

LA JOLLA PHARMACEUTICAL CO  
Form 10-K  
February 25, 2016  
UNITED STATES  
SECURITIES AND EXCHANGE COMMISSION  
WASHINGTON, DC 20549

FORM 10-K

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2015

OR

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from \_\_\_\_\_ to \_\_\_\_\_

Commission file number: 1-36282

LA JOLLA PHARMACEUTICAL COMPANY  
(Exact name of registrant as specified in its charter)

California 33-0361285  
(State or other jurisdiction of incorporation or organization) (I.R.S. Employer Identification Number)

10182 Telesis Court, 6th Floor, San Diego, CA 92121  
(Address of principal executive offices, including Zip Code)

Registrant's telephone number, including area code: (858) 207-4264

Securities registered pursuant to Section 12(b) of the Act:  
Title of each class Name of each exchange on which registered  
Common Stock, Par Value \$0.0001 per share The NASDAQ Capital Market

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes  No

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. Yes  No

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes  No

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Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes  No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of the Form 10-K or any amendment to this Form 10-K.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer	<input type="checkbox"/>	Accelerated filer	<input checked="" type="checkbox"/>
Non-accelerated filer	<input type="checkbox"/> (Do not check if a smaller reporting company)	Smaller reporting company	<input type="checkbox"/>

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes  No

The aggregate market value of voting and non-voting common stock held by non-affiliates of the registrant as of June 30, 2015 totaled approximately \$270,367,000. As of February 22, 2016, there were 18,254,009 shares of the Company's common stock, \$0.0001 par value, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

None.

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## FORWARD-LOOKING STATEMENTS

This report contains forward-looking statements as that term is defined in the Private Securities Litigation Reform Act of 1995. Forward-looking statements can be identified by words such as “intends,” “believes,” “anticipates,” “indicates,” “plans,” “expects,” “suggests,” “may,” “should,” “potential,” “designed to,” “will” and similar references. These statements relate to future events or the Company’s anticipated future results of operations. These statements are only predictions and involve known and unknown risks, uncertainties and other factors, which may cause actual results to be materially different from these forward-looking statements. The Company cautions readers not to place undue reliance on any such forward-looking statements, which speak only as of the date they were made. Certain of these risks, uncertainties, and other factors are described in greater detail in the Company’s filings with the U.S. Securities and Exchange Commission (SEC), all of which are available free of charge on the SEC’s web site [www.sec.gov](http://www.sec.gov). These risks include, but are not limited to, risks relating to: the timing for commencement of clinical studies, the anticipated timing for completion of such studies, and the anticipated timing for regulatory actions; the success of future development activities for LJPC-501, LJPC-401, LJPC-30Sa and LJPC-30Sb; potential indications for which LJPC-501, LJPC-401, LJPC-30Sa and LJPC-30Sb may be developed; and the expected duration over which the Company’s cash balances will fund its operations.

Important factors that could cause our actual results and financial condition to differ materially from those indicated in the forward-looking statements include, among others:

- the risk that our clinical trials with our product candidates may not be successful in evaluating their safety and tolerability or providing evidence of efficacy;
- the successful and timely completion of clinical trials;
- our plans and timing with respect to seeking regulatory approvals and uncertainties regarding the regulatory process;
- the availability of funds and resources to pursue our research and development projects, including clinical trials with our product candidates;
- uncertainties associated with obtaining and enforcing patents;
- the potential commercialization of any of our drug candidates that receive regulatory approval;
- our estimates for future performance;
- our estimates regarding our capital requirements and our needs for, and ability to obtain, additional financing; and
- those risk factors identified in this Annual Report on Form 10-K under the heading “Risk Factors” and in other filings the Company periodically makes with the SEC.

Forward-looking statements contained in this Annual Report on Form 10-K speak as of the date hereof, and we do not undertake to update any of these forward-looking statements to reflect a change in our views or events or circumstances that occur after the date of this Annual Report on Form 10-K. In addition, please see the “Risk Factors” section of this Annual Report on Form 10-K. These risk factors may be updated from time to time by our future filings under the Exchange Act.

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## PART I

In this report, all references to "we," "our," "us," "La Jolla" and "the Company" refer to La Jolla Pharmaceutical Company, a California corporation.

### Item 1. Business.

#### Overview

La Jolla Pharmaceutical Company is a biopharmaceutical company focused on the discovery, development and commercialization of innovative therapies intended to significantly improve outcomes in patients suffering from life-threatening diseases. We have several product candidates in development. LJPC-501 is our proprietary formulation of angiotensin II for the potential treatment of catecholamine-resistant hypotension. LJPC-401 is our novel formulation of hepcidin for the potential treatment of conditions characterized by iron overload, such as hereditary hemochromatosis, beta thalassemia, sickle cell disease and myelodysplastic syndrome. LJPC-30Sa and LJPC-30Sb are our next-generation gentamicin derivatives for the potential treatment of serious bacterial infections and rare genetic disorders, such as cystic fibrosis and Duchenne muscular dystrophy.

#### LJPC-501

LJPC-501 is our proprietary formulation of angiotensin II. Angiotensin II, the major bioactive component of the renin-angiotensin system, serves as one of the body's central regulators of blood pressure. We are developing LJPC-501 for the treatment of catecholamine-resistant hypotension (CRH), which is an acute, life-threatening condition in which blood pressure drops to dangerously low levels in patients who respond poorly to current treatments. Angiotensin II has been shown to raise blood pressure in a randomized, placebo-controlled clinical trial in CRH, which was recently published in the journal *Critical Care*, as well as in animal models of hypotension. Preclinical pharmacology studies that we have conducted have demonstrated that catecholamine resistance may be in part a result of reduced endogenous production of angiotensin II. In October 2014, we presented positive data from a preclinical study of LJPC-501 for the treatment of CRH.

We initiated a Phase 3 clinical trial with LJPC-501 for the treatment of CRH, called the ATHOS (Angiotensin II for the Treatment of High-Output Shock) 3 trial, in March 2015. In February 2015, we reached agreement with the U.S. Food and Drug Administration (FDA) on a Special Protocol Assessment (SPA) for this multicenter, randomized, double-blind, placebo-controlled, Phase 3 clinical trial. In accordance with the SPA, the primary efficacy endpoint for the ATHOS 3 registration trial is increase in blood pressure at three hours. The ATHOS 3 trial is designed to enroll approximately 315 patients. Patients are to be randomized in a 1:1 fashion to receive either: (i) LJPC-501 plus standard-of-care vasopressors; or (ii) placebo plus standard-of-care vasopressors. Randomized patients are to receive their assigned treatment via continuous IV infusion for up to seven days. The primary efficacy endpoint in the study is to compare the change in mean arterial pressure in patients with CRH who receive an IV infusion of LJPC-501 plus standard-of-care vasopressors to those that receive placebo plus standard-of-care vasopressors. Secondary endpoints include comparison of changes in cardiovascular Sequential Organ Failure Assessment (SOFA) scores and the safety and tolerability of LJPC-501 in patients with CRH. Results from ATHOS 3 are expected by the end of 2016.

#### LJPC-401

LJPC-401 is our novel formulation of hepcidin. Hepcidin, an endogenous peptide hormone, is the body's naturally occurring regulator of iron absorption and distribution. Hepcidin prevents excessive iron accumulation in vital organs, such as the liver and heart, where it can cause significant damage and even result in death.

We are developing LJPC-401 for the potential treatment of iron overload, which occurs as a result of diseases such as hereditary hemochromatosis (HH), beta thalassemia, sickle cell disease (SCD) and myelodysplastic syndrome (MDS). HH is a disease caused by a genetic deficiency in hepcidin that results in excessive iron accumulation. HH is the most common genetic disease in Caucasians and causes liver cirrhosis, liver cancer, heart disease and/or failure, diabetes, arthritis and joint pain. Beta thalassemia, SCD and MDS are genetic diseases of the blood that can cause life-threatening anemia and usually require frequent and life-long blood transfusions. These blood transfusions cause excessive iron accumulation in the body, which is toxic to vital organs, such as the liver and heart. In addition, the underlying anemia causes excessive iron accumulation independent of blood transfusions.

LJPC-401 has been shown to be effective in reducing serum iron in preclinical testing. In October 2015, we initiated a Phase 1 clinical trial of LJPC-401 in patients at risk of iron overload due to conditions such as HH, beta thalassemia, SCD and MDS. In January 2016, we reported interim results from this study that suggested a dose-dependent reduction in serum iron following a single dose of LJPC-401. We expect to report complete results from our Phase 1 dose-escalation study in the second half of 2016.

In September 2015, we received a positive opinion from the European Medicines Agency (EMA) Committee for Orphan Medicinal Products (COMP), which the European Commission subsequently adopted in October 2015, for designation of LJPC-401 as an orphan medicinal product for the treatment of beta thalassemia intermedia and major.

#### LJPC-30Sa and LJPC-30Sb

LJPC-30Sa and LJPC-30Sb are our next-generation gentamicin derivatives. Despite kidney toxicity, gentamicin has become one of the most commonly prescribed hospital antibiotics due to its broad spectrum of antimicrobial efficacy. Gentamicin consists primarily of a mixture of four distinct but closely related chemical entities that may contribute differentially to the product's toxicity profile.

LJPC-30Sa and LJPC-30Sb are purified components of the currently marketed gentamicin product that retain the biologic activity of gentamicin, yet appear to lack the traditional kidney toxicity associated with it. We are developing LJPC-30Sa and LJPC-30Sb not only for the potential treatment of serious bacterial infections but also for the potential treatment of rare genetic disorders, such as cystic fibrosis and Duchenne muscular dystrophy.

We believe that gentamicin's ability to induce a lack of fidelity in gene transcription, intrinsic to its antimicrobial mechanism of action, can also be leveraged in the correction of certain human genetic mutations that lead to rare genetic disorders, such as cystic fibrosis and Duchenne muscular dystrophy. In spite of favorable short-term clinical proof-of-efficacy data in cystic fibrosis, development of gentamicin as a chronic treatment for these genetic diseases has been limited by its toxicity profile.

Following a pre-investigational new drug application (IND) meeting with the FDA, we have received guidance that we may proceed with a proposed Phase 1 clinical trial following the submission of an IND.

#### GCS-100 and LJPC-1010

GCS-100 and LJPC-1010 are our polysaccharide-based galectin-3 inhibitors. As part of our portfolio reprioritization in May 2015, the development of these product candidates was discontinued. We are exploring out-licensing opportunities for these product candidates.

#### Manufacturing

We do not currently own or operate manufacturing facilities for the production of clinical or commercial quantities of any of our product candidates. We rely on a small number of third-party manufacturers to produce our compounds and expect to continue to do so to meet the preclinical and clinical requirements of our potential product candidates and for all of our commercial needs. We do not have long-term agreements with any of these third parties. We require in our manufacturing and processing agreements that all third-party contract manufacturers and processors produce active pharmaceutical ingredients (API) and finished products in accordance with the FDA's current Good Manufacturing Practices (cGMP) and all other applicable laws and regulations. We maintain confidentiality agreements with potential and existing manufacturers in order to protect our proprietary rights related to our drug candidates.

With regard to our lead product candidate, LJPC-501, we use third parties to supply API and to formulate, fill and finish our final product. After sourcing the API for LJPC-501 from independent suppliers, we use different third parties to formulate the bulk drug product and complete the process by filling bulk drug product into vials. To date, LJPC-501 has been manufactured in small quantities for preclinical studies and clinical trials. If LJPC-501 is approved for commercial sale, we will need to manufacture the product in larger quantities. Significant scale-up of manufacturing requires additional process development and validation studies, which the FDA must review and approve. We are currently starting the process of completing this scale-up and validation work. If approved, the commercial success of LJPC-501, in the near-term, will be dependent upon the ability of our contract manufacturers to produce product in commercial quantities at competitive costs of

manufacture. If LJPC-501 receives regulatory approval, we plan to scale-up manufacturing through our third-party manufacturers with the objective of realizing important economies of scale. These scale-up activities will take time to implement, require additional capital investment, process development, validation studies and FDA approval. We cannot guarantee that we will be successful in achieving competitive manufacturing costs through such scale-up activities.

### Patents and Proprietary Technologies

Patents and other proprietary rights are important to our business. As part of our strategy to protect our current product candidates and to provide a foundation for future products, we have filed a number of patent applications and have licensed rights from third parties for other patent applications related to our product candidates.

As of December 31, 2015, we owned or had the rights to 25 issued patents (14 U.S. and 11 foreign), and 45 pending applications (14 U.S. and 31 foreign). These patents and patent applications owned or licensed by us cover our LJPC-501, LJPC-401, LJPC-30Sa and LJPC-30Sb programs, as well as other programs (discontinued GCS-100 and LJPC-1010 and new development programs).

Description	United States			Foreign		
	Issued	Pending	Expiration	Issued	Pending	Expiration
LJPC-501	1	4	2029 - 2035	—	10	2034 - 2035
LJPC-401	1	1	2022	10	3	2022
LJPC-30Sa and 30Sb	1	2	2027 - 2036	—	—	N/A
Other	11	7	2025 - 2036	1	18	2025 - 2035

In addition to those above, we plan to file additional patent applications that, if issued, would provide further protection for LJPC-501, LJPC-401, LJPC-30Sa and LJPC-30Sb. Although we believe the bases for these patents and patent applications are sound, they are untested; and there is no assurance that they will not be successfully challenged. There can be no assurance that any patent previously issued will be of commercial value, that any patent applications will result in issued patents of commercial value, or that our technology will not be held to infringe patents held by others.

### Competition

The biotechnology and pharmaceutical industries are subject to rapid technological change. Competition from domestic and foreign biotechnology companies, large pharmaceutical companies and other institutions is intense and expected to increase. A number of companies are pursuing the development of pharmaceuticals in our targeted areas.

### Government Regulation

#### Pharmaceutical Regulation

If and when we market any pharmaceutical products in the U.S., they will be subject to extensive government regulation. Likewise, if we seek to market and distribute any such products abroad, they would also be subject to extensive foreign government regulation.

In the U.S., the FDA regulates pharmaceutical products. FDA regulations govern the testing, research and development activities, manufacturing, quality, storage, advertising, promotion, labeling, sale and distribution of pharmaceutical products. Accordingly, there is a rigorous process for the approval of new drugs and ongoing oversight of marketed products. We are also subject to foreign regulatory requirements governing clinical trials and drug products if products are tested or marketed abroad. The approval process outside the U.S. varies from jurisdiction

to jurisdiction and the time required may be longer or shorter than that required for FDA approval.

See Item 1A. Risk Factors of this Annual Report on Form 10-K for a discussion of the factors that could adversely impact our development of commercial products and industry regulation.

## Regulation in the U.S.

The FDA testing and approval process requires substantial time, effort and money. We cannot assure you that any of our product candidates will ever obtain approval. The FDA approval process for new drugs includes, without limitation:

- preclinical studies;
- submission in the U.S. of an IND for clinical trials conducted in the U.S.;
- adequate and well-controlled human clinical trials to establish safety and efficacy of the product;
- review of a New Drug Application (NDA) in the U.S.; and
- inspection of the facilities used in the manufacturing of the drug to assess compliance with the FDA's current cGMP regulations.

The FDA monitors the progress of trials conducted in the U.S. under an IND and may, at its discretion, re-evaluate, alter, suspend or terminate testing based on the data accumulated to that point and the FDA's benefit-risk assessment with regard to the patients enrolled in the trial. The FDA may also withdraw approval for an IND for that drug if deemed warranted. Furthermore, even after regulatory approval is obtained, under certain circumstances, such as later discovery of previously unknown problems, the FDA can withdraw approval or subject the drug to additional restrictions.

## Preclinical Testing

The testing and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our product candidates will be granted on a timely basis, if at all. Preclinical studies include laboratory evaluation of the product, as well as animal studies to assess the potential safety and effectiveness of the product. Most of these studies must be performed according to Good Laboratory Practices, a system of management controls for laboratories and research organizations to ensure the consistency and reliability of results.

An IND is the request for authorization from the FDA to administer an investigational new drug product to humans. The IND includes information regarding the preclinical studies, the investigational product's chemistry and manufacturing, supporting data and literature, and the investigational plan and protocol(s). Clinical trials may begin 30 days after an IND is received, unless the FDA raises concerns or questions about the conduct of the clinical trials. If concerns or questions are raised, an IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can proceed. An IND must become effective before human clinical trials begin.

## Clinical Trials

Clinical trials involve the administration of the product candidate that is the subject of the trial to volunteers or patients under the supervision of a qualified principal investigator and in accordance with a clinical trial protocol, which sets forth details, such as the study objectives and the safety and effectiveness criteria to be evaluated. Each clinical trial must be reviewed and approved by an independent institutional review board (IRB) in the U.S. or ethics committee in the European Union (EU) at each institution at which the study will be conducted. The IRB or ethics committee will consider, among other things, ethical factors, safety of human subjects and the possible liability of the institution arising from the conduct of the proposed clinical trial. In addition, clinical trials in the U.S. must be performed according to good clinical practices, which are enumerated in FDA regulations and guidance documents. Some studies include oversight by an independent group of experts, known as a data safety monitoring board, which provides authorization for whether a study may move forward based on certain data from the study and may stop the clinical trial if it determines that there is an unacceptable safety risk for subjects or on other grounds.

The FDA may order the temporary, or permanent, discontinuation of a clinical trial at any time, or impose other sanctions, if it believes that the clinical trial is not being conducted in accordance with FDA requirements or presents an unacceptable risk to the clinical trial patients. An IRB may also require the clinical trial at the site to be halted, either temporarily or permanently, for failure to comply with the IRB's requirements, or may impose other conditions.

Clinical trials in the U.S. typically are conducted in sequential phases: Phases 1, 2, 3 and 4. The phases may overlap. The FDA may require that we suspend clinical trials at any time on various grounds, including if the FDA makes a finding that the subjects participating in the trial are being exposed to an unacceptable health risk.

In Phase 1 clinical trials, the investigational product is usually tested on a small number of healthy volunteers to determine safety, any adverse effects, proper dosage, absorption, metabolism, distribution, excretion and other drug effects. Follow-on Phase 1b clinical trials may also evaluate efficacy with respect to trial participants.

In Phase 2 clinical trials, the investigational product is usually tested on a limited number of patients (generally up to several hundred) to preliminarily evaluate the efficacy of the drug for specific, targeted indications, determine dosage tolerance and optimal dosage, and identify possible adverse effects and safety risks. Multiple Phase 2 clinical trials may be conducted to obtain information prior to beginning Phase 3 clinical trials.

In Phase 3 clinical trials, the investigational product is administered to an expanded patient population to support proof of concept and efficacy claims, provide evidence of clinical efficacy and to further test for safety, generally at multiple clinical sites.

In Phase 4 clinical trials or other post-approval commitments, additional studies and patient follow-up are conducted to gain experience from the treatment of patients in the intended therapeutic indication. FDA may require a commitment to conduct post-approval Phase 4 studies as a condition of approval. Additional studies and follow-up may be conducted to document a clinical benefit where drugs are approved under accelerated approval regulations and based on surrogate endpoints. In clinical trials, surrogate endpoints are alternative measurements of the symptoms of a disease or condition that are substituted for measurements of observable clinical symptoms. Failure to timely conduct Phase 4 clinical trials and follow-up could result in withdrawal of approval for products approved under accelerated approval regulations.

We cannot assure you that any of our current or future clinical trials will result in approval to market our products.

#### Clinical Data Review and Approval in the U.S.

The data from the clinical trials, together with preclinical data and other supporting information that establishes a drug candidate's safety, are submitted to the FDA in the form of an NDA, or NDA supplement (for approval of a new indication if the product candidate is already approved for another indication). Under applicable laws and FDA regulations, FDA reviews the NDA within 60 days of receipt of the NDA to determine whether the application will be accepted for filing based on FDA's threshold determination that the NDA is sufficiently complete to permit substantive review. If deemed complete, the FDA will "file" the NDA, thereby triggering substantive review of the application. The FDA can refuse to file any NDA that it deems incomplete or not properly reviewable.

The FDA has established internal substantive review goals of ten months for most NDAs. The FDA has various programs, including Fast Track, priority review, and accelerated approval, which are intended to expedite or simplify the process for reviewing drugs, and/or provide for approval based on surrogate endpoints. Even if a drug qualifies for one or more of these programs, the FDA may later decide that the drug no longer meets the conditions for qualification or that the period for FDA review or approval will not be shortened. Generally, drugs that may be eligible for these programs are those for serious or life-threatening conditions, those with the potential to address unmet medical needs, and those that offer meaningful benefits over existing treatments. For example, Fast Track is a process designed to facilitate the development, and expedite the review, of drugs to treat serious diseases and fill an unmet medical need. The request may be made at the time of IND submission and generally no later than the pre-NDA meeting. The FDA will respond within 60 calendar days of receipt of the request. Priority review, which is requested at the time of an NDA submission, is designed to give drugs that offer major advances in treatment or provide a treatment where no adequate therapy exists, an initial review within six months as compared to a standard review time of ten months. Although Fast Track and priority review do not affect the standards for approval, the FDA

will attempt to facilitate early and frequent meetings with a sponsor of a Fast Track designated drug and expedite review of the application for a drug designated for priority review. Accelerated approval provides an earlier approval of drugs to treat serious diseases, and that fill an unmet medical need based on a surrogate endpoint. The FDA, however, is not legally required to complete its review within these periods, and these performance goals may change over time.

If the FDA approves the NDA, it will issue an approval letter authorizing the commercial marketing of the drug with prescribing information for specific indications. As a condition of NDA approval, the FDA may require a risk evaluation and mitigation strategy (REMS) to help ensure that the benefits of the drug outweigh the potential risks. REMS can include medication guides, communication plans for healthcare professionals, and elements to assure safe use. Additionally, the FDA will inspect the facility or the facilities at which the drug is manufactured. Moreover, product approval may require substantial post-approval testing and surveillance to monitor the drug's safety or efficacy. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing. In many cases, the outcome of the review, even if generally favorable, is not an actual approval, but a "complete response" that

generally outlines the deficiencies in the submission, which may require substantial additional testing, or information, in order for the FDA to reconsider the application. If, or when, those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter.

Satisfaction of FDA requirements or similar requirements of state, local, and foreign regulatory agencies typically takes several years and requires the expenditure of substantial financial resources. Information generated in this process is susceptible to varying interpretations that could delay, limit or prevent regulatory approval at any stage of the process. Accordingly, the actual time and expense required to bring a product to market may vary substantially. We cannot assure you that we will submit applications for required authorizations to manufacture and/or market potential products or that any such application will be reviewed and approved by the appropriate regulatory authorities in a timely manner, if at all. Data obtained from clinical activities is not always conclusive and may be susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. Success in early stage clinical trials does not ensure success in later stage clinical trials. Even if a product candidate receives regulatory approval, the approval may be significantly limited to specific disease states, patient populations and dosages, or have conditions placed on it that restrict the commercial applications, advertising, promotion or distribution of these products.

Once issued, the FDA may withdraw product approval if ongoing regulatory standards are not met or if safety problems occur after the product reaches the market. In addition, the FDA may require testing and surveillance programs to monitor the safety or effectiveness of approved products which have been commercialized, and the FDA has the power to prevent or limit further marketing of a product based on the results of these post-marketing programs. The FDA may also request or require additional Phase 4 clinical trials after a product is approved. The results of Phase 4 clinical studies can confirm the effectiveness of a product candidate and can provide important safety information to augment the FDA's voluntary adverse drug reaction reporting system. Any products manufactured or distributed by us pursuant to FDA approvals would be subject to continuing regulation by the FDA, including record-keeping requirements and reporting of adverse experiences with the drug. Drug manufacturers and their subcontractors are required to register their establishments with the FDA and certain state agencies and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP, which impose certain procedural and documentation requirements upon us and our third-party manufacturers. We cannot be certain that we, or our present or future suppliers, will be able to comply with the cGMP regulations and other FDA regulatory requirements.

In addition, both before and after approval is sought, we are required to comply with a number of FDA requirements. For example, we are required to report certain adverse reactions and production problems, if any, to the FDA, and to comply with certain limitations and other requirements concerning advertising and promotion for our products. In addition, quality control and manufacturing procedures must continue to conform to cGMP after approval, and the FDA periodically inspects manufacturing facilities to assess compliance with continuing cGMP. In addition, discovery of problems, such as safety problems, may result in changes in labeling or restrictions on a product manufacturer or NDA holder, including removal of the product from the market.

The FDA closely regulates the marketing and promotion of drugs. Approval may be subject to post-marketing surveillance and other record-keeping and reporting obligations, and involve ongoing requirements. Product approvals may be withdrawn if compliance with regulatory standards is not maintained or if problems occur following initial marketing. A company can make only those claims relating to safety and efficacy that are approved by the FDA. Failure to comply with these requirements can result in adverse publicity, warning letters, corrective advertising and potential civil and criminal penalties.

Clinical Trial Conduct and Product Approval Regulation in Non-U.S. Jurisdictions

In addition to regulations in the U.S., we may be subject to a variety of foreign regulations governing clinical trials and commercial sales and distribution of our products. Our clinical trials conducted in the EU must be done under an Investigational Medicinal Product Dossier (IMPD) and the oversight of an ethics committee. If we market our products in foreign countries, we also will be subject to foreign regulatory requirements governing marketing approval for pharmaceutical products. The requirements governing the conduct of clinical trials, product approval, pricing and reimbursement vary widely from country to country. Whether or not FDA approval has been obtained, approval of a product by the comparable regulatory authorities of foreign countries must be obtained before manufacturing or marketing the product in those countries. The approval process varies from country to country and the time required for such approvals may differ substantially from that required for FDA approval. There is no assurance that any future FDA approval of any of our product candidates will result in similar foreign approvals or vice versa. The process for clinical trials in the EU is similar, and trials are heavily scrutinized by the designated ethics committee.

### Section 505(b)(2) Applications

Some of our product candidates may be eligible for submission of applications for approval under the FDA's Section 505(b)(2) approval process, which provides an alternate path to FDA approval for new or improved formulations or new uses of previously approved products. Section 505(b)(2) was enacted as part of the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act, and allows approval of NDAs that rely, at least in part, on studies that were not conducted by or for the applicant and to which the applicant has not obtained a right of reference. Such studies can be provided by published literature, or the FDA can rely on previous findings of safety and efficacy for a previously approved drug. If the 505(b)(2) applicant can establish that reliance on the FDA's previous approval is scientifically appropriate, it may eliminate the need to conduct certain preclinical or clinical studies of the new product. Section 505(b)(2) applications may be submitted for drug products that represent a modification (e.g., a new indication or new dosage form) of an eligible approved drug. In such cases, the additional information in 505(b)(2) applications necessary to support the change from the previously approved drug is frequently provided by new studies submitted by the applicant. Because a Section 505(b)(2) application relies in part on previous studies or previous FDA findings of safety and effectiveness, preparing 505(b)(2) applications is generally less costly and time-consuming than preparing an NDA based entirely on new data and information from a full set of clinical trials. The FDA may approve the new product candidate for all, or some, of the label indications for which the referenced product has been approved, as well as for any new indication sought by the Section 505(b)(2) applicant. The law governing Section 505(b)(2) or FDA's current policies may change in such a way as to adversely affect our applications for approval that seek to utilize the Section 505(b)(2) approach. Such changes could result in additional costs associated with additional studies or clinical trials and delays.

The FDA provides that reviews and/or approvals of applications submitted under Section 505(b)(2) will be delayed in various circumstances. For example, the holder of the NDA for the listed drug may be entitled to a period of market exclusivity during which the FDA will not approve, and may not even review, a Section 505(b)(2) application from other sponsors. If the listed drug is claimed by one or more patents that the NDA holder has listed with the FDA, the Section 505(b)(2) applicant must submit a certification with respect to each such patent. If the 505(b)(2) applicant certifies that a listed patent is invalid, unenforceable or not infringed by the product that is the subject of the Section 505(b)(2) application, it must notify the patent holder and the NDA holder. If, within 45 days of providing this notice, the NDA holder sues the 505(b)(2) applicant for patent infringement, the FDA will not approve the Section 505(b)(2) application until the earlier of a court decision favorable to the Section 505(b)(2) applicant or the expiration of 30 months. The regulations governing marketing exclusivity and patent protection are complex, and it is often unclear how they will be applied in particular circumstances.

### Drug Enforcement Agency Regulation

Our research and development processes involve the controlled use of hazardous materials, including chemicals. Some of these hazardous materials are considered to be controlled substances and subject to regulation by the U.S. Drug Enforcement Agency (DEA). Controlled substances are those drugs that appear on one of five schedules promulgated and administered by the DEA under the Controlled Substances Act (CSA). The CSA governs, among other things, the distribution, recordkeeping, handling, security and disposal of controlled substances. We must be registered by the DEA in order to engage in these activities, and are subject to periodic and ongoing inspections by the DEA and similar state drug enforcement authorities to assess ongoing compliance with the DEA's regulations. Any failure to comply with these regulations could lead to a variety of sanctions, including the revocation, or a denial of renewal, of the DEA registration, injunctions or civil or criminal penalties.

### Third-Party Payor Coverage and Reimbursement

Although none of our current product candidates have been approved or commercialized for any indication as of the date of this report, if they are approved for marketing, commercial success of our product candidates will depend, in part, upon the availability of coverage and reimbursement from third-party payors at the federal, state and private levels. Government payor programs, including Medicare and Medicaid, private healthcare insurance companies and managed care plans have attempted to control costs by limiting coverage and the amount of reimbursement for particular procedures or drug treatments. The U.S. Congress and state legislatures, from time to time, propose and adopt initiatives aimed at cost containment. Ongoing federal and state government initiatives directed at lowering the total cost of healthcare will likely continue to focus on healthcare reform, the cost of prescription pharmaceuticals and on the reform of the Medicare and Medicaid payment systems.

Examples of how limits on drug coverage and reimbursement in the U.S. may cause reduced payments for drugs in the future include:

- changing Medicare reimbursement methodologies;
- fluctuating decisions on which drugs to include in formularies;
- revising drug rebate calculations under the Medicaid program or requiring that new or additional rebates be provided to Medicare, Medicaid, other federal or state healthcare programs; and
- reforming drug importation laws.

Some third-party payors also require pre-approval of coverage for new drug therapies before they will reimburse healthcare providers that use such therapies. While we cannot predict whether any proposed cost-containment measures will be adopted or otherwise implemented in the future, the announcement or adoption of these proposals could have a material adverse effect on our ability to obtain adequate prices for our product candidates and to operate profitably.

Reimbursement systems in international markets vary significantly by country and, within some countries, by region. Reimbursement approvals must be obtained on a country-by-country basis. In many foreign markets, including markets in which we hope to sell our products, the pricing of prescription pharmaceuticals is subject to government pricing control. In these markets, once marketing approval is received, pricing negotiations could take significant additional time. As in the U.S., the lack of satisfactory reimbursement or inadequate government pricing of any of our products would limit widespread use and lower potential product revenues.