

As filed with the Securities and Exchange Commission on October 25, 2004  
Registration Statement No. 333-

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

**FORM S-3**

REGISTRATION STATEMENT UNDER THE SECURITIES ACT OF 1933

**HYBRIDON, INC.**

(Exact name of registrant as specified in its charter)

**Delaware**  
(State or other jurisdiction of incorporation or organization)

**04-3072298**  
(I.R.S. Employer Identification No.)

**345 Vassar Street**  
**Cambridge, Massachusetts 02139**  
**(617) 679-5500**  
(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

**Sudhir Agrawal, D. Phil.**  
**President and Chief Executive Officer**  
**Hybridon, Inc.**  
**345 Vassar Street**  
**Cambridge, Massachusetts 02139**  
**(617) 679-5500**  
(Name, address, including zip code, and telephone number, including area code, of agent for service)

Copies to:  
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*Approximate date of commencement of proposed sale to public:* As soon as practicable after this Registration Statement becomes effective.

If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box.

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.  \_\_\_\_\_

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.  \_\_\_\_\_

If delivery of the prospectus is expected to be made pursuant to Rule 434, please check the following box.

CALCULATION OF REGISTRATION FEE

Title of Shares to be Registered	Amount to be Registered (1)	Proposed Maximum Offering Price Per Share(2)	Proposed Maximum Aggregate Offering Price(2)	Amount of Registration Fee
Common Stock, \$0.001 par value per share	11,020,600	\$0.52	\$5,730,712	\$727

(1) Consists of (a) 8,823,400 shares of common stock and 2,197,200 shares of common stock issuable upon the exercise of common stock purchase warrants and (b) additional shares, of a currently indeterminable amount, as may from time to time become issuable by reason of stock splits, stock dividends and other similar transactions, which shares are registered hereunder pursuant to Rule 416 under the Securities Act.

(2) Estimated solely for purposes of calculating the registration fee pursuant to Rule 457(c) under the Securities Act and based upon the average of the high and low prices on the American Stock Exchange on October 21, 2004.

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The Company hereby amends this Registration Statement on such date or dates as may be necessary to delay its effective date until the Company shall file a further amendment which specifically states that this Registration Statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933 or until the Registration Statement shall become effective on such date as the Commission, acting pursuant to said Section 8(a), shall determine.

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The information in this prospectus is not complete and may be changed. The selling stockholders named in this prospectus may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities and the selling stockholders named in this prospectus are not soliciting offers to buy these securities in any jurisdiction where the offer or sale is not permitted.

Subject to completion, dated October 25, 2004

PROSPECTUS

HYBRIDON, INC.

11,020,600 SHARES OF COMMON STOCK

This prospectus relates to the resale from time to time of up to 11,020,600 shares of common stock of Hybridon, Inc. by the selling stockholders identified in this prospectus. We will not receive any proceeds from the sale of the shares offered by this prospectus.

The selling stockholders identified in this prospectus, or their pledgees, donees, transferees or other successors-in-interest, may offer the shares from time to time through public or private transactions at prevailing market prices, at prices related to prevailing market prices or at privately negotiated prices.

Our common stock is traded on the American Stock Exchange under the symbol "HBY." On October 22, 2004, the closing sale price of our common stock on the American Stock Exchange was \$0.53 per share. You are urged to obtain current market quotations for the common stock.

Investing in our common stock involves a high degree of risk. See "Risk Factors" beginning on page 2.

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

The date of this prospectus is October 25, 2004.

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We have not authorized anyone to provide you with information different from that contained or incorporated by reference in this prospectus. The selling stockholders 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 is accurate only as of the date of this prospectus, regardless of the time of delivery of this prospectus or of any sale of common stock.

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## PROSPECTUS SUMMARY

*This summary highlights important features of this offering and the information included or incorporated by reference in this prospectus. This summary may not contain all of the information that is important to you. You should read the entire prospectus carefully, including "Risk Factors" beginning on page 2, before deciding to invest in our common stock.*

### Hybridon, Inc.

We are engaged in the discovery and development of novel therapeutics using synthetic DNA. Our activities are primarily based on two technology platforms:

- Our immunomodulatory oligonucleotide, or IMO<sup>TM</sup>, technology modulates responses of the immune system using synthetic DNA containing specific sequences that mimic bacterial DNA.
- Our antisense technology uses synthetic DNA to block the production of disease causing proteins at the cellular level.

We are currently conducting clinical trials of two drug candidates. We plan to initiate in the fourth quarter of 2004 a phase 2 clinical trial in the United States of IMOXine<sup>TM</sup> (also known as HYB2055), our lead second generation IMO compound for the treatment of metastatic or recurrent renal cell carcinoma. We have in progress a phase 1/2 clinical trial in the United States of GEM<sup>®</sup>231, a second generation antisense compound, in combination with irinotecan, and a phase 1 trial of IMOXine for the treatment of solid tumor cancers. We have also completed a separate phase 1 trial of HYB2055 in healthy volunteers in the United Kingdom.

### Corporate Information

Our executive offices are located at 345 Vassar Street, Cambridge, MA 02139, our telephone number is (617) 679-5500 and our Internet address is [www.hybridon.com](http://www.hybridon.com). The information on our Internet website is not incorporated by reference in this prospectus and should not be considered to be part of this prospectus. Our website address is included in this prospectus as an inactive technical reference only. Unless the context otherwise requires, references in this prospectus to "Hybridon," "we," "us," and "our" refer to Hybridon, Inc.

Hybridon<sup>®</sup> and GEM<sup>®</sup> are our registered trademarks. IMO<sup>TM</sup>, IMOXine<sup>TM</sup> and Amplivax<sup>TM</sup> are also our trademarks. All other trademarks and service marks are the property of their respective owners.

### The Offering

Common Stock offered by selling stockholders.	11,020,600 shares, including 2,197,200 shares issuable upon the exercise of warrants held by the selling stockholders.
Use of proceeds.	We will not receive any proceeds from the sale of shares in this offering.
American Stock Exchange symbol.	HBV

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## RISK FACTORS

*Investing in our common stock involves a high degree of risk. You should carefully consider the risks and uncertainties described below in addition to the other information included or incorporated by reference in this prospectus before purchasing our common stock. If any of the following risks actually occurs, our business, financial condition or results of operations would likely suffer, possibly materially. In that case, the trading price of our common stock could fall, and you may lose all or part of the money you paid to buy our common stock.*

### **Risks Relating to Our Financial Results and Need for Financing**

***We have incurred substantial losses and expect to continue to incur losses. We will not be successful unless we reverse this trend.***

We have incurred losses in every year since our inception, except for 2002 when our recognition of revenues under a license and collaboration agreement resulted in us reporting net income for that year. As of June 30, 2004, we had incurred operating losses of approximately \$292.5 million. We expect to continue to incur substantial operating losses in future periods. These losses, among other things, have had and will continue to have an adverse effect on our stockholders' equity, total assets and working capital.

We have received no revenues from the sale of drugs. To date, almost all of our revenues have been from collaborative and license agreements and the sale of manufactured synthetic DNA and reagent products by our Hybridon Specialty Products Division prior to our selling that division in September 2000. We have devoted substantially all of our efforts to research and development, including clinical trials, and we have not completed development of any drugs. Because of the numerous risks and uncertainties associated with developing drugs, we are unable to predict the extent of any future losses, whether or when any of our products will become commercially available, or when we will become profitable, if at all.

***We will need additional financing, which may be difficult to obtain. Our failure to obtain necessary financing or doing so on unattractive terms could adversely affect our discovery and development programs and other operations.***

We will require substantial funds to conduct research and development, including preclinical testing and clinical trials of our drugs. We will also require substantial funds to conduct regulatory activities and to establish commercial manufacturing, marketing and sales capabilities. We believe that, based on our current operating plan, our existing cash and cash equivalents and short-term investments, including the \$4.7 million in net proceeds that we received from the private placement of securities that we consummated with the selling stockholders in August 2004, will be sufficient to fund our cash requirements until midway through the third quarter of 2005. We will need to raise additional funds to operate our business beyond such time.

Additional financing may not be available to us when we need it or may not be available to us on favorable terms. We could be required to seek funds through arrangements with collaborators or others that may require us to relinquish rights to some of our technologies, drug candidates or drugs which we would otherwise pursue on our own. In addition, if we raise additional funds by issuing equity securities, our then existing stockholders will experience dilution. The terms of any financing may adversely affect the holdings or the rights of existing stockholders. If we are unable to obtain adequate funding on a timely basis or at all, we may be required to significantly curtail one or more of our discovery or development programs. For example, we significantly curtailed expenditures on our research and development programs during 1999 and 2000 because we did not have sufficient funds available to advance these programs at planned levels.

### **Risks Relating to Our Business, Strategy and Industry**

***We are depending heavily on the success of HYB2055, our lead 2nd generation IMO compound, which is in clinical development. If we are unable to commercialize this product, or experience significant delays in doing so, our business will be materially harmed.***

We are investing a significant portion of our time and financial resources in the development of HYB2055, our lead 2nd generation IMO compound. We anticipate that in the near term our ability to generate product revenues will depend heavily on the successful development and commercialization of this product. The commercial success of this product will depend on several factors, including the following:

- successful completion of clinical trials;
- receipt of marketing approvals from the United States Food and Drug Administration, or FDA, and similar foreign regulatory authorities;
- establishing commercial manufacturing arrangements with third party manufacturers;
- launching commercial sales of the product, whether alone or in collaboration with others; and
- acceptance of the product in the medical community and with third party payors.

Our efforts to commercialize this product are at an early stage, as we are currently conducting a phase 1 clinical trial of this product candidate in the United States. We have also completed a separate phase 1 trial of this product in the United Kingdom. If we are not successful in commercializing this product, or are significantly delayed in doing so, our business will be materially harmed.

***If our clinical trials are unsuccessful, or if they are significantly delayed, we may not be able to develop and commercialize our products.***

We may not be able to successfully complete any clinical trial of a potential product within any specified time period. In some cases, we may not be able to complete the trial at all. Moreover, clinical trials may not show our potential products to be both safe and efficacious. Thus, the FDA and other regulatory authorities may not approve any of our potential products for any indication.

In order to obtain regulatory approvals for the commercial sale of our products, we will be required to complete extensive clinical trials in humans to demonstrate the safety and efficacy of our drug candidates. In 2003, we commenced phase 1 clinical trials of HYB2055, in healthy subjects and in oncology patients, and we plan to initiate a phase 2 clinical trial in the fourth quarter of 2004. We are currently conducting a phase 1/2 clinical trial of GEM231 in combination with irinotecan, for the treatment of solid tumor cancer. We may not be able to obtain authority from the FDA or other equivalent foreign regulatory agencies to complete these trials or commence and complete any other clinical trials.

We may license HYB2055 and other of our products to third parties for use in different fields or indications than we are pursuing for such products. For instance, we have licensed HYB2055 to Immune Response Corporation for use as an adjuvant in the development of a vaccine for HIV infection at the same time as we are seeking to develop the product for cancer therapy. If these third parties conduct clinical trials of our products and the clinical trial results are adverse with respect to our products, such clinical trial results may adversely affect the timing and success of the clinical development of our products.

The results from preclinical testing of a drug candidate that is under development may not be predictive of results that will be obtained in human clinical trials. In addition, the results of early human clinical trials may not be predictive of results that will be obtained in larger scale, advanced stage clinical trials. A failure of one or more of our clinical trials can occur at any stage of testing. We may experience numerous unforeseen events during, or as a result of, preclinical testing and the clinical trial process that could delay or prevent our ability to receive regulatory approval or commercialize our products, including:

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- regulators or institutional review boards may not authorize us to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- our preclinical tests or clinical trials may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional preclinical testing or clinical trials or we may abandon projects that we expect to be promising;
- we might have to suspend or terminate our clinical trials if the participating patients are being exposed to unacceptable health risks;
- regulators or institutional review boards may require that we hold, suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements;
- the cost of our clinical trials may be greater than we currently anticipate; and
- the effects of our products may not be the desired effects or may include undesirable side effects or the products may have other unexpected characteristics.

As an example, in 1997, after reviewing the results from the clinical trial of GEM91, our lead 1st generation antisense compound at the time, we determined not to continue the development of GEM91 and suspended all clinical trials of this product candidate.

The rate of completion of clinical trials is dependent in part upon the rate of enrollment of patients. Patient accrual is a function of many factors, including:

- the size of the patient population,
- the proximity of patients to clinical sites,
- the eligibility criteria for the study,
- the nature of the study,
- the existence of competitive clinical trials, and
- the availability of alternative treatments.

Our product development costs will increase if we experience delays in our clinical trials. We do not know whether planned clinical trials will begin as planned, will need to be restructured or will be completed on schedule, if at all. Significant clinical trial delays also could allow our competitors to bring products to market before we do and impair our ability to commercialize our products.

***We face substantial competition which may result in others discovering, developing or commercializing drugs before or more successfully than us.***

The biotechnology industry is highly competitive and characterized by rapid and significant technological change. We face, and will continue to face, intense competition from organizations such as pharmaceutical and biotechnology companies, as well as academic and research institutions and government agencies. Some of these organizations are pursuing products based on technologies similar to our technologies. Others have developed and are marketing products, or are pursuing other technological approaches designed to produce products, that are competitive with our product candidates in the therapeutic effect these competitive products have on diseases targeted by our product candidates. Our competitors may discover, develop or commercialize products or other novel technologies that are more effective, safer or less costly than any that we are developing. Our competitors may also obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours.

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Many of our competitors are substantially larger than we are and have greater capital resources, research and development staffs and facilities than we have. In addition, many of our competitors are more experienced than we are in drug discovery, development and commercialization, obtaining regulatory approvals and drug manufacturing and marketing.

We anticipate that the competition with our products and technologies will be based on a number of factors including product efficacy, safety, availability and price.

The timing of market introduction of our products and competitive products will also affect competition among products. We expect the relative speed with which we can develop products, complete the clinical trials and approval processes and supply commercial quantities of the products to the market to be important competitive factors. Our competitive position will also depend upon our ability to attract and retain qualified personnel, to obtain patent protection or otherwise develop proprietary products or processes and to secure sufficient capital resources for the period between technological conception and commercial sales.

***Because the products that we may develop will be based on new technologies and therapeutic approaches, the market may not be receptive to these products upon their introduction.***

The commercial success of any of our products for which we may obtain marketing approval from the FDA or other regulatory authorities will depend upon their acceptance by the medical community and third party payors as clinically useful, cost-effective and safe. Many of the products that we are developing are based upon technologies or therapeutic approaches that are relatively new and unproven. The FDA has only granted marketing approval for one product based on antisense technology which is currently being marketed by another company for the treatment of cytomegalovirus retinitis, an infectious disease, in patients with AIDS. The FDA has not granted marketing approval to any products based on technology similar to IMO technology and no such products are currently being marketed. As a result, it may be more difficult for us to achieve regulatory approval or market acceptance of our products. Our efforts to educate the medical community on these potentially unique approaches may require greater resources than would be typically required for products based on conventional technologies or therapeutic approaches. The safety, efficacy, convenience and cost-effectiveness of our products as compared to competitive products will also affect market acceptance.

***Competition for technical and management personnel is intense in our industry, and we may not be able to sustain our operations or grow if we are unable to attract and retain key personnel.***

Our success is highly dependent on the retention of principal members of our technical and management staff, including Sudhir Agrawal. Dr. Agrawal serves as our President and Chief Executive Officer. Dr. Agrawal has made significant contributions to the field of nucleic acid chemistry and is named as an inventor on over 200 patents and patent applications worldwide. Dr. Agrawal provides the scientific leadership for our research and development activities and directly supervises our research staff. The loss of Dr. Agrawal's services would be detrimental to our ongoing scientific progress.

We are a party to an employment agreement with Dr. Agrawal, but this agreement may be terminated by us or Dr. Agrawal for any reason or no reason at any time upon notice to the other party. We do not carry key man life insurance for Dr. Agrawal.

Furthermore, our future growth will require hiring a significant number of qualified technical and management personnel. Accordingly, recruiting and retaining such personnel in the future will be critical to our success. There is intense competition from other companies and research and academic institutions for qualified personnel in the areas of our activities. If we are not able to continue to attract and retain, on acceptable terms, the qualified personnel necessary for the continued development of our business, we may not be able to sustain our operations or grow.



## Regulatory Risks

*We may not be able to obtain marketing approval for products resulting from our development efforts.*

All of the products that we are developing or may develop in the future will require additional research and development, extensive preclinical studies and clinical trials and regulatory approval prior to any commercial sales. This process is lengthy, often taking a number of years, is uncertain and is expensive. Since our inception, we have conducted clinical trials of a number of compounds. In 1997, we determined not to continue clinical development of GEM91, our lead product candidate at the time. Currently, we are conducting clinical trials of two compounds, HYB2055 and GEM231.

We may need to address a number of technological challenges in order to complete development of our products. Moreover, these products may not be effective in treating any disease or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining regulatory approval or prevent or limit commercial use.

*We are subject to comprehensive regulatory requirements, which are costly and time consuming to comply with; if we fail to comply with these requirements, we could be subject to adverse consequences and penalties.*

The testing, manufacturing, labeling, advertising, promotion, export and marketing of our products are subject to extensive regulation by governmental authorities in Europe, the United States and elsewhere throughout the world.

In general, submission of materials requesting permission to conduct clinical trials may not result in authorization by the FDA or any equivalent foreign regulatory agency to commence clinical trials. In addition, submission of an application for marketing approval to the relevant regulatory agency following completion of clinical trials may not result in the regulatory agency approving the application if applicable regulatory criteria are not satisfied, and may result in the regulatory agency requiring additional testing or information.

Any regulatory approval of a product may contain limitations on the indicated uses for which the product may be marketed or requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the product. Any product for which we obtain marketing approval, along with the facilities at which the product is manufactured, any post-approval clinical data and any advertising and promotional activities for the product will be subject to continual review and periodic inspections by the FDA and other regulatory agencies.

Both before and after approval is obtained, violations of regulatory requirements may result in:

- the regulatory agency's delay in approving, or refusal to approve, an application for approval of a product;
- restrictions on such products or the manufacturing of such products;
- withdrawal of the products from the market;
- warning letters;
- voluntary or mandatory recall;
- fines;
- suspension or withdrawal of regulatory approvals;
- product seizure;
- refusal to permit the import or export of our products;
- injunctions or the imposition of civil penalties; and

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- criminal penalties.

*We have only limited experience in regulatory affairs and our products are based on new technologies; these factors may affect our ability or the time we require to obtain necessary regulatory approvals.*

We have only limited experience in filing the applications necessary to gain regulatory approvals. Moreover, the products that result from our research and development programs will likely be based on new technologies and new therapeutic approaches that have not been extensively tested in humans. The regulatory requirements governing these types of products may be more rigorous than for conventional drugs. As a result, we may experience a longer regulatory process in connection with obtaining regulatory approvals of any product that we develop.

### **Risks Relating to Collaborators**

*We need to establish collaborative relationships in order to succeed.*

An important element of our business strategy includes entering into collaborative relationships for the development and commercialization of products based on our discoveries. We face significant competition in seeking appropriate collaborators. Moreover, these arrangements are complex to negotiate and time-consuming to document. We may not be successful in our efforts to establish collaborative relationships or other alternative arrangements.

The success of collaboration arrangements will depend heavily on the efforts and activities of our collaborators. Our collaborators will have significant discretion in determining the efforts and resources that they will apply to these collaborations. The risks that we face in connection with these collaborations include the following:

- disputes may arise in the future with respect to the ownership of rights to technology developed with collaborators;
- disagreements with collaborators could delay or terminate the research, development or commercialization of products, or result in litigation or arbitration;
- we may have difficulty enforcing the contracts if one of our collaborators fails to perform;
- our collaborators may terminate their collaborations with us, which could make it difficult for us to attract new collaborators or adversely affect the perception of us in the business or financial communities;
- collaborators have considerable discretion in electing whether to pursue the development of any additional drugs and may pursue technologies or products either on their own or in collaboration with our competitors that are similar to or competitive with our technologies or products that are the subject of the collaboration with us; and
- our collaborators may change the focus of their development and commercialization efforts. Pharmaceutical and biotechnology companies historically have re-evaluated their priorities following mergers and consolidations, which have been common in recent years in these industries. The ability of our products to reach their potential could be limited if our collaborators decrease or fail to increase spending relating to such products.

Given these risks, it is possible that any collaborative arrangements into which we enter may not be successful. Previous collaborative arrangements to which we were a party with F. Hoffmann-La Roche and G.D. Searle & Co. both were terminated prior to the development of any product. The failure of any of our collaborative relationships could delay our drug development or impair commercialization of our products.

## Risks Relating to Intellectual Property

***If we are unable to obtain patent protection for our discoveries, the value of our technology and products will be adversely affected.***

Our patent positions, and those of other drug discovery companies, are generally uncertain and involve complex legal, scientific and factual questions.

Our ability to develop and commercialize drugs depends in significant part on our ability to:

- obtain patents;
- obtain licenses to the proprietary rights of others on commercially reasonable terms where needed;
- operate without infringing upon the proprietary rights of others;
- prevent others from infringing on our proprietary rights; and
- protect trade secrets.

We do not know whether any of our patent applications or those patent applications which we license will result in the issuance of any patents. Our issued patents and those that may issue in the future, or those licensed to us, may be challenged, invalidated or circumvented, and the rights granted thereunder may not provide us proprietary protection or competitive advantages against competitors with similar technology. Furthermore, our competitors may independently develop similar technologies or duplicate any technology developed by us. Because of the extensive time required for development, testing and regulatory review of a potential product, it is possible that, before any of our products can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thus reducing any advantage of the patent.

Because patent applications in the United States and many foreign jurisdictions are typically not published until 18 months after filing, or in some cases not at all, and because publications of discoveries in the scientific literature often lag behind actual discoveries, neither we nor our licensors can be certain that we or they were the first to make the inventions claimed in issued patents or pending patent applications, or that we or they were the first to file for protection of the inventions set forth in these patent applications.

***Third parties may own or control patents or patent applications and require us to seek licenses, which could increase our development and commercialization costs, or prevent us from developing or marketing products.***

We may not have rights under some patents or patent applications related to our products. Third parties may own or control these patents and patent applications in the United States and abroad. Therefore, in some cases, to develop, manufacture, sell or import some of our products, we or our collaborators may choose to seek, or be required to seek, licenses under third party patents issued in the United States and abroad or under patents that might issue from United States and foreign patent applications. In such event, we would be required to pay license fees or royalties or both to the licensor. If licenses are not available to us on acceptable terms, we or our collaborators may not be able to develop, manufacture, sell or import these products.

***We may lose our rights to patents, patent applications or technologies of third parties if our licenses from these third parties are terminated. In such an event, we might not be able to develop or commercialize products covered by the licenses.***

We are party to nine royalty-bearing license agreements under which we have acquired rights to patents, patent applications and technology of third parties. Under these licenses we are obligated to pay royalties on net sales by us of products or processes covered by a valid claim of a patent or patent application licensed to us. We also are required in some cases to pay a specified percentage of any sublicense income that we may receive. These licenses impose various commercialization, sublicensing, insurance and other obligations on us. Our failure to comply with these requirements could result in termination of the licenses. These licenses generally will otherwise

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remain in effect until the expiration of all valid claims of the patents covered by such licenses or upon earlier termination by the parties. The issued patents covered by these licenses expire at various dates ranging from 2006 to 2022. If one or more of these licenses is terminated, we may be delayed in our efforts, or be unable, to develop and market the products that are covered by the applicable license or licenses.

***We may become involved in expensive patent litigation or other proceedings, which could result in our incurring substantial costs and expenses or substantial liability for damages or require us to stop our development and commercialization efforts.***

There has been substantial litigation and other proceedings regarding patent and other intellectual property rights in the biotechnology industry. We may become a party to various types of patent litigation or other proceedings regarding intellectual property rights from time to time even under circumstances where we are not practicing and do not intend to practice any of the intellectual property involved in the proceedings. For instance, in 2002, we became involved in an interference declared by the United States Patent and Trademark Office involving a patent application exclusively licensed by us from University of Massachusetts Medical Center, or UMMC, and three patents issued to the National Institutes of Health. In addition, in 2003, we became involved in an interference declared by the United States Patent and Trademark Office involving another patent exclusively licensed to us from UMMC and a patent application assigned jointly to the University of Montreal and The Massachusetts Institute of Technology. We are neither practicing nor intending to practice the intellectual property involved in either of the interferences of which we are involved. As of September 1, 2004, both interferences are still proceeding.

The cost to us of any patent litigation or other proceeding, including the interferences referred to above, even if resolved in our favor, could be substantial. Some of our competitors may be able to sustain the cost of such litigation or proceedings more effectively than we can because of their substantially greater financial resources. If any patent litigation or other proceeding is resolved against us, we or our collaborators may be enjoined from developing, manufacturing, selling or importing our drugs without a license from the other party and we may be held liable for significant damages. We may not be able to obtain any required license on commercially acceptable terms or at all.

Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace. Patent litigation and other proceedings may also absorb significant management time.

### **Risks Relating to Product Manufacturing, Marketing and Sales and Reliance on Third Parties**

***Because we have limited manufacturing experience, we are dependent on third-party manufacturers to manufacture products for us. If we cannot rely on third-party manufacturers, we will be required to incur significant costs and devote significant efforts to establish our own manufacturing facilities and capabilities.***

We have limited manufacturing experience and no commercial scale manufacturing capabilities. In order to continue to develop our products, apply for regulatory approvals and ultimately commercialize products, we need to develop, contract for or otherwise arrange for the necessary manufacturing capabilities.

We currently rely upon third parties to produce material for preclinical and clinical testing purposes and expect to continue to do so in the future. We also expect to rely upon third parties to produce materials that may be required for the commercial production of our products.

There are a limited number of manufacturers that operate under the FDA's current good manufacturing practices regulations capable of manufacturing our products. As a result, we may have difficulty finding manufacturers for our products with adequate capacity for our needs. If we are unable to arrange for third party manufacturing of our products on a timely basis, or to do so on commercially reasonable terms, we may not be able to complete development of our products or market them.

Reliance on third party manufacturers entails risks to which we would not be subject if we manufactured products ourselves, including:

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- reliance on the third party for regulatory compliance and quality assurance,
- the possibility of breach of the manufacturing agreement by the third party because of factors beyond our control,
- the possibility of termination or nonrenewal of the agreement by the third party, based on its own business priorities, at a time that is costly or inconvenient for us,
- the potential that third party manufacturers will develop know-how owned by such third party in connection with the production of our products that is necessary for the manufacture of our products, and
- reliance upon third party manufacturers to assist us in preventing inadvertent disclosure or theft of our proprietary knowledge.

Between September 2000 and March 2004, we purchased oligonucleotides for preclinical and clinical testing from Avecia Biotechnology under a manufacturing agreement. Since the expiration of our manufacturing agreement with Avecia in March 2004, Avecia has continued to provide oligonucleotides to us under the terms of that agreement while the parties work to establish a new agreement. We are continuing to purchase oligonucleotides from Avecia for use in clinical trials. If we are unable to enter into a new manufacturing arrangement with Avecia or a new contract manufacturer on a timely basis or at all, our ability to supply the product needed for our clinical trials could be materially impaired.

***We have no experience selling, marketing or distributing products and no internal capability to do so.***

If we receive regulatory approval to commence commercial sales of any of our products, we will face competition with respect to commercial sales, marketing and distribution. These are areas in which we have no experience. To market any of our products directly, we would need to develop a marketing and sales force with technical expertise and with supporting distribution capability. In particular, we would need to recruit a large number of experienced marketing and sales personnel. Alternatively, we could engage a pharmaceutical or other healthcare company with an existing distribution system and direct sales force to assist us. However, to the extent we entered into such arrangements, we would be dependent on the efforts of third parties. If we are unable to establish sales and distribution capabilities, whether internally or in reliance on third parties, our business would suffer materially.

***If third parties on whom we rely for clinical trials do not perform as contractually required or as we expect, we may not be able to obtain regulatory approval for or commercialize our products and our business may suffer.***

We do not have the ability to independently conduct the clinical trials required to obtain regulatory approval for our products. We depend on independent clinical investigators, contract research organizations and other third party service providers in the conduct of the clinical trials of our products and expect to continue to do so. We rely heavily on these parties for successful execution of our clinical trials, but do not control many aspects of their activities. We are responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with standards, commonly referred to as good clinical practices, for conducting, recording and reporting clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Our reliance on third parties that we do not control does not relieve us of these responsibilities and requirements. Third parties may not complete activities on schedule or may not conduct our clinical trials in accordance with regulatory requirements or our stated protocols. The failure of these third parties to carry out their obligations could delay or prevent the development, approval and commercialization of our products. If we seek to conduct any of these activities ourselves in the future, we will need to recruit appropriately trained personnel and add to our infrastructure.

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***If we are unable to obtain adequate reimbursement from third party payors for any products that we may develop or acceptable prices for those products, our revenues and prospects for profitability will suffer.***

Most patients will rely on Medicare and Medicaid, private health insurers and other third party payors to pay for their medical needs, including any drugs we may market. If third party payors do not provide adequate coverage or reimbursement for any products that we may develop, our revenues and prospects for profitability will suffer. The Congress recently enacted a limited prescription drug benefit for Medicare recipients in the Medicare Prescription Drug and Modernization Act of 2003. While the program established by this statute may increase demand for our products, if we participate in this program, our prices will be negotiated with drug procurement organizations for Medicare beneficiaries and are likely to be lower than we might otherwise obtain. Non-Medicare third party drug procurement organizations may also base the price they are willing to pay on the rate paid by drug procurement organizations for Medicare beneficiaries.

A primary trend in the United States healthcare industry is toward cost containment. In addition, in some foreign countries, particularly the countries of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take six to 12 months or longer after the receipt of regulatory marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost effectiveness of our product candidates or products to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in commercialization of our products.

Third party payors are challenging the prices charged for medical products and services, and many third party payors limit reimbursement for newly-approved healthcare products. In particular, third party payors may limit the indications for which they will reimburse patients who use any products that we may develop. Cost control initiatives could decrease the price we might establish for products that we may develop, which would result in lower product revenues to us.

***We face a risk of product liability claims and may not be able to obtain insurance.***

Our business exposes us to the risk of product liability claims that is inherent in the manufacturing, testing and marketing of human therapeutic drugs. Although we have product liability and clinical trial liability insurance that we believe is adequate, this insurance is subject to deductibles and coverage limitations. We may not be able to obtain or maintain adequate protection against potential liabilities. If we are unable to obtain insurance at acceptable cost or otherwise protect against potential product liability claims, we will be exposed to significant liabilities, which may materially and adversely affect our business and financial position. These liabilities could prevent or interfere with our commercialization efforts.

### **Risks Relating to an Investment in Our Common Stock**

***Our corporate governance structure, including provisions in our certificate of incorporation and by-laws, our stockholder rights plan and Delaware law, may prevent a change in control or management that stockholders may consider desirable.***

Section 203 of the Delaware General Corporation Law and our certificate of incorporation, by-laws and stockholder rights plan contain provisions that might enable our management to resist a takeover of our company or discourage a third party from attempting to take over our company. These provisions include:

- a classified board of directors,
- limitations on the removal of directors,
- limitations on stockholder proposals at meetings of stockholders,
- the inability of stockholders to act by written consent or to call special meetings, and
- the ability of our board of directors to designate the terms of and issue new series of preferred stock without

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stockholder approval.

These provisions could have the effect of delaying, deferring, or preventing a change in control of us or a change in our management that stockholders may consider favorable or beneficial. These provisions could also discourage proxy contests and make it more difficult for you and other stockholders to elect directors and take other corporate actions. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock.

***Our stock price has been and may in the future be extremely volatile. In addition, because an active trading market for our common stock has not developed, our investors' ability to trade our common stock may be limited. As a result, investors may lose all or a significant portion of their investment.***

Our stock price has been volatile. During the period from January 1, 2002 to September 1, 2004, the closing sale price of our common stock ranged from a high of \$1.77 per share to a low of \$0.42 per share. The stock market has also experienced significant price and volume fluctuations, and the market prices of biotechnology companies in particular have been highly volatile, often for reasons that have been unrelated to the operating performance of particular companies. The market price for our common stock may be influenced by many factors, including:

- results of clinical trials of our product candidates or those of our competitors;
- the regulatory status of our product candidates;
- failure of any of our product candidates, if approved, to achieve commercial success;
- the success of competitive products or technologies;
- regulatory developments in the United States and foreign countries;
- developments or disputes concerning patents or other proprietary rights;
- the departure of key personnel;
- variations in our financial results or those of companies that are perceived to be similar to us;
- our cash resources;
- the terms of any financing conducted by us;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors and issuance of new or changed securities analysts' reports or recommendations; and
- general economic, industry and market conditions.

In addition, our common stock has historically been traded at low volume levels and may continue to trade at low volume levels. As a result, any large purchase or sale of our common stock could have a significant impact on the price of our common stock and it may be difficult for investors to sell our common stock in the market without depressing the market price for the common stock or at all.

As a result of the foregoing, investors may not be able to resell their shares at or above the price they paid for such shares. Investors in our common stock must be willing to bear the risk of fluctuations in the price of our common stock and the risk that the value of their investment in our stock could decline.

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***Our former independent public accountant, Arthur Andersen LLP, has been found guilty of a federal obstruction of justice charge. Arthur Andersen LLP has not consented to the inclusion of its audit report with respect to our consolidated financial statements in this prospectus, and you may be unable to exercise effective remedies against it in any legal action.***

Our former independent public accountant, Arthur Andersen LLP, provided us with auditing services for prior fiscal periods through December 31, 2001, including issuing an audit report with respect to our audited consolidated financial statements as of and for the year ended December 31, 2001, which report is included in our annual report on Form 10-K for the year ended December 31, 2003 and is incorporated by reference in this prospectus. On June 15, 2002, a jury in Houston, Texas found Arthur Andersen LLP guilty of a federal obstruction of justice charge arising from the federal government's investigation of Enron Corp. On August 31, 2002, Arthur Andersen LLP ceased practicing before the Securities and Exchange Commission.

We were unable to obtain Arthur Andersen LLP's consent to include its report with respect to our audited consolidated financial statements as of and for the year ended December 31, 2001 in our annual report on Form 10-K for the year ended December 31, 2003, in this prospectus or in any other filing that we may make with the SEC. As a result, you may not have an effective remedy against Arthur Andersen LLP in connection with a material misstatement or omission with respect to those audited consolidated financial statements or any filing that we may make with the Securities and Exchange Commission. In addition, even if you were able to assert such a claim, as a result of its conviction and other lawsuits, Arthur Andersen LLP may fail or otherwise have insufficient assets to satisfy claims made by investors or by us that might arise under federal securities laws or otherwise relating to any alleged material misstatement or omission with respect to our audited consolidated financial statements.

#### **SPECIAL NOTE REGARDING FORWARD-LOOKING INFORMATION**

This prospectus and the documents we incorporate by reference contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. All statements, other than statements of historical facts, included or incorporated in this prospectus regarding our strategy, future operations, financial position, future revenues, projected costs, prospects, plans and objectives of management are forward-looking statements. The words "anticipates," "believes," "estimates," "expects," "intends," "may," "plans," "projects," "will," "would" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this prospectus, particularly under the heading "Risk Factors," that we believe could cause actual results or events to differ materially from the forward-looking statements that we make. In addition, any forward-looking statements represent our estimates only as of the date this prospectus is filed with the SEC and should not be relied upon as representing our estimates as of any subsequent date. We do not assume any obligation to update any forward-looking statements.

#### **USE OF PROCEEDS**

We will not receive any proceeds from the sale of the shares offered pursuant to this prospectus. The selling stockholders will receive all of the proceeds from the sale of the shares of common stock offered by this prospectus. For information about the selling stockholders, see "Selling Stockholders."

The selling stockholders will pay any underwriting discounts and commissions and expenses incurred by the selling stockholders for brokerage, accounting, tax or legal services or any other expenses incurred by the selling stockholders in disposing of the shares. We will bear all other costs, fees and expenses incurred in effecting the registration of the shares covered by this prospectus, including all registration and filing fees and fees and expenses of our counsel and our accountants.



**SELLING STOCKHOLDERS**

The shares of common stock covered by this prospectus include:

- 8,823,400 shares of common stock that we issued to the selling stockholders in a private placement on August 27, 2004;
- 1,764,680 shares of common stock issuable upon exercise of warrants to purchase common stock which we issued to the selling stockholders in connection with their purchase of shares of common stock in the private placement, which we refer to as the investor warrants; and
- 432,520 shares of common stock issuable upon exercise of warrants to purchase common stock, which we refer to as the dealer warrants, which we issued to Pillar Investments Limited, which acted as a non-exclusive financial advisor to us in connection with the private placement of our securities to investors outside of the United States.

The table below sets forth, to our knowledge, information about the selling stockholders as of September 1, 2004.

We do not know when or in what amounts a selling stockholder may offer shares for sale. The selling stockholders may sell any or all of the shares offered by this prospectus. Because the selling stockholders may offer all or some of the shares pursuant to this offering, and because there are currently no agreements, arrangements or understandings with respect to the sale of any of the shares, we cannot estimate the number of shares that will be held by the selling stockholders after completion of this offering. For purposes of this table, however, we have assumed that, after completion of this offering, none of the shares covered by this prospectus will be held by the selling stockholders.

Beneficial ownership is determined in accordance with the rules of the SEC, and includes voting or investment power with respect to shares. Shares of common stock issuable upon exercise of warrants or stock options that are exercisable within 60 days after September 1, 2004 are deemed outstanding for computing the percentage ownership of the person holding the warrants or options but are not deemed outstanding for computing the percentage ownership of any other person. Unless otherwise indicated below, to our knowledge, all persons named in the table have sole voting and investment power with respect to the shares of common stock beneficially owned by them, except to the extent authority is shared by spouses under applicable law. The inclusion of any shares in this table does not constitute an admission of beneficial ownership for the person named below.

Name of Selling Stockholder (1)	Shares of Common Stock Beneficially Owned Prior to Offering		Number of Shares of Common Stock Being Offered	Shares of Common Stock to be Beneficially Owned After Offering	
	Number	Percentage		Number	Percentage
Biomedical Offshore Value Fund Ltd.	4,261,316(2)	3.8%	1,733,520	2,527,796	2.3%
Biomedical Value Fund L.P.	5,714,078(3)	5.1%	342,600	5,371,478	4.8%
Banque Saudi Fransi	6,476,342(4)	5.8%	5,190,240	1,286,102	1.2%
Optima Life Sciences Limited	10,472,215(5)	9.3%	3,321,720	7,150,495	6.3%
Pillar Investments Limited	1,020,229(6)	*%	432,520	587,709	*%

\* Less than one percent.

(1) The term “selling stockholders” includes donees, pledgees, transferees or other successors-in-interest selling shares received after the date of this prospectus from a selling stockholder as a gift, pledge, partnership distribution or other non-sale related transfer.

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- (2) Includes 674,516 shares of common stock issuable upon the exercise of warrants held by Biomedical Offshore Value Fund Ltd..
- (3) Includes 876,478 shares of common stock issuable upon the exercise of warrants held by Biomedical Value Fund L.P.
- (4) Includes 865,040 shares of common stock issuable upon the exercise of warrants held by Banque Saudi Fransi.
- (5) Includes 2,203,734 shares of common stock issuable upon the exercise of warrants held by Optima Life Sciences Limited.
- (6) Includes 1,020,229 shares of common stock issuable upon the exercise of warrants held by Pillar Investments Limited.

### **Relationships with Selling Stockholders**

Except for the selling stockholders listed below, no selling stockholder has had any position, office or other material relationship with us or our affiliates since September 1, 2001.

#### *Optima Life Sciences Limited and Pillar Investment Limited*

One of our directors, Youssef El-Zein, is a director of Optima Life Sciences Limited and Pillar Investment Limited. Pillar Investment Limited is the manager and investment advisor of Optima.

Pillar Investment Limited acted as a placement agent for non-U.S. investors for us in connection with our August 2004 private placement under the terms of an engagement letter dated August 27, 2004. Under the terms of the engagement letter, we paid Pillar Investment Limited \$287,000 in cash and issued Pillar Investment Limited warrants to purchase 432,520 shares of common stock at an exercise price of \$0.67 per share as fees in connection with the participation of non-U.S. investors in our August 2004 private placement.

Pillar Investment Limited acted as a placement agent for us in connection with our August 2003 private placement under the terms of an engagement letter dated April 18, 2003 with Pillar Investment Limited and PrimeCorp Finance S.A. Under the terms of the engagement letter, we paid Pillar Investment Limited \$300,319 in cash and issued Pillar Investment Limited warrants to purchase 587,709 shares of common stock at an exercise price of \$1.00 per share as fees in connection with the participation of non-U.S. investors in our August 2003 private placement.

Since September 1, 2001, Pillar S.A., an affiliate of Pillar Investment Limited and Mr. El-Zein, has provided consulting services to us relating to international investor relations, employment contracts with our management team and various transactions in which we have engaged, such as proxy solicitation and our repurchase of common stock in 2003. For consulting services provided since September 1, 2001, we have paid Pillar a total of \$357,500 in cash, including \$38,500 in the twelve months ended September 1, 2002, \$265,000 in the twelve months ended September 1, 2003, and \$54,000 in the twelve months ended September 1, 2004.

### **DESCRIPTION OF CAPITAL STOCK**

We are authorized to issue 185,000,000 shares of common stock and 5,000,000 shares of preferred stock, \$0.01 par value per share, of which 1,500,000 are designated series A convertible preferred stock and 150,000 shares are designated series C junior participating preferred stock. As of September 1, 2004, there were 110,887,609 shares of common stock outstanding, 655 shares of series A convertible preferred stock outstanding, no shares of series C junior participating preferred stock outstanding and no other shares of preferred stock issued and outstanding.

The material terms and provisions of our common stock, our preferred stock, our preferred stock purchase rights and each other class of our securities that qualifies or limits our common stock, are described in our

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Registration Statement on Form 8-A dated December 4, 2003 which is incorporated by reference in this prospectus. For the complete terms of our common stock, preferred stock and preferred stock purchase rights, please refer to our certificate of incorporation, by-laws and stockholder rights plan that we have filed with the SEC. The terms of these securities may also be affected by the General Corporation Law of the State of Delaware.

### **PLAN OF DISTRIBUTION**

The selling shareholders may offer and sell the shares covered by this prospectus from time to time. The term "selling stockholders" includes donees, pledgees, transferees or other successors-in-interest selling shares received after the date of this prospectus from the selling stockholders as a gift, pledge, partnership distribution or other transfer. The selling stockholders will act independently of us in making decisions with respect to the timing, manner and size of each sale. Such sales may be made on one or more exchanges or in the over-the-counter market or otherwise, at prices and under terms then prevailing or at prices related to the then current market price or in negotiated transactions. The selling stockholders may sell their shares by one or more of, or a combination of, the following methods:

- purchases by a broker-dealer as principal and resale by such broker-dealer for its own account pursuant to this prospectus;
- ordinary brokerage transactions and transactions in which the broker solicits purchasers;
- block trades in which the broker-dealer so engaged will attempt to sell the shares as agent but may position and resell a portion of the block as principal to facilitate the transaction;
- an over-the-counter distribution;
- in privately negotiated transactions; and
- in options transactions.

In addition, the selling stockholders may sell any shares that qualify for sale pursuant to Rule 144 under Rule 144 rather than pursuant to this prospectus.

In connection with distributions of the shares or otherwise, the selling stockholders may enter into hedging transactions with broker-dealers or other financial institutions. In connection with such transactions, broker-dealers or other financial institutions may engage in short sales of the common stock in the course of hedging the positions they assume with selling stockholders. The selling stockholders may also sell the common stock short and redeliver the shares to close out such short positions. The selling stockholders may also enter into option or other transactions with broker-dealers or other financial institutions which require the delivery to such broker-dealer or other financial institution of shares offered by this prospectus, which shares such broker-dealer or other financial institution may resell pursuant to this prospectus, as supplemented or amended to reflect such transaction. The selling stockholders may also pledge shares to a broker-dealer or other financial institution, and, upon a default, such broker-dealer or other financial institution, may effect sales of the pledged shares pursuant to this prospectus, as supplemented or amended to reflect such transaction. In effecting sales, broker-dealers or agents engaged by the selling stockholders may arrange for other broker-dealers to participate. Broker-dealers or agents may receive commissions, discounts or concessions from the selling stockholders in amounts to be negotiated immediately prior to the sale.

In offering the shares covered by this prospectus, the selling stockholders and any broker-dealers who execute sales for the selling stockholders may be deemed to be "underwriters" within the meaning of the Securities Act in connection with such sales. Any profits realized by the selling stockholders and the compensation of any broker-dealers may be deemed to be underwriting discounts and commissions.

In order to comply with the securities laws of some states, if applicable, the shares must be sold in those states only through registered or licensed brokers or dealers. In addition, some states may restrict the selling

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stockholders from selling their shares unless the shares have been registered or qualified for sale in the applicable state or an exemption from the registration or qualification requirement is available and is complied with.

We have advised the selling stockholders that the anti-manipulation rules of Regulation M under the Exchange Act may apply to sales of shares in the market and to the activities of the selling stockholders and their affiliates. In addition, we will make copies of this prospectus available to the selling stockholders for the purpose of satisfying the prospectus delivery requirements of the Securities Act. The selling stockholders may indemnify any broker-dealer that participates in transactions involving the sale of the shares against some liabilities, including liabilities arising under the Securities Act.

At the time a particular offer of shares is made, if required, we will distribute a prospectus supplement that will set forth the number of shares being offered and the terms of this offering, including the name of any underwriter, dealer or agent, the purchase price paid by any underwriter, any discount, commission and other item constituting compensation, any discount, commission or concession allowed or reallocated or paid to any dealer, and the proposed selling price to the public. In addition, we may amend or supplement this prospectus from time to time to describe a specific plan of distribution.

We have agreed to indemnify the selling stockholders against some liabilities, including some liabilities under the Securities Act.

We have agreed with the selling stockholders to use our best efforts to cause the registration statement of which this prospectus constitutes a part to remain effective until the earlier of:

- such time as all of the shares covered by this prospectus and held by the selling stockholders are eligible to be sold under Rule 144 of the Securities Act without restriction by the volume limitations of Rule 144(e) of the Securities Act; and
- such time as all of the shares covered by this prospectus have been sold pursuant to the registration statement of which this prospectus constitutes a part, to or through a broker or dealer or underwriter in a public securities transaction or in a transaction exempt from the registration and prospectus delivery requirements of the Securities Act such that all transfer restrictions and restrictive legends, if any, are removed upon the consummation of such sale.

## **LEGAL MATTERS**

The validity of the shares offered by this prospectus has been passed upon by Wilmer Cutler Pickering Hale and Dorr LLP.

## **EXPERTS**

Ernst & Young LLP, an independent registered accounting firm, have audited our consolidated financial statements included in our Annual Report on Form 10-K for the years ended December 31, 2003 and 2002, as set forth in their report, which is incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements as of and for the years ended December 31, 2003 and 2002 are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

Our consolidated financial statements as of and for the year ended December 31, 2001 appearing in our Annual Report on Form 10-K have been audited by Arthur Andersen LLP, independent accountants. On August 31, 2002, Arthur Andersen LLP ceased practicing before the SEC. Therefore, Arthur Andersen LLP did not participate in the preparation of the Annual Report on Form 10-K, did not re-issue its audit report with respect to these financial statements and did not consent to the inclusion of its report in the Annual Report on Form 10-K or this prospectus. For more information, see "Risk Factors — Our former independent public accountant, Arthur Andersen LLP, has been found guilty of a federal obstruction of justice charge. Arthur Andersen LLP has not consented to the inclusion of its audit report with respect to our consolidated financial statements in this prospectus, and you may be unable to exercise effective remedies against it in any legal action."

## WHERE YOU CAN FIND MORE INFORMATION

We file reports, proxy statements and other documents with the SEC. You may read and copy any document we file at the SEC's public reference room at Judiciary Plaza Building, 450 Fifth Street, N.W., Room 1024, Washington, D.C. 20549. You should call 1-800-SEC-0330 for more information on the public reference room. Our SEC filings are also available to you on the SEC's Internet site at <http://www.sec.gov>.

This prospectus is part of a registration statement that we filed with the SEC. The registration statement contains more information than this prospectus regarding us and our common stock, including certain exhibits and schedules. You can obtain a copy of the registration statement from the SEC at the address listed above or from the SEC's Internet site.

## INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

The SEC requires us to "incorporate" into this prospectus information that we file with the SEC in other documents. This means that we can disclose important information to you by referring to other documents that contain that information. The information incorporated by reference is considered to be part of this prospectus. Information contained in this prospectus and information that we file with the SEC in the future and incorporate by reference in this prospectus automatically updates and supersedes previously filed information. We incorporate by reference the documents listed below and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, prior to the sale of all the shares covered by this prospectus.

- (1) Our Annual Report on Form 10-K for the year ended December 31, 2003, as amended on April 29, 2004.
- (2) Our Quarterly Report on Form 10-Q for the quarter ended March 31, 2004;
- (3) Our Quarterly Report on Form 10-Q for the quarter ended June 30, 2004;
- (4) Our Current Report on Form 8-K dated April 15, 2004;
- (5) Our Current Report on Form 8-K dated April 16, 2004;
- (6) Our Current Report on Form 8-K dated August 27, 2004;
- (7) Our Current Report on Form 8-K dated September 27, 2004;
- (8) The description of our capital stock contained in our Registration Statement on Form 8-A dated December 4, 2003, including any amendments or reports filed for the purpose of updating that description; and
- (9) All of our filings pursuant to the Exchange Act after the date of filing the initial registration statement and prior to effectiveness of the registration statement.

You may request a copy of these documents, which will be provided to you at no cost, by writing or telephoning us using the following contact information below. We will provide copies of the exhibits to these filings only if they are specifically incorporated by reference in these filings.

Hybridon, Inc.  
345 Vassar Street  
Cambridge, Massachusetts 02139  
Attention: Investor Relations  
(617) 679-5500

**PART II**  
**INFORMATION NOT REQUIRED IN PROSPECTUS**

**Item 14. Other Expenses of Issuance and Distribution.**

The following table sets forth the various expenses to be incurred in connection with the sale and distribution of the securities being registered hereby (except any underwriting discounts and commissions), all of which will be borne by Hybridon. All amounts shown are estimates except the SEC registration fee.

Filing Fee — Securities and Exchange Commission	\$ 727
Legal fees and expenses	20,000
Accounting fees and expenses	10,000
Miscellaneous expenses	9,273
	<hr/>
Total Expenses	\$40,000
	<hr/>

**Item 15. Indemnification of Directors and Officers.**

Article EIGHTH of the Registrant's Restated Certificate of Incorporation provides that no director of the Registrant shall be personally liable for any monetary damages for any breach of fiduciary duty as a director, except to the extent that the Delaware General Corporation Law prohibits the elimination or limitation of liability of directors for breach of fiduciary duty.

Article NINTH of the Registrant's Restated Certificate of Incorporation provides that a director or officer of the Registrant (a) shall be indemnified by the Registrant against all expenses (including attorneys' fees), judgments, fines and amounts paid in settlement incurred in connection with any litigation or other legal proceeding (other than an action by or in the right of the Registrant) brought against him by virtue of his position as a director or officer of the Registrant if he acted in good faith and in a manner he reasonably believed to be in, or not opposed to, the best interests of the Registrant, and, with respect to any criminal action or proceeding, had no reasonable cause to believe his conduct was unlawful and (b) shall be indemnified by the Registrant against all expense (including attorneys' fees) and amounts paid in settlement incurred in connection with any action by or in the right of the Registrant brought against him by virtue of his position as a director or officer of the Registrant if he acted in good faith and in a manner he reasonably believed to be in, or not opposed to, the best interests of the Registrant, except that no indemnification shall be made with respect to any matter as to which such person shall have been adjudged to be liable to the Registrant, unless a court determines that, despite such adjudication but in view of all of the circumstances, he is entitled to indemnification of such expenses. Notwithstanding the foregoing, to the extent that a director or officer has been successful, on the merits or otherwise, including, without limitation, the dismissal of an action without prejudice, he is required to be indemnified by the Registrant against all expenses (including attorneys' fees) incurred in connection therewith. Expenses shall be advanced to a director or officer at his request, provided that he undertakes to repay the amount advanced if it is ultimately determined that he is not entitled to indemnification for such expenses.

Indemnification is required to be made unless the Registrant determines that the applicable standard of conduct required for indemnification has not been met. In the event of a determination by the Registrant that the director or officer did not meet the applicable standard of conduct required for indemnification, or if the Registrant fails to make an indemnification payment within 60 days after such payment is claimed by such person, such person is permitted to petition the court to make an independent determination as to whether such person is entitled to indemnification. As a condition precedent to the right of indemnification, the director or officer must give the Registrant notice of the action for which indemnity is sought and the Registrant has the right to participate in such action or assume the defense thereof.

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Article NINTH of the Registrant's Restated Certificate of Incorporation further provides that the indemnification provided therein is not exclusive, and provides that in the event that the Delaware General Corporation Law is amended to expand the indemnification permitted to directors or officers the Registrant must indemnify those persons to the full extent permitted by such law as so amended.

Section 145 of the Delaware General Corporation law provides that a corporation has the power to indemnify a director, officer, employee or agent of the corporation and certain other persons serving at the request of the corporation in related capacities against amounts paid and expense incurred in connection with an action or proceeding to which he is or is threatened to be made a party by reason of such position, if such person shall have acted in good faith and in a manner he reasonably believed to be in or not opposed to the best interests of the corporation, and, in any criminal proceeding, if such person had no reasonable cause to believe his conduct was unlawful; provided that, in the case of actions brought by or in the right of the corporation, no indemnification shall be made with respect to any matter as to which such person shall have been adjudged to be liable to the corporation unless and only to the extent that the adjudicating court determines that such indemnification is proper under the circumstances.

Hybridon has obtained directors and officers insurance for the benefit of its directors and its officers.

### **Item 16. Exhibits**

The exhibits listed in the Exhibit Index immediately preceding the exhibits are filed as part of this Registration Statement on Form S-3.

### **Item 17. Undertakings.**

The undersigned Registrant hereby undertakes:

(1) To file, during any period in which offers or sales are being made, a post-effective amendment to this Registration Statement:

(i) To include any prospectus required by Section 10(a)(3) of the Securities Act of 1933, as amended (the "Securities Act");

(ii) To reflect in the prospectus any facts or events arising after the effective date of this Registration Statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in this Registration Statement. Notwithstanding the foregoing, any increase or decrease in the volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than 20 percent change in the maximum aggregate offering price set forth in the "Calculation of Registration Fee" table in the effective Registration Statement; and

(iii) To include any material information with respect to the plan of distribution not previously disclosed in this Registration Statement or any material change to such information in this Registration Statement;

*provided, however*, that paragraphs (1)(i) and (1)(ii) do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in periodic reports filed with or furnished to the Commission by the Registrant pursuant to Section 13 or Section 15(d) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), that are incorporated by reference in this Registration Statement.

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(2) That, for the purposes of determining any liability under the Securities Act, each post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at the time shall be deemed to be the initial *bona fide* offering thereof.

(3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.

The Registrant hereby undertakes that, for purposes of determining any liability under the Securities Act, each filing of the Registrant's annual report pursuant to Section 13(a) or 15(d) of the Exchange Act (and, where applicable, each filing of an employee benefit plan's annual report pursuant to Section 15(d) of the Exchange Act) that is incorporated by reference in this Registration Statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof.

Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers and controlling persons of the Registrant pursuant to the indemnification provisions described herein, or otherwise, the Registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the Registrant of expenses incurred or paid by a director, officer or controlling person of the Registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the Registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.



**SIGNATURES**

Pursuant to the requirements of the Securities Act of 1933, as amended, the Registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this Registration Statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Cambridge, Commonwealth of Massachusetts, on October 19, 2004.

**HYBRIDON, INC.**

By: /s/ Sudhir Agrawal

\_\_\_\_\_  
Sudhir Agrawal  
President and Chief Executive Officer

**SIGNATURES AND POWER OF ATTORNEY**

We, the undersigned officers and directors of Hybridon, Inc., hereby severally constitute and appoint Robert G. Andersen and Sudhir Agrawal and each of them singly, our true and lawful attorneys with full power to any of them, and to each of them singly, to sign for us and in our names in the capacities indicated below the Registration Statement on Form S-3 filed herewith and any and all pre-effective and post-effective amendments to said Registration Statement and generally to do all such things in our name and behalf in our capacities as officers and directors to enable Hybridon, Inc. to comply with the provisions of the Securities Act of 1933, as amended, and all requirements of the Securities and Exchange Commission, hereby ratifying and confirming our signatures as they may be signed by our said attorneys, or any of them, to said Registration Statement and any and all amendments thereto.

Pursuant to the requirements of the Securities Act of 1933, as amended, this Registration Statement has been signed by the following persons in the capacities and on the dates indicated.

<u>Signature</u>	<u>Title</u>	<u>Date</u>
<u>/s/ James B. Wyngaarden</u> James B. Wyngaarden, M.D.	Chairman of the Board of Directors	October 19, 2004
<u>/s/ Sudhir Agrawal</u> Sudhir Agrawal, D. Phil.	Chief Executive Officer, President and Director (Principal Executive Officer)	October 19, 2004
<u>/s/ Robert G. Andersen</u> Robert G. Andersen	Chief Financial Officer, Vice President of Operations, Treasurer and Secretary (Principal Financial and Accounting Officer)	October 19, 2004
<u>/s/ Youssef El-Zein</u> Youssef El-Zein	Director	October 19, 2004
<u>/s/ C. Keith Hartley</u> C. Keith Hartley	Director	October 19, 2004

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<u>/s/ William S. Reardon</u> William S. Reardon	Director	October 18, 2004
<u>/s/ Alison Taunton-Rigby</u> Alison Taunton-Rigby	Director	October 14, 2004
<u>/s/ Paul C. Zamecnik</u> Paul C. Zamecnik, M.D.	Director	October 19, 2004

EXHIBIT INDEX

<b>EXHIBIT NUMBER</b>	<b>DESCRIPTION</b>
4.1 (1)	Restated Certificate of Incorporation of the Registrant, as amended.
4.2 (2)	Amended and Restated By-laws of the Registrant.
5.1	Opinion of Wilmer Cutler Pickering Hale and Dorr LLP.
23.1	Consent of Ernst & Young LLP.
23.2	Consent of Wilmer Cutler Pickering Hale and Dorr LLP, included in Exhibit 5.1 filed herewith.
24.1	Power of Attorney (See page II-4 of this Registration Statement).

(1) Incorporated by reference to Exhibits to the Registrant's Registration Statement on Form 8-A dated December 4, 2003 (File No. 001-31918).

(2) Incorporated by reference to Exhibits to the Registrant's Registration Statement on Form S-1. (File No. 33-99024)

October 25, 2004  
Hybridon, Inc.  
345 Vassar Street  
Cambridge, MA 02139-4818

60 STATE STREET  
BOSTON, MA 02109  
+1 617 526 6000  
+1 617 526 5000 fax  
wilmerhale.com

Re: Registration Statement on Form S-3

Ladies and Gentlemen:

This opinion is furnished to you in connection with a Registration Statement on Form S-3 (the "Registration Statement") to be filed with the Securities and Exchange Commission (the "Commission") under the Securities Act of 1933, as amended (the "Securities Act"), for the registration of an aggregate of 11,020,600 shares of Common Stock, \$0.001 par value per share (the "Shares"), of Hybridon, Inc., a Delaware corporation (the "Company"). All of the Shares are being registered on behalf of certain stockholders of the Company (the "Selling Stockholders"). The Shares include 8,823,400 shares of Common Stock (the "Issued Shares") that are held by the Selling Stockholders and 2,197,200 shares of Common Stock (the "Warrant Shares") issuable upon the exercise of warrants held by the Selling Stockholders.

We are acting as counsel for the Company in connection with the registration for resale of the Shares. We have examined signed copies of the Registration Statement to be filed with the Commission. We have also examined and relied upon minutes of meetings of the stockholders and the Board of Directors of the Company as provided to us by the Company, stock record books of the Company as provided to us by the Company, the Certificate of Incorporation and By-Laws of the Company, each as restated and/or amended to date, and such other documents as we have deemed necessary for purposes of rendering the opinions hereinafter set forth.

In our examination of the foregoing documents, we have assumed the genuineness of all signatures, the authenticity of all documents submitted to us as originals, the conformity to original documents of all documents submitted to us as copies, the authenticity of the originals of such latter documents and the legal competence of all signatories to such documents.

Our opinion below, insofar as it relates to the Issued Shares being fully paid, is based solely on a certificate of the Chief Financial Officer of the Company confirming the Company's receipt of the consideration called for by the applicable resolutions authorizing the issuance of such Issued Shares.

We assume that the appropriate action will be taken, prior to the offer and sale of the Shares by the Selling Stockholders, to register and qualify the Shares for sale under all applicable state securities or "blue sky" laws.

We express no opinion herein as to the laws of any state or jurisdiction other than the state laws of the Commonwealth of Massachusetts, the General Corporation Law of the State of Delaware and the federal laws of the United States of America.

Based upon and subject to the foregoing, we are of the opinion that the Shares have been duly authorized, that the Issued Shares are validly issued, fully paid and nonassessable and that the Warrant Shares, when issued, sold and delivered in accordance with the provisions of the warrants, will be validly issued, fully paid and nonassessable.

Hybridon, Inc.  
October 25, 2004  
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It is understood that this opinion is to be used only in connection with the offer and sale of the Shares while the Registration Statement is in effect.

Please note that we are opining only as to the matters expressly set forth herein, and no opinion should be inferred as to any other matters. This opinion

is based upon currently existing statutes, rules, regulations and judicial decisions, and we disclaim any obligation to advise you of any change in any of these sources of law or subsequent legal or factual developments which might affect any matters or opinions set forth herein.

We hereby consent to the filing of this opinion with the Commission as an exhibit to the Registration Statement in accordance with the requirements of Item 601(b)(5) of Regulation S-K under the Securities Act and to the use of our name therein and in the related prospectus under the caption "Legal Matters." In giving such consent, we do not hereby admit that we are in the category of persons whose consent is required under Section 7 of the Securities Act or the rules and regulations of the Commission.

Very truly yours,

WILMER CUTLER PICKERING  
HALE AND DORR LLP

By: /s/ Stuart M. Falber

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Stuart M. Falber, Partner

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the reference to our firm under the caption "Experts" in the Registration Statement (Form S-3) and related Prospectus of Hybridon, Inc. for the registration of 11,020,600 shares of its common stock and to the incorporation by reference therein of our report dated January 24, 2004 (except for Note 18, as to which date is February 2, 2004), with respect to the consolidated financial statements of Hybridon, Inc. included in its Annual Report (Form 10-K) for the year ended December 31, 2003, filed with the Securities and Exchange Commission.

/s/ Ernst & Young LLP

October 21, 2004