White Paper: DEA Imposes Extra Layer of Regulations on Manufacturers of FDA-Approved Prescription Drugs To Alleviate Pain

Norwich Pharma Services
6826 State Highway 12
Norwich, NY 13815 USA
Tel: 607.335.3000
www.norwichpharma.com

DEA Imposes Extra Layer of Regulations on Manufacturers of FDA-Approved Prescription Drugs To Alleviate Pain

Pain therapeutics rank as one of pharmaceutical industry's key growth sectors, thanks to the "graying" population, scientific advances in understanding the neurological pathways underlying pain perception, and clinicians' improved awareness of pain management.

Several market research reports have predicted that prescription pain therapeutics could prove to be commercially lucrative to pharmaceutical and biotechnology companies.[1] In early 2014, one report predicted that the sales of prescription drugs for pain management would increase over the next four years at a compound annual growth rate of 3.84 percent.[2] According to another market research forecast, the global market for these drugs would reach $60 billion in 2015.[3] In 2010, the global market was estimated at $28.6 billion.[4]

Because prescription pain medications too often have been diverted into the illegal drug trade, development, manufacturing, and distribution are much more complicated for these drugs than for other prescription therapeutics. To produce prescription pain medications in the U.S., manufacturing facilities must abide by the rules and regulations of two federal agencies: the Food and Drug Administration (FDA) and the Drug Enforcement Agency (DEA), an arm of the U.S. Department of Justice that is charged with enforcing the Comprehensive Drug Abuse Prevention and Control Act, better known as the Controlled Substances Act (CSA).

Once a new prescription pain drug is approved by the FDA[5], DEA in consultation with the U.S. Department of Health and Human Services assigns the medication to one of five categories named Schedule I, II, III, IV, and V. The assignment is based on such factors as the compound's relative abuse or misuse, safety, its actual or relative potential for being addictive, FDA's approved medical use of the agent, and scientific evidence about the drug's pharmacological effect.[6] The compounds assigned to Schedule I, II, III, IV, and V are commonly referred to as controlled substances and include not only pain control drugs but also stimulants, such as MDMA ("ecstasy"), and psychedelics, such as LSD (lysergic acid diethylamide).

U.S. law prohibits the manufacture, distribution, or use of Schedule I controlled substances, which include heroin and LSD[7], for patient treatment because their addictive and abuse potential are high, and they're not approved for medical use and cannot be safely used even under medical supervision. However, with DEA's approval, a manufacturer can legally produce a very limited supply of Schedule I substances for research that the agency regards as scientifically important. The labs that conduct research with Schedule I substances must be registered with the DEA and are required to install security systems to safeguard the drugs.[8]

Because the drugs assigned to Schedules II to V have legitimate medical uses, DEA allows the manufacture, distribution, and prescription of these medications in the U.S., in accordance with the agency's as well as FDA's rules and regulations. The higher the schedule number, the less potentially addictive the substances in that category. Thus, Schedule II drugs, which include the opiates codeine and morphine, are potentially more addictive than Schedule V medications, which include such medications as the anti-seizure drug ezogabine.[6]

To prevent the diversion of Schedule II to V controlled substances for illegal use, DEA requires that the supply chain for these drugs be restricted to DEA-registered U.S. based manufacturers, distributors, hospitals, clinics, physicians, dentists, and retail pharmacies. This closed system helps insure that controlled substances are under the control of a DEA-registered entity during the manufacture, transport, storage, delivery, and dispensing of the drug. Only when controlled substances reach the patient or are destroyed according to DEA regulations are they legally allowed to exit the closed system.[8]

To register with DEA as a developer or manufacturer of controlled substances, pharmaceutical companies and contract development and manufacturing organizations (CDMOs) must apply for and receive an application for a Manufacturing Authorization and a Controlled Drugs Domestic License. As part of the agency's evaluation of the application, DEA inspects the manufacturing facility to insure that it adheres to security and record-keeping requirements. The agency's regulations and requirements for facilities that manufacture controlled substances are included in the Title 21 Code of Federal Regulations, published on the DEA's website.[7]

The manufacture of controlled substances demands a much higher level of security, record-keeping, and inventory control than are legally required for the production of other prescription medicines. Schedule I and II substances must be stored in specially constructed vaults or highly rated safes.[6] Because DEA requires less security for Schedule III, IV, and V drugs, they can be safeguarded in less costly structures, such as locked fenced cages inside the manufacturing facility. DEA also requires manufacturing facilities for all controlled substances to be externally protected with, for example, perimeter fences and gates with detector activated surveillance.

DEA regulations recommend, but do not require, that manufacturing facilities carefully screen job applicants for criminal records and use of illicit controlled substances.[8] Although not required by the DEA, periodic, unscheduled substance abuse screening of employees is regarded as a best practice in the industry. Employees involved in the manufacture of controlled substances must complete training programs on DEA rules and regulations as well as Good Manufacturing Practice (cGMP).

By establishing an annual aggregate production quota (APQ), DEA limits the nationwide supply of Schedule I and II agents. Each year's APQ is based on available data on sales and inventories of these controlled substances and FDA's estimates of drug usage.[6] The APQ for a specific year is announced during the preceding year. For example, DEA published the APQ for 2014 in the September 2013 issue of Federal Register.[9]

DEA also assigns an annual individual production quota (PQ) to each registered manufacturer. To obtain a PQ for the following year, the manufacturer must submit DEA form 189 to the agency by April 1. Applications must be submitted for each schedule of controlled substances that the manufacturer plans to produce. Suppliers of bulk raw materials to manufacturers must apply for their individual quotas by May 1.[9] DEA sets each manufacturing facility's PQ based on not only APQ but also the current nationwide inventory of the controlled substance, projected demand for the medication, changes that have occurred in the accepted medical uses of the drug, and the economic and physical availability of

the raw materials to produce the medication. If the manufacturing facility currently produces controlled substances, its annual application for a PQ must identify the amount of the drug that the facility manufactured and disposed during the current and past two previous years.

A DEA-registered manufacturer must maintain accurate, up-to-date records on each controlled substance that it produces, delivers, and disposes. Manufacturers of Schedule I and II substances and specific narcotics in Schedules III and IV must enter the information in DEA's Automation of Reports and Consolidated Orders Systems (ARCOS). ARCOS enables DEA to track the movement of these controlled substances in the closed supply chain. According to a DEA publication, the agency views the requirement that manufacturers post up-to-date information on ARCOS as "sufficient to discourage many forms of diversion. It actually serves large drug corporations as an internal check to uncover diversion, such as pilferage by employees." [6]

A manufacturer with multiple DEA-registered facilities must maintain separate files for each site. In addition, records on Schedule I and II substances must be maintained separate from files on Schedule III, IV, and V drugs.

DEA-registered manufacturers must submit detailed annual reports by the end of January of the following year. Thus, the deadline for the 2014 annual report will be January 31, 2015. The information collected from the annual reports of registered manufacturers and distributors creates a dataset that DEA taps for analysis. The agency uses the dataset to compile its own annual report to the United Nations Office of Drug and Crime,[9] which focuses on the international illegal drug trade. This U.N. body is empowered by three international treaties to which the U.S. is a signatory. The treaties form the basis for the statutory framework of the CSA and much of the country's drug control policy.[8]

Between 10 to 11 percent of all drug prescriptions written in the U.S. are for pharmaceutical controlled substances.[8] The rules and regulations of DEA that govern the development, production, and distribution of these substances are complex and demanding. Thus, a pharmaceutical company that plans to outsource the manufacture of its prescription pain medication should carefully check the CDMO's track record of adhering to the regulations of both FDA and DEA.

References

1. The Global Pain Therapeutics Market, 4th Edition: Market Trends & R&D Insights. Available at: http://www.bloomberg.com/apps/news?pid=newsarchive&sid=aWlaJtk7RI4A
2. Global Pain Management Drugs Market 2014-2018. Available at: http://www.reportbuyer.com/pharma_healthcare/therapeutic/global_pain_management_drugs_market_2014_2018.html
3. Pain Management Market Ripe with Immediate Opportunities. Genetic Engineering and Biotechnology News. Available at: http://www.genengnews.com/gen-articles/pain-management-market-ripe-with-immediate-opportunities/4123/
4. Pain Management Therapeutics Market to 2017 – Price Competition to Intensify Following Patent Expiries of Lyrica and Cymbalta. Available at: http://www.gbiresearch.com/Report.aspx?ID=Pain-Management-Therapeutics-Market-to-2017-Price-Competition-to-Intensify-Following-Patent-Expiries-of-Lyrica-and-Cymbalta&
5. 2013 National Rx Drug Abuse Summit. Remarks by Margaret A. Hamburg, M.D., Commissioner of Food and Drugs. Available at: http://www.fda.gov/newsevents/speeches/ucm346315.htm
6. Drugs of Abuse. A DEA Resource Guide 2011. Available at: http://www.justice.gov/dea/docs/drugs_of_abuse_2011.pdf
7. Title 21 Code of Federal Regulations. Part 1300-END. Available at: http://www.deadiversion.usdoj.gov/21cfr/cfr/index.html
8. The Controlled Substances Act: Regulatory Requirements. Congressional Research Service. Dec. 13, 2012. Available at: http://www.fas.org/sgp/crs/misc/RL34635.pdf
9. Obtaining DEA Quota Manufacture Controlled Substances. DEA Chronicles. May 6, 2013. Available at: http://deachronicles.quarles.com/2013/05/obtaining-dea-quota-to-manufacture-controlled-substances/
10. Year-End Reports. DOE. Available at: http://www.deadiversion.usdoj.gov/mtgs/man_imp_exp/conf_2013/kavanagh.pdf#search=year-end%20reports