United States quickly severed.

The FDA continues to crack down on compliance at facilities to ensure good manufacturing practice (GMP) requirements are met, with an increase in presence and 'zero-notice' inspections at Asia-based facilities in particular. Although potentially disruptive, greater focus on compliance is highly valued in an industry in which quality and safety are of utmost importance. "As the FDA and other regulatory agencies continue to push back more and more, we have seen a trend with the FDA being very hard in Asia," related Anil Kripalani, president at Ash Ingredients. "In 2016, 14 warning letters were issued to manufacturers in China (44 worldwide). In 2017, between January and March, it has been 6 in China (17 worldwide). When we started, the supply chain was not so closely scrutinized. We welcome the increasing scrutiny as it has given us an advantage over our competitors as we have taken proactive steps to be in compliance."

Ash Ingredients, based in New Jersey, specializes in the manufacturing, sourcing and development of advanced intermediaries and fine chemicals. In conjunction with Longchem Chemical Co., based in China, the company forms half of Ash Longchem. Increased inspections, warning letters and import alerts across the board are however taking their toll on the market. "The FDA's presence in India and China has greatly increased and seemingly every month a major player gets knocked out with a warning letter or import alert," stated Melissa Authelet, director, regulatory and compliance at Rochem, a U.S.-based distributor focused on bringing Chinese products into the U.S. market. "This can have huge repercussions throughout the supply chain, with manufacturers in the United States experiencing drug shortages, and so on."

By being more stringent and ensuring adherence to the same quality standards and regulations the FDA continues to protect patients by barring low-quality and potentially harmful products from the U.S. market.

Harmonizing the Global Framework

With increasingly globalized supply chains and companies expanding their geographical footprints the differences in regulation between markets pose a challenge for many companies.

Speaking from the perspective of a manufacturer, Kristin Brancato, vice president and general manager at Cyalume Specialty Products, asserted: "We may characterize the period that lies behind us as one of a "double standard" of regulatory requirements for the manufacture of API's: the level demanded by the U.S. FDA and that required by the rest of the world. Fierce competition on one hand, coupled with the very strict limitations imposed by regulatory requirements in only some parts of the market have been the source of numerous dilemmas for the API industry. The fact that FDA compliance and high manufacturing costs go hand-in-hand has made it extremely difficult for manufacturers to supply the entire global market and at the same time maintain competitiveness."

Whilst the most pronounced disparities are between the U.S. market and less-regulated ones, there are also some key differences between the U.S. and European framework which are now being addressed. For example, the FDA and EMA agreed in March 2017 to recognize each other's audit reports through a reciprocal agreement. Previously, companies in Europe were required to audit suppliers every two to three years after inspection by the regulatory authority, whereas in the United States, the product can be received with impunity once the producer has been passed by the FDA. The result will likely be fewer inspections and greater cohesion and efficiency. The general trend is towards increased global alignment. —

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Another big difference is that European companies have a qualified person (QP), who releases the product from the factory to the general public on behalf of the marketing authorization holder. That QP has special recognized qualifications and is personally responsible for releasing the batch. This is the lynch pin of the safety of the consumer, because it focuses the QP completely and increases accountability. There is an equivalent mechanism in the United States, but there is no designated individual to take responsibility; each company may select and allocate a person with this responsibility.

- Rino Coladangelo,
CEO,
Rephine

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