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| **Item 1A.** | **RISK FACTORS** |

This report and other documents we file with the SEC contain forward-looking statements that are based on current expectations, estimates, forecasts and projections about us, our future performance, our business, our beliefs and our management’s assumptions. These statements are not guarantees of future performance and involve certain risks, uncertainties and assumptions that are difficult to predict. You should carefully consider the risks and uncertainties our business faces. The risks described below are not the only ones we face. Our business is also subject to the risks that affect many other companies, such as employment relations, general economic conditions, geopolitical events and international operations. Further, additional risks not currently known to us or that we currently believe are immaterial may in the future materially and adversely affect our business, operations, liquidity and stock price.

*Our sales depend on coverage and reimbursement from third-party payers, and pricing and reimbursement pressures may affect our profitability.*

Sales of our products depend on the availability and extent of coverage and reimbursement from third-party payers, including government healthcare programs and private insurance plans. Governments and private payers continue to pursue initiatives to contain costs and manage drug utilization. These payers are increasingly focused on the effectiveness, benefits and costs of similar treatments, which could result for our products in lower reimbursement rates or narrower populations for whom payers will reimburse. Continued intense public scrutiny of the price of drugs and other healthcare costs, together with payer dynamics, may limit our ability to set or adjust the price of our products based on their value, which could have a material adverse effect on our business. In the United States, the public discussions of drug pricing issues are likely to continue.

*—Changing federal coverage and reimbursement policies and practices have impacted and may continue to impact access to and sales of our products*

A substantial portion of our U.S. business relies on reimbursement from U.S. federal government healthcare programs and commercial insurance plans regulated by the U.S. federal and state governments. See Item 1. Business—Reimbursement. Our business has and will continue to be impacted by legislative actions changing U.S. federal reimbursement policy. For example, in February 2018, the U.S. Congress passed legislation requiring biopharmaceutical manufacturers to provide greater discounts beginning in 2019 on products dispensed to patients in the coverage gap between the initial coverage limit of Medicare Part D and the program’s catastrophic-coverage threshold, which will reduce our net product sales relating to such patients. Additional legislative proposals have been introduced by members of Congress to overhaul provisions of the Patient Protection and ACA, to allow commercial-level re-importation of prescription medications from Canada or other countries and to enable Medicare to negotiate drug prices with biopharmaceutical manufacturers. Congressional focus on drug pricing has increased since the Democrats took control of the U.S. House of Representatives in November 2018. For example, in January 2019, the chair of the House Oversight and Reform Committee sent letters to twelve different biopharmaceutical manufacturers, including Amgen, seeking documents and detailed information about such companies’ drug pricing. Both that committee and the Senate Finance Committee held committee hearings in January 2019 on the topic of drug pricing and have indicated that further committee hearings on the topic are likely.

Also our business has been and is expected to continue to be impacted by changes in U.S. federal reimbursement policy resulting from executive actions, federal regulations, or federal demonstration projects. For example, in May 2018, the U.S. presidential administration released a drug pricing “blueprint” and requested public comment on an array of policy ideas intended to increase competition, improve the negotiating power of the federal government, reduce drug prices and lower patient out-of-pocket costs. This blueprint includes a number of policy ideas with the potential to significantly impact, whether individually or collectively, our industry. Such proposals include moving coverage and reimbursement for Medicare Part B drugs into Medicare

22

Part D, instituting a competitive acquisition program for Part B drugs in which competing third-party vendors take on the financial risk of acquiring drugs and billing Medicare, removing the safe harbor protection under the federal anti-kickback statute for drug rebates paid to payers, and requiring the inclusion of drug price information in direct-to-consumer drug advertising.

Since that time, the president and/or federal agencies, such as CMS, have announced a number of demonstration projects, recommendations and proposals to implement various elements described in the drug pricing blueprint. CMS, the federal agency responsible for administering Medicare and overseeing state Medicaid programs and Health Insurance Marketplaces, has substantial power to implement policy changes or demonstration projects that can quickly and significantly affect how drugs, including our products, are covered and reimbursed. For example, in October 2018, President Trump announced that CMS was evaluating a pilot program proposed to initially cover fifty percent of spending on Part B single-source drugs referred to as the “International Price Index” that would, among other things, set the Medicare payment amount for such single-source drugs to more closely align with international drug prices. CMS has taken additional actions to implement other elements described in the administration’s drug-pricing blueprint, including issuing guidance to allow certain Medicare plans offered by private insurance companies to require that patients receiving Medicare Part B drugs first try a drug preferred by the plan before such plan will cover another therapy and proposing lower reimbursement rates for new Part B drugs. And on January 31, 2019, the U.S. Department of Health and Human Services released a proposal to revise the federal anti-kickback statute safe harbor regulations to exclude from safe harbor protection certain rebates and other forms of remuneration paid by a manufacturer of prescription drugs to Medicaid managed care organizations or plan sponsors under Medicare Part D, either directly or through PBMs.

Further, CMS has undertaken demonstration projects to test care models, such as the CMS Oncology Care Model, which provides participating physician practices with performance-based financial incentives that aim to manage or reduce Medicare costs without negatively impacting the efficacy of care. We believe the Oncology Care Model has reduced utilization of certain of our oncology products by participating physician practices and may continue to do so in the future. In addition, CMS has solicited suggestions regarding other potential care models.

In this dynamic environment, we are unable to predict which or how many of these various federal policy, legislative or regulatory changes may ultimately be enacted, to the extent that these or other federal government initiatives decrease or modify the coverage or reimbursement available for our products, limit our ability to offer co-pay payment assistance to commercial patients, require that we pay increased rebates or shift other costs to us, limit or impact our decisions regarding the pricing of biopharmaceutical products or otherwise reduce the use of our U.S. products, such actions could have a material adverse effect on our business and results of operations.

We also face risks relating to the reporting of pricing data that affects the reimbursement of and discounts provided for our products. Government price reporting regulations are complex and may require a manufacturer to update certain previously submitted data. If our submitted pricing data are incorrect, we may become subject to substantial fines and penalties or other government enforcement actions, which could have a material adverse effect on our business and results of operations. In addition, as a result of restating previously reported price data, we also may be required to pay additional rebates and provide additional discounts.

*—Changing state reimbursement and pricing actions may impact access to and have impacted and may continue to impact sales of our products*

At the state level, government actions or ballot initiatives can also affect how our products are covered and reimbursed and/or create additional pressure on our pricing decisions. A number of states have adopted, and many other states have discussed and debated and are considering, new pricing actions, including proposals designed to require biopharmaceutical manufacturers to publicly report proprietary pricing information, limit price increases or to place a maximum price ceiling or cap on biopharmaceutical products. Existing and proposed state pricing laws have added complexity to the pricing of drugs and may already be impacting industry pricing decisions. For example, in October 2017, California enacted a drug-pricing transparency bill that requires biopharmaceutical manufacturers to notify health insurers and government health plans at least 60 days before scheduled prescription drug price increases that exceed certain thresholds. Other states are seeking to change the way their states pay for drugs for patients covered by state programs. For example, in August 2018 the Ohio Department of Medicaid ordered that all the state’s Medicaid managed care plans terminate and renegotiate contracts with PBMs to eliminate the drug purchasing model in which PBMs bill the state more than they reimburse pharmacists for filling Medicaid patient prescriptions. In January 2019, California’s governor issued an executive order expanding state Medicaid coverage and directing state agencies and programs to consolidate drug purchases and to negotiate drug prices with manufacturers. Other states could adopt similar approaches or could pursue different policy changes in a continuing effort to reduce their costs. Ultimately, as with U.S. federal government actions, existing or future state government actions or ballot initiatives may also have a material adverse effect on our product sales, business and results of operations.

23

*—U.S. commercial payer actions have impacted and may continue to impact access to and sales of our products*

Payers, including healthcare insurers, PBMs and group purchasing organizations, increasingly seek ways to reduce their and their respective members’ costs. With increasing frequency, payers are adopting benefit plan changes that shift a greater portion of drug costs to patients. Such measures include more limited benefit plan designs, high deductible plans, higher patient co-pay or coinsurance obligations and limitations on patients’ use of manufacturer commercial co-pay payment assistance programs (including through co-pay accumulator adjustment or maximization programs). Payers have sought and will likely continue to seek price discounts or rebates in connection with the placement of our products on their formularies or those they manage, particularly in treatment areas where the payer has taken the position that multiple branded products are therapeutically comparable. Payers also control costs by imposing restrictions on access to or usage of our products, such as requiring that patients first try a drug preferred by the payer or receive the payer’s prior authorization before covering the product, or that patients use a mail-order pharmacy or mail-order pharmacy or a limited network of fully-owned specialty pharmacies; payers may also choose to exclude certain indications for which our products are approved or even choose to exclude coverage entirely. For example, the burdensome administrative processes required for physicians to demonstrate or document that the patients for whom Repatha® has been prescribed meet payer utilization management criteria has limited and may continue to limit patient access to Repatha® treatment. In an effort to reduce barriers to access, we reduced the net price of Repatha® by providing greater discounts and rebates to payers, including PBMs that administer Medicare Part D prescription drug plans. However, affordability of patient out-of-pocket co-pay cost has and may continue to limit patient use. For example, a very high percentage of Medicare patients have abandoned their Repatha®prescriptions rather than pay their co-pay payment. In late 2018 and early 2019, we introduced a set of new NDCs to make Repatha® available at a lower list price to attempt to address affordability for patients, particularly those on Medicare. Despite the recent net and list price reductions, payers may continue to restrict patient access, change formulary coverage for Repatha®, seek further discounts or rebates or take other actions that could reduce our sales of Repatha®. Further, our introduction of the new NDCs may not be rapidly adopted by payers, which could continue to limit patient use and could also reduce our sales of Repatha®.

Significant consolidation in the health insurance industry has resulted in a few large insurers and PBMs exerting greater pressure in pricing and usage negotiations with drug manufacturers, significantly increasing discounts and rebates required of manufacturers and limiting patient access and usage. For example, in the United States, the top three PBMs now oversee greater than two-thirds of prescription claims as well as government and commercial covered lives. The consolidation among insurers, PBMs and other payers, including through integrated delivery systems and/or with specialty or mail-order pharmacies and pharmacy retailers, has increased the negotiating leverage such entities have over us and other drug manufacturers and has resulted in greater price discounts, rebates and fees for other services being realized by those payers. For example, during the fourth quarter of 2018, two of the nation’s largest PBMs, Express Scripts and CVS Health, completed their combinations with major insurance companies Cigna and Aetna, respectively. Additional consolidation would further increase the leverage of such entities. Ultimately, additional discounts, rebates, coverage or plan changes, restrictions or exclusions imposed by these commercial payers could have a material adverse effect on our product sales, business and results of operations.

*—Government and commercial payer actions outside the United States have impacted and will continue to impact access to and sales of our products*

Outside the United States, we expect countries will continue to take actions to reduce their drug expenditures. See Item 1. Business—Reimbursement. International reference pricing (IRP) has been widely used by many countries outside the United States to control costs based on an external benchmark of a product’s price in other countries. IRP policies can quickly and frequently change and may not reflect differences in the burden of disease, indications, market structures, or affordability differences across countries or regions. In addition, countries may refuse to reimburse or may restrict the reimbursed population for a product when their national health technology assessments do not consider a medicine to demonstrate sufficient clinical benefit beyond existing therapies or that it does not meet certain cost effectiveness thresholds. For example, despite the EMA’s May 2018 approval of Repatha® for the treatment of patients with established atherosclerotic disease, reimbursement for Repatha® in France and Germany has remained limited to narrower patient populations (such as those with homozygous familial hypercholesterolemia) following national health technology assessments in mid-2018. While the pricing and reimbursement process in those countries remains ongoing, these assessments currently limit our efforts in France and Germany to expand Repatha® access to the broader patient population covered by the approved label. Failure to obtain coverage and reimbursement for our products, a deterioration in their existing coverage and reimbursement, or a decline in the timeliness or certainty of payment by payers to physicians and other providers could negatively impact the ability or willingness of healthcare providers to prescribe our products for their patients or could otherwise negatively affect the use of our products or the prices we receive for them. Such changes could have a material adverse effect on our product sales, business and results of operations.

*We currently face competition from biosimilars and expect to face increasing competition from biosimilars and generics in the future.*

We currently face competition from biosimilars in both Europe and the United States, and we expect to face increasing biosimilar and/or generics competition this year and beyond. Expiration or successful challenge of applicable patent rights or

24

expiration of an applicable exclusivity period would accelerate such competition, and we expect to face more litigation regarding the validity and/or scope of our patents. Our products may also experience greater competition from lower-cost biosimilars or generics that come to market when branded products that compete with our products lose their own patent protection. To the extent that governments adopt more permissive approval frameworks and competitors are able to obtain broader or expedited marketing approval for biosimilars and generics, the rate of increased competition for our products could accelerate.

In the EU, biosimilars are evaluated for marketing authorization pursuant to a set of general and product class-specific guidelines. In addition, in an effort to spur biosimilar utilization and/or increase potential healthcare savings, some EU countries have adopted and others are attempting to adopt biosimilar uptake measures such as requiring physician prescribing quotas or promoting switching or pharmacy substitution of biosimilars for the corresponding reference products, and other countries may adopt similar measures. Some EU countries impose automatic price reductions upon market entry of one or more biosimilar competitors. While the degree of competitive impact of biosimilar competition differs between EU countries and between products, in the EU the overall use of biosimilars and the rate at which product sales of innovative products are being impacted by biosimilar competition is increasing.

In the United States, the ACA authorized the FDA to approve biosimilars via a separate, abbreviated pathway. See Item 1. Business—Government Regulation—Regulation in the United States—Approval of Biosimilars. The first biosimilar entrant into the U.S. market, Sandoz’s Zarxio®, is a biosimilar version of NEUPOGEN® and was launched in the United States in 2015. Since then, the FDA has approved additional biosimilars, including biosimilar versions of ENBREL, Neulasta® and EPOGEN®, and a growing number of companies have announced that they are also developing biosimilar versions of our products. Two biosimilar versions of Neulasta® are now marketed in the United States and others may receive approval in 2019. Impact to our Neulasta® sales could accelerate as additional competitors are launched. See Item 1. Business—Marketing, Distribution and Selected Marketed Products—Competition. The approved biosimilar version of EPOGEN® has also launched in the United States, and we are currently involved in patent litigation with the manufacturer of the approved version of ENBREL. Manufacturers of biosimilars may attempt to compete with our products by offering lower list prices, greater discounts or rebates, or contracts that offer longer-term pricing or a broader portfolio of other products. Companies pursuing development of biosimilar versions of our products have challenged and may continue to challenge our patents well in advance of the expiration of our material patents. For information related to our biosimilars and generics patent litigation, see Part IV—Note 20, Contingencies and commitments, to the Consolidated Financial Statements. See *Our intellectual property positions may be challenged, invalidated or circumvented, or we may fail to prevail in present and future intellectual property litigation.* The U.S. pathway includes the option for biosimilar products that meet certain criteria to be approved as interchangeable with their reference products. Some companies currently developing or already marketing biosimilars may seek to register their products as interchangeable biosimilars, which could make it easier for pharmacists to substitute those biosimilars for our reference products or could encourage prescribers or payers who are inclined to select the interchangeable biosimilar over our innovative products or our biosimilars. In addition, critics of the 12-year exclusivity period in the biosimilar pathway law will likely continue to seek to shorten the data exclusivity period and/or to encourage the FDA to interpret narrowly the law’s provisions regarding which new products receive data exclusivity. For example, the FDA is considering whether subsequent changes to a licensed biologic would be protected by the remainder of the reference product’s original 12-year exclusivity period (a concept known in the generic drug context as “umbrella exclusivity”). If the FDA were to decide that umbrella exclusivity does not apply to biological reference products or were to make other changes to the exclusivity period, this could expose us to biosimilar competition at an earlier time. There also have been, and may continue to be, public, legislative, and FDA efforts to promote price competition through policies enabling easier generic and biosimilar entry, including efforts to lower standards for demonstrating biosimilarity or interchangeability and provide greater clarity for how to do so, and through changes to the reimbursement policies for biologics.

Upon the expiration or loss of patent protection for one of our small-molecule products, we can lose the majority of revenues for that product in a very short period of time. See Item 1. Business—Marketing, Distribution and Selected Marketed Products—Competition. Our U.S. composition of matter patent for Sensipar®, a small-molecule product, expired in March 2018. We are engaged in litigation with a number of companies seeking to market generic versions of Sensipar® surrounding our U.S. formulation patent that expires in September 2026. Several of these generic versions of Sensipar® have been approved by the FDA, and the manufacturer of one of the approved generic versions began selling its product in late 2018 before reaching a settlement agreement with us in early January 2019. We were subsequently sued by a manufacturer of another approved generic version of Sensipar® who is contending that provisions of its own settlement agreement with Amgen have been triggered by the first manufacturer’s at-risk launch, giving this second manufacturer a right to market its own generic version under its settlement agreement. See Part IV—Note 20, Contingencies and commitments, to the Consolidated Financial Statements. While no generic versions of Sensipar®are currently available for sale, one or more other companies may elect to launch their approved generic versions at-risk prior to the conclusion of our ongoing litigation, or may seek and obtain a judicial declaration that they are permitted to launch their generic versions. If this happens, our product sales for Sensipar® could be materially and adversely affected.

While we are unable to predict the precise impact of biosimilars and generics on our products, we are currently facing and expect to face greater competition in the United States, Europe and elsewhere this year and beyond as a result of biosimilar and

25

generic competition and downward pressure on our product prices and sales. This competition has had and could increasingly have a material adverse effect on our product sales, business and results of operations.

*Our products face substantial competition.*

We operate in a highly competitive environment. See Item 1. Business—Marketing, Distribution and Selected Marketed Products—Competition. We expect that our products will compete with new drugs currently in development, drugs currently approved for other indications that may later be approved for the same indications as those of our products and drugs approved for other indications that are used off-label. Large pharmaceutical companies and generics manufacturers of pharmaceutical products are expanding into the biotechnology field, and some pharmaceutical companies and generics manufacturers have formed partnerships to pursue biosimilars. In addition, some of our competitors may have technical, competitive or other advantages over us for the development of technologies and processes or greater experience in particular therapeutic areas, and consolidation among pharmaceutical and biotechnology companies can enhance such advantages. These advantages may make it difficult for us to compete with them to successfully discover, develop and market new products and for our current products to compete with new products or new product indications they may bring to market. As a result, our products may compete against products that offer higher rebates or discounts, lower prices, equivalent or superior performance, better safety profiles, easier administration, earlier market availability or other competitive features. If we are unable to compete effectively, this could reduce sales, which could have a material adverse effect on our business and results of operations.

*Our intellectual property positions may be challenged, invalidated or circumvented, or we may fail to prevail in present and future intellectual property litigation.*

Our success depends in part on our ability to obtain and defend patent rights and other intellectual property rights that are important to the commercialization of our products and product candidates. The patent positions of pharmaceutical and biotechnology companies can be highly uncertain and often involve complex legal, scientific and factual questions. Driven by cost pressures, efforts to limit or weaken patent protection for our industry are increasing. Third parties may challenge, invalidate or circumvent our patents and patent applications relating to our products, product candidates and technologies. Challenges to patents may come from potential competitors or from parties other than those who seek to market a potentially-infringing product. In addition, our patent positions might not protect us against competitors with similar products or technologies because competing products or technologies may not infringe our patents. For certain of our product candidates, there are third parties who have patents or pending patent applications that they may claim necessitate payment of a royalty or prevent us from commercializing these product candidates in certain territories. Patent disputes are frequent, costly and can preclude, delay or increase the cost of commercialization of products. We have been in the past, and are currently and expect to be in the future, involved in patent litigation. These matters have included and may in the future include litigation with manufacturers of products that purport to be biosimilars of certain of our products for patent infringement and for failure to comply with certain provisions of the Biologics Price Competition and Innovation Act. A determination made by a court, agency or tribunal concerning infringement, validity, enforceability, injunctive or economic remedy, or the right to patent protection, for example, are typically subject to appellate or administrative review. Upon review, such initial determinations may be afforded little or no deference by the reviewing tribunal and may be affirmed, reversed, or made the subject of reconsideration through further proceedings. A patent dispute or litigation may not discourage a potential violator from bringing the allegedly-infringing product to market prior to a final resolution of the dispute or litigation. The period from inception until resolution of a patent dispute or litigation is subject to the availability and schedule of the court, agency or tribunal before which the dispute or litigation is pending. We may be subject to competition during this period and may not be able to recover fully from the losses, damages, and harms we incur from infringement by the competitor product even if we prevail. Moreover, if we lose or settle current or future litigations at certain stages or entirely, we could be subject to competition and/or significant liabilities, be required to enter into third-party licenses for the infringed product or technology or be required to cease using the technology or product in dispute. In addition, we cannot guarantee that such licenses will be available on terms acceptable to us, or at all.

Further, under the Hatch-Waxman Act, our products approved by the FDA under the FDCA may be the subject of patent litigation with generics competitors before expiry of the five-year period of data exclusivity provided for under the Hatch-Waxman Act and prior to the expiration of the patents listed for the product. Likewise, our innovative biologic products may be the subject of patent litigation prior to the expiration of our patents and, with respect to competitors seeking approval as a biosimilar or interchangeable version of our products, prior to the 12-year exclusivity period provided under the ACA. In addition, we are facing patent litigation involving claims that the biosimilar product candidates we are working to develop infringe the patents of other companies that manufacture, market or sell the applicable reference products. For example, we are currently engaged in litigation in the United States regarding MVASITM, KANJINTITMand AMJEVITATM, and in Europe we are engaged in litigation regarding AMGEVITATM. While we may attempt to challenge the patents held by the companies manufacturing, marketing or selling the applicable reference products, our efforts may be unsuccessful. Alternatively, such patents may contribute to a decision by us to not pursue all of the same labeled indications as are held by these companies. For information related to our patent litigation, see Part IV—Note 20, Contingencies and commitments, to the Consolidated Financial Statements.

26

Certain of the existing patents on our products have expired. See Item 1. Business—Marketing, Distribution and Selected Marketed Products—Patents. As our patents expire, competitors are able to legally produce and market similar products or technologies, including biosimilars, which may have a material adverse effect on our product sales, business and results of operations. In addition, competitors may be able to invalidate, design around or otherwise circumvent our patents and sell competing products.

*Guidelines and recommendations published by various organizations can reduce the use of our products.*

Government agencies promulgate regulations and guidelines directly applicable to us and to our products. Professional societies, practice management groups, insurance carriers, physicians’ groups, private health and science foundations and organizations involved in various diseases also publish guidelines and recommendations to healthcare providers, administrators and payers, as well as patient communities. Recommendations by government agencies or other groups and organizations may relate to such matters as usage, dosage, route of administration and use of related therapies. In addition, a growing number of organizations are providing assessments of the value and pricing of biopharmaceutical products, and even organizations whose guidelines have historically been focused on clinical matters have begun to incorporate analyses of the cost effectiveness of various treatments into their treatment guidelines and recommendations. Value assessments may come from private organizations that publish their findings and offer recommendations relating to the products’ reimbursement by government and private payers. Some companies and payers have announced pricing and payment decisions based in part on the assessments of private organizations. For example, CVS Caremark indicated in August 2018 that it will begin utilizing third-party cost effectiveness analyses to make formulary and coverage determinations for newly-approved drugs. In addition, government health technology assessment organizations in many countries make reimbursement recommendations to payers in their jurisdictions based on the clinical effectiveness, cost-effectiveness and service impact of new, emerging and existing medicines and treatments. Such health technology assessment organizations may recommend reimbursement for our product for a narrower indication than was approved by applicable regulatory agencies or may recommend against reimbursement entirely. Such recommendations or guidelines may affect our reputation, and any recommendations or guidelines that result in decreased use, dosage or reimbursement of our products could have a material adverse effect on our product sales, business and results of operations. In addition, the perception by the investment community or stockholders that such recommendations or guidelines will result in decreased use and dosage of our products could adversely affect the market price of our common stock.

*Our current products and products in development cannot be sold without regulatory approval.*

Our business is subject to extensive regulation by numerous state and federal government authorities in the United States, including the FDA, and by foreign regulatory authorities, including the EMA. We are required in the United States and in foreign countries to obtain approval from regulatory authorities before we manufacture, market and sell our products. Once our products are approved, the FDA and other U.S. and foreign regulatory agencies have substantial authority to require additional testing and reporting, perform inspections, change product labeling or mandate withdrawals of our products. Failure to comply with applicable regulatory requirements may subject us to administrative and/or judicially imposed sanctions or monetary penalties as well as reputational and other harms. The sanctions could include the FDA’s or foreign regulatory authorities’ refusals to approve pending applications, delays in obtaining or withdrawals of approvals, delays or suspensions of clinical trials, warning letters, product recalls or seizures, total or partial suspensions of our operations, injunctions, fines, civil penalties and/or criminal prosecutions.

Obtaining and maintaining regulatory approvals have been, and will continue to be, increasingly difficult, time-consuming and costly. Legislative bodies or regulatory agencies could enact new laws or regulations, change existing laws or regulations, or change their interpretations of laws or regulations at any time, which could affect our ability to obtain or maintain approval of our products or product candidates. The rate and degree of change in existing laws and regulations and regulatory expectations have accelerated in established markets, and regulatory expectations continue to evolve in emerging markets.We are unable to predict whether and when any further changes to laws or regulatory policies affecting our business could occur, such as changes to laws or regulations governing manufacturer communications concerning drug products and drug product candidates, and whether such changes could have a material adverse effect on our product sales, business and results of operations. In the United States, a partial federal government shutdown halted the work of many federal agencies and their employees from late December 2018 through late January 2019. While federal employees have since returned to work, a subsequent extended shutdown could result in reductions or delays of FDA’s activities, including with respect to our ongoing clinical programs, our manufacturing of our products and product candidates, and our product approvals.

Regulatory authorities may also question the sufficiency for approval of the endpoints we select for our clinical trials. A number of our products and product candidates have been evaluated in clinical trials using surrogate endpoints that measure an effect that is known to correlate with an ultimate clinical endpoint. For example, a therapeutic oncology product candidate may be evaluated for its ability to extend the length of time during and after the treatment that a patient lives without the disease worsening, measured by progression-free survival (PFS). Demonstrating that the product candidate produces a statistically significant improvement in PFS does not necessarily mean that the product candidate will show a statistically significant improvement in overall survival, or the time that the patients remain alive. In the cardiovascular setting, a heart disease therapeutic

27

candidate may be evaluated for its ability to reduce LDL-C levels, as elevated LDL-C level has been a surrogate endpoint for cardiovascular events such as death, heart attack and stroke. The use of surrogate endpoints such as PFS and LDL-C reduction, in the absence of other measures of clinical benefit, may not be sufficient for broad usage or approval even when such results are statistically significant. Regulatory authorities could also add new requirements, such as the completion of enrollment in a confirmatory study or the completion of an outcomes study or a meaningful portion of an outcomes study, as conditions for obtaining approval or obtaining an indication. For example, our initial FDA application for Repatha® sought approval for a broader patient population based on data demonstrating that Repatha® reduced LDL-C levels. However, the FDA initially approved Repatha® in 2015 only for a subset of those patients, citing among other things the absence of positive outcomes data showing that Repatha® prevents cardiovascular events. In December 2017, the FDA granted broader approval of Repatha® to reduce the risk of certain cardiovascular events, and also to be used, alone or in combination with other lipid-lowering therapies, for the treatment of adults with primary hyperlipidemia to reduce LDL-C, only after our large phase 3 outcomes study evaluating the ability of Repatha® to prevent cardiovascular events met its primary composite endpoint and key secondary composite endpoint. There may also be situations in which demonstrating the efficacy and safety of a product candidate may not be sufficient to gain regulatory approval unless superiority to other existing treatment options can be shown. The imposition of additional requirements or our inability to meet them in a timely fashion or at all may delay our clinical development and regulatory filing efforts, delay or prevent us from obtaining regulatory approval for new product candidates or new indications for existing products, or prevent us from maintaining our current labels.

Some of our products have been approved by U.S. and foreign regulatory authorities on an accelerated or conditional basis with full approval conditioned upon fulfilling the requirements of regulators. For example, in March 2018, we announced that the FDA approved BLINCYTO®under accelerated approval for the treatment of adults and children with B-cell precursor ALL in first or second complete remission with minimal residual disease greater than or equal to 0.1 percent. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Regulatory authorities are placing greater focus on monitoring products originally approved on an accelerated or conditional basis and on whether the sponsors of such products have met the conditions of the accelerated or conditional approvals. If we are unable to fulfill the regulators’ requirements that were conditions of a product’s accelerated or conditional approval and/or if regulators re-evaluate the data or risk-benefit profile of our product, the conditional approval may not result in full approval or may be revoked or not renewed. Alternatively, we may be required to change the product’s labeled indications or even withdraw the product from the market.

Safety problems or signals can arise as our products and product candidates are evaluated in clinical trials, including investigator sponsored studies, or as our marketed products are used in clinical practice. We are required to continuously collect and assess adverse events reported to us and to communicate to regulatory agencies these adverse events and safety signals regarding our products. Regulatory agencies periodically perform inspections of our pharmacovigilance processes, including our adverse event reporting. In the United States, for our products with approved REMS (see Item 1. Business—Government Regulation—Post-approval Phase), we are required to submit periodic assessment reports to the FDA to demonstrate that the goals of the REMS are being met. REMS and other risk management programs are designed to ensure that a drug’s benefits outweigh the risks, and vary in the elements they contain. If the FDA is not satisfied with the results of the periodic assessment reports we submit for any of our REMS, the FDA may also modify our REMS or take other regulatory actions, such as implementing revised or restrictive labeling. The drug delivery devices approved for use in combination with our products are also subject to regulatory oversight and review for safety and malfunctions. If regulatory agencies determine that we or other parties (including our clinical trial investigators, those operating our patient support programs or licensees of our products) have not complied with the applicable reporting, other pharmacovigilance or other safety or quality assessment requirements, we may become subject to additional inspections, warning letters or other enforcement actions, including fines, marketing authorization withdrawal and other penalties. Our product candidates and marketed products can also be affected by safety problems or signals occurring with respect to products that are similar to ours or that implicate an entire class of products. Further, as a result of clinical trials, including sub-analyses or meta-analyses of earlier clinical trials (a meta-analysis involves the use of various statistical methods to combine results from previous separate but related studies) performed by us or others, concerns may arise about the sufficiency of the data or studies underlying a product’s approved label. Such actual or perceived safety problems or concerns can lead to:

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| • | revised or restrictive labeling for our products, or the potential for restrictive labeling that may result in our decision not to commercialize a product candidate; |

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| • | requirement of risk management activities or other regulatory agency compliance actions related to the promotion and sale of our products; |

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| • | mandated post-marketing commitments or pharmacovigilance programs for our approved products; |

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| • | product recalls of our approved products; |

28

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| • | required changes to the processes used in the manufacture of our products, which could increase our manufacturing costs and affect the availability of contract manufacturers we may utilize to assist in such manufacturing; |

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| • | revocation of approval for our products from the market completely, or within particular therapeutic areas or patient types; |

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| • | increased timelines or delays in being approved by the FDA or other regulatory bodies; and/or |

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| • | fewer treatments or product candidates being approved by regulatory bodies. |

For example, the FDA is currently evaluating our BLA for EVENITYTMfor the treatment of postmenopausal women with osteoporosis at high risk of fracture. In January 2018, the FDA’s BRUDAC recommended that the FDA approve EVENITYTM, but also suggested that the FDA require appropriate post-marketing review to evaluate a potential cardiovascular risk seen in one of the EVENITYTM pivotal clinical trials. See Item 1. Business—Significant Developments. While the FDA is not bound to follow the recommendations of its advisory committees, it often does; if the FDA approves EVENITYTM it may require that we complete a post-marketing study, which could be time consuming and costly.

In addition to our innovative products, we are working to develop and commercialize biosimilar versions of a number of products currently manufactured, marketed and sold by other pharmaceutical companies. In some markets, there is not yet a legislative or regulatory pathway for the approval of biosimilars. In the United States, the ACA provided for such a pathway; while the FDA continues to implement it, discussions continue as to the evidence needed to demonstrate biosimilarity or interchangeability for specific products. See *We currently face competition from biosimilars and expect to face increasing competition from biosimilars and generics in the future.* Delays or uncertainties in the development or implementation of such pathways could result in delays or difficulties in getting our biosimilar products approved by regulatory authorities, subject us to unanticipated development costs or otherwise reduce the value of the investments we have made in the biosimilars area. Further, we cannot predict whether any repeal or reform of the ACA would affect the biosimilar pathway or have a material adverse effect on our development of biosimilars or on our marketed biosimilars. In addition, if we are unable to bring our biosimilar products to market on a timely basis, and secure “first-to-market” or other advantageous positions, our future biosimilar sales and results of operations could be materially and adversely affected.

*We may not be able to develop commercial products despite significant investments in R&D.*

Amgen invests heavily in R&D. Successful product development in the biotechnology industry is highly uncertain, and very few R&D projects produce commercial products. Product candidates, including biosimilar product candidates, or new indications for existing products (collectively, product candidates) that appear promising in the early phases of development may fail to reach the market for a number of reasons, such as:

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| • | the product candidate did not demonstrate acceptable clinical trial results even though it demonstrated positive preclinical trial results, for reasons that could include changes in the standard of care of medicine; |

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| • | the product candidate was not effective or not more effective than currently available therapies in treating a specified condition or illness; |

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| • | the product candidate was not cost effective in light of existing therapeutics; |

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| • | the product candidate had harmful side effects in animals or humans; |

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| • | the necessary regulatory bodies, such as the FDA or EMA, did not approve the product candidate for an intended use; |

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| • | the product candidate was not economical for us to manufacture and commercialize; |

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| • | other parties had or may have had proprietary rights relating to our product candidate, such as patent rights, and did not let us sell it on reasonable terms, or at all; |

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| • | we and certain of our licensees, partners, contracted organizations or independent investigators may have failed to effectively conduct clinical development or clinical manufacturing activities; |

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| • | the pathway to regulatory approval or reimbursement for product candidates was uncertain or not well-defined; and |

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| • | the biosimilar product candidate failed to demonstrate the requisite biosimilarity to the applicable reference product, or was otherwise determined by a regulatory authority to not meet applicable standards for approval. |

We have spent considerable time, energy and resources developing our expertise in human genetics with the belief that genetics could meaningfully aid our search for new medicines and help guide our research and development decisions and investments. We have focused our R&D strategy on drug targets validated by genetic or other compelling human evidence. However,

29

product candidates based on genetically validated targets remain subject to the uncertainties of the drug development process and may not reach the market for a number of reasons, including the factors listed above.

A number of our product candidates have failed or been discontinued at various stages in the product development process. For example, in May 2015, we terminated our participation in the co-development and commercialization of brodalumab with AstraZeneca. The decision was based on events of suicidal ideation and behavior in the brodalumab program, which we believed likely would necessitate restrictive labeling that would limit the appropriate patient population. Inability to bring a product to market or a significant delay in the expected approval and related launch date of a new product for any of the reasons discussed could potentially have a negative impact on our product sales and earnings and could result in a significant impairment of in-process research and development (IPR&D) or other intangible assets.

*We must conduct clinical trials in humans before we commercialize and sell any of our product candidates or existing products for new indications.*

Before we sell any products, we must conduct clinical trials to demonstrate that our product candidates are safe and effective for use in humans. The results of those clinical trials are used as the basis to obtain approval from regulatory authorities such as the FDA and EMA. See *Our current products and products in development cannot be sold without regulatory approval*. We are required to conduct clinical trials using an appropriate number of trial sites and patients to support the product label claims. The length of time, number of trial sites and number of patients required for clinical trials vary substantially, and we may spend several years and incur substantial expense in completing certain clinical trials. In addition, we may have difficulty finding a sufficient number of clinical trial sites and patients to participate in our clinical trials, particularly if competitors are conducting clinical trials in similar patient populations. Patients may withdraw from clinical trials at any time, and privacy laws and/or other restrictions in certain countries may restrict the ability of clinical trial investigators to conduct further follow-up on such patients, which may adversely affect the interpretation of study results. Delays and complications in planned clinical trials can result in increased development costs, associated delays in regulatory approvals and in product candidates reaching the market and revisions to existing product labels.

Further, to increase the number of patients available for enrollment in our clinical trials, we have and will continue to open clinical sites and enroll patients in a number of locations where our experience conducting clinical trials is more limited, including Russia, India, China, South Korea, the Philippines, Singapore and some Central and South American countries, either through utilization of third-party contract clinical trial providers entirely or in combination with local staff. Conducting clinical trials in locations where we have limited experience requires substantial time and resources to understand the unique regulatory environments of individual countries. Further, we must ensure the timely production, distribution and delivery of the clinical supply of our product candidates to numerous and varied clinical trial sites. If we fail to adequately manage the design, execution and diverse regulatory aspects of our large and complex clinical trials or to manage the production or distribution of our clinical supply, corresponding regulatory approvals may be delayed or we may fail to gain approval for our product candidates or could lose our ability to market existing products in certain therapeutic areas or altogether. If we are unable to market and sell our products or product candidates or to obtain approvals in the timeframe needed to execute our product strategies, our business and results of operations could be materially and adversely affected.

We rely on independent third-party clinical investigators to recruit patients and conduct clinical trials on our behalf in accordance with applicable study protocols, laws and regulations. Further, we rely on unaffiliated third-party vendors to perform certain aspects of our clinical trial operations. In some circumstances, we enter into co-development arrangements with other pharmaceutical and medical devices companies that provide for the other company to conduct certain clinical trials for the product we are co-developing or to develop a diagnostic test used in screening patients for our clinical trials. See *Some of our pharmaceutical pipeline and of our commercial product sales relies on collaborations with third parties, which may adversely affect the development and sale of our products.*We also may acquire companies that have past or ongoing clinical trials or rights to products or product candidates for which clinical trials have been or are being conducted. These trials may not have been conducted to the same standards as ours; however, once an acquisition has been completed we assume responsibility for the conduct of these trials, including any potential risks and liabilities associated with the past and prospective conduct of those trials. If regulatory authorities determine that we or others, including our licensees or co-development partners, or the independent investigators or vendors selected by us, our co-development partners or by a company we have acquired or from which we have acquired rights to a product or product candidate, have not complied with regulations applicable to the clinical trials, those authorities may refuse or reject some or all of the clinical trial data or take other actions that could delay or otherwise negatively impact our ability to obtain or maintain marketing approval of the product or indication. In addition, delays or failures to develop diagnostic tests for our clinical trials can affect the timely enrollment of such trials and lead to delays or inability to obtain marketing approval. If we were unable to market and sell our products or product candidates, our business and results of operations could be materially and adversely affected.

In addition, some of our clinical trials utilize drugs manufactured and marketed by other pharmaceutical companies. These drugs may be administered in clinical trials in combination with one of our products or product candidates or in a head-to-head

30

study comparing the products’ or product candidates’ relative efficacy and safety. In the event that any of these vendors or pharmaceutical companies have unforeseen issues that negatively impact the quality of their work product or create a shortage of supply, or if we are otherwise unable to obtain an adequate supply of these other drugs, our ability to complete our applicable clinical trials and/or evaluate clinical results may also be negatively impacted. As a result, such quality or supply problems could adversely affect our ability to timely file for, gain or maintain regulatory approvals worldwide.

Clinical trials must be designed based on the current standard of medical care. However, in certain diseases, such as cancer, the standard of care is evolving rapidly. In such diseases, the duration of time needed to complete certain clinical trials may result in the design of such clinical trials being based on standards of medical care that are no longer the current standards by the time such trials are completed, limiting the utility and application of such trials. We may not obtain favorable clinical trial results and therefore may not be able to obtain regulatory approval for new product candidates or new indications for existing products and/or maintain our current product labels. Participants in clinical trials of our products and product candidates may also suffer adverse medical events or side effects that could, among other factors, delay or terminate clinical trial programs and/or require additional or longer trials to gain approval.

Even after a product is on the market, safety concerns may require additional or more extensive clinical trials as part of a risk management plan for our product or for approval of a new indication. For example, in connection with the June 2011 ESA label changes, we agreed to and conducted additional clinical trials examining the use of ESAs in CKD. Additional clinical trials we initiate, including those required by the FDA, could result in substantial additional expense and the outcomes could result in further label restrictions or the loss of regulatory approval for an approved indication, each of which could have a material adverse effect on our product sales, business and results of operations. Additionally, any negative results from such trials could materially affect the extent of approvals, the use, reimbursement and sales of our products, our business and results of operations.

*Some of our products are used with drug delivery or companion diagnostic devices that have their own regulatory, manufacturing and other risks.*

Many of our products and product candidates may be used in combination with a drug delivery device, such as an injector or other delivery system. For example, Neulasta® is available as part of the Neulasta®Onpro®kit, and our AutoTouch®reusable auto-injector is used with Enbrel Mini® single-dose prefilled cartridges. In addition, some of our products or product candidates may also require the use of a companion diagnostic device such as a device that determines whether the patient is eligible to use our drug or that helps ensure its safe and effective use. Our product candidates or expanded indications of our products used with such devices may not be approved or may be substantially delayed in receiving regulatory approval if development of such devices is delayed, such devices do not also gain or maintain regulatory approval or clearance, or if such devices do not remain commercially available. When approval of the product and device is sought under a single marketing drug application, the increased complexity of the review process may delay receipt of regulatory approval. In addition, some of these devices may be provided by single-source unaffiliated third-party companies. We are dependent on the sustained cooperation and effort of those third-party companies both to supply the devices and, in some cases, to conduct the studies required for approval or clearance by the applicable regulatory agencies. We are also dependent on those third-party companies continuing to meet applicable regulatory or other requirements. Failure to successfully develop, modify, or supply the devices, delays in or failures of the Amgen or third-party studies, or failure of us or the third-party companies to obtain or maintain regulatory approval or clearance of the devices could result in increased development costs; delays in, or failure to obtain or maintain, regulatory approval; and/or associated delays in a product candidate reaching the market or in the addition of new indications for existing products. We are also required to collect and assess user complaints, adverse events, and malfunctions regarding our devices, and actual or perceived safety problems or concerns with a device used with our product can lead to regulatory actions and impacts to our products. See*Our current products and products in development cannot be sold without regulatory approval.* Additionally, regulatory agencies conduct routine monitoring and conduct inspections to identify and evaluate potential issues with our devices. For example, in 2017 the FDA reported on its adverse event reporting system that it is evaluating our Neulasta® Onpro® kit. Loss of regulatory approval or clearance of a device that is used with our product may also result in the removal of our product from the market. Further, failure to successfully develop, supply, or gain or maintain approval for these devices could adversely affect sales of the related, approved products.

*Some of our pharmaceutical pipeline and of our commercial product sales relies on collaborations with third parties, which may adversely affect the development and sale of our products.*

We depend on alliances with other companies, including pharmaceutical and biotechnology companies, vendors and service providers, for the development of a portion of the products in our pharmaceutical pipeline and for the commercialization and sales of certain of our commercial products. For example, we have collaborations with third parties under which we share development rights, obligations and costs and/or commercial rights and obligations. See Item 1. Business—Business Relationships.

Failures by these parties to meet their contractual, regulatory, or other obligations to us, or any disruption in the relationships between us and these third parties, could have a material adverse effect on our pharmaceutical pipeline and business. In addition, our collaborative relationships for research and development and/or commercialization and sales often extend for many years and

31

may give rise to disputes regarding the relative rights, obligations and revenues of us and our collaboration partners, including the ownership or prosecution of intellectual property and associated rights and obligations. This could result in the loss of intellectual property rights or protection, delay the development and sale of potential pharmaceutical products, impact the effective sale and delivery of our commercialized products and lead to lengthy and expensive litigation, administrative proceedings or arbitration.

*The adoption and interpretation of new tax legislation or exposure to additional tax liabilities could affect our profitability.*

We are subject to income and other taxes in the United States and other jurisdictions in which we do business. As a result, our provision for income taxes is derived from a combination of applicable tax rates in the various places we operate. Significant judgment is required for determining our provision for income tax.

Our tax returns are routinely examined by tax authorities in the United States and other jurisdictions in which we do business, and a number of audits are currently underway. Tax authorities, including the Internal Revenue Service (IRS), are becoming more aggressive in their audits and are particularly focused on the allocations of income and expense among tax jurisdictions. As previously disclosed, we received a Revenue Agent Report (RAR) from the IRS for the years 2010, 2011 and 2012. The RAR proposes to make significant adjustments that relate primarily to the allocation of profits between certain of our entities in the United States and the U.S. territory of Puerto Rico. In November 2017, we received a modified RAR that revised the IRS’s calculation but continued to propose substantial adjustments. We disagree with the proposed adjustments and are pursuing resolution with the IRS administrative appeals office, which currently has jurisdiction over the matter. If we deem necessary, we will vigorously contest the proposed adjustments through the judicial process. Although final resolution of this complex matter is not likely within the next 12 months, such resolution could have a material negative impact on our consolidated financial statements. We believe our accrual for income tax liabilities is appropriate based on past experience, interpretations of tax law, and judgments about potential actions by tax authorities; however, due to the complexity of the provision for income taxes, the ultimate resolution of any tax matters may result in payments greater or less than amounts accrued.

Our provision for income taxes and results of operations in the future could be adversely affected by changes to our operating structure, changes in the mix of income and expenses in countries with differing tax rates, changes in the valuation of deferred tax assets and liabilities, and changes in applicable tax laws, regulations or administrative interpretations thereof. The 2017 Tax Act is complex and further regulations and interpretations are still being issued. We could face audit challenges on how we apply the new law that could have a negative impact on our provision for income taxes. A change to the U.S. tax system, such as a repeal or modification of the 2017 Tax Act, a change to the tax system in a jurisdiction where we have significant operations, such as the U.S. territory of Puerto Rico, or changes in tax law in the United States or other jurisdictions where we do business, could have a material and adverse effect on our business and on the results of our operations.

*We perform a substantial majority of our commercial manufacturing activities at our facility in the U.S. territory of Puerto Rico and a substantial majority of our clinical manufacturing activities at our facility in Thousand Oaks, California; significant disruptions or production failures at these facilities could significantly impair our ability to supply our products or continue our clinical trials.*

The global supply of our products and product candidates for commercial sales and for use in our clinical trials is significantly dependent on the uninterrupted and efficient operation of our manufacturing facilities, in particular those in the U.S. territory of Puerto Rico and Thousand Oaks, California. See *Manufacturing difficulties, disruptions or delays could limit supply of our products and limit our product sales*.

We currently perform a substantial majority of our clinical manufacturing activities at our facility in Thousand Oaks, California. A substantial disruption in our ability to operate our Thousand Oaks, California manufacturing facility could materially and adversely affect our ability to supply our product candidates for use in our clinical trials, leading to delays in development of our product candidates.

In addition, we currently perform a substantial majority of our commercial manufacturing activities at our facility in the U.S. territory of Puerto Rico. In late September 2017, Hurricane Maria made landfall on the island of Puerto Rico. The hurricane destroyed residential and commercial buildings, agriculture, communications networks and most of Puerto Rico’s electric grid. While the critical manufacturing areas of our commercial manufacturing facility were not significantly impacted by the storm, the restoration of electrical service on the island was a slow process, and our facility operated with electrical power from back-up diesel powered generators for some time. In January 2018, we reconnected to the Puerto Rico electric grid but have continued to use diesel generators as needed when sufficient electric power has not been reliably available. Further instability of the electric grid could require us to increase the use of our generators or even return to using them exclusively. In addition, future storms or other disasters or events could cause a more significant impact to our manufacturing operations. A substantial disruption in our ability to operate our Puerto Rico manufacturing facility (whether due to problems with the facility itself, the infrastructure and services available on the island, the unavailability of raw materials or supplies from vendors, the unavailability of key staff or otherwise) or get supplies and manufactured products transported to and from that location could materially and adversely affect

32

our ability to supply our products and affect our product sales. See *Manufacturing difficulties, disruptions or delays could limit supply of our products and limit our product sales*.

The impact of Hurricane Maria placed greater stress on the island’s already challenged economy. Prior to Hurricane Maria, the government of Puerto Rico was unable to pay its roughly $72 billion in debt. In June 2016, the U.S. Congress passed the Puerto Rico Oversight, Management, and Economic Stability Act (PROMESA), which established a Financial Oversight and Management Board (Oversight Board) to provide fiscal oversight through the development and approval of fiscal plans and budgets for Puerto Rico and to assist in its debt restructuring. In May 2017, after negotiations for debt restructuring with creditors were unsuccessful, the Oversight Board approved and certified the filing in the U.S. District Court for the District of Puerto Rico of a voluntary petition under Title III of PROMESA for the government of Puerto Rico and certain of its governmental entities, including the Puerto Rico Electric Power Authority (PREPA). Title III of PROMESA provides Puerto Rico with a judicial process for restructuring its debt similar to, but not identical to, Chapter 9 of the U.S. Bankruptcy Code. The Governor of Puerto Rico declared a state of emergency and authorized a moratorium on the payment of general obligation bonds and other debts issued by certain instrumentalities, which moratorium has been extended and may continue to be extended while the Oversight Board is in effect. Given the severe conditions in Puerto Rico after Hurricane Maria, resolution of Puerto Rico’s debt situation through the PROMESA judicial process has been delayed. In the case of PREPA, the effects of Hurricane Maria and several changes in PREPA’s management have delayed reconstruction efforts.

In June 2018, the Oversight Board certified a budget for Puerto Rico’s fiscal year 2019 that imposes significant expense reductions across the government. The Title III Court upheld government challenges to the budget, and the Governor and Legislature of Puerto Rico have now filed appeals before the U.S. Court of Appeals for the First Circuit. In addition, certain non-governmental entities have brought suit claiming the appointment process of the Oversight Board members set forth in PROMESA conflicts with the appointments clause of the U.S. Constitution. If the First Circuit were to hold that PROMESA has a constitutional infirmity and that actions taken by the Oversight Board are invalid, the commencement of all Title III proceedings could be invalid. In such event, the current debt restructuring process and the debtholder litigation stay under Title III of PROMESA could be in jeopardy.

In October 2018, the fiscal plan for Puerto Rico was updated, including a projected increase in federal disaster funding and projected material deficits once the stimulus effects of the disaster recovery dissipate. The fiscal plan stresses the importance of structural reforms to address Puerto Rico’s challenging economic and demographic trends that may be difficult to implement as well as have a material adverse impact on our consolidated financial statements.

In addition, the 2017 Tax Act will no longer permit deferral of U.S. taxation on Puerto Rico earnings of U.S. companies (or their foreign subsidiaries), although these earnings generally will be taxed in the United States at a reduced 10.5% rate. Given Puerto Rico’s challenged economy and hurricane recovery needs, it may be difficult for Puerto Rico to sustain or grow its manufacturing base due to competition from other foreign locations subject to a similar level of U.S. taxation, or U.S. locations due to the reduction in the U.S. corporate tax rate from 35% to 21%. The manufacturing sector contributes more than 45% of Puerto Rico’s gross domestic product, and multinational companies with Puerto Rico operations contribute approximately 30% of Puerto Rico’s revenue base.

While PROMESA and the actions above continue to be important factors in moving Puerto Rico toward economic stability, there is still a risk that Puerto Rico’s ongoing economic challenges, the effects of Hurricane Maria and the potential impact of the 2017 Tax Act could negatively affect the territorial government’s provision of utilities or other services in Puerto Rico that we use in the operation of our business, create the potential for increased taxes or fees to operate in Puerto Rico, result in a migration of workers from Puerto Rico to the mainland United States, or make it more expensive or difficult for us to operate in Puerto Rico, which could materially and adversely affect our ability to supply our products and affect our product sales.

*We rely on third-party suppliers for certain of our raw materials, medical devices and components.*

We rely on unaffiliated third-party suppliers for certain raw materials, medical devices and components necessary for the manufacturing of our commercial and clinical products. Certain of those raw materials, medical devices and components are proprietary products of those unaffiliated third-party suppliers and are specifically cited in our drug applications with regulatory agencies so that they must be obtained from that specific sole source or sources and could not be obtained from another supplier unless and until the regulatory agency approved such supplier. For example, Insulet Corporation is our single-source of the on-body injector for our Neulasta®Onpro®kit. Also, certain of the raw materials required in the commercial and clinical manufacturing of our products are sourced from other countries and/or derived from biological sources, including mammalian tissues, bovine serum and human serum albumin.

Among the reasons we may be unable to obtain these raw materials, medical devices and components include:

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| • | regulatory requirements or action by regulatory agencies or others; |

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| • | adverse financial or other strategic developments at or affecting the supplier, including bankruptcy; |

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| • | unexpected demand for or shortage of raw materials, medical devices or components; |

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| • | failure to comply with our quality standards which results in quality and product failures, product contamination and/or recall; |

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| • | a material shortage, contamination, recall and/or restrictions on the use of certain biologically derived substances or other raw materials; |

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| • | discovery of previously unknown or undetected imperfections in raw materials, medical devices or components; and |

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| • | labor disputes or shortages, including from the effects of health emergencies and natural disasters. |

For example, in prior years we have experienced shortages in certain components necessary for the formulation, fill and finish of certain of our products in our Puerto Rico facility. Further quality issues that result in unexpected additional demand for certain components may lead to shortages of required raw materials or components (such as we have experienced with EPOGEN® glass vials). We may experience similar or other shortages in the future resulting in delayed shipments, supply constraints, clinical trial delays, contract disputes and/or stock-outs of our products. These or other similar events could negatively impact our ability to satisfy demand for our products or conduct clinical trials, which could have a material adverse effect on our product sales, business and results of operations.

*Manufacturing difficulties, disruptions or delays could limit supply of our products and limit our product sales.*

Manufacturing biologic human therapeutic products is difficult, complex and highly regulated. We currently are involved in the manufacture of many of our products and plan to manufacture many of our product candidates. In addition, we currently use third-party contract manufacturers to produce, or assist in the production of, a number of our products, and we currently use contract manufacturers to produce, or assist in the production of, a number of our late-stage product candidates and drug delivery devices. See Item 1. Business—Manufacturing, Distribution and Raw Materials—Manufacturing. Our ability to adequately and timely manufacture and supply our products (and product candidates to support our clinical trials) is dependent on the uninterrupted and efficient operation of our facilities and those of our third-party contract manufacturers, which may be impacted by:

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| • | capacity of manufacturing facilities; |

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| • | contamination by microorganisms or viruses, or foreign particles from the manufacturing process; |

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| • | natural or other disasters, including hurricanes, earthquakes, volcanoes or fires; |

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| • | labor disputes or shortages, including the effects of health emergencies or natural disasters; |

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| • | compliance with regulatory requirements; |

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| • | changes in forecasts of future demand; |

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| • | timing and actual number of production runs and production success rates and yields; |

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| • | updates of manufacturing specifications; |

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| • | contractual disputes with our suppliers and contract manufacturers; |

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| • | timing and outcome of product quality testing; |

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| • | power failures and/or other utility failures; |

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| • | breakdown, failure, substandard performance or improper installation or operation of equipment; and/or |

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| • | delays in the ability of the FDA or foreign regulatory agencies to provide us necessary reviews, inspections and approvals, including as a result of a subsequent extended U.S. federal government shutdown. |

If any of these or other problems affect production in one or more of our facilities or those of our third-party contract manufacturers, or if we do not accurately forecast demand for our products or the amount of our product candidates required in clinical trials, we may be unable to increase production in our unaffected facilities to meet demand. If the efficient manufacture and supply of our products or product candidates is interrupted, we may experience delayed shipments, delays in our clinical trials, supply constraints, stock-outs, adverse event trends, contract disputes and/or recalls of our products. From time to time we have initiated recalls of certain lots of our products. For example, in July 2014 we initiated a voluntary recall of an Aranesp® lot distributed in the EU after particles were detected in a quality control sample following distribution of that lot, and in April 2018 we initiated a precautionary recall of two batches of Vectibix® distributed in Switzerland after potential crimping defects were discovered in the metal seals on the product vials. If we are at any time unable to provide an uninterrupted supply of our products to patients,

34

we may lose patients and physicians may elect to prescribe competing therapeutics instead of our products, which could have a material adverse effect on our product sales, business and results of operations.

Our manufacturing processes, those of our third-party contract manufacturers and those of certain of our third-party service providers must undergo regulatory approval processes and are subject to continued review by the FDA and other regulatory authorities. It can take longer than five years to build, validate and license another manufacturing plant and it can take longer than three years to qualify and license a new contract manufacturer or service provider. If we elect or are required to make changes to our manufacturing processes because of new regulatory requirements, new interpretations of existing requirements or other reasons, this could increase our manufacturing costs and result in delayed shipments, delays in our clinical trials, supply constraints, stock-outs, adverse event trends or contract negotiations or disputes. Such manufacturing challenges may also occur if our existing contract manufacturers are unable or unwilling to implement such changes.

If regulatory authorities determine that we or our third-party contract manufacturers or certain of our third-party service providers have violated regulations or if authorities restrict, suspend or revoke our prior approvals, they could prohibit us from manufacturing our products or conducting clinical trials or selling our marketed products until we or the affected third-party contract manufacturers or third-party service providers comply, or indefinitely. Such issues may also delay the approval of product candidates we have submitted for regulatory review, even if such product candidates are not directly related to the products, devices or processes at issue with regulators. Because our third-party contract manufacturers and certain of our third-party service providers are subject to the FDA and foreign regulatory authorities, alternative qualified third-party contract manufacturers and third-party service providers may not be available on a timely basis or at all. If we or our third-party contract manufacturers or third-party service providers cease or interrupt production or if our third-party contract manufacturers and third-party service providers fail to supply materials, products or services to us, we may experience delayed shipments, delays in our clinical trials, supply constraints, contract disputes, stock-outs and/or recalls of our products. Additionally, we distribute a substantial volume of our commercial products through our primary distribution centers in Louisville, Kentucky for the United States and in Breda, Netherlands for Europe and much of the rest of the world. We also conduct all the labeling and packaging of our products distributed in Europe and much of the rest of the world in Breda. Our ability to timely supply products is dependent on the uninterrupted and efficient operations of our distribution and logistics centers, our third-party logistics providers and our labeling and packaging facility in Breda. Further, we rely on commercial transportation, including air and sea freight, for the distribution of our products to our customers, which may be negatively impacted by natural disasters or security threats.

*Concentration of sales at certain of our wholesaler distributors and at one free-standing dialysis clinic business and consolidation of private payers may negatively impact our business.*

Certain of our distributors, customers and payers have substantial purchasing leverage, due to the volume of our products they purchase or the number of patient lives for which they provide coverage. The substantial majority of our U.S. product sales is made to three pharmaceutical product wholesaler distributors: AmerisourceBergen Corporation, McKesson Corporation and Cardinal Health, Inc. These distributors, in turn, sell our products to their customers, which include physicians or their clinics, dialysis centers, hospitals and pharmacies. One of our products, EPOGEN®, is sold primarily to free-standing dialysis clinics. DaVita owns or manages a large number of the outpatient dialysis facilities located in the United States and accounts for approximately 70% of all EPOGEN®sales. Similarly, as discussed above, there has been significant consolidation in the health insurance industry, including that a small number of PBMs now oversee a substantial percentage of total covered lives in the United States. See *Our sales depend on coverage and reimbursement from third-party payers, and pricing and reimbursement pressures may affect our profitability*. The three largest PBMs in the United States are now part of major health insurance providers. The growing concentration of purchasing and negotiating power by these entities may put pressure on our pricing due to their ability to extract price discounts on our products, fees for other services or rebates, negatively impacting our bargaining position, sales and/or profit margins. In addition, decisions by these entities to purchase or cover less or none of our products in favor of competitive products could have a material adverse effect on our product sales, business and results of operations due to their purchasing volume. Further, if one of our significant wholesale distributors encounters financial or other difficulties and becomes unable or unwilling to pay us all amounts that such distributor owes us on a timely basis or at all, it could negatively impact our business and results of operations. In addition, if one of our significant wholesale distributors becomes insolvent or otherwise unable to continue its commercial relationship with us in its present form, it could significantly disrupt our business and adversely affect our product sales, our business and results of operations unless suitable alternatives are timely found or lost sales are absorbed by another distributor.

*Our efforts to acquire other companies or products and to integrate their operations may not be successful, and may result in unanticipated costs, delays or failures to realize the benefits of the transactions.*

We seek innovation through significant investment in both internal R&D and external transactions including collaborations, partnering, alliances, licenses, joint ventures, mergers and acquisitions (acquisition activity). We have an ongoing process of evaluating such potential acquisition activity opportunities that we expect will contribute to our future growth and expand our geographic footprint, product offerings and/or our R&D pipeline. Acquisitions or similar arrangements may be complex, time

35

consuming and expensive and may result in unanticipated costs, delays or other operational or financial problems related to integrating the acquired company and business with our company, which may result in the diversion of our management’s attention from other business issues and opportunities. We may pay substantial amounts of cash, incur debt or issue equity securities to pay for acquisition activities, which could adversely affect our liquidity or result in dilution to our stockholders, respectively. Failures or difficulties in integrating or retaining new personnel or in integrating the operations of the businesses we acquire (including their technology, compliance programs, distribution and general business operations and procedures), while preserving important R&D, distribution, marketing, promotion and other relationships, may affect our ability to grow and may result in our incurring asset impairment or restructuring charges.

*Our sales and operations are subject to the risks of doing business internationally, including in emerging markets.*

As we continue our expansion efforts in emerging markets around the world, through acquisitions and licensing transactions as well as through the development and introduction of our products in new markets, we face numerous risks to our business. There is no guarantee that our efforts and strategies to expand sales in emerging markets will succeed. Emerging market countries may be especially vulnerable to periods of global and local political, legal, regulatory and financial instability, including sovereign debt issues and/or the imposition of international sanctions in response to certain state actions. We may also be required to increase our reliance on third-party agents and unfamiliar operations and arrangements previously utilized by companies we partner with or acquire in emerging markets. See *We must conduct clinical trials in humans before we commercialize and sell any of our product candidates or existing products for new indications*. As we expand internationally, we are subject to fluctuations in foreign currency exchange rates relative to the U.S. dollar. While we have a program in place that is designed to reduce our exposure to foreign currency exchange rate fluctuations through foreign currency hedging arrangements, our hedging efforts do not completely offset the effect of these fluctuations on our revenues and earnings. Our international operations and business may also be subject to less protective intellectual property or other applicable laws, diverse data privacy and protection requirements, changing tax laws and tariffs, trade restrictions or other barriers designed to protect industry in the home country against foreign competition, far-reaching anti-bribery and anti-corruption laws and regulations and/or evolving legal and regulatory environments. These legal and operational challenges along with government controls, the challenges of attracting and retaining qualified personnel and obtaining and/or maintaining necessary regulatory or pricing approvals of our products may result in a material adverse impact on our international product sales, business and results of operations.

*Our business may be affected by litigation and government investigations.*

We and certain of our subsidiaries are involved in legal proceedings. See Part IV—Note 20, Contingencies and commitments, to the Consolidated Financial Statements. Civil and criminal litigation is inherently unpredictable, and the outcome can result in costly verdicts, fines and penalties, exclusion from federal healthcare programs and/or injunctive relief that affect how we operate our business. Defense of litigation claims can be expensive, time consuming and distracting, and it is possible that we could incur judgments or enter into settlements of claims for monetary damages or change the way we operate our business, which could have a material adverse effect on our product sales, business and results of operations. In addition, product liability is a major risk in testing and marketing biotechnology and pharmaceutical products. We may face substantial product liability exposure in human clinical trials and for products we sell after regulatory approval. Product liability claims, regardless of their merits, could be costly and divert management’s attention and could adversely affect our reputation and the demand for our products. We and certain of our subsidiaries have previously been named as defendants in product liability actions for certain of our products.

We are also involved in government investigations that arise in the ordinary course of our business. In recent years, there has been a trend of increasing government investigations and litigations against companies operating in our industry, both in the United States and around the world. Our business activities outside of the United States are subject to the FCPA and similar anti-bribery or anti-corruption laws, regulations or rules of other countries in which we operate, including the UK Bribery Act. We cannot ensure that all our employees, agents, contractors, vendors, licensees, partners or collaborators will comply with all applicable laws and regulations. In 2012, we finalized a settlement agreement with the U.S. government and various other parties to settle certain allegations regarding our sales and marketing practices and agreed to operate under a corporate integrity agreement with the OIG of the U.S. Department of Health and Human Services, which was formally closed out in August 2018. We may see new government investigations of or actions against us citing novel theories of recovery. Any of these results could have a material adverse effect on our business and results of operations.

*A breakdown, cyberattack or information security breach could compromise the confidentiality, integrity and availability of our information technology systems and network-connected control systems and our data, interrupt the operation of our business and affect our reputation.*

To achieve our business objectives, we rely to a large extent upon sophisticated information technology systems and network-connected control systems, some of which are managed, hosted, provided or serviced by third parties. Internal or external events that compromise the confidentiality, integrity and availability of our systems and data may significantly interrupt the operation of our business, result in significant costs and/or affect our reputation.

36

Our information technology systems are highly integrated into our business, including our R&D efforts, our clinical and commercial manufacturing processes and our product sales and distribution processes. The complexity and interconnected nature of our systems makes them potentially vulnerable to breakdown or other service interruptions. Our systems are also subject to frequent cyberattacks. As the cyber-threat landscape evolves, these attacks are growing in frequency, sophistication and intensity, and are becoming increasingly difficult to detect. Such attacks could include the use of key loggers or other harmful and virulent malware, including ransomware or other denials of service, and can be deployed through malicious websites, the use of social engineering and/or other means. Attacks such as those seen with other multi-national companies, including some of our peers, could leave us unable to utilize key business systems or access important data needed to operate our business, including developing, gaining regulatory approval for, manufacturing, selling and distributing our products. For example, in 2017, a pharmaceutical company experienced a cyberattack involving virulent malware that significantly disrupted its operations, including its research and sales operations and the production of some of its medicines and vaccines. As a result of the cyberattack, its orders and sales for certain products in certain markets were negatively impacted. Our systems also contain and utilize a high volume of sensitive data, including intellectual property, trade secrets, financial information, regulatory information, strategic plans, sales trends and forecasts, litigation materials or personal information belonging to us, our staff, our patients, customers and/or other business partners. In some cases, we utilize third-party service providers to process, store, manage or transmit such data, which may increase our risk. Intentional or inadvertent data privacy or security breaches (including cyberattacks) by employees, service providers, nation states, organized crime organizations, “hacktivists” or others, pose risks that our sensitive data may be exposed to unauthorized persons, our competitors, or the public. Finally, domestic and global government regulators, our key business partners, suppliers with whom we do business, companies that provide us or our partners with important business services and companies we may acquire may face similar risks, and security breaches of their systems could adversely affect our security, leave us without access to important systems, products, raw materials, components, services or information or expose our confidential data. For example, we distribute our products in the United States primarily through three pharmaceutical wholesalers, and a security breach that impairs the distribution operations of our wholesalers could significantly impair our ability to deliver our products to healthcare providers.

Although in the past we have experienced system breakdowns, attacks and information security breaches, we do not believe such breakdowns, attacks and breaches have had a material adverse effect on our business or results of operations. We continue to invest in the monitoring, protection, and resilience of our critical or sensitive data and systems. However, there can be no assurance that our efforts will detect, prevent or fully recover systems or data from all breakdowns, service interruptions, attacks, or breaches of our systems that could adversely affect our business and operations and/or result in the loss of critical or sensitive data, which could result in financial, legal, business or reputational harm to us or impact our stock price. While we maintain cyber-liability insurance, our insurance is not sufficient to cover us against all losses that could potentially result from a service interruption, breach of our systems or loss of our critical or sensitive data.

*Global economic conditions may negatively affect us and may magnify certain risks that affect our business.*

Our operations and performance have been, and may continue to be, affected by global economic conditions. Financial pressures may cause government or other third-party payers to more aggressively seek cost containment measures. See *Our sales depend on coverage and reimbursement from third-party payers, and pricing and reimbursement pressures may affect our profitability*. As a result of global economic conditions, some third-party payers may delay or be unable to satisfy their reimbursement obligations. Job losses or other economic hardships may also affect patients’ ability to afford health care as a result of increased co-pay or deductible obligations, greater cost sensitivity to existing co-pay or deductible obligations, lost healthcare insurance coverage or for other reasons. We believe such conditions have led and could continue to lead to reduced demand for our products, which could have a material adverse effect on our product sales, business and results of operations. Economic conditions may also adversely affect the ability of our distributors, customers and suppliers to obtain the liquidity required to buy inventory or raw materials and to perform their obligations under agreements with us, which could disrupt our operations. Although we monitor our distributors’, customers’ and suppliers’ financial condition and their liquidity to mitigate our business risks, some of our distributors, customers and suppliers may become insolvent, which could have a material adverse effect on our product sales, business and results of operations.

We maintain a significant portfolio of investments disclosed as cash equivalents and marketable securities on our consolidated balance sheets. The value of our investments may be adversely affected by interest rate fluctuations, downgrades in credit ratings, illiquidity in the capital markets and other factors that may result in other-than-temporary declines in the value of our investments. Any of those events could cause us to record impairment charges with respect to our investment portfolio or to realize losses on sales of investments.

*Our stock price is volatile.*

Our stock price, like that of our peers in the biotechnology and pharmaceutical industries, is volatile. Our revenues and operating results may fluctuate from period to period for a number of reasons. Events such as a delay in product development, changes to our expectations or strategy or even a relatively small revenue shortfall may cause financial results for a period to be

37

below our expectations or projections. As a result, our revenues and operating results and, in turn, our stock price may be subject to significant fluctuations. Announcements or discussions, including via social media channels, of possible restrictive actions by government or private payers that would impact our business or industry if ultimately enacted or adopted may also cause our stock price to fluctuate, whether or not such restrictive actions ever actually occur. Similarly, actual or perceived safety issues with our products or similar products or unexpected clinical trial results can have an immediate and rapid impact on our stock price, whether or not our operating results are materially impacted.

*We may not be able to access the capital and credit markets on terms that are favorable to us, or at all.*

The capital and credit markets may experience extreme volatility and disruption which may lead to uncertainty and liquidity issues for both borrowers and investors. We expect to access the capital markets to supplement our existing funds and cash generated from operations in satisfying our needs for working capital; capital expenditure and debt service requirements; our plans to pay dividends and repurchase stock; and other business initiatives we plan to strategically pursue, including acquisitions and licensing activities. In the event of adverse capital and credit market conditions, we may be unable to obtain capital market financing on similar favorable terms, or at all, which could have a material adverse effect on our business and results of operations. Changes in credit ratings issued by nationally recognized credit-rating agencies could adversely affect our ability to obtain capital market financing and the cost of such financing and have an adverse effect on the market price of our securities.

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