ARENA PHARMACEUTICALS INC
Form 424B5
January 13, 2005

QuickLinks -- Click here to rapidly navigate through this document

The information contained in this prospectus supplement is not complete and may be changed. The registration statement filed with the Securities and Exchange Commission relating to these securities has been declared effective. This prospectus supplement and the accompanying prospectus are not an offer to sell these securities and are not soliciting an offer to buy these securities in any state where the offer or sale is not permitted.

Subject to Completion, Dated January 13, 2005

**This filing is made pursuant to
Rule 424(b)(5) under
the Securities Act of 1933
in connection with
Registration No. 333-115670**

6,000,000 Shares

Common Stock

$ per share

Arena Pharmaceuticals, Inc. is offering 6,000,000 shares.

The common stock is listed on the Nasdaq National Market under the symbol "ARNA." On January 10, 2005, the last reported sale price of the common stock on the Nasdaq National Market was $6.45 per share.

Investing in the common stock involves risks. See "Risk Factors" beginning on page S-9 of this prospectus supplement.

	Per Share	Total
Price to the public	$	$
Underwriting discount		
Proceeds to Arena		

We have granted an over-allotment option to the underwriters. Under this option, the underwriters may elect to purchase a maximum of 900,000 additional shares from us within 30 days following the date of this prospectus supplement to cover over-allotments.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus supplement or the accompanying prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

CIBC World Markets **Piper Jaffray**

Needham & Company, Inc.

Granite Financial Group, Inc.

Morgan Joseph

The date of this prospectus supplement (to the prospectus dated June 18, 2004) is , 2005

Table of Contents

About this Prospectus Supplement

We provide information to you about this offering of shares of our common stock in two separate documents that are bound together: (1) this prospectus supplement, which describes the specific details regarding this offering; and (2) the accompanying prospectus, which provides general information, some of which may not apply to this offering. Generally, when we refer to this "prospectus," we are referring to both documents combined. If information in this prospectus supplement is inconsistent with the accompanying prospectus, you should rely on this prospectus supplement.

You should rely only on information contained in or incorporated by reference into this prospectus supplement and the accompanying prospectus. We have not, and the underwriters have not, authorized anyone to provide you with information that is different. We are offering to sell and seeking offers to buy shares of our common stock only in jurisdictions where offers and sales are permitted. The information contained in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein are accurate only as of their respective dates, regardless of the time of delivery of this prospectus supplement or of any sale of our common stock.

Prospectus Supplement Summary

This summary highlights selected information contained in other parts of this prospectus supplement and the accompanying prospectus. Because it is a summary, it does not contain all of the information that you should consider before investing in our shares. You should read the entire prospectus supplement and accompanying prospectus and the documents incorporated by reference herein and therein carefully.

The Company

We are a biopharmaceutical company with a pipeline of internally discovered small molecule product candidates that target G protein-coupled receptors, or GPCRs. Two of our product candidates are in clinical trials: APD356 for the treatment of obesity is in a Phase 2 clinical trial; and APD125 for the treatment of insomnia is in a Phase 1 clinical trial. We also have active collaborations with two major pharmaceutical companies, Ortho-McNeil Pharmaceutical, Inc., a Johnson & Johnson company, for the treatment of type 2 diabetes, and Merck & Co., Inc., for the treatment of atherosclerosis and related disorders. Our product candidates act on or through known and orphan GPCRs, and have been discovered using our GPCR-focused drug discovery technologies and capabilities. We believe these technologies and capabilities will allow us to continue to discover novel product candidates in our therapeutic areas of focus, which are metabolic, central nervous system (or CNS), cardiovascular and inflammatory diseases.

APD356

Our most advanced product candidate is APD356, a novel and selective 5-HT_{2C} receptor agonist, for the treatment of obesity. In animal models, APD356 appears to lower body fat without affecting lean body mass. Obesity and a related condition known as metabolic syndrome affect tens of millions of adults and children in the United States and pose a serious long-term threat to their health and welfare.

Our preclinical studies show APD356 stimulates the 5-HT_{2C} serotonin receptor more selectively than fenfluramine and dexfenfluramine. Based on these studies, we believe that APD356 is less likely to cause the cardiovascular side effects associated with fenfluramine and dexfenfluramine. Until 1997, Wyeth marketed fenfluramine and dexfenfluramine, serotonin-releasing agents and non-selective serotonin receptor agonists, which were often used in combination with phentermine for the treatment of obesity. The combination of fenfluramine or dexfenfluramine with phentermine is commonly referred to as fen-phen. Despite their efficacy as appetite suppressants, both fenfluramine and dexfenfluramine were withdrawn from the market in 1997 after reported incidences of heart valve disease and pulmonary hypertension associated with their usage.

We have completed single and multiple dose Phase 1 clinical trials of APD356. Results from these trials identified the maximum tolerated dose, indicated that APD356 was well tolerated with food, showed no apparent drug effect on heart valves or pulmonary artery pressure, and demonstrated an effect which we believe is a clinically meaningful signal of pharmacology.

Based on these results, in December 2004 we began a randomized, double-blinded, multiple-dose, 28-day Phase 2 clinical trial of APD356 in obese subjects. We expect that the trial will compare doses of 1 mg, 5 mg and 15 mg of APD356 to placebo, evaluating weight loss after administration once daily for 28 days. We expect to announce initial results from this trial in the second quarter of 2005.

APD125

Our lead product candidate for insomnia, APD125, is a novel and selective 5-HT_{2A} receptor inverse agonist. Currently marketed drugs for insomnia generally activate the GABA-A receptor in the brain, and cause a general CNS-suppressive effect. While these drugs are effective at initiating sleep, they have side effects including the risk of developing tolerance to the drug and the potential for causing a sensation of dullness and lethargy upon awakening, often referred to as the "hangover effect." In addition, these drugs are DEA-scheduled controlled substances due to their potential for abuse.

APD125 selectively targets the 5-HT_{2A} receptor and acts through a different mechanism than currently marketed insomnia drugs. We believe that APD125 may not have the side effects associated with such drugs. In our animal studies, APD125 improved the quality of sleep and appeared to promote sleep onset. Based on these animal data, we believe that APD125 has the potential to improve the treatment of insomnia over GABA-A hypnotics.

In December 2004, we initiated a Phase 1 clinical trial of APD125 in healthy volunteers. This dose-ranging study will evaluate the safety, tolerability, and pharmacokinetics of single doses of APD125. We expect to announce results from this trial in the middle of 2005. Depending on the results of this trial, we intend to initiate multiple-dose tolerability and single-dose pharmacology trials.

19AJ / Ortho-McNeil Collaboration

Our lead product candidate for diabetes targets an orphan GPCR, which we call 19AJ, found in the pancreas. We believe 19AJ represents a novel mechanism for generating a new class of drugs for diabetes that may offer advantages over current approaches. Our preclinical results indicate that stimulating the 19AJ receptor allows beta cells to produce insulin more efficiently in response to changes in blood glucose levels. We have discovered potent, selective and orally available small molecule agonists of the receptor that improve glucose tolerance and lower blood glucose levels in animal models of diabetes. The 19AJ mechanism is glucose dependent, so that in our animal studies our compounds only lowered blood glucose when it rose above normal levels, such as after a meal. Our preclinical results indicate that these compounds do not lower normal fasting baseline glucose levels in animal models and, therefore, do not cause hypoglycemia, unlike the glucose-insensitive sulphonylureas.

In December 2004, we entered into a collaboration and license agreement with Ortho-McNeil to further develop compounds for the potential treatment of type 2 diabetes and other disorders. Our two lead compounds are currently in preclinical development with Ortho-McNeil. We received a $17.5 million upfront payment and two milestone payments of $2.5 million each. We are eligible to receive up to $295.0 million in milestone payments for each compound, as well as royalty payments associated with Ortho-McNeil's commercialization of any drugs discovered under the agreement. These milestone payments include development and approval milestone payments of up to $132.5 million for the first indication and $62.5 million for the second indication for each compound, and up to $100.0 million in sales milestone payments for each product resulting from the collaboration.

Merck Cardiovascular Collaboration

In October 2002, we entered into a research and licensing agreement with Merck to collaborate on three GPCRs to develop therapeutics for atherosclerosis and related disorders. We believe one or more of these GPCRs plays a role in regulating plasma lipid profiles, including HDL cholesterol, the so-called "good cholesterol," and is responsible for HDL-raising activity of niacin. In October 2004, Merck extended and expanded our collaboration and selected one of our compounds for preclinical development. To date, we have received $19.5 million from Merck in upfront and milestone payments and an equity investment. We may receive additional milestone payments of up to $34.0 million for Merck's clinical and marketing achievements, as well as royalty payments associated with Merck's

commercialization of any drugs discovered under the agreement. In addition, we have received research funding from Merck since the inception of our collaboration, and Merck has agreed to pay us $5.7 million a year for collaboration research through October 2007.

Other Research and Development Programs

In addition to our Merck collaboration, our programs in the cardiovascular area include ones directed toward the prevention of thrombosis and cardiac reperfusion injury. We have identified novel GPCRs that we believe are involved in both conditions, and are currently evaluating lead compounds in animal models. For inflammatory diseases, we have discovered small molecule compounds which can be orally administered and that act to target GPCRs in the immune system to inhibit the production of TNF-α. For CNS diseases, we are developing small molecules targeting a GPCR through a different mechanism than serotonin or norepinephrine, and have confirmed that inhibitors of this GPCR show activity in animal models of depression and anxiety. For metabolic diseases, we are working on a series of orphan GPCR targets other than 19AJ in order to develop orally available therapies to treat type 1 and type 2 diabetes. We also have discovery programs focused on several different GPCRs implicated in obesity.

Our GPCR Technologies and Project Genesis

Our product candidates have resulted from our GPCR-focused drug discovery technologies, capabilities and programs, including Constitutively Activated Receptor Technology, or CART, our Melanophore technology and Project Genesis. CART allows us to discover drug-like compounds by activating the GPCR to mimic the biological response that occurs when the native ligand binds to the receptor. Our patented Melanophore technology is a broadly applicable high-throughput screen for GPCRs. We have substantially completed our efforts under Project Genesis, a program to identify human GPCRs, determine where these GPCRs are expressed in normal and diseased tissues, and utilize our CART and Melanophore technologies to screen against our chemical libraries.

Our Strategy

The key elements of our scientific and business strategy are to:

- continue to advance our lead programs;
- discover and develop additional small molecule product candidates targeting GPCRs;
- focus on attractive market opportunities;
- retain significant commercial rights and/or economic value for our product candidates;
- continue to build our development capabilities; and
- maintain strong research discovery capabilities.

Recent Developments

As of December 31, 2004, our cash, cash equivalents and short-term investments available for sale was $113.3 million. This does not include upfront and milestone payments totaling $22.5 million paid to us in January 2005 by Ortho-McNeil under our collaboration.

The Offering

Common stock offered by Arena	6,000,000 shares
Common stock to be outstanding after this offering	32,566,419 shares
Use of proceeds	We intend to use the net proceeds from this offering for the clinical and preclinical development of our internally discovered product candidates, for discovery research for new product candidates and for general corporate purposes, including working capital. In the event the effective net price to us per share from this offering is less than $6.72, the holders of our Series B Convertible Preferred Stock may require us to redeem all or some of their outstanding preferred shares. Accordingly, if the price at which we sell shares to the public in this offering is less than approximately $7.22 per share, this redemption right may be triggered. The aggregate redemption price at December 31, 2004 was approximately $36.5 million, and accrues interest at 4.0% annually. We may be able to satisfy a portion of this amount with shares of our common stock if certain criteria are met.
Nasdaq National Market symbol	ARNA

The number of shares of common stock to be outstanding after this offering as reflected in the table above is based on the actual number of shares outstanding as of December 31, 2004, which was 26,566,419, and does not include, as of that date:

- 4,861,899 shares of common stock issuable upon conversion of our Series B-1 Convertible Preferred Stock at a conversion price of $7.50 per share;
- 1,486,200 shares of common stock issuable upon the exercise of outstanding warrants at an exercise price of $10.00 per share;
- 2,780,399 shares of common stock issuable upon the exercise of outstanding options at a weighted average exercise price of $8.66 per share;
- 1,547,383 shares of common stock available for future issuance under our equity compensation plans;
- 690,268 shares of common stock available for future issuance under our 2001 Employee Stock Purchase Plan;
- 151,669 shares of common stock available for future issuance under our Deferred Compensation Plan; and
- up to 2,092,857 shares of common stock issuable from unit warrants held by our Series B-1 Convertible Preferred stockholders at a weighted average exercise price of $7.65 per share.

Unless otherwise stated, all information contained in this prospectus supplement assumes no exercise of the over-allotment option granted to the underwriters.

Summary Consolidated Financial Data

The following table sets forth our summary consolidated financial data. This data has been derived from our audited consolidated financial statements for the years ended December 31, 2001, 2002 and 2003, and our unaudited consolidated financial statements for the nine month periods ended September 30, 2003 and 2004, and as of September 30, 2004, all of which are incorporated by reference into this prospectus supplement. You should read this information in conjunction with "Management's Discussion and Analysis of Financial Condition and Results of Operations" and our financial statements and the related notes, which are incorporated by reference into this prospectus supplement. The results of operations for interim periods are not necessarily indicative of operating results for the full year.

	Year Ended December 31,			Nine Months Ended September 30,	
	2001	2002	2003	2003	2004
				(Unaudited)	
Consolidated Statements of Operations Data:					
Revenues:					
Total revenues	$ 18,059,999	$ 19,421,765	$ 12,834,279	$ 11,217,885	$ 11,565,000
Expenses:					
Research and development	22,864,250	44,399,136	50,885,417	37,762,310	42,055,010
General and administrative	5,390,446	7,499,011	8,553,910	6,026,989	7,610,225
Amortization of deferred compensation	4,239,740	2,264,934	3,236,087	2,554,791	1,167,378
Amortization of acquired technology	1,280,830	1,586,127	1,621,220	1,215,915	1,215,915
Total operating expenses	33,775,266	55,749,208	64,296,634	47,560,005	52,048,528
Interest income and other, net	8,832,543	3,497,505	4,402,916	3,892,735	(143,808)
Net loss	(6,882,724)	(32,829,938)	(47,059,439)	(32,449,385)	(40,627,336)
Dividends on redeemable convertible preferred Stock			(26,858)		(1,071,612)
Accretion of discount related to redeemable convertible preferred stock			(35,516)		(1,388,912)
Net loss allocable to common stockholders	$ (6,882,724)	$ (32,829,938)	$ (47,121,813)	$ (32,449,385)	$ (43,087,860)
Net loss per share allocable to common stockholders, basic and diluted	$ (0.28)	$ (1.19)	$ (1.74)	$ (1.17)	$ (1.70)
Shares used in calculating net loss per share allocable to common stockholders, basic and diluted	24,989,067	27,487,537	27,159,234	27,725,907	25,313,716

	September 30, 2004	
	Actual	As Adjusted
Consolidated Balance Sheet Data (unaudited):		
Cash, cash equivalents and short-term investments available for sale	$ 118,579,684	$ 154,587,684
Working capital	116,263,524	152,271,524
Total assets	190,464,264	226,472,264
Financing obligation, including deferred interest	13,194,494	13,194,494
Accumulated deficit	(150,613,338)	(150,613,338)
Stockholders' equity	140,996,302	177,004,302

The as adjusted consolidated balance sheet data gives effect to the sale of 6,000,000 shares of common stock offered by us in this offering at an assumed public offering price of $6.45 per share, after deducting the underwriting discount and our estimated offering expenses.

The as adjusted consolidated balance sheet data does not give effect to any redemption of our outstanding Series B-1 Convertible Preferred Stock. In the event the effective net price to us per share from this offering is less than $6.72, the holders of our Series B Convertible Preferred Stock may require us to redeem all or some of their outstanding preferred shares. The aggregate redemption price at December 31, 2004, was approximately $36.5 million, and accrues interest at 4.0% annually. We may be able to satisfy a portion of this amount with shares of our common stock if certain criteria are met.

Risk Factors

You should consider carefully the risks described below, together with other information in this prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein, before you make a decision to invest in our common stock. If any of the following events actually occur, our business, operating results, prospects or financial condition could be materially and adversely affected. This could cause the trading price of our common stock to decline and you may lose all or part of your investment. The risks described below are not the only ones that we face. Additional risks not presently known to us or that we currently deem immaterial may also affect our business operations.

Risks Relating to Our Business

We will need additional funds to conduct our planned research and development efforts, and we may not be able to obtain such funds.

We had losses of $43.1 million for the nine months ended September 30, 2004, and we had an accumulated deficit of $150.6 million from our inception in April 1997 through September 30, 2004. Our losses have resulted in large part from the significant research and development expenditures we have made in seeking to identify and validate new drug targets and compounds that could become marketed drugs.

We expect our operating expenses over the next several years will be significant and that we will continue to have significant operating losses in the near term, even if we or our collaborators are successful in advancing compounds discovered using our technologies.

We do not have any commercial products. It takes many years and potentially hundreds of millions of dollars to successfully develop a preclinical or early clinical compound into a marketed drug. Even with the anticipated proceeds from this offering, we will have substantially less money than we would need to successfully develop a compound into a marketed drug. Additional financing may not be available to us or may not be available on terms that you or we believe are favorable.

Our stock has not performed as well as the stock of many of our peers for some time, and we presently are aware of only a small number of securities analysts covering our stock, which means limited third-party information is available to investors. We believe that institutional and other investors value third-party information in making investment decisions regarding our stock. These factors, and many others, may affect our ability to access capital markets.

If additional financing is not available, we may be required to delay, reduce the scope of or eliminate one or more of our research or development programs.

We expect to announce results for our two most advanced product candidates by the middle of 2005, and our stock price could decline significantly based on those clinical results.

By the middle of 2005, we expect to announce results from separate clinical trials currently in progress for our two most advanced product candidates, APD356 and APD125. These results may not be favorable or viewed favorably by us or third parties, including investors, analysts and potential collaborators. Biotechnology company stock prices have declined significantly in certain instances where clinical results were not favorable, were perceived negatively or otherwise did not meet expectations. Unfavorable results or negative perceptions regarding the results of our clinical trials of APD356, APD125, or any of our other product candidates could cause our stock price to decline significantly.

Clinical trials for our product candidates are expensive, time consuming and their outcome is uncertain.

Clinical trials are very expensive and difficult to design and implement. The clinical trial process is also time consuming. We estimate that the clinical trials of our most advanced drug candidates will continue for several years, but may take significantly longer to complete. Before we can obtain regulatory approval for the commercial sale of any product candidate that we wish to develop, we are required to complete extensive clinical trials in humans to demonstrate its safety and efficacy. The timing of the commencement, continuation and completion of clinical trials may be subject to significant delays relating to various causes, including:

- our inability to manufacture or obtain sufficient quantities of materials for use in clinical trials;
- delays in obtaining regulatory approvals to commence a study;
- delays in identifying and reaching agreement on acceptable terms with prospective clinical trial sites;
- slower than expected rates of patient recruitment and enrolment;
- uncertain dosing issues;
- inability or unwillingness of medical investigators to follow our clinical protocols;
- variability in the number and types of subjects available for each study and resulting difficulties in identifying and enrolling subjects who meet trial eligibility criteria;
- scheduling conflicts with participating clinicians and clinical institutions;
- difficulty in maintaining contact with subjects after treatment, resulting in incomplete data;
- unforeseen safety issues or side effects;
- lack of effectiveness during the clinical trials; or
- other regulatory delays.

The results of preclinical studies and initial clinical trials are not necessarily predictive of future results, and our current product candidates may not have favorable results in later testing or trials.

Preclinical tests and Phase 1 and Phase 2 clinical trials are not primarily designed to test the efficacy of a product candidate, but rather to test safety, to study pharmacokinetics and pharmacodynamics, and to understand the product candidate's side effects at various doses and schedules. Success in preclinical or animal studies and early clinical trials does not ensure that later large-scale trials will be successful nor does it predict final results. Favorable results in early trials may not be repeated in later trials.

A number of companies in the biotechnology industry have suffered significant setbacks in advanced clinical trials, even after promising results in earlier trials. Clinical results are frequently susceptible to varying interpretations that may delay, limit or prevent regulatory approvals. Negative or inconclusive results or adverse medical events during a clinical trial could cause a clinical trial to be delayed, repeated or terminated. In addition, failure to construct appropriate clinical trial protocols could result in the test or control group experiencing a disproportionate number of adverse events and could cause a clinical trial to be repeated or terminated.

Initial clinical trials of APD356 have been conducted only in small numbers of subjects. Preclinical data and the limited clinical results we have obtained for APD356 may not predict results from studies in larger numbers of subjects drawn from more diverse populations, and also may not predict the ability of APD356 to achieve a sustained reduction in bodyweight, or to do so safely. We have designed

APD356 to more selectively stimulate the 5-HT_{2C} serotonin receptor because we believe this selectivity may avoid the cardiovascular side effects associated with fenfluramine and dexfenfluramine, both of which were withdrawn from the market in 1997 after reported incidences of heart valve disease and pulmonary hypertension associated with their usage. We may not be correct in this belief, however, and APD356's selectivity profile may not avoid the undesired side effects. Moreover, the potential relationship between the activity of APD356 and fenfluramine and dexfenfluramine may result in increased FDA regulatory scrutiny of the safety of our product candidates and may raise potential adverse publicity in the marketplace. In response to our IND submission for APD356, the FDA requested that we provide an assessment of the abuse potential of APD356 as well as plans for cardiac valve monitoring during Phase 2 and Phase 3 clinical trials. We have submitted to the FDA our plan for cardiac valve monitoring and our communication with the FDA on these issues is on-going. Preclinical data also may not predict the ability of APD125 to be effective at initiating sleep and/or improving sleep quality.

We will be required to demonstrate through larger-scale clinical trials that these product candidates are safe and effective for use in a diverse population before we can seek regulatory approvals for their commercial sale. There is typically an extremely high rate of attrition from the failure of product candidates proceeding through clinical trials. To date, long-term safety and efficacy have not yet been demonstrated in clinical trials for any of our product candidates. If APD356 or APD125 fails to demonstrate sufficient safety and efficacy in any clinical trial, we will experience potentially significant delays in, or be required to abandon development of, that product candidate. We expect to announce the results of clinical trials for both APD356 and APD125 by the middle of 2005. However, if we delay or abandon our development efforts related to APD356 or APD125, or any other product candidate, we may not be able to generate sufficient revenues to continue our operations at the current level or become profitable, our reputation in the industry and in the investment community would likely be significantly damaged, and our stock price is likely to decrease significantly.

Our research and development programs are in early stages of development, and may not result in the commencement of clinical trials.

Our research and development programs are in the discovery, preclinical or early clinical stage of development. The process of discovering compounds with therapeutic potential is expensive, time-consuming and unpredictable. Similarly, the process of conducting preclinical studies of compounds that we discover requires the commitment of a substantial amount of our technical, financial and human resources. We may not discover additional compounds with therapeutic potential, and any of the compounds for which we are conducting preclinical studies may not result in the commencement of clinical trials. If we are unable to identify and develop new product candidates, we may not be able to establish or maintain a clinical development pipeline or generate revenue.

The technologies on which we rely may not result in the discovery or development of commercially viable products.

Our GPCR technologies allow us to discover drug-like compounds that act on receptor subtypes of known GPCRs and novel GPCRs where the native ligands have not been identified. These methods of identifying, prioritizing and screening molecular targets are unproven approaches to the identification of drug leads that may possess therapeutic potential, and may not result in the regulatory approval and commercialization of any therapeutic products. We do not believe that there are any drugs on the market that have been discovered or developed using our proprietary technologies. If we are unable to identify additional product candidates using our proprietary drug discovery technologies, we may not be able to maintain a clinical development pipeline or generate revenues.

Another company, organization or individual could have, or could develop, a technology using GPCRs to discover and develop compounds into drugs more effectively or more efficiently than our screening and other technologies. Such a technology could render our technologies, in particular our constitutively activated receptor technology, or CART, and Melanophore technology, obsolete or noncompetitive.

Our product candidates are subject to extensive regulation, which can be costly and time consuming, cause unanticipated delays, or prevent the receipt of the required approvals to commercialize products.

The clinical development, manufacturing, labeling, packaging, storage, record-keeping, advertising, promotion, export, marketing, and distribution of our product candidates are subject to extensive regulation by the FDA and other regulatory agencies in the United States and by comparable governmental authorities in foreign markets. Neither we nor our collaborators are permitted to market our potential products in the United States until we receive regulatory approval from the FDA. Neither we nor our collaborators have received marketing approval for any of our product candidates. The process of obtaining regulatory approval is expensive, often takes many years, and can vary substantially based upon the type, complexity and novelty of the products involved. A new drug approval, or NDA, application must be supported by extensive clinical and preclinical data regarding manufacturing, process and controls to demonstrate the safety and effectiveness of the product candidate. Approval policies or regulations may change. Moreover, failure to comply with the FDA and other applicable foreign and United States regulatory requirements may subject us to administrative or judicially imposed sanctions. These include warning letters, civil and criminal penalties, injunctions, product seizure and detention, product recalls, total or partial suspension of production, and refusal to approve pending NDAs, or supplements to approved NDAs.

In addition, we have not previously filed NDAs with the FDA. This lack of experience may impede our ability to obtain FDA approval in a timely manner, if at all, for our product candidates for which development and commercialization is our responsibility. Despite the time and expense invested, regulatory approval is very uncertain and never guaranteed and we could encounter problems that cause us to abandon clinical trials or to repeat or perform additional preclinical testing and clinical trials. The FDA has substantial discretion in the drug approval process. The number of preclinical studies and clinical trials that will be required for FDA approval varies depending on the product candidate, the disease or condition that the product candidate is designed to address, and the regulations applicable to any particular drug candidate. The FDA can delay, limit or deny approval of a product candidate for many reasons, including:

not finding a product candidate safe and effective;

not finding the data from preclinical testing and clinical trials sufficient;

not approving of our or a third-party manufacturers' processes or facilities; or

due to changes in its approval policies or the adoption of new regulations.

Because, in part, of the early stage of our product candidate research and development process, we cannot predict whether or not regulatory approval will be obtained for any product we develop. Only two of our product candidates, APD356 and APD125, are undergoing clinical trials. Compounds developed by us, alone or with other parties, may not prove to be safe and effective in clinical trials and may not meet all of the applicable regulatory requirements needed to receive marketing approval. Administering any of our product candidates to humans may produce undesirable side effects. These side effects could interrupt, delay or halt clinical trials of our product candidates and could result in the FDA or other regulatory authorities denying approval of our product candidates for any or all of the targeted indications. If regulatory approval of a product is granted, the approval will be limited to those disease states and conditions for which the product is demonstrated through clinical trials to be safe

and effective. Failure to obtain regulatory approval will delay or prevent us from commercializing products. These risks also apply to the development activities of our collaborators, and we do not expect any drugs resulting from our collaborators' research and development efforts to be commercially available for many years, if ever. The FDA, other regulatory authorities, our collaborators or we may suspend or terminate clinical trials at any time. Any failure or significant delay in completing clinical trials for our drug candidates, or in receiving regulatory approval for the sale of any drugs resulting from our product candidates, may severely harm our business and reputation.

If we are not successful in advancing our lead programs, we may have to curtail some of our activities.

If we are not successful in achieving additional milestones under our cardiovascular collaboration with Merck or our 19AJ collaboration with Ortho-McNeil, or developing or partnering APD356 or APD125 or any of our other lead programs, we may not be able to raise new financing or generate significant partnering revenues in the short term. If we do not receive new financing or partnering revenues, we may need to license some or all of our programs on financial terms that are unfavorable to us. Also, without additional financing or partnering revenues, we would need to re-evaluate our strategy of moving multiple drug discovery and development programs forward while at the same time maintaining our research and discovery capabilities. Based on such evaluation, we may need to significantly curtail some of our current and planned programs and expenditures. We do not know what programs, if any, we would need to curtail, but we believe narrowing our pipeline would reduce our opportunity for success.

Our revenues depend upon the actions of our existing and potential collaborations.

Our revenues depend upon the success of our existing collaborations and on our ability to enter into new collaborations. We will receive little additional revenue under our existing collaboration agreements if our own or our collaborators' research, development or, ultimately, marketing efforts are unsuccessful, or if our agreements are terminated early. Typically, our collaborators (and not us) control the development of compounds into drugs after we have met early preclinical scientific milestones, and we are not entitled to the more significant milestone payments under our agreements until our collaborators have advanced compounds into clinical testing, which may not occur for many years, if ever. We cannot guarantee that any of the development, approval or sales milestones in our existing or future collaborations will be satisfied, or that we will receive any payments for the achievement of those milestones.

For the nine months ended September 30, 2004, revenues recognized under our collaboration with Merck represented approximately 96.4% of our total revenues. On December 20, 2004, we entered into a collaboration and license agreement with Ortho-McNeil for which we received an upfront payment of $17.5 million in January 2005. In addition, we received milestone payments totaling $5.0 million upon Ortho-McNeil's selection of two Arena-discovered compounds for preclinical development in January 2005. We expect substantially all of our revenues for 2005 will be derived from our collaborations with Merck and Ortho-McNeil. Our revenues will be materially impacted if:

- our agreement with either Merck or Ortho-McNeil is terminated;
- our collaborators do not devote their time and financial resources to develop compounds under our collaborations;
- our collaborators dispute whether we have achieved a milestone, rights to a particular receptor or compound, or other terms of our agreements;

- our collaborators use alternative technologies to our technologies and compete with us in developing products; or

- our collaborators experience failures in the discovery or development of compounds identified with our technologies or in the clinic or marketplace with other products that cause them to discontinue or slow down our collaboration.

Our ability to enter into new collaborations depends on the outcomes of our preclinical and clinical testing. We do not control these outcomes. In addition, even if our testing is successful, pharmaceutical companies may not partner with us on terms that we believe are acceptable until we have advanced our product candidates into the clinic and, possibly, through a Phase 2 clinical trial, if at all.

Our collaboration agreements with Merck and Ortho-McNeil may be terminated in certain circumstances.

The term of our amended collaborative research program with Merck is three years from October 21, 2004. Merck can terminate this program: (i) for "Technical Grounds," by giving 30 days prior notice, if both Merck and we agree that Technical Grounds have occurred; or (ii) in the event of our change in control (as defined in the agreement), by giving 30 days prior notice. Technical Grounds include circumstances where: (1) our joint research committee (a committee of an equal number of Merck and our representatives) concludes that (a) a significant adverse event affecting all the targets, all program compounds and all active compounds under the program has arisen during the conduct of the program, or (b) continuation of the program is no longer scientifically promising because the role of all the targets proves incorrect, or none of the targets are valid as a suitable target for development of a pharmaceutical product; or (2) Merck's patent department, upon consultation with our patent attorneys, makes a reasonable determination that valid third-party patent rights block the achievement of significant program goals.

In addition, either party can terminate the agreement if the other party breaches its material obligations under the agreement by causes and reasons within its control, has not cured such breach within 90 days of receiving a letter requesting such cure, and there is no dispute as to whether such breach has occurred. In lieu of terminating the agreement, however, Merck can terminate the research program and certain other aspects of the agreement after giving 90 days prior notice if we materially breach our obligations during the course of the program and fail to cure such breach, if such default cannot be cured within such 90-day period, or if we do not commence and diligently continue good faith efforts to cure such default during such period.

Our agreement with Ortho-McNeil will continue until the expiration of Ortho-McNeil's payment obligations for research funding, milestone payments and royalties, unless the agreement is terminated earlier by either party. We and Ortho-McNeil each have the right to terminate the agreement early if the other party commits an uncured material breach of its obligations. Further, Ortho-McNeil may terminate the agreement without cause during the term of the research program, provided that in such event it pays us the balance of its research funding obligation in a lump sum, unless the termination is due to a change of control of Arena (as defined in the agreement), in which case Ortho-McNeil may terminate either the agreement or the research program under the agreement, without the payment of additional research funding to us. At any time after the end of the research program, Ortho-McNeil may terminate the agreement by providing us at least 60 days prior written notice. Upon termination of the agreement, all rights to the compounds developed under the collaboration will revert to us.

We may have conflicts with our collaborators that could delay or prevent the development or commercialization of our product candidates.

We may have conflicts with our collaborators, such as conflicts concerning the interpretation of clinical data, the achievement of milestones, or the ownership of intellectual property developed during the collaboration. If any conflicts arise with Ortho-McNeil, Merck or any other collaborators, such collaborator may act in its self-interest, which may be adverse to our best interests. Any such disagreement could result in one or more of the following, each of which could delay or prevent the development or commercialization of our product candidates, and in turn prevent us from generating revenues:

- unwillingness on the part of a collaborator to pay us research funding, milestone payments or royalties we believe are due to us under a collaboration;
- uncertainty regarding ownership of intellectual property rights arising from our collaborative activities, which could prevent us from entering into additional collaborations;
- unwillingness on the part of a collaborator to keep us informed regarding the progress of its development and commercialization activities or to permit public disclosure of the results of those activities; or
- slowing or cessation of a collaborator's development or commercialization efforts with respect to our product candidates.

Drug discovery and development is intensely competitive in the therapeutic areas on which we focus. If our competitors develop treatments that are approved faster, marketed better or demonstrated to be more effective than our product candidates, our commercial opportunity will be reduced or eliminated.

We focus our efforts on GPCRs. Because GPCRs are an important target class for drug discovery efforts, we believe that many pharmaceutical and biotechnology companies and other organizations have internal drug discovery programs focused on GPCRs. Many of the drugs that we or our collaborators are attempting to discover and develop would compete with existing therapies. In addition, many companies are pursuing the development of new drugs that target the same diseases and conditions that we target. Many of our competitors, particularly large pharmaceutical companies, have substantially greater research and development capabilities and greater financial, scientific and human resources than we do. Companies that complete clinical trials, obtain required regulatory agency approvals and commence commercial sale of their drugs before we do for the same indication may achieve a significant competitive advantage, including certain patent and FDA marketing exclusivity rights. In addition, our competitors may develop drugs with fewer side effects, more desirable characteristics (such as route of administration or frequency of dosing) or greater efficacy than our drugs, if any, for the same indication. Any results from our research and development efforts, or from our joint efforts with our existing or any future collaborators, may not compete successfully with existing or newly discovered products or therapies.

Consolidation and setbacks in our industry and our or our collaborator's inability to obtain acceptable prices for drugs could make partnering more difficult and diminish our revenues.

Consolidation in the pharmaceutical and biotechnology industry, setbacks caused by safety concerns relating to high-profile drugs like Vioxx and Celebrex, competition from generic drugs and litigation may have an adverse effect on us. In addition, pharmaceutical companies may be less willing to enter into a new collaboration if they are integrating a new operation as a result of a merger or acquisition, if their therapeutic areas of focus change following a merger, or if they have reduced research budgets as a result of some financial setback.

Our and our collaborators' ability to commercialize future drugs will depend in part on government regulation and the reimbursement policies of government authorities, private health insurers and other third-party payors. Government and third-party payors are increasingly attempting to contain healthcare costs by limiting coverage and reimbursement levels for new drugs. These efforts may limit our commercial opportunities by reducing the amount a potential collaborator is willing to pay to license our programs or product candidates in the future by reducing the potential revenues that we and our collaborators could generate from drug sales.

We rely on third parties to conduct our clinical trials. If those parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to advance our product candidates in a timely manner or at all.

In the course of our discovery, preclinical testing and clinical trials, we have relied and continue to rely on third parties, including laboratories, investigators, clinical research organizations and manufacturers, to perform critical services for us. For example, we are relying on contract clinical sites to conduct our clinical trials for APD356 and APD125. Clinical research organizations will be responsible for many aspects of the trials, including finding and enrolling subjects for testing and administering the trials. These third parties may not be available when we need them or, if they are available, may not comply with all regulatory and contractual requirements or may not otherwise perform their services in a timely or acceptable manner. These independent third parties may also have relationships with other commercial entities, some of which may compete with us. As a result of our dependence on third parties, we may face delays or failures outside of our direct control. These risks also apply to the development activities of our collaborators, and we do not expect any drugs resulting from our collaborators' research and development efforts to be commercially available for many years, if ever.

Any performance failure on the part of a third-party manufacturer could delay clinical development or regulatory approval of our product candidates. Third-party manufacturers often encounter difficulties involving production yields, quality control and quality assurance, as well as shortages of qualified personnel. The manufacturers are subject to ongoing periodic unannounced inspection by the FDA, the DEA and corresponding state agencies to ensure strict compliance with cGMP and other applicable government regulations and corresponding foreign standards; however, we do not have control over third-party manufacturers' compliance with these regulations and standards. If one of our manufacturers fails to maintain compliance, the production of our product candidates could be interrupted, resulting in delays, additional costs and potentially lost revenues.

We may engage in strategic transactions that could impact our liquidity, increase our expenses and present significant distractions to our management.

From time to time we consider strategic transactions, such as acquisitions of companies, asset purchases and out-licensing or in-licensing compounds developed by us or others. Additional potential transactions we may consider include a variety of different business arrangements, including spin-offs, strategic partnerships, joint ventures, restructurings, divestitures, business combinations and investments. Any such transaction may require us to incur non-recurring or other charges, may increase our near and long-term expenditures and may pose significant integration challenges or disrupt our management or business, which could harm our operations and financial results.

Our efforts will be seriously jeopardized if we are unable to retain and attract key employees.

Our success depends on the continued contributions of our principal management, development and scientific personnel, and the ability to hire and retain key personnel, particularly in the clinical development area as we transition more of our programs from research into drug development. We

face intense competition for such personnel. The loss of services of any principal member of our management or scientific staff, particularly Jack Lief, our President and Chief Executive Officer, and Dominic P. Behan, Ph.D., our Senior Vice President and Chief Scientific Officer, could adversely impact our operations and ability to raise additional capital. To our knowledge, neither Mr. Lief nor Dr. Behan plans to leave, retire or otherwise disassociate with us in the near future.

We may encounter significant delays or problems with our new chemical development facility.

We have a chemical development facility for process research, the scale-up and production of intermediates and other compounds for research and development purposes, and the production of active pharmaceutical ingredients.

We may encounter delays and problems in operating our chemical development facility due to:

- governmental approvals, permits and regulation of the facility;
- accidents during operation of the facility;
- failure of equipment for the facility;
- delays in receiving raw materials from suppliers;
- natural or other disasters; or
- other factors inherent in operating a complex manufacturing facility.

We may not be able to operate our chemical development facility in a cost-effective manner or in a time frame that is consistent with our expected future manufacturing needs.

We use biological materials, hazardous materials, chemicals and radioactive compounds.

Our research and development activities involve the use of potentially harmful biological materials as well as hazardous materials, chemicals and various radioactive compounds that could be hazardous to human health, safety or the environment. These materials and various wastes resulting from their use are stored at our facility pending ultimate use and disposal. We cannot completely eliminate the risk of contamination, which could cause:

- an interruption of our research and development efforts;
- injury to our employees and others;
- environmental damage resulting in costly clean up; and
- liabilities under federal, state and local laws and regulations governing the use, storage, handling and disposal of these materials and specified waste products.

In such an event, we could be held liable for any resulting damages, and any such liability could exceed our resources. Although we believe that we carry insurance in amounts and type that we consider commercially reasonable, we do not have insurance coverage for losses relating to an interruption of our research and development efforts caused by contamination, and we cannot be certain that the coverage or coverage limits of our insurance policies will be adequate.

We may incur substantial liabilities from any product liability claims if our insurance coverage for those claims is inadequate.

We face an inherent risk of product liability exposure related to the testing of our product candidates in human clinical trials, and will face an even greater risk if we sell our product candidates

commercially. An individual may bring a liability claim against us if one of our product candidates causes, or merely appears to have caused, an injury. If we cannot successfully defend ourselves against the product liability claim, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for our product candidates;
- injury to our reputation;
- withdrawal of clinical trial subjects;
- costs of related litigation;
- substantial monetary awards to subjects or other claimants;
- loss of revenues; and
- the inability to commercialize our product candidates.

We have product liability insurance that covers our clinical trials up to an annual aggregate limit of $5.0 million. We intend to expand our insurance coverage to include the sale of commercial products if marketing approval is obtained for any of our product candidates. However, insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost and we may not be able to obtain insurance coverage that will be adequate to satisfy any liability that may arise.

In the event we are unable to satisfy the regulatory requirements relating to internal controls over financial reporting, or if our internal controls are not effective, our business and our stock price could suffer.

Section 404 of the Sarbanes-Oxley Act of 2002 requires companies to do a comprehensive evaluation of their internal controls, and our independent registered public accounting firm and we are required to perform an evaluation of our internal controls over financial reporting. We have a timeline and schedule of activities that we believe are appropriate to comply with the requirements of Section 404; however, these requirements will be effective for the first time for our fiscal year ended December 31, 2004, and neither we nor our independent registered public accounting firm have previously performed an evaluation on our business under these new rules. Our business and stock price may be adversely affected if we or our auditors cannot conclude that our internal controls are effective.

We may incur increased costs as a result of recently enacted changes in laws and regulations relating to corporate governance matters.

Changes in the laws and regulations affecting public companies, including the provisions of the Sarbanes-Oxley Act of 2002 and rules adopted by the Securities and Exchange Commission and by the Nasdaq National Market, may result in increased costs to us. These laws, rules and regulations could make it more difficult or costly for us to obtain certain types of insurance, including director and officer liability insurance, and we may be forced to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. The impact of these events could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers. We cannot predict or estimate the amount or timing of additional costs we may incur to respond to their requirements.

Our operations might be interrupted by the occurrence of a natural disaster or other catastrophic event.

We depend on our collaborators, contractors and vendors and on our laboratories and other facilities for the continued operation of our business. Natural disasters or other catastrophic events, including terrorist attacks, power interruptions, wildfires and other fires, actions of animal rights activists, earthquakes and wars could disrupt our operations or those of our collaborators, contractors and vendors. Even though we believe we carry reasonably adequate business interruption and liability insurance, and our contractors may carry liability insurance, that protect us in certain events, we might suffer losses as a result of business interruptions that exceed the coverage available under our and our contractors' insurance policies or for which we or our contractors do not have coverage. For example, we are not insured against a terrorist attack. Any natural disaster or catastrophic event could have a significant negative impact on our operations and financial results.

Even if any of our product candidates receives regulatory approval, our product candidates will still be subject to extensive post-market regulation.

If we or our collaborators receive regulatory approval for our drug candidates, we will also be subject to ongoing FDA obligations and continued regulatory review, such as continued safety reporting requirements, and we may also be subject to additional FDA post-marketing obligations, all of which may result in significant expense and limit our ability to commercialize our product.

If any of our product candidates receive United States regulatory approval, the FDA may still impose significant restrictions on the indicated uses for which the product may be marketed or impose ongoing requirements for potentially costly post-approval studies. In addition, regulatory agencies subject a product, its manufacturer and the manufacturer's facilities to continual review and periodic inspections. The subsequent discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, may result in restrictions on the marketing of that product, and could include withdrawal of the product from the market. Failure to comply with applicable regulatory requirements may result in:

issuance of warning letters by the FDA;

fines and other civil penalties;

criminal prosecutions;

injunctions, suspensions or revocations of marketing licenses;

suspension of any ongoing clinical trials;

suspension of manufacturing;

delays in commercialization;

refusal by the FDA to approve pending applications or supplements to approved applications filed by us or our collaborators;

refusals to permit products to be imported or exported to or from the United States;

restrictions on operations, including costly new manufacturing requirements; and

product recalls or seizures.

The FDA's policies may change and additional government regulations may be enacted that could prevent or delay regulatory approval of our drug candidates or further restrict or regulate post-approval activities. We cannot predict the likelihood, nature or extent of adverse government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are

not able to maintain regulatory compliance, we might not be permitted to market our drugs and our business could suffer.

In order to market any products outside of the United States, we and our collaborators must establish and comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy. Approval procedures vary among countries and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from that required to obtain FDA approval. The regulatory approval process in other countries may include all of the risks associated with FDA approval as well as additional presently unanticipated risks. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others. Failure to obtain regulatory approval in other countries or any delay or setback in obtaining such approval could have the same adverse effects associated with regulatory approval in the United States, including the risk that our product candidates may not be approved for all indications requested and that such approval may be subject to limitations on the indicated uses for which the product may be marketed.

Risks Relating to Our Intellectual Property

Our success is dependent on intellectual property rights held by us and third parties and our interest in these rights is complex and uncertain.

Our success will depend on our own and on our collaborators' abilities to obtain, secure and defend patents. In particular, the patents directed to compounds discovered using our technologies are important to commercializing drugs. We have numerous U.S. and foreign patent applications pending for our technologies, including patent applications on drug lead discovery techniques using CART, genetically altered GPCRs, GPCRs that we have discovered, new uses for previously discovered GPCRs, and compounds discovered using CART and Melanophore and other technologies. The procedures for obtaining a patent in the U.S. and in most foreign countries are complex. These procedures require an analysis of the scientific technology related to the invention and many legal issues. Consequently, the analysis of our patent applications will be complex and time consuming. Our patent position is very uncertain and we do not know when, or if, we will obtain additional patents for our technologies.

As of December 31, 2004, we owned, in part or in whole, or had exclusively licensed the following patents: 14 in the United States, 11 in European countries, six in Australia, five in New Zealand, one in Japan, one in Singapore, and one in Israel. In addition, as of December 31, 2004, we had approximately 243 patent applications before the United States Patent and Trademark Office, foreign patent offices and international patent authorities. There is no assurance that any of these patent applications will issue, or that any of the patents will be enforceable or will cover a drug product or other commercially significant product or method. Our most advanced compounds, including APD356 and APD125, are the subject of patent applications and not patents. In 2000, the United States Patent and Trademark Office began issuing broad patent claims that could allow patent holders to control the use of all drug products that modulate a particular drug target or GPCR, regardless of whether the infringing drug product bears any structural resemblance to a chemical compound known to the patent holder at the time of patent filing. The question of whether these new patent claims are valid is highly controversial and the subject of intense litigation. Whether we or our competitors are able to obtain and enforce such patent claims, particularly as they apply to the GPCRs that are the subject of our drug development activities, may have a significant impact on our potential revenues from any drugs that we are able to develop.

We also rely on trade secrets to protect our technologies. However, trade secrets are difficult to protect. We require our employees to contractually agree not to improperly use our trade secrets or disclose them to others, but we may be unable to determine if our employees have conformed or will

conform with their legal obligations under these agreements. We also require collaborators, service providers and consultants to enter into confidentiality agreements, but we may not be able to adequately protect our trade secrets or other proprietary information in the event of any unauthorized use or disclosure or the lawful development by others of this information. Many of our employees and consultants were, and many of them may currently be, parties to confidentiality agreements with other pharmaceutical and biotechnology companies, and the use of our technologies could violate these agreements. In addition, third parties may independently discover our trade secrets or proprietary information.

Some of our academic institution licensors, research collaborators and scientific advisors have rights to publish data and information to which we have rights. We generally seek to prevent our partners from disclosing scientific discoveries before we have the opportunity to file patent applications on such discoveries. In some of our collaborations we do not have control over our partners' ability to disclose their own discoveries under the collaboration and in some of our academic collaborations we are limited to relatively short periods to review a proposed publication and file a patent application. If we cannot maintain the confidentiality of our technologies and other confidential information in connection with our collaborations, our ability to receive patent protection or protect our proprietary information will be impaired.

A dispute regarding the infringement or misappropriation of our proprietary rights or the proprietary rights of others could be costly and result in delays in our research and development activities.

Our commercial success also depends upon our ability to develop, manufacture, market and sell our product candidates and conduct our research and development activities without infringing or misappropriating the proprietary rights of third parties. There are many patents and patent applications filed, and that may be filed, by others relating to drug discovery and development programs that could be determined to be similar, identical or superior to ours or our licensors or collaborators. We may be exposed to future litigation by third parties based on claims that our product candidates, technologies or activities infringe the intellectual property rights of others. Numerous U.S. and foreign issued patents and pending patent applications owned by others exist in the area of GPCRs, some of which purport to allow the patent holder to control the use of all drug products that modulate a particular drug target or GPCR, regardless of whether the infringing drug product bears any structural resemblance to a chemical compound known to the patent holder at the time of patent filing. Numerous U.S. and foreign issued patents and pending patent applications owned by others also exist in the therapeutic areas in which we are developing products. These could materially affect our ability to develop our drug candidates or sell our products, and our activities, or those of our licensors or collaborators, could be determined to infringe these patents. Because patent applications can take many years to issue, there may be currently pending applications, unknown to us, which may later result in issued patents that our product candidates or technologies may infringe. There also may be existing patents, of which we are not aware, that our product candidates or technologies may inadvertently infringe. Further, there may be issued patents and pending patent applications in fields relevant to our business, of which we are or may become aware, that we believe we do not infringe or that we believe are invalid or relate to immaterial portions of our overall drug discovery and development efforts. We cannot assure you that third parties holding any of these patents or patent applications will not assert infringement claims against us for damages or seeking to enjoin our activities. We also cannot assure you that, in the event of litigation, we will be able to successfully assert any belief we may have as to non-infringement, invalidity or immateriality, or that any infringement claims will be resolved in our favor.

In addition, third parties may infringe or misappropriate our proprietary rights, and we may have to institute costly legal action to protect our intellectual property rights. We may not be able to afford the costs of enforcing or defending our intellectual property rights against third parties.

Other organizations, companies and individuals are seeking proprietary positions on genomics information that overlap with the government sponsored project to sequence the human genome. Our activities, or those of our licensors or collaborators, could be affected by conflicting positions that may exist between any overlapping genomics information made available publicly as a result of the government sponsored project and genomics information that other organizations, companies or individuals consider to be proprietary.

There could be significant litigation and other administrative proceedings in our industry that affect us regarding patent and other intellectual property rights. Any legal action or administrative action against us, or our collaborators, claiming damages or seeking to enjoin commercial activities relating to our drug discovery and development programs could:

- require us, or our collaborators, to obtain a license to continue to use, manufacture or market the affected products, methods or processes, which may not be available on commercially reasonable terms, if at all;
- prevent us from importing, making, using, selling or offering to sell the subject matter claimed in patents held by others and subject us to potential liability for damages;
- consume a substantial portion of our managerial, scientific and financial resources; or
- be costly, regardless of the outcome.

Furthermore, because of the substantial amount of pre-trial document and witness discovery required in connection with intellectual property litigation, there is risk that some of our confidential information could be compromised by disclosure during this type of litigation. In addition, during the course of this kind of litigation, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the trading price of our common stock.

We have been contacted from time to time by third parties regarding their intellectual property rights, sometimes asserting that we may need a license to use their technologies. If we fail to obtain any required licenses or make any necessary changes to our technologies, we may be unable to develop or commercialize some or all of our product candidates.

We cannot protect our intellectual property rights throughout the world.

Filing patents on all of our drug discovery technologies throughout the world would be prohibitively expensive. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own drug products. These products may compete with our products and may not be covered by any of our patent claims or other intellectual property rights.

Patent law outside the United States is also uncertain and many countries are currently reviewing and revising patent laws, particularly with respect to biotechnology and pharmaceutical inventions. The laws of some countries do not protect our intellectual property rights to the same extent as U.S. laws. It may be necessary or useful for us to participate in proceedings to determine the validity of our, or our competitors', foreign patents, which could result in substantial cost and divert our efforts and attention from other aspects of our business.

Risks Relating to Our Securities

Our stock price will likely be volatile, and your investment in our stock could decline in value.

Our stock price has fluctuated historically. From January 1, 2003 to December 31, 2004, the market price of our stock was as low as $3.48 per share and as high as $8.57 per share.

Very few biotechnology products being tested will ultimately receive FDA approval, and a biotechnology company may experience a significant drop in its stock price based on an adverse clinical

trial result or regulatory action. Our stock price may fluctuate significantly, depending on a variety of factors, including:

- our success or failure in clinical trials, including, in the near term, the results from our clinical trials for either APD356 or APD125;
- the timing of the discovery of drug leads and the development of our product candidates;
- entering into a new collaboration or modifying or terminating an existing collaboration;
- the timing and receipt by us of milestone and royalty payments or failing to achieve and receive the same, if any;
- changes in the research and development budgets of our existing or potential collaborators;
- others introducing new drug discovery techniques or new drugs that target the same diseases and conditions that we or our collaborators target;
- regulatory actions; and
- expenses related to, and the results of, litigation and other proceedings relating to intellectual property rights or other matters.

We are not able to control all of these factors. Period-to-period comparisons of our financial results are not necessarily indicative of our future performance. In addition, if our revenues or results of operations in a particular period do not meet stockholders' or analysts' expectations, our stock price may decline and such decline could be significant.

Holders of our Series B Convertible Preferred Stock may require us to redeem their Series B Convertible Preferred Stock under certain circumstances, including if the effective net price to us per share from this offering is less than $6.72 per share.

On December 24, 2003, we completed the private placement to two institutional investors of (i) an aggregate of 3,500 shares of our Series B-1 Convertible Preferred Stock, (ii) seven-year warrants to purchase up to an aggregate of 1,486,200 shares of our common stock at an exercise price of $10.00 per share and (iii) unit warrants to purchase for a period of approximately 16 months from December 24, 2003 up to $11.5 million of our Series B-2 Convertible Preferred Stock and additional seven-year warrants to purchase up to 450,000 shares of our common stock at an exercise price of $10.00 per share. The exercise price of our outstanding seven-year warrants are subject to adjustment in certain circumstances, including if the effective net price to us per share from this offering is less than $6.72 and the gross proceeds from this offering are less than $35.0 million. Any warrants issued upon exercise of our unit warrants will have similar anti-dilution protections for future issuances.

The holders of our Series B Convertible Preferred Stock may require us to redeem their shares of the applicable series of Series B Convertible Preferred Stock after December 24, 2005, at a price equal to the amount of the original holder's original investment, plus all accrued but unpaid dividends thereon to the date of payment and any applicable penalties, if, following the 21st month anniversary of the original issue date of the applicable series of Series B Convertible Preferred Stock (the 21st month anniversary of the original issue date of the Series B-1 Convertible Preferred Stock will be September 24, 2005), the closing price of our common stock for any 30 consecutive trading days is below the applicable conversion price for the Series B Convertible Preferred Stock (the conversion price of the Series B-1 Convertible Preferred Stock is $7.50).

Also, the holders of the Series B Convertible Preferred Stock may require us to redeem their shares if we issue common stock or common stock equivalents (excluding, among other things, certain common stock and common stock equivalents issued or issuable (a) to our officers, directors, employees or consultants, (b) in connection with certain strategic partnerships or joint ventures, and (c) in connection with certain mergers and acquisitions) for an effective net price to us per share of less than $6.72, in

the case of the Series B-1 Convertible Preferred Stock, or a price to be determined based on a formula, in the case of Series B-2 Convertible Preferred Stock. Accordingly, if the effective net price to us per share from this offering is less than $6.72, the holders of our Series B Convertible Preferred Stock may require us to redeem all or some of their outstanding preferred shares. "Effective net price" is not defined in the Certificate of Designations governing our Series B Convertible Preferred Stock. The holders of our Series B Convertible Preferred Stock may assert that effective net price should be calculated as the amount we receive after paying the underwriting discount and other expenses of this offering. We estimate that our expenses relating to this offering will be approximately $370,000. Accordingly, if the price at which we sell shares to the public in this offering is less than approximately $7.22 per share, this redemption right may be triggered.

In addition to the foregoing redemption rights, at any time following the occurrence of a "Triggering Event," a holder of the Series B Convertible Preferred Stock may require us to repurchase all or any portion of the Series B Convertible Preferred Stock then held by such holder at a price per share equal to the greater of 115.0% of the stated value or the market value (as calculated under the Certificate of Designations for the Series B-1 Convertible Preferred Stock and the Series B-2 Convertible Preferred Stock) of such shares of Series B Convertible Preferred Stock plus all accrued but unpaid dividends thereon to the date of payment. "Triggering Events" include any of the following events: (a) immediately prior to a bankruptcy event; (b) we fail for any reason to timely deliver a certificate evidencing any securities to a purchaser or the exercise or conversion rights of the holders are otherwise suspended for other than a permissible reason; (c) any Event (as defined in the Registration Rights Agreement with the Series B Convertible Preferred Stock holders) occurs and remains uncured for 60 days; (d) we fail to make any cash payment required under the Series B Convertible Preferred Stock transaction documents and such failure is not timely cured; (e) the issuance of a going concern opinion by our independent registered public accounting firm that is not timely cured; (f) we breach a section of the Series B Convertible Preferred Stock purchase agreement relating to indebtedness and subordination; or (g) we default in the timely performance of any other obligation under the Series B Convertible Preferred Stock transaction documents and such default is not timely cured. We will also be required to redeem any shares of the Series B Convertible Preferred Stock that remain outstanding on the fifth anniversary of their issuance at a price equal to the amount of the original holder's original investment, plus all accrued but unpaid dividends thereon to the date of such payment. "Triggering Event" is specifically defined in the Certificate of Designations for the Series B-1 Convertible Preferred Stock and the Series B-2 Convertible Preferrred Stock.

The aggregate redemption price of our Series B Convertible Preferred Stock at December 31, 2004 was approximately $36.5 million, and accrues interest at 4.0% annually. If we are required to redeem all or some of the currently outstanding shares of our Series B Convertible Preferred Stock, we may be able to pay a portion of the redemption price using shares of our common stock if certain other enumerated conditions are satisfied, including:

- we have sufficient number of shares of common stock available for issuance;
- the shares of common stock to be issued are registered under an effective registration statement or are otherwise available for sale under Rule 144(k) under the Securities Act;
- our common stock is listed on The Nasdaq National Market or other eligible market;
- the shares to be issued can be issued without violating the rules of The Nasdaq National Market or any applicable trading market or a provision of our certificate of designations; and
- no bankruptcy event has occurred.

If we are permitted to satisfy a portion of a redemption by using shares of our common stock, and if we elect to do so, the number of shares to be issued to holders of Series B Convertible Preferred Stock will be determined by dividing their cash redemption price by the lesser of the conversion price or

95.0% of the average of the volume weighted average price of our common stock for either 10 or 15 trading days.

There can be no assurance that we will not have to redeem the Series B Convertible Preferred Stock in connection with this offering or otherwise, or, if we do have to redeem the stock, that we will be able to pay a portion of the redemption price using shares of our common stock. If we use common stock to redeem a portion of the Series B Convertible Preferred Stock, your ownership interest may be significantly diluted. If we are required or elect to redeem shares of the Series B Convertible Preferred Stock using cash, we may not have sufficient cash to redeem these shares or to continue our planned research and discovery activities. In such event we may try to raise additional capital by issuing new stock, but there can be no assurance that capital will be available on acceptable terms or at all.

There are a substantial number of shares of our common stock eligible for future sale in the public market, and the sale of these shares could cause the market price of our common stock to fall.

There were 26,566,419 shares of our common stock outstanding as of December 31, 2004. The outstanding shares of our Series B-1 Convertible Preferred Stock are convertible into up to 4,861,899 shares of common stock at $7.50 per share of common stock. Holders of the Series B-1 Convertible Preferred Stock are entitled to receive a 4.0% annual dividend that is payable by issuing common stock or by increasing the amount of common stock that is issuable upon conversion of the Series B-1 Convertible Preferred Stock. In addition, holders of our Series B-1 Convertible Preferred Stock own warrants to acquire common stock and unit warrants to acquire Series B-2 Convertible Preferred Stock and additional warrants to acquire common stock, which, if exercised and converted, would obligate us to issue up to 3,579,057 additional shares of common stock at a weighted average exercise price of $8.62 per share. In addition, as of December 31, 2004, there were 2,780,399 common stock options issued and outstanding under our equity compensation plans at a weighted average exercise price of $8.66, 1,547,383 additional shares of common stock issuable under our equity compensation plans, 690,268 shares of common stock reserved for issuance under our 2001 Employee Stock Purchase Plan and 151,669 shares issuable under our Deferred Compensation Plan. A substantial number of the shares described above, when issued upon exercise, will be available for immediate resale in the public market. The market price of our common stock could fall as a result of such resales due to the increased number of shares available for sale in the market.

Any future equity or debt issuances by us may have dilutive or adverse effects on our existing stockholders.

We have financed our operations, and we expect to continue to finance our operations, primarily by issuing and selling our common stock or securities convertible into or exercisable for shares of our common stock. In light of our need for additional financing, we may issue additional shares of common stock or additional convertible securities that could dilute your ownership in our company and may include terms that give new investors rights that are superior to yours. Moreover, any issuances by us of equity securities may be at or below the prevailing market price of our common stock and in any event may have a dilutive impact on your ownership interest, which could cause the market price of our common stock to decline. The terms of our Series B Convertible Preferred Stock limit our ability to engage in certain equity issuances.

We may also raise additional funds through the incurrence of debt, and the holders of any debt we may issue would have rights superior to your rights in the event we are not successful and are forced to seek the protection of the bankruptcy laws. The terms of our Series B Convertible Preferred Stock limits our ability to incur debt.

Our largest stockholders may take actions that are contrary to your interests, including selling their stock.

A small number of our stockholders hold a significant amount of our outstanding stock. These stockholders may support competing transactions and have interests that are different from yours. In addition, the average number of shares of our stock that trade each day is generally low. As a result, sales of a large number of shares of our stock by these large stockholders or other stockholders within a short period of time could adversely affect our stock price.

Holders of our Series B Convertible Preferred Stock have the right to purchase up to 50% of the shares we offer in certain transactions. If the aggregate gross proceeds to us from this offering are less than $35.0 million, we will need to obtain a waiver of this right.

In this offering, we intend to raise in excess of $35.0 million in aggregate gross proceeds. In the event the aggregate gross proceeds to us from this offering are less than $35.0 million, the holders of our Series B Convertible Preferred Stock will have the right to purchase up to 50% of the shares offered by us in this offering, in which event we intend to obtain a waiver of this right.

Provisions of our Series B Convertible Preferred Stock may prevent or make it more difficult for us to raise funds or take certain other actions.

Provisions of our Series B Convertible Preferred Stock require us to obtain approval of the preferred stockholders, or otherwise trigger rights of first refusal or payment provisions, to (i) offer or sell new securities, other than in specified underwritten offerings or strategic partnerships or joint venture and certain other exceptions, (ii) sell or issue common stock or securities issuable into common stock below certain prices, (iii) incur debt or allow liens on our property, other than certain permitted debt and liens, (iv) amend our certificate of incorporation so as to affect adversely any rights of the preferred stockholders, (v) authorize or create a new class of stock that will be senior or equal to the Series B Convertible Preferred Stock in terms of dividends, redemption or distribution of assets, (vi) use more than $25.0 million in cash for acquisitions or (vii) take certain other actions. These provisions may make it more difficult for us to take certain corporate actions and could delay, discourage or prevent future financings.

Our rights agreement and certain provisions in our charter documents and Delaware law could delay or prevent a change in management or a takeover attempt that you may consider to be in your best interest.

We have adopted certain anti-takeover provisions, including a stockholders' rights plan, dated as of October 30, 2002, between us and Computershare Trust Company, Inc., as Rights Agent, as amended on December 24, 2003. The rights plan will cause substantial dilution to any person who attempts to acquire us in a manner or on terms not approved by our board of directors.

The rights agreement and Certificate of Designations for the Series B Convertible Preferred Stock, as well as other provisions in our certificate of incorporation and by-laws and under Delaware law, could delay or prevent the removal of directors and other management and could make more difficult a merger, tender offer or proxy contest involving us that you may consider to be in your best interest. For example, these provisions:

- allow our board of directors to issue preferred stock without stockholder approval;
- limit who can call a special meeting of stockholders;
- eliminate stockholder action by written consent; and
- establish advance notice requirements for nomination for election to the board of directors or for proposing matters to be acted upon at stockholders meetings.

We may allocate the net proceeds from this offering in ways that you and other stockholders may not approve.

We intend to use the net proceeds from this offering:

- for the clinical and preclinical development of our internally discovered product candidates;
- for discovery research for new product candidates; and
- for general corporate purposes, including working capital.

Our management will, however, have broad discretion in the application of the net proceeds from this offering and could spend the proceeds in ways that do not necessarily improve our operating results or enhance the value of our common stock. The proceeds may be used to pay the redemption price for some or all of the outstanding Series B Convertible Preferred Stock, if the holders are entitled to, and elect to, have their

preferred stock redeemed.

Forward-Looking Statements

This prospectus supplement and the accompanying prospectus, including the documents that we incorporate by reference herein and therein, contain "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. These forward-looking statements can generally be identified as such because the context of the statement will include words such as "may," "will," "intends," "plans," "believes," "anticipates," "expects," "estimates," "predicts," "potential," "continue," or "opportunity," the negative of these words or words of similar import. Similarly, statements that describe our future plans, strategies, intentions, expectations, objectives, goals or prospects are also forward-looking statements. Discussions containing these forward-looking statements may be found, among other places, in the "Business" section of this prospectus supplement and the "Business" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" sections incorporated by reference from our most recent Annual Report on Form 10-K and our Quarterly Reports on Form 10-Q for the quarters ended subsequent to our filing of such Annual Report on Form 10-K with the SEC, as well as any amendments thereto reflected in subsequent filings with the SEC. These forward-looking statements are based largely on our expectations and projections about future events and future trends affecting our business, and are subject to risks and uncertainties that could cause actual results to differ materially from those anticipated in the forward-looking statements. The risks and uncertainties include, among others, those noted in "Risk Factors" above.

In addition, past financial and/or operating performance is not necessarily a reliable indicator of future performance and you should not use our historical performance to anticipate results or future period trends. We can give no assurances that any of the events anticipated by the forward-looking statements will occur or, if any of them do, what impact they will have on our results of operations and financial condition. Except as required by law, we undertake no obligation to publicly revise our forward-looking statements to reflect events or circumstances that arise after the filing of this prospectus supplement or the filing of the accompanying prospectus or documents incorporated by reference herein and therein that include forward-looking statements.

Use of Proceeds

We estimate that the net proceeds from the sale of the shares of common stock we are offering will be approximately $36.0 million. If the underwriters exercise the over-allotment option in full, the net proceeds of the shares we sell will be approximately $41.5 million. "Net proceeds" is what we expect to receive after paying the underwriting discount and other expenses of this offering. For the purpose of estimating net proceeds, we are assuming that the public offering price will be $6.45 per share.

We intend to use the net proceeds from this offering for the clinical and preclinical development of our internally discovered product candidates, for discovery research for new product candidates, and for general corporate purposes, including working capital.

After December 24, 2005, if the closing price of our common stock is below $7.50 for any 30 consecutive trading days after September 24, 2005, the holders of our Series B-1 Convertible Preferred Stock may require us to redeem all or some of their outstanding preferred shares at a price of $7.50 per share, plus all accrued but unpaid dividends thereon. In the event the effective net price to us per share from this offering is less than $6.72, the holders of our Series B-1 Convertible Preferred Stock also will be entitled to require us to redeem their outstanding preferred shares following the date on which the shares in this offering are sold. Accordingly, if the price at which we sell shares to the public in this offering is less than approximately $7.22 per share, this redemption right may be triggered. Should the holders of our Series B Convertible Preferred Stock qualify for and request redemption, we may be able to pay a portion of the redemption price using shares of our common stock if certain criteria are met. We intend to use our common stock to satisfy a portion of this redemption obligation to the extent permitted. However, such criteria may not be met and, accordingly, all or substantially all of the proceeds from this offering may be used to redeem our outstanding Series B-1 Convertible Preferred Stock if the effective net price to us per share from this offering is less than $6.72 and the holders exercise their accelerated redemption rights. The aggregate redemption price at December 31, 2004 was approximately $36.5 million, and accrues interest at 4.0% annually.

The timing and amount of our actual expenditures will be based on many factors, including the timing and success of our clinical trials, whether we partner any of our internal programs, whether we choose to curtail some of our research activities and whether the holders of our Series B Convertible Preferred Stock have the right and elect to have their preferred stock redeemed. As a result, we will retain broad discretion in determining how we will allocate the net proceeds from this offering.

Until we use the net proceeds of this offering, we intend to invest the funds in short-term, investment grade, interest bearing securities.

Dividend Policy

We have never paid any cash dividends on our capital stock. We anticipate that we will retain earnings, if any, to support operations and to finance the growth and development of our business. Therefore, we do not expect to pay cash dividends in the foreseeable future. In addition, we are prohibited from paying cash dividends on any of our capital stock other than our Series B Convertible Preferred Stock without the approval of the holders of the Series B Convertible Preferred Stock.

Capitalization

The following table shows:

Our capitalization on September 30, 2004.

Our capitalization on September 30, 2004, assuming the completion of this offering at an assumed public offering price of $6.45 per share, less the underwriting discount and estimated offering expenses payable by us.

	September 30, 2004	
	Actual	As Adjusted
	(Unaudited)	
Financing obligation, including deferred interest	$ 13,194,494	$ 13,194,494
Redeemable Convertible Preferred Stock	28,263,485	28,263,485
Common stock, $.0001 par value; 67,500,000 shares authorized, 25,638,656 issued and outstanding, actual; 67,500,000 shares authorized, 31,638,656 shares issued and outstanding, as adjusted	2,880	3,480
Additional paid-in capital	315,843,330	351,850,730
Treasury stock	(23,070,000)	(23,070,000)
Accumulated other comprehensive loss	(82,908)	(82,908)
Deferred compensation	(1,083,662)	(1,083,662)
Accumulated deficit	(150,613,338)	(150,613,338)
Total stockholders' equity	140,996,302	177,004,302
Total capitalization	$ 182,454,281	$ 218,462,281

The number of shares of common stock as reflected in the actual and as adjusted columns above is based on the actual number of shares outstanding as of September 30, 2004, and does not include, as of that date:

4,813,129 shares of common stock issuable upon conversion of our Series B-1 Convertible Preferred Stock at a conversion price of $7.50 per share;

1,486,200 shares of common stock issuable upon the exercise of outstanding warrants at an exercise price of $10.00 per share;

2,788,749 shares of common stock issuable upon exercise of outstanding options at a weighted average exercise price of $8.69 per share;

1,555,033 shares of common stock available for future issuance under our equity compensation plans;

718,699 shares of common stock available for future issuance under our 2001 Employee Stock Purchase Plan;

97,501 shares of common stock available for future issuance under our Deferred Compensation Plan;

937,500 shares of common stock issued to Merck in October 2004 at $8.00 per share; and

up to 2,092,857 shares of common stock issuable from unit warrants held by our Series B-1 Convertible Preferred stockholders at a weighted average exercise price of $7.65 per share.

The as adjusted column data does not give effect to any redemption of our outstanding Series B-1 Convertible Preferred Stock. In the event the effective net price to us per share from this offering is less than $6.72, the holders of our Series B Convertible Preferred Stock may require us to redeem all or some of their outstanding preferred shares. The aggregate redemption price at December 31, 2004, was approximately $36.5 million, and accrues interest at 4.0% annually. We may be able to satisfy a portion of this amount with shares of our common stock if certain criteria are met.

Dilution

Our unaudited net tangible book value on September 30, 2004 was approximately $131.1 million, or $5.11 per share of common stock. "Net tangible book value" is total assets minus the sum of liabilities and intangible assets. "Net tangible book value per share" is net tangible book value divided by the total number of common stock shares outstanding.

After giving effect of the sale of 6,000,000 shares of common stock offered by us in this offering, our pro forma net tangible book value on September 30, 2004 would have been $167.1 million, or $5.28 per share of common stock. The adjustments made to determine pro forma net tangible book value per share are the following:

- an increase in total assets to reflect the net proceeds of the offering as described under "Use of Proceeds" (assuming that the public offering price will be $6.45 per share); and
- the addition of the number of shares offered by this prospectus supplement to the number of shares outstanding.

The following table illustrates the pro forma increase in net tangible book value of $0.17 per share and the dilution (the difference between the offering price per share and net tangible book value per share) to new investors:

Assumed public offering price per share	$	6.45
Net tangible book value per share as of September 30, 2004	$	5.11
Increase in net tangible book value per share attributable to offering	$	0.17
Pro forma net tangible book value per share as of September 30, 2004, after giving effect to the offering	$	5.28
Dilution per share to new investors in the offering	$	1.17

The following table shows the difference between existing stockholders and new investors with respect to the number of shares purchased from us, the total consideration paid and the average price paid per share. The table assumes that the public offering price will be $6.45 per share.

	Shares Purchased		Total Consideration		
	Number	Percent	Amount	Percent	Average Price Per Share
Existing stockholders	25,638,656	81.0%	$ 289,557,670	88.2%	$ 11.29
New investors	6,000,000	19.0%	$ 38,700,000	11.8%	$ 6.45
Total	31,638,656	100.0%	$ 328,257,670	100.0%	$ 10.38

The above discussion and tables are based on 25,638,656 common shares outstanding at September 30, 2004, and excludes:

- 4,813,129 shares of common stock issuable upon conversion of our Series B-1 Convertible Preferred Stock at a conversion price of $7.50 per share;
- 1,486,200 shares of common stock issuable upon the exercise of outstanding warrants at an exercise price of $10.00 per share;
- 2,788,749 shares of common stock issuable upon exercise of outstanding options at a weighted average exercise price of $8.69 per share;
- 1,555,033 shares of common stock available for future issuance under our equity compensation plans;
- 718,699 shares of common stock available for future issuance under our 2001 Employee Stock Purchase Plan;

97,501 shares of common stock available for future issuance under our Deferred Compensation Plan;

937,500 shares of common stock issued to Merck in October 2004 at $8.00 per share; and

up to 2,092,857 shares of common stock issuable from unit warrants held by our Series B-1 Convertible Preferred stockholders at a weighted average exercise price of $7.65 per share.

Business

We are a biopharmaceutical company with a pipeline of internally discovered small molecule product candidates identified through our focus on G protein-coupled receptor, or GPCR, drug discovery and technologies. GPCRs are a class of receptors that mediate the majority of cell-to-cell communication within humans. A high percentage of today's prescription drugs target one or more GPCRs. Our goal is to discover, develop, and commercialize novel, orally available drugs that address major unmet medical needs by targeting known and novel GPCRs. Our integrated drug discovery platform allows us to determine GPCR function, tissue and cell distribution, and relation to disease. We focus on four therapeutic areas: metabolic, central nervous system (or CNS), cardiovascular and inflammatory diseases. We believe our technologies and integrated discovery and development capabilities will allow us to continue to build our pipeline of unique and selective product candidates.

We believe that approved GPCR-based drugs target about 60, or 30%, of the approximately 190 known GPCRs, predominantly in the biogenic amine family, a sub-family of class I GPCRs. The GPCRs are categorized as "known" because their naturally occurring, or native, ligands have been identified. Scientists have used molecular cloning in combination with the sequencing of the human genome to identify both additional receptor subtypes of known GPCRs as well as novel GPCRs. These novel GPCRs are categorized as "orphan" GPCRs because their native ligands have not been identified. We believe orphan GPCRs offer promise for the development of novel GPCR-based therapeutics, and, therefore, are a major focus of our discovery research.

We intend to commercialize our product candidates independently and with partners. We have retained commercial rights for our most advanced development programs, except for our diabetes partnership with Ortho-McNeil Pharmaceutical, Inc., a Johnson & Johnson company, and our cardiovascular collaboration with Merck & Co., Inc.

In 2004, we made significant progress, including:

- announcing results for single and multiple dose Phase 1 clinical trials of our product candidate for obesity, APD356;
- initiating a Phase 2 study of APD356;
- initiating a Phase 1 clinical trial of our product candidate for insomnia, APD125;
- announcing a two-year extension and expansion of our cardiovascular collaboration with Merck and receiving three milestone payments and an equity investment totaling $15.5 million; and
- establishing a world-wide partnership with Ortho-McNeil for our diabetes program, 19AJ, under which we received an upfront payment of $17.5 million and two milestone payments totaling $5.0 million in January 2005.

Our Strategy

The key elements of our scientific and business strategy are to:

- *Continue to advance our lead programs.* We intend to advance our current product candidates, either alone or in conjunction with pharmaceutical and biotechnology companies, through clinical development and, if successful, commercialization.
- *Discover and develop additional small molecule product candidates targeting GPCRs.* We intend to continue to develop orally available, small molecule compounds for GPCRs identified or validated by our research efforts.

Focus on attractive market opportunities. Obesity, insomnia, diabetes and thrombosis each represent multi-billion dollar market opportunities. We intend to continue to focus on these and other programs with attractive commercial potential.

Retain significant commercial rights and/or economic value for our product candidates. We intend to maximize the value of our product candidates through either internal development or commercial partnerships in which we retain significant economic value and/or targeted copromotion rights.

Continue to build our development capabilities. To capitalize on our discoveries, we plan to continue to expand our clinical development capabilities as our product candidates enter into, and move through, clinical trials.

Maintain strong research discovery capabilities. Our proprietary technologies, including CART and Melanophore, and our drug discovery infrastructure, have allowed us to identify a number of GPCR targets and novel compounds. We believe these and other discoveries will continue to fuel our pipeline.

Our Research & Development Programs

Our product candidates range from being in a Phase 2 clinical trial to the early stages of drug research. The following table summarizes our most advanced internal and partnered research and development programs:

APD356

Our most advanced product candidate, which we call APD356, is a novel and selective 5-HT_{2C} receptor agonist for obesity. Obesity and a related condition known as metabolic syndrome affect tens of millions of adults and children in the United States. and pose a serious long-term threat to their health and welfare. Medical treatment options for obesity and metabolic syndrome are currently very limited.

Our preclinical studies show APD356 stimulates the 5-HT_{2C} serotonin receptor more selectively than fenfluramine and dexfenfluramine. Based on these studies, we believe that APD356 is less likely to cause the cardiovascular side effects associated with fenfluramine and dexfenfluramine. Until 1997, Wyeth marketed fenfluramine and dexfenfluramine, serotonin-releasing agents and non-selective serotonin receptor agonists, which were often used in combination with phentermine for the treatment of obesity. The combination of fenfluramine or dexfenfluramine with phentermine is commonly referred to as fen-phen. Despite their efficacy as appetite suppressants, both fenfluramine and dexfenfluramine were withdrawn from the market in 1997 after reported incidences of heart valve disease and pulmonary hypertension associated with their usage.

Mechanism and Preclinical Data. APD356 selectively stimulates the 5-HT_{2C} serotonin receptor, a GPCR located in the hypothalamus. We have conducted preclinical studies examining the activity and 5-HT receptor subtype specificity of APD356. In these studies, APD356 demonstrated a high affinity and specificity for the 5-HT_{2C} receptor, with approximately 15-fold and 100-fold selectivity over the 5-HT_{2A} and 5-HT_{2B} receptors, respectively, and no pharmacologic activity at other serotonin receptors. In addition, in these studies, APD356 did not release serotonin. Fenfluramine releases serotonin, and its primary metabolite, norfenfluramine, also has activity at the 5-HT_{2B} receptor. Because of its selectivity, we believe that APD356 is less likely to cause the cardiovascular side effects associated with fenfluramine and dexfenfluramine.

In a free-fed rat model, APD356 reduced total food intake in a dose-dependent manner. APD356 dosed once, orally at 6 mg/kg, 12 mg/kg and 24 mg/kg reduced food intake approximately 12% to 25% over 22 hours compared to a saline control. In the same model, dexfenfluramine dosed once, orally at 0.3 mg/kg, 1 mg/kg, and 3 mg/kg reduced food intake approximately 10% to 30% over the same time period.

In an obese rat model, APD356 caused dose-dependent reductions in body weight after 14 days of oral administration. APD356 dosed at 4.5 mg/kg, 9 mg/kg, 18 mg/kg twice-daily, and 36 mg/kg once-daily reduced bodyweight by approximately 3%, 6%, 11%, and 12%, respectively. We believe this compares favorably to Meridia, a drug marketed by Abbott Laboratories, which reduced bodyweight by approximately 12% when dosed at 6 mg/kg once-daily in the same model. The reductions in bodyweight caused by APD356 appear to be due to lowered body fat, as lean body mass in the obese rats was unaffected at all APD356 doses.

Clinical Development. In July 2004, we announced results from a three-part Phase 1a study of APD356. In part A, safety was assessed in 45 subjects who received single doses of APD356. We began dose escalation at 10 mg and ended at 40 mg due to CNS-related side effects, including nausea, dizziness, headache and disorientation. Doses of 10 mg and 20 mg were well tolerated. In part B, we evaluated the effect of food consumption on APD356 absorption and pharmacokinetics in 12 volunteers, and found that APD356 was well-tolerated with food, and that food neither reduced maximum concentrations of the drug reached in the blood nor the amount of the drug absorbed. Finally, in part C, we evaluated the effect of single doses of APD356 on food intake in 20 subjects in a four-period crossover study. Each subject received single doses of placebo and 0.1 mg, 1 mg, or 10 mg doses of APD356 in random order over four successive weeks, and two hours after each dosing was offered a standard test meal in a controlled setting. In this way, subjects acted as their own control. At the 10 mg dose, average food intake declined 6.5% versus the placebo period, which is not statistically significant. Excluding a single outlier, who ate more than twice as much during period one (which also was the period in which he received the highest dose) as during each of the other three periods, average food intake declined 10.7%, which would be statistically significant. We believe this effect is a clinically meaningful signal of pharmacology.

In November 2004, we announced results from a Phase 1b clinical safety trial of APD356 in obese volunteers. In this trial, 27 subjects (15 males and 12 females) with an average body mass index, or

BMI, of 31, and a BMI range of 25 to 58, were enrolled. Participants were administered 3 mg, 10 mg and 20 mg doses of APD356 or placebo daily for 14 days in successive cohorts of nine subjects (six received APD356 and three received placebo) and remained within a Phase 1 unit throughout the dosing period. Participants were instructed to maintain their usual exercise patterns, and were offered sufficient food to maintain their desired intake levels. APD356 was well tolerated; there were no severe or serious adverse events reported, no withdrawals due to an adverse event, and no reports of euphoria, dysphoria, or disorientation. The most common side effects, occurring primarily at the 20 mg dosage level, were headache and nausea, sometimes with vomiting. These side effects were occasional and generally mild in nature. APD356 continued to demonstrate very predictable pharmacokinetic behavior, similar to that found in its Phase 1a trial. The maximum plasma concentration and exposures increased in proportion with increasing doses of APD356, and there were no apparent gender differences in pharmacokinetic parameters. Based on a comparison of echocardiograms taken at screening with those taken at the end of treatment and two and three months thereafter, there was no apparent drug effect on heart valves or pulmonary artery pressure. This Phase 1b study was neither designed nor powered to detect significant weight change between treatment groups. When compared with placebo, none of the mean changes in weight in the groups that received APD356 were statistically significant.

Based on these results, in December 2004 we began a randomized, double-blinded, multiple-dose, 28-day Phase 2 clinical trial of APD356 in obese subjects. We expect that the trial will compare doses of 1 mg, 5 mg and 15 mg of APD356 to placebo, evaluating weight loss after administration once daily for 28 days. We expect to announce initial results from this trial in the second quarter of 2005.

Intellectual Property. We have patent applications covering compositions of matter for APD356 and related compounds, and related methods of treatment, pending in 26 countries including the United States and Japan, and before the European Patent Office, or EPO. In addition, we have a pending patent application covering the synthetic route for APD356 before the World Intellectual Property Organization, or WIPO, designating all contracting states. We also have a patent application that covers the particular hydrate and crystal form of APD356 that we intend to use in late-phase clinical trials and perhaps commercially.

APD125

Our lead product candidate for insomnia, which we call APD125, is a novel and selective 5-HT_{2A} receptor inverse agonist in a Phase 1 clinical trial. According to the National Institutes of Health, as many as 25% of Americans report occasional sleeping problems, and insomnia is a chronic problem for about 10% of the population. In these cases, the lack of restful sleep impairs the person's ability to carry out daily responsibilities because they are too tired or have trouble concentrating. However, only a fraction of those suffering from insomnia seek medical treatment, as fewer than 10% of adults with this disorder report using medication for treatment. Currently marketed therapies include Ambien, marketed by sanofi-aventis, zaleplon, an off-patent compound, and various benzodiazepines, including Valium. These therapies generally work by activating the GABA-A receptor in the brain, and cause a general CNS-suppressive effect. While these drugs are effective at initiating sleep, they have side effects including the risk of developing tolerance to the drug and the potential for causing a sensation of dullness and lethargy upon awakening, often referred to as the "hangover effect." In addition, these drugs are DEA-scheduled controlled substances due to their potential for abuse. Despite these limitations, current medications for insomnia are expected to have worldwide sales in excess of $2 billion in 2005.

Mechanism and Preclinical Data. APD125 is our lead compound in a series we have discovered that selectively target the 5-HT_{2A} receptor. APD125 acts through a different mechanism than currently marketed insomnia drugs, and we believe that APD125 may not have the side effects associated with

such drugs. In our animal studies, we have demonstrated that APD125 increases both the quality and total time of non-REM sleep, the most restorative phase of the sleep cycle in humans, while having no effect on REM (rapid eye movement or dream) sleep. In addition, APD125 appeared to reduce sleep onset latency. The total increase in non-REM sleep time was manifested by fewer bouts of longer duration, indicating an increase in sleep consolidation. In addition, animals treated with APD125 showed an increase in delta power during non-REM sleep, a brain wave activity associated with increased sleep intensity. The improvements in non-REM duration and quality observed with APD125 administration were at least as robust as those observed with a prototypic GABA-A hypnotic control drug, Ambien. However, unlike Ambien, APD125 did not adversely affect REM sleep in these studies. We believe these animal data suggest that APD125 has the potential to improve the treatment of insomnia over GABA-A hypnotics.

Clinical Development. In December 2004, we initiated a Phase 1 clinical trial of APD125 in healthy volunteers. This dose-ranging study will evaluate the safety, tolerability and pharmacokinetics of single doses of APD125. We expect to announce results from this trial in the middle of 2005. Depending on the results of this trial, we intend to initiate multiple-dose tolerability and single-dose pharmacology trials.

Intellectual Property. We have patent applications covering compositions of matter for APD125 and related compounds, and related methods of treatment pending in the United States, Taiwan, Argentina, and Malaysia, and before the WIPO, designating all contracting states, and the EPO. We expect to file in early 2005 patent applications covering APD125 and related methods of treatment in nine additional jurisdictions that are not contracting states of the WIPO. We also have a pending patent application covering the synthetic route for APD125 before the WIPO, designating all contracting states.

19AJ / Ortho-McNeil Collaboration

Our lead product candidate for diabetes targets an orphan GPCR, which we call 19AJ, found in the pancreas. Our two lead compounds for this target are currently in preclinical development in partnership with Ortho-McNeil. Diabetes is a major worldwide disease. The International Diabetes Foundation has estimated that in 2001 there were 177 million adults with diabetes worldwide, an increase of 17% over the number in 2000. This estimate includes 21.4 million in the United States and 32.2 million in the European Union. Approximately 90%, or 160 million, of diabetics suffer from type 2 diabetes, the adult-onset form of the disease. Type 2 diabetes is characterized by inadequate response to insulin and/or inadequate secretion of insulin as blood glucose levels rise. Therapies for type 2 diabetes are directed toward correcting the body's inadequate response with oral medications, or directly modifying insulin levels through direct injection of insulin or insulin analogs.

Oral medications for type 2 diabetes include insulin releasers such as Glyburide, insulin sensitizers such as Actos and Avandia and agents which slow the uptake of glucose into the bloodstream such as Precose and Glyset. The worldwide market for oral diabetes medications was expected to exceed $10 billion in 2004. However, a significant portion of type 2 diabetics fail oral medication and require injected insulin therapy. Current oral medications for type 2 diabetes have a number of side effects, including hypoglycemia, weight gain and edema. Numerous pharmaceutical and biotechnology companies are seeking to develop insulin sensitizers, novel insulin formulations and other therapeutics to improve the treatment of diabetes.

Mechanism and Preclinical Data. 19AJ is a receptor that we have found to be preferentially expressed in beta cells, the cells in the pancreas responsible for producing insulin in response to increases in blood glucose. The pharmaceutical industry has discovered three main mechanisms that have resulted in beta-cell therapeutics: GLP-1 receptor peptide agonists, DPP-IV inhibitors and sulphonylureas. We believe 19AJ represents a novel mechanism for generating a new class of drugs for diabetes that may offer advantages over current approaches. Our preclinical results indicate that stimulating the 19AJ

receptor allows beta cells to produce insulin more efficiently in response to changes in blood glucose levels. In addition, we have found in these studies that stimulation of the 19AJ receptor leads to increased levels and activity of intracellular factors thought to be involved in the preservation of beta cells. Unlike the GLP-1 receptor, we have found that the 19AJ receptor is amenable to small molecule drug development. We have discovered potent, selective and orally available small molecule agonists of the receptor that improve glucose tolerance and lower blood glucose levels in animal models of diabetes. The 19AJ mechanism is glucose dependent, so that in our animal studies our compounds only lowered blood glucose when it rose above normal levels, such as after a meal. Our preclinical results indicate these compounds do not lower normal fasting baseline glucose levels in animal models and, therefore, do not cause hypoglycemia, unlike the glucose-insensitive sulphonylureas.

Development Plans and Partnership Status. In December 2004, we entered into a collaboration and license agreement with Ortho-McNeil to further develop compounds for the potential treatment of type 2 diabetes and other disorders. Our two lead compounds are currently in preclinical development with Ortho-McNeil. In January 2005, we received a $17.5 million upfront payment, and two milestones payments of $2.5 million each. We are eligible to receive up to $295.0 million in milestone payments for each compound, as well as royalty payments associated with Ortho-McNeil's commercialization of any drugs discovered under the agreement. These milestone payments include development and approval milestone payments of up to $132.5 million for the first indication and $62.5 million for the second indication for each compound, and up to $100.0 million in sales milestone payments for each product resulting from the collaboration.

Intellectual Property. We have patent applications covering composition of matter for the two most advanced preclinical lead compounds in our 19AJ program and related methods of treatment pending in the United States, Taiwan, Argentina, and Malaysia, and before the WIPO, designating all contracting states. We expect to file in early 2005 patent applications covering the two 19AJ lead compounds and related methods of treatment in nine additional jurisdictions that are not contracting states of the WIPO. We also expect to file in early 2005 a patent application covering the synthetic routes for the two 19AJ lead compounds.

Merck Cardiovascular Collaboration

In October 2002, we entered into a research and licensing agreement with Merck to collaborate on three GPCRs to develop therapeutics for atherosclerosis and related disorders. We believe one or more of these GPCRs plays a role in regulating plasma lipid profiles, including HDL cholesterol, the so-called "good cholesterol," and is responsible for the HDL-raising activity of niacin. In October 2004, Merck extended and expanded our collaboration and selected one of our compounds for preclinical development. To date, we have received $19.5 million from Merck in upfront and milestone payments and an equity investment. We may receive additional milestone payments of up to $34.0 million for Merck's clinical and marketing achievements, as well as royalty payments associated with Merck's commercialization of any drugs discovered under the agreement. In addition, we have received research funding from Merck since the inception of our collaboration, and Merck has agreed to pay us $5.7 million a year for collaboration research through October 2007.

There are very successful drugs available for lowering LDL cholesterol. However, development of novel, effective therapies to increase HDL cholesterol remains a major focus of research. We believe that such therapies may reduce the risk of atherosclerotic heart disease and compete in the large anti-hyperlipidemic market.

Other Research and Development Programs

Cardiovascular. In addition to our Merck collaboration, our programs in the cardiovascular area include ones directed toward the prevention of thrombosis and cardiac reperfusion injury. The

American Heart Association estimates that in the United States alone over 12 million people alive in 2001 have survived either a myocardial infarction or a stroke. To reduce the risk of future events, many subjects receive daily anti-platelet therapy. In 2003, worldwide sales of Plavix, a leading antithrombotic marketed by Bristol-Myers Squibb, exceeded $2.4 billion.

Platelet aggregation results in the formation of a blood clot and vessel occlusion leading to cardiovascular disease such as myocardial infarction and stroke. There are several important signals that increase the platelet aggregation response, such as thrombin, ADP, epinephrine, prostaglandins and collagen. Activated platelets are a rich source of a secondary signal, serotonin, that when released into the blood acts to amplify the aggregation response produced by the various primary signals. This serotonin-induced amplification process is mediated through 5-HT_{2A} receptors present on platelets. We have developed potent and selective small molecule inhibitors of the 5-HT_{2A} receptor that can block the serotonin-amplified aggregation response and have antithrombotic activity in animal models. In contrast to our 5-HT_{2A} lead compounds for insomnia which distributes significantly to the CNS, we have designed our lead antithrombotic compounds to have limited exposure to the brain through the blood-brain barrier. Moreover, in animal models, these compounds demonstrate a better therapeutic index due to a separation of antithrombotic activity from the increased bleeding that may be seen as a treatment effect of currently marketed products. Acute myocardial infarction, which is commonly known as a heart attack, is often followed by heart failure in survivors. Myocardial infarction, and often heart failure, are direct consequences of atherosclerosis, and both remain major causes of death. We have identified certain GPCRs that we believe play a role in these processes and are seeking to identify small molecules directed at these GPCR targets that we believe could provide cardio-protection following myocardial infarction.

Inflammatory Disorders. We are developing small molecule therapeutics that target GPCRs involved in the inflammatory process. TNF-α is an important pro-inflammatory mediator in diseases such as rheumatoid arthritis. Biologic therapeutics, such as Enbrel, Remicade and Humira, function to inhibit the activity of TNF-α. In 2003, worldwide sales of these three drugs exceeded $3.3 billion. However, biologic treatments are expensive and restricted to intravenous or subcutaneous administration. We have discovered small molecule compounds which can be orally administered and that in preclinical studies act to target GPCRs in the immune system to inhibit the production of TNF-α. We plan to continue to test the efficacy of these molecules in animal models of inflammatory diseases, such as arthritis, in 2005.

Diseases such as inflammatory bowel disease, which includes Crohn's disease and ulcerative colitis, and asthma, are initiated and exacerbated by an aberrant inflammatory response. Immune cells such as monocytes, dendritic cells, eosinophils, neutrophils, mast cells and specific T cell subsets play a role in these diseases. We have identified GPCRs that are found in specific immune cell types. We believe these GPCRs modulate the inflammatory process, and we are applying our screening technologies to these targets to identify small molecules that could activate or inhibit these GPCRs.

CNS Disorders. Many GPCRs are found predominately in the brain or the CNS, and, therefore, we believe targeting GPCRs provides an opportunity to selectively treat various CNS diseases. Many approved drugs for indications ranging from insomnia and narcolepsy to depression, schizophrenia, and Parkinson's disease target GPCRs. Our discovery efforts in CNS disorders are focused on indications with large market opportunities where current therapies have significant limitations. For example, we are developing small molecules targeting a GPCR through a different mechanism than serotonin or norepinephrine, and have confirmed that inhibitors of this GPCR show activity in animal models of depression and anxiety. We intend to continue our research and development of these compounds.

Other Diabetes Programs. For metabolic diseases, we are working on a series of orphan GPCR targets other than 19AJ in order to develop orally available therapies to treat type 1 and type 2 diabetes. We are focusing our discovery efforts on approximately 10 known and orphan GPCR targets that we

believe regulate important mechanisms involved in glucose control. For example, we are conducting research with receptors that may act to regulate glucose uptake, glucose absorption, insulin sensitivity, insulin secretion, lipid levels and production of glucose in the liver. In order to treat general metabolic disease, we have prioritized GPCRs that have the potential to modulate blood glucose and lipid levels. We have identified selective small molecule agonists to an orphan receptor we call 20PO. In preclinical studies, oral administration of these compounds improved glucose tolerance in a standard glucose tolerance test and lowered free fatty acids *in vivo*. We believe that agonists to the 20PO receptor have potential for the treatment of diabetes and lipid disorders.

Other Obesity Programs. In addition to APD356 and other compounds that act on the 5-HT_{2C} serotonin receptor, we have discovery programs focused on several different GPCRs implicated in obesity. Our drug discovery efforts are directed at identifying novel product candidates that target GPCRs in the CNS and peripheral tissues to reduce fat mass in people. We have identified both known and orphan GPCRs expressed in the hypothalamus, an area of the brain known to be critical for regulating satiety and metabolism, that we believe regulate food intake and weight. We have also identified targets in fat cells that may represent targets for obesity. We have identified early lead compounds for obesity targets other than the 5-HT_{2C} serotonin receptor, and are currently evaluating these compounds for their ability to reduce food intake and body weight.

Our Proprietary GPCR Technologies and Programs

Our product candidates have resulted from our GPCR-focused drug discovery technologies, capabilities and programs, including Constitutively Activated Receptor Technology, or CART, our Melanophore technology and Project Genesis.

CART

Traditional ligand-based drug screening methods require the time-consuming identification and use of the receptor's native ligand to discover small molecule compounds that will bind at, or close to, the native ligand's binding site on the receptor. In contrast, we have developed technologies that do not require the use of the native ligand. Instead, we are able to activate the GPCR so that the G protein signals without the presence of the native ligand. We call this Constitutively Activated Receptor Technology, or CART. CART allows us to discover drug-like compounds by activating the GPCR to mimic the biological response that occurs when the native ligand binds to the receptor. Therefore, CART avoids a major bottleneck in drug discovery efforts at orphan receptors by eliminating the step of first identifying the native ligand. We have found that CART can be applied broadly to GPCRs.

Screening using CART allows us to simultaneously identify drug leads that act as receptor activators, or agonists, which increase the detected biological response, or act as receptor inhibitors, which decrease the detected response. We can also identify inverse agonists, which inhibit ligand-independent, as well as ligand-dependent, receptor activity.

We believe that CART offers several key advantages for drug discovery over traditional screening techniques that require the use of the native ligand including:

- not requiring prior identification of the native ligand for an orphan receptor;
- enhancing the detection of, and allowing us to simultaneously identify, both receptor inhibitor and receptor activator drug leads;
- allowing for the identification of drug leads that inhibit both ligand-independent and ligand-dependent activity; and
- providing the ability to discover novel and improved therapeutics directed at known receptors.

Melanophore Technology

Our patented Melanophore technology is a broadly applicable high-throughput screen for GPCRs. When a GPCR is activated (either by a ligand or independent of a ligand through CART), the GPCR couples to one or more G proteins, including those belonging to the Gs, Gq, and Gi/o classes. Melanophore technology can detect GPCRs that couple to major G protein classes. We believe our Melanophore technology is, therefore, also well-suited for studies of orphan receptors whose coupling parameters are unknown. We believe Melanophore technology provides us with a robust, reproducible, high-throughput and low-cost means for identifying and optimizing GPCR agonists, antagonists, and inverse agonists, and is sensitive enough to detect the constitutive activity of many GPCRs.

Project Genesis

We have substantially completed our efforts under Project Genesis, a program to identify human GPCRs, determine where these GPCRs are expressed in normal and diseased tissues, and utilize our CART and Melanophore technologies to screen against our chemical libraries.

Through Project Genesis, we have learned, among other things, where and how GPCRs function in the body and how they interact with the small molecule chemicals that modulate their activity. We believe that this knowledge will allow us to more efficiently advance our therapeutic programs. We are applying medicinal chemistry to further develop the small molecule leads identified through screening.

Corporate Collaborations

In addition to Ortho-McNeil and Merck, we have entered into strategic collaborations with other pharmaceutical and biotechnology companies to discover and develop novel drug leads using our GPCR technologies. We intend to continue to pursue collaborations in an effort to access our partners' research, drug development, manufacturing, marketing and financial resources.

Intellectual Property

Our success depends in large part on our ability to protect our proprietary technology, compounds and information, and to operate without infringing the proprietary rights of third parties. We rely on a combination of patent, trade secret, copyright, and trademark laws, as well as confidentiality agreements, licensing agreements, and other agreements, to establish and protect our proprietary rights.

As of December 31, 2004, we owned or had exclusively licensed the following patents: 14 in the United States, 11 in European countries, six in Australia, five in New Zealand, one in Japan, one in Singapore, and one in Israel. In addition, as of December 31, 2004, we had approximately 243 patent applications before the United States Patent and Trademark Office, foreign patent offices and international patent authorities. These patents and patent applications are directed to drug lead discovery techniques using CART, genetically altered GPCRs, GPCRs that we have discovered, new uses for previously discovered GPCRs, and compounds discovered using CART and Melanophore and other technologies. There is no assurance that any of these patent applications will issue, or that any of the patents will be enforceable or cover a drug product or other commercially significant product or method. Except for the U.S. patents relating to our Melanophore technology, the term of all of our other current patents commenced, and our future patents, if any, will commence, on the date of issuance and terminate 20 years from the earliest effective filing date of the patent application. Since our U.S. Melanophore patents were issued under now superceded rules that provided a patent term of 17 years from the date of issuance, the term of these patents are scheduled to end in 2012. Because the time from filing to issuance of biotechnology patent applications is often more than three years, the resulting term of our pending patent applications, if any, on our products and technologies may be substantially less than

20 years. In the United States, patent term extensions are available for certain delays in patent office proceedings and United States Food and Drug Administration, or FDA, approval. However, due to the specific requirements for obtaining these extensions, there is no assurance that our patents will be afforded extensions even if we encounter significant delays in patent office proceedings or FDA approval.

We seek patent protection for our key inventions, including clinical candidates and product candidates we identify, routes for chemical synthesis, CART, new receptors that we discover, and genetically altered receptors. It has generally been possible to obtain broad composition of matter patents on novel chemical compounds. It has also generally been possible to obtain broad method patents for techniques and procedures for screening and drug-identification technologies. It has generally been more difficult to obtain broad composition of matter patents for nucleic acid and amino acid sequences. However, it has been possible to obtain patents that protect specific sequences and functional equivalents of those sequences. Furthermore, intellectual property law allows for separate and distinct patents for novel, altered genetic sequences that have improved properties over previously disclosed sequences. We believe that we can obtain patents on certain of our CART-activated receptor sequences because they are not functional equivalents of the natural version of the receptor. We expect to continue to develop other means of activating GPCRs for drug screening and to file patent applications with respect thereto.

In March 2003, we became aware that the Japanese Patent Office had issued a Notification of Reasons for Revocation of our Japanese patent. In subsequent proceedings, we succeeded in having our Japanese patent on our Melanophore technology reinstated with a narrower claim scope, which we do not believe materially impacts our ability to utilize the Melanophore technology.

In addition to patent protection, we rely on trade secrets, proprietary know-how, and continuing technological advances to develop and maintain our competitive position. To maintain the confidentiality of our trade secrets and proprietary information, all of our employees are required to enter into and adhere to an employee confidentiality and invention assignment agreement, laboratory notebook policy, and invention disclosure protocol, as a condition of employment. Additionally, our employee confidentiality and invention assignment agreement requires that our employees not bring to us, or use without proper authorization, any third-party proprietary technology. We also require our consultants and collaborators that have access to proprietary property and information to execute confidentiality and invention rights agreements in our favor before beginning their relationship with us. While such arrangements are intended to enable us to better control the use and disclosure of our proprietary property and provide for our ownership of proprietary technology developed on our behalf, they may not provide us with meaningful protection for such property and technology in the event of unauthorized use or disclosure.

Competition

The biotechnology and pharmaceutical industries are highly competitive and are subject to rapid and significant change. We face significant competition from organizations that are pursuing the same or similar technologies. We also face significant competition from organizations that are pursuing drugs that would compete with the product candidates we are developing. We may not be able to compete successfully against these organizations, which include many large and well-financed and experienced pharmaceutical and biotechnology companies, as well as academic and research institutions and government agencies.

The focus of our scientific and business strategy is GPCRs. We believe that many pharmaceutical and biotechnology companies and other organizations have internal drug discovery programs focused on GPCRs. In addition, other companies have attempted to overcome the problems associated with

traditional drug screening by embarking on a variety of alternative strategies. Developments by others may render our product candidates or technologies obsolete or noncompetitive.

Our present competitors with respect to APD356 include Abbott, which markets Meridia, and Roche, which markets Xenical. A potential future competitor is sanofi-aventis, which is developing rimonabant, a cannabinoid-1 blocker. In addition, we are aware of potentially competing $5\text{-}HT_{2C}$ programs at Roche and GlaxoSmithKline.

In addition to the marketed compounds described above under the APD125 discussion, Pfizer/Neurocrine have submitted an NDA for Indiplon, and Sepracor has recently received FDA approval for Lunesta, formally called Estorra. We believe sanofi-aventis and Eli Lilly have been developing potentially competing $5\text{-}HT_{2A}$ programs for insomnia.

Many of our existing and potential competitors have substantially greater product development capabilities and financial, scientific, and marketing resources than we do. Additional consolidation in the pharmaceutical industry may result in even more resources being concentrated with our competitors. As a result, our competitors may be able to devote greater resources than we can to the research, development, marketing, and promotion of drug discovery techniques or therapeutic products, or to adapt more readily to technological advances than we can. Accordingly, our competitors may succeed in obtaining patent protection, receiving FDA approval, or commercializing products before we do.

We expect to encounter significant competition for the principal product candidates we are developing. Companies that complete clinical trials, obtain regulatory approvals, and commence commercial sales of their products before us may achieve a significant competitive advantage. Furthermore, we will be competing against companies with substantially greater manufacturing, marketing, distributing, and selling capabilities, and any product candidate that we successfully develop may compete with existing therapies that have long histories of safe and effective use.

We rely on our collaborators for support of development programs and for the manufacturing and marketing of product candidates. Our collaborators may be conducting multiple product development efforts within the same disease areas that are the subject of their agreements with us, which may negatively impact the development of drugs that they discover that are subject to our agreements. Generally, our agreements with our collaborators do not preclude them from pursuing development efforts in one or more therapeutic areas of interest in which we have internal development efforts ongoing. In addition, we face and will continue to face intense competition from other companies for such collaborative arrangements, and technological and other developments by others may make it more difficult for us to establish such relationships.

Employees

As of December 31, 2004, we had 288 employees, including 239 in research and development and 49 in administration. None of our employees is covered by a collective bargaining agreement. We consider our relationship with our employees to be good.

Management

Directors and Senior Management

The directors and senior management of the Company are as follows:

Name	Age	Position
Jack Lief(1)	58	CEO, President and Director
K.A. Ajit-Simh	52	Vice President, Quality Systems
Dominic P. Behan, Ph.D.	41	Senior Vice President, Chief Scientific Officer and Director
Robert E. Hoffman, C.P.A.	39	Vice President, Finance and Chief Accounting Officer
Paul W. Maffuid, Ph.D.	49	Vice President, Pharmaceutical Development
Louis J. Scotti	49	Vice President, Marketing and Business Development
William R. Shanahan, Jr., M.D., J.D.	56	Vice President, Chief Medical Officer
Steven W. Spector, J.D.	39	Senior Vice President, General Counsel and Secretary
Donald D. Belcher(1)(2)(3)(4)	66	Director
Scott H. Bice, J.D.(2)(3)(4)	61	Director
Duke K. Bristow, Ph.D.(3)(5)	47	Director
Harry F. Hixson, Jr., Ph.D.(1)(5)	66	Director
J. Clayburn La Force Jr., Ph.D.(2)(3)(4)(5)	76	Director
Tina S. Nova, Ph.D.(1)(4)	51	Director
Robert L. Toms, Sr., J.D.(3)(5)	69	Director

(1) Member of the Strategy Committee

(2) Member of the Audit Committee

(3) Member of the Corporate Governance Committee

(4) Member of the Nominating Committee

(5) Member of the Compensation Committee

Jack Lief, CEO, President and Director. Mr. Lief is a co-founder of Arena and has served as a director and our President and Chief Executive Officer since April 1997. Mr. Lief also serves as a director of TaiGen Biotechnology Co., Ltd. Mr. Lief has been selected to become the chairperson of BIOCOM in March of 2005. BIOCOM is a life science industry association representing more than 450 member companies in San Diego and Southern California. From 1995 to April 1997, Mr. Lief served as an advisor and consultant to numerous biopharmaceutical organizations. From 1989 to 1994, Mr. Lief served as Senior Vice President, Corporate Development and Secretary of Cephalon, Inc., a biopharmaceutical company. From 1983 to 1989, Mr. Lief served as Director of Business Development and Strategic Planning for Alpha Therapeutic Corporation, a manufacturer of biological products. Mr. Lief joined Abbott Laboratories, a pharmaceutical company, in 1972, where he served until 1983, most recently as the head of International Marketing Research. Mr. Lief holds a B.A. from Rutgers University and a M.S. in Psychology (Experimental and Neurobiology) from Lehigh University.

K.A. Ajit-Simh, Vice President, Quality Systems. Mr. Ajit-Simh has served as our Vice President, Quality Systems since January 2004. Mr. Ajit-Simh provided regulatory compliance services to several companies in the United States and internationally from 1999 to the end of 2003. Mr. Ajit-Simh held various positions of increasing responsibility at Mallinckrodt Inc. from 1975 to 1985, Baxter Healthcare from 1986 to 1989, Abbott BioTech from 1989 to 1992, and Cytel Corporation from 1992 to 1999. In

addition, he has been an instructor at the University of California, San Diego since 1994, teaching classes in regulatory compliance and quality control/assurance. He also teaches courses in Good Manufacturing Practices and Advanced Quality Control and Assurance at San Diego State University as part of the graduate program in Regulatory Affairs. Mr. Ajit-Simh received a B.Sc. degree in Biology and Chemistry from Banglore University and a M.S. in Cell Biology from St. Louis University, Missouri.

Dominic P. Behan, Ph.D., Senior Vice President, Chief Scientific Officer and Director. Dr. Behan is a co-founder of Arena and has served as a director since April 2000, and as our Senior Vice President and Chief Scientific Officer since June 2004. Dr. Behan served as our Vice President, Research from April 1997 to June 2004. From 1993 to January 1997, Dr. Behan directed various research programs at Neurocrine Biosciences, Inc., a public biopharmaceutical company. From 1990 to 1993, Dr. Behan was engaged in research at the Salk Institute. Dr. Behan holds a B.Sc. in Biochemistry from Leeds University, England, and a Ph.D. in Biochemistry from Reading University, England.

Robert E. Hoffman, C.P.A., Vice President, Finance and Chief Accounting Officer. Mr. Hoffman has served as our Vice President, Finance since April 2000, and also serves as our Chief Accounting Officer. Mr. Hoffman previously served as our Controller from August 1997 to April 2000. From 1994 to 1997, Mr. Hoffman served as Assistant Controller for Document Sciences Corporation, a software company. Mr. Hoffman is a member of the Association of Bioscience Financial Officers, and is a director of the San Diego County Credit Union. Mr. Hoffman holds a B.B.A. from St. Bonaventure University and is licensed as a C.P.A. in the state of California.

Paul W. Maffuid, Ph.D., Vice President, Pharmaceutical Development. Dr. Maffuid has served as our Vice President, Pharmaceutical Development since November 2002. He previously served as our Director of Pharmaceutical Development from November 2001 to November 2002. From May 1999 to November 2001, Dr. Maffuid served as Executive Director in Pharmaceutical Development at Magellan Laboratories, Inc., a pharmaceutical development company. From 1994 to 1999, Dr. Maffuid served in various positions at Amylin Pharmaceuticals, Inc., a biotechnology company, including as Senior Director Pharmaceutical Development. From 1990 to 1994, Dr. Maffuid served in various positions at Glaxo Research Institute, a pharmaceutical company, including as Group Leader in Analytical Chemistry. Dr. Maffuid holds a Ph.D. in Organic Chemistry from the University of California, San Diego.

Louis J. Scotti, Vice President, Marketing and Business Development. Mr. Scotti has served as our Vice President, Marketing and Business Development since September 2002. He previously served as our Vice President, Business Development from August 1999 to September 2002. From June 1998 to July 1999, Mr. Scotti served as President and Chief Executive Officer for ProtoMed, Inc., a biopharmaceutical company. From April 1996 to June 1998, Mr. Scotti served as Executive Director of Licensing for Ligand Pharmaceuticals Incorporated, a drug discovery company. From 1986 to 1995, Mr. Scotti served in various positions at Reed & Carnrick Pharmaceuticals, a pharmaceutical company, most recently as Vice President of Marketing and Business Development. Mr. Scotti holds a B.S.E. in Biomedical Engineering from the University of Pennsylvania.

William R. Shanahan, Jr., M.D., J.D., Vice President, Chief Medical Officer. Dr. Shanahan has served as our Vice President, Chief Medical Officer since March 2004. From August 2000 to March 2004, Dr. Shanahan served as Chief Medical Officer for Tanox, Inc., a biopharmaceutical company. From October 1994 to August 2000, Dr. Shanahan held various positions at Isis Pharmaceuticals, a biopharmaceutical company, most recently as Vice President, Drug Development. From 1989 to 1994, he served as Director, Clinical Research for Pfizer Central Research, a pharmaceutical company. From 1986 to 1989, he held various positions at Searle Research & Development, a pharmaceutical company subsequently acquired by Pfizer, most recently as Director, Clinical Research. Dr. Shanahan holds an

A.B. from Dartmouth College, a M.D. from the University of California, San Francisco and a J.D. from Loyola University, Chicago.

Steven W. Spector, J.D., Senior Vice President, General Counsel and Secretary. Mr. Spector has served as our Senior Vice President and General Counsel since June 2004. Mr. Spector served as our Vice President and General Counsel from October 2001 to June 2004. Mr. Spector also serves as our Secretary and as a director of ChemNavigator. Prior to joining Arena, Mr. Spector was a partner with the law firm of Morgan, Lewis & Bockius LLP, where he worked from 1991 to October 2001. Mr. Spector was a member of the Morgan Lewis Technology Steering Committee. Mr. Spector was our outside corporate counsel from 1998 to October 2001. Mr. Spector holds B.A. and J.D. degrees from the University of Pennsylvania.

Donald D. Belcher, Director. Mr. Belcher has served as a member of our Board of Directors since December 2003. Mr. Belcher served as Chairman of the Board of Directors of Banta Corporation, a printing and supply-chain management company, from May 1995 to April 2004, Chief Executive Officer from January 1995 to October 2002 and President from September 1994 to January 2001. Mr. Belcher holds a B.A. from Dartmouth College and an M.B.A. from the Stanford University Graduate School of Business.

Scott H. Bice, J.D., Director. Mr. Bice has served as a member of our Board of Directors since December 2003. Since June 2000, Mr. Bice has been the Robert C. Packard Professor at the University of Southern California Law School, where he served as Dean from 1980 to June 2000. Mr. Bice has experience on several corporate boards, including Imagine Films, from 1992 to 1994, Western and Residence Mutual Insurance Companies, from 1996 to 2003, and Jenny Craig, from 1996 to 2002. Mr. Bice holds a B.S. in finance and a J.D. from the University of Southern California.

Duke K. Bristow, Ph.D., Director. Dr. Bristow has served as a member of our Board of Directors since October 2002. Dr. Bristow is an economist and is the Program Director for a research program in entrepreneurship, corporate governance and corporate finance in the Harold Price Center for Entrepreneurial Studies at the Anderson Graduate School of Management at the University of California, Los Angeles. Prior to his arrival at UCLA in 1990, Dr. Bristow worked for ten years at Eli Lilly and Company, holding various management positions in the Pharmaceutical Division, Medical Device Division, Diagnostics Division and in Corporate Finance. Dr. Bristow has been a member of the board of directors of Landec Corporation since September 2004. Dr. Bristow received his Ph.D. in Financial Economics at UCLA, his M.B.A. from Indiana University and his B.S. in Chemical Engineering from Purdue University.

Harry F. Hixson, Jr., Ph.D., Director. Dr. Hixson has served as member of our Board of Directors since September 2004. Dr. Hixson has served as Chairman of BrainCells Inc. since December 2003 and as Chief Executive Officer since July 2004. Dr. Hixson served as Chief Executive Officer of Elitra Pharmaceuticals, a biopharmaceutical company, from February 1998 until May 2003. Dr. Hixson held various management positions with Amgen, Inc., a biopharmaceutical company from 1985 until 1991, most recently as President and Chief Operating Officer. Dr. Hixson is currently Chairman of Sequenom, Inc., a genomics company and a Director of Discovery Partners International, Inc., a pharmaceutical services company. Dr. Hixson holds a B.S. in Chemical Engineering from Purdue University, an M.B.A. from the University of Chicago and a Ph.D. in Physical Biochemistry from Purdue University.

J. Clayburn La Force Jr., Ph.D., Director. Dr. La Force has served as a member of our Board of Directors since October 2002. Dr. La Force has served as a professor of Economics at the University of California, Los Angeles since 1962, and served as Dean of the Anderson School of Management at University of California, Los Angeles from July 1978 to June 1993. From 1969 to 1978, Dr. La Force served as the Chairman of the Economics Department at UCLA. Dr. La Force currently serves as a

member of the Board of Directors of CancerVax Corporation, an oncology focused company, and on the following registered investment companies: BlackRock Closed-End Funds, Payden Funds, Mezler Payden, Provident Investment Counsel Funds, and Advisors Series Trust. Dr. La Force holds an A.B. in Economics from San Diego State College and an M.A. in Economics and a Ph.D. in Economics from the University of California, Los Angeles.

Tina S. Nova, Ph.D., Director. Dr. Nova has served as a member of our Board of Directors since September 2004. Dr. Nova is a co-founder of Genoptix, Inc., a provider of personalized medicine services, and has served as its President and Chief Executive Officer and as a member of its Board of Directors since March 2000. Previously, Dr. Nova was a co-founder of Nanogen, Inc., a provider of molecular diagnostic tests, where she served as Chief Operating Officer and President from 1994 to January 2000. From 1992 to 1994, Dr. Nova served as Chief Operating Officer of Selective Genetics, a targeted therapy, biotechnology company. From 1988 to 1992, Dr. Nova held various director-level positions with Ligand Pharmaceuticals Incorporated, most recently serving as Executive Director of New Leads Discovery. Dr. Nova has also held various research and management positions with Hybritech, Inc., a former subsidiary of Eli Lilly & Company, a pharmaceutical company. In addition, Dr. Nova is the life science sector representative to the Independent Citizen's Oversight Committee overseeing the implementation of the California stem cell initiative, Proposition 71. Dr. Nova holds a B.S. in Biological Sciences from the University of California, Irvine and a Ph.D. in Biochemistry from the University of California, Riverside.

Robert L. Toms, Sr., J.D., Director. Mr. Toms has served as a member of our Board of Directors since December 2003. Since December 2001, Mr. Toms has worked as an attorney in private practice. Mr. Toms was Of Counsel from July 1998 to November 2001 to Christie, Parker & Hale, a patent and trademark law firm. Previously, Mr. Toms served as the Commissioner of Corporations for the State of California. Mr. Toms holds a B.A. from Bob Jones University and a J.D. from Duke University School of Law.

Underwriting

We have entered into an underwriting agreement with the underwriters named below. CIBC World Markets Corp. is acting as representative of the underwriters.

The underwriting agreement provides for the purchase of a specific number of shares of common stock by each of the underwriters. The underwriters' obligations are several, which means that each underwriter is required to purchase a specified number of shares, but is not responsible for the commitment of any other underwriter to purchase shares. Subject to the terms and conditions of the underwriting agreement, each underwriter has severally agreed to purchase the number of shares of common stock set forth opposite its name below:

Underwriter	Number of Shares
CIBC World Markets Corp.	
Piper Jaffray & Co.	
Needham & Company, Inc.	
Granite Financial Group, Inc.	
Morgan Joseph & Co. Inc.	
Total	6,000,000

The underwriters have agreed to purchase all of the shares offered by this prospectus supplement (other than those covered by the over-allotment option described below) if any ar