

Risk Factors Comparison 2025-03-10 to 2024-03-15 Form: 10-K

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To enforce these requirements, the DEA conducts periodic inspections of registered establishments that handle controlled substances. Failure to maintain compliance with applicable requirements, especially security and recordkeeping and as manifested in loss or diversion or inability to account for all controlled substances, can result in administrative, civil, or criminal enforcement action that could have a material adverse effect on our business, results of operations, and financial condition. The DEA may seek civil penalties, refuse to renew necessary registrations, or initiate administrative proceedings to revoke those registrations. The DEA may also reduce or deny quota to manufacturing facilities based on non-compliance with these requirements. In certain circumstances, violations could result in criminal proceedings. Individual states also independently regulate controlled substances. Legislative and Regulatory Initiatives for Opioids In response to widespread prescription opioid abuse, the United States government and a number of state legislatures have enacted legislation and regulations intended to fight the opioid epidemic. The number and scope of legislative and regulatory actions, particularly in the last three years, emphasize the severity of the opioid epidemic and its impact on our society. The FDA has stated that addressing prescription drug abuse is a priority and has reaffirmed that the development of abuse-deterrent opioids is a key part of that strategy. Recent actions to address the opioid abuse epidemic include:

- **FDA guidance:** In April 2015, the FDA adopted final guidance regarding studies and clinical trials that should be conducted to demonstrate that a given formulation has abuse-deterrent properties, how those studies and clinical trials will be evaluated, and what product labeling claims may be approved based on the results of those studies and clinical trials. The guidance describes four categories of abuse-deterrence studies and clinical trials: Categories 1, 2, and 3 consist of pre-marketing studies and clinical trials designed to evaluate a product candidate's potentially abuse-deterrent properties under controlled conditions, while Category 4, post-marketing clinical trials and studies, assesses the real-world impact of abuse-deterrent formulations. The final guidance also provides examples of product label claims that may be made based on the results of the corresponding studies and clinical trials.
- **FDA Opioids Action Plan:** In February 2016, the FDA released an action plan to address the opioid abuse epidemic and reassess the FDA's approach to opioid medications. The FDA's plan is part of a broader initiative led by the U. S. Department of Health and Human Services ("HHS"), to address opioid-related overdose, death, and dependence.
- **CDC Prescribing Guidelines:** In November 2022, the CDC released a new Guideline for Prescribing Opioids for Pain to update their 2016 Guidelines. The new guidance includes recommendations for managing acute (duration of < 1 month), subacute (duration of 1 – 3 months), and chronic (duration of > 3 months) pain. The guideline addresses the following four areas: 1) determining whether or not to initiate opioids for pain, 2) selecting opioids and determining opioid dosages, 3) deciding duration of initial opioid prescription and conducting follow-up, and 4) assessing risk and addressing potential harms of opioid use. ~~The guideline addresses the following four areas: 1) determining whether or not to initiate opioids for pain, 2) selecting opioids and determining opioid dosages, 3) deciding duration of initial opioid prescription and conducting follow-up, and 4) assessing risk and addressing potential harms of opioid use.~~
- **FDA Drug Safety Communication:** In April 2023, the FDA issued a communication that in the ongoing effort to address the nation's opioid crisis, it was making several updates to the prescribing information of opioid pain medicines to provide additional guidance on their use. The changes include label updates addressing addiction, abuse and misuse as well as life-threatening respiratory depression, accidental ingestion, risks from concomitant use with other CNS depressants, neonatal withdrawal and opioid analgesic risk evaluation and mitigation strategy.
- **Enhanced Warnings and Safety Labeling:** In March 2016, the FDA announced required enhanced warnings for immediate-release opioid pain medications related to risks of misuse, abuse, addiction, overdose, and death. Subsequently, there have been several class-wide labeling changes, including the addition of boxed warnings relating to serious risks of using certain opioids medications along with benzodiazepines and other central nervous system depressants, including alcohol (Decembers 2016); and additional information relating to the new class-wide REMS (Septembers 2018).
- **Enactment of the Comprehensive Addiction and Recovery Act ("CARA"):** In 2016, the CARA was enacted to address the national epidemics of prescription opioid abuse and heroin use. Consistent with the initiatives of HHS, this legislation sought to, among other things, expand the availability of naloxone for law enforcement and other first responders; form an interagency task force to develop best practices for pain management with opioid medications; and provide resources to improve state monitoring of controlled substances, including opioids. In 2018, CARA 2.0 was introduced as follow-up legislation to limit initial prescriptions for opioids to 3 days, while exempting initial prescriptions for chronic care, cancer care, hospice or end of life care, and palliative care.
- **Enactment of the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act ("SUPPORT Act"):** In November 2018, the SUPPORT Act was enacted as a comprehensive legislative response to the continuing opioid epidemic. It includes a number of measures directed towards regulation and improvement of treatment for substance use-disorder and increased coverage by CMS of medically assisted treatment options. In addition, the SUPPORT Act requires HHS to report to Congress on existing barriers to access to abuse-deterrent opioid formulations by Medicare Part C and D beneficiaries. It also includes a number of requirements directed at reducing the potential for oversupply of opioids to reduce the potential for misuse and diversion.

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