

The existence of price differentials within the EU due to the different national pricing and reimbursement laws leads to significant parallel trade flows.

Government Regulation

The pharmaceutical industry is subject to extensive global regulations by regional, country, state and local agencies. The Federal Food, Drug, and Cosmetic Act, other Federal statutes and regulations, various state statutes and regulations (including newly enacted state laws regulating drug price transparency, rebates and drug spending), and laws and regulations of foreign governments govern to varying degrees the testing, approval, production, labeling, distribution, post-market surveillance, advertising, dissemination of information and promotion of our products. The lengthy process of laboratory and clinical testing, data analysis, manufacturing, development and regulatory review necessary for required governmental approvals is extremely costly and can significantly delay product introductions in a given market. Promotion, marketing, manufacturing and distribution of pharmaceutical products are extensively regulated in all major world markets. In addition, our operations are subject to complex Federal, state, local and foreign environmental and occupational safety laws and regulations. We anticipate that the laws and regulations affecting the manufacture and sale of current products and the introduction of new products will continue to require substantial scientific and technical effort, time and expense as well as significant capital investments.

The FDA is of particular importance in the U.S. It has jurisdiction over virtually all of our activities and imposes requirements covering the testing, safety, effectiveness, manufacturing, labeling, marketing, advertising and post-marketing surveillance of our products. In many cases, the FDA requirements have increased the amount of time and money necessary to develop new products and bring them to market in the U.S. The regulatory review process is a resource intensive undertaking for both the FDA and the pharmaceutical manufacturer. Improvements in the efficiency of this process can have significant impact on bringing new therapies to patients more quickly. The FDA can employ several tools to expedite certain applications, including fast track designation, accelerated approval and others. Recently, the FDA Oncology Center of Excellence (OCE) established two new pilot projects to test novel approaches to regulatory review for oncology drugs: the Real-Time Oncology Review (RTOR) and the Assessment Aid (AAid). Under the AAid pilot program, the FDA approved *Empliciti* on November 6, 2018 for an additional multiple myeloma indication in combination with pomalidomide and dexamethasone for the treatment of adult patients who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor. This approval was achieved more than 7 weeks before the priority review Prescription Drug User Fee Act (PDUFA) date.

The FDA mandates that drugs be manufactured, packaged and labeled in conformity with cGMP established by the FDA. In complying with cGMP regulations, manufacturers must continue to expend time, money and effort in production, recordkeeping and quality control to ensure that products meet applicable specifications and other requirements to ensure product safety and efficacy. The FDA periodically inspects our drug manufacturing facilities to ensure compliance with applicable cGMP requirements. Failure to comply with the statutory and regulatory requirements subjects us to possible legal or regulatory action, such as suspension of manufacturing, seizure of product or voluntary recall of a product. Adverse experiences with the use of products must be reported to the FDA and could result in the imposition of market restrictions through labeling changes or product removal. Product approvals may be withdrawn if compliance with regulatory requirements is not maintained or if problems concerning safety or efficacy occur following approval.

The Federal government has extensive enforcement powers over the activities of pharmaceutical manufacturers, including authority to withdraw or delay product approvals, to commence actions to seize and prohibit the sale of unapproved or non-complying products, to halt manufacturing operations that are not in compliance with cGMPs, and to impose or seek injunctions, voluntary recalls, civil, monetary and criminal penalties. Such a restriction or prohibition on sales or withdrawal of approval of products marketed by us could materially adversely affect our business, financial condition and results of operations and cash flows.

Marketing authorization for our products is subject to revocation by the applicable governmental agencies. In addition, modifications or enhancements of approved products or changes in manufacturing locations are in many circumstances subject to additional FDA approvals, which may or may not be received and may be subject to a lengthy application process.

The distribution of pharmaceutical products is subject to the PDMA as part of the Federal Food, Drug, and Cosmetic Act, which regulates such activities at both the Federal and state level. Under the PDMA and its implementing regulations, states are permitted to require registration of manufacturers and distributors that provide pharmaceuticals even if such manufacturers or distributors have no place of business within the state. States are also permitted to adopt regulations limiting the distribution of product samples to licensed practitioners. The PDMA also imposes extensive licensing, personnel recordkeeping, packaging, quantity, labeling, product handling and facility storage and security requirements intended to prevent the sale of pharmaceutical product samples or other product diversions.

The FDA Amendments Act of 2007 imposed additional obligations on pharmaceutical companies and delegated more enforcement authority to the FDA in the area of drug safety. Key elements of this legislation give the FDA authority to (1) require that companies conduct post-marketing safety studies of drugs, (2) impose certain safety related drug labeling changes, (3) mandate risk mitigation measures such as the education of healthcare providers and the restricted distribution of medicines, (4) require companies to publicly disclose data from clinical studies and (5) pre-review television advertisements.