

MANHATTAN PHARMACEUTICALS INC
Form 10KSB
March 31, 2005

UNITED STATES SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-KSB

Annual Report pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 for the fiscal year ended December 31, 2004

Transition Report pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 for the transition period from ___ to ___

Commission File Number 0-27282

MANHATTAN PHARMACEUTICALS, INC.
(Exact name of issuer as specified in its charter)

Delaware
(State or other jurisdiction of
incorporation or organization)

36-3898269
(IRS Employer Identification No.)

(212) 582-3950
(Issuer's telephone number)

(Former Name, Former Address and Former Fiscal Year, if Changed Since Last Report)

Securities registered pursuant to Section 12(b) of the Exchange Act:

None

Securities registered pursuant to Section 12(g) of the Exchange Act:

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

Check if there is no disclosure of delinquent filers pursuant to Item 405 of Regulation S-B is not contained herein, and no disclosure will be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-KSB or any amendment to this Form 10-KSB.

The issuer's revenues for the fiscal year ended December 31, 2004 were \$0.

As of March 21, 2005 there were 29,608,883 outstanding shares of common stock, par value \$.001 per share.

The aggregate market value of the voting common stock of the issuer held by non-affiliates of the issuer on March 21, 2005 based on the closing price of the common stock as quoted by the NASD Over-the-Counter Bulletin Board on such date was \$47,966,390.

Transitional Small Business Disclosure Format: Yes No

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References to the “Company,” the “Registrant,” “we,” “us,” or “our” or in this Annual Report on Form 10-KSB refer to Manhattan Pharmaceuticals, Inc., a Delaware corporation, and our consolidated subsidiaries, together taken as a whole, unless the context indicates otherwise.

Forward-Looking Statements

This Annual Report on Form 10-KSB contains statements that are not historical but are forward-looking in nature, including statements regarding the expectations, beliefs, intentions or strategies regarding the future. In particular, the “Risk Factors” section following Item 1 and the “Management’s Discussion and Analysis of Financial Condition and Results of Operations” section in Item 6 of this annual report include forward-looking statements that reflect our current views with respect to future events and financial performance. We use words such as we “expect,” “anticipate,” “believe,” and “intend” and similar expressions to identify forward-looking statements. Investors should be aware that actual results may differ materially from our expressed expectations because of risks and uncertainties inherent in future events, particularly those risks identified in the subsection entitled “Risk Factors” following Item 1 in this Annual Report, and should not unduly rely on these forward looking statements.

PART I

ITEM 1. DESCRIPTION OF BUSINESS

Overview

We are engaged in the business of developing and commercializing biomedical and pharmaceutical technologies. We aim to acquire proprietary rights to these technologies by licensing or otherwise acquiring an ownership interest, funding their research and development and eventually bringing the technologies to market. We do not have any drugs or other products available for sale, but we are currently researching and developing two biomedical technologies:

- Oleoyl-estrone, an orally administered hormone attached to a fatty-acid that has been shown to cause significant weight loss in preclinical animal studies regardless of dietary modifications; and
- Lingual spray propofol, a proprietary lingual spray technology to deliver propofol for pre-procedural sedation prior to diagnostic, therapeutic or endoscopic procedures.

Although we are primarily focused on developing these technologies, we continue to seek to acquire proprietary rights to other biomedical and pharmaceutical technologies, by licensing or acquiring an ownership interest, funding their research and development and bringing the technologies to market. We have signed a letter of intent to acquire Tarpan Therapeutics, Inc. (“Tarpan”), a privately-held, New York-based biopharmaceutical company developing dermatological therapeutics, in an all stock transaction. Upon consummation of the transaction, Tarpan shareholders will own approximately 20% of the shares of Manhattan on a fully-diluted basis. Upon the close of the Tarpan transaction, our expanded therapeutic portfolio will consist of three product candidates having the potential to address various large, underserved medical markets. Through the acquisition, we will acquire Tarpan’s primary product candidate, PTH (1-34), a peptide believed to be a regulator of epidermal cell growth and differentiation.

Several of Tarpan’s stockholders are directors or significant stockholders of our company. For example, Joshua Kazam, Timothy McInerney, David Tanen and Dr. Michael Weiser, all directors of our company, collectively hold approximately 13.4 percent of Tarpan’s outstanding common stock. In addition, Dr. Lindsay Rosenwald and various trusts established for the benefit of Dr. Rosenwald and members of his immediate family collectively beneficially own approximately 46 percent of Tarpan’s common stock and beneficially own approximately 26 percent our common stock. Because of these relationships, our board has established a committee of disinterested directors to consider the Tarpan transaction. Although not yet closed, we anticipate completing the transaction with Tarpan in the near future.

We were incorporated originally under the name “Atlantic Pharmaceuticals, Inc.” and in March 2000, we changed our name to “Atlantic Technology Ventures, Inc.” On February 21, 2003, we completed a “reverse” acquisition of privately-held Manhattan Research Development, Inc. (formerly known as Manhattan Pharmaceuticals, Inc.), a Delaware corporation. To effect this transaction, Manhattan Pharmaceuticals Acquisition Corp., a wholly-owned subsidiary of Atlantic Technology Ventures, merged with and into Manhattan Research Development, with Manhattan Research Development surviving as a wholly owned subsidiary of Atlantic Technology Ventures. In accordance with the terms of the merger, the outstanding shares of common stock of Manhattan Research Development automatically converted into an aggregate of approximately 80 percent of the outstanding common stock of Atlantic Technology Ventures (after giving effect to the transaction). While in connection with the merger, Atlantic Technology Ventures changed its name to “Manhattan Pharmaceuticals, Inc.”, for accounting purposes, Manhattan Research Development was treated as the acquiring company. Accordingly, when we refer to our business or financial information for periods prior to the merger, we are referring to the business and financial information of Manhattan Research Development, unless the context indicates otherwise.

Oleoyl-estrone

We acquired the rights to develop and commercialize oleoyl-estrone, a hormone modified by an attachment to a fatty acid, pursuant to a February 2002 license agreement with Oleoylestrone Development, S.L., a Spanish corporation. Oleoyl-estrone is an orally administered small molecule that has been shown to cause significant weight loss in preclinical animal studies regardless of dietary modifications. We believe that oleoyl-estrone causes weight loss in two ways. First, the scientific community believes that weight loss is regulated by a part of the hypothalamus, located in the brain, called the ponderostat. It is believed that the ponderostat regulates the body’s weight in a manner similar to the way in which a thermostat regulates a room’s temperature. Preclinical studies suggest that oleoyl-estrone resets the ponderostat, telling the body that a lower weight is normal. We believe that this signal then decreases appetite, which leads to weight loss that may be maintained even after oleoyl-estrone treatment is discontinued. Second, fat cells that have been treated with oleoyl-estrone appear to shrink in size, indicating a local effect of oleoyl-estrone acting directly on cells. The apparent dual effect of oleoyl-estrone leads us to believe that the drug has the potential to cause weight loss in a variety of obese and overweight patients.

Oleoyl-estrone was initially developed by researchers at the University of Barcelona (“UB”) in Spain. Through a decade of research, scientists of the Nitrogen-Obesity Research Group at UB noted that hormones that effect metabolism play a significant role in body weight regulation. At the same time, the obesity research community suggested that weight is regulated by the ponderostat, a central mechanism in the hypothalamus of the brain believed to set the point of ideal weight. Researchers at UB believe that a hormone controls the ponderostat, raising or lowering body weight by changing the central set point for the entire body.

After examining the available work related to estrogens, changes in body weight and body fat percentage (such as during pregnancy), researchers at UB noted that the estrogen-like hormone, estrone, was elevated in the blood of both obese men and women. Initially thought to be a simple estrogen, UB researchers noticed that although estrone levels were elevated, very few obese men manifest the effects of elevated estrogen levels. Further testing revealed that oleoyl-estrone was the main form of estrone that existed in obese patients. The researchers suggested that when cells become filled with fat they produce oleoyl-estrone, signaling the brain to lose weight. They further suggested that fat cells in obese people do not produce sufficiently high levels of oleoyl-estrone to signal the ponderostat to suppress appetite and cause weight loss. Based on this concept, investigators at UB believed that they could induce weight loss by increasing levels of oleoyl-estrone in obese individuals. When oleoyl-estrone was given to rats, the rats lost weight in a dose-dependent manner, supporting the idea that oleoyl-estrone is a primary weight loss signal produced by fat cells. At the doses employed, no side effects were observed in the rats and, in female rats, uterine size remained unchanged, indicating that oleoyl-estrone did not act as an estrogen.

In January 2005, the United States Food and Drug Administration (“FDA”) accepted our filed Investigational New Drug Application (“IND”) for the human clinical testing of oleoyl estrone. This IND allowance moves us forward into the next stage of oleoyl-estrone’s development and was granted on the preclinical chemistry, manufacturing, and safety data which we submitted to the FDA.

In February 2005, we began dosing patients in our first Phase I trial of oleoyl-estrone in Basel, Switzerland to evaluate the safety and tolerability of defined doses of orally administered oleoyl-estrone in obese adults, in accordance with FDA guidelines. The objective of this human Phase I dose-escalation study is to determine the pharmacokinetic profile of oleoyl-estrone, as well as its safety and tolerability in obese adult volunteers of both genders. In total, 36 obese volunteers will be randomized to receive a single dose of either OE or a placebo, in a dose-escalating manner. The Swiss medical regulatory authority, SwissMedic, issued its formal approval to initiate such a trial last month. The trial is being conducted under the IND Application recently accepted by the FDA in February 2005 and the results will be used as a part of the U.S. regulatory approval process.

Lingual Spray Propofol

On April 4, 2003, we entered into a License and Development Agreement (the “Propofol License”) with NovaDel Pharma Inc. (“NovaDel”) for the worldwide, exclusive rights to NovaDel’s proprietary lingual spray technology to deliver propofol for preprocedural sedation prior to diagnostic, therapeutic or endoscopic procedures.

Propofol is currently delivered in an oily emulsion for intravenous infusion for induction and maintenance of general anesthesia or “monitored anesthesia care” in operating rooms, or deep sedation in intensive care units. Propofol has previously not been available for dosing via a convenient route of administration for office-based and other ambulatory uses. Accordingly, we have filed a patent application for this new method of use. Other patent applications are being prepared related to our non-oily, novel formulation.

We believe that delivering propofol via this proprietary delivery system provides many advantages over currently formulated sedatives. In addition to the convenience and ease of administration, we believe the lingual spray route will eliminate delayed onset and poor coordination of timing associated with administering oral sedatives, and allow for rapid clinical responses typical of intravenous delivery (i.e., less than 5 minutes). Lingual spray propofol is intended to allow patients to tolerate unpleasant procedures, by relieving anxiety and producing a pleasant, short-term amnesia. Particularly in children and adults unable to cooperate, mild sedation expedites the conduct of numerous ambulatory procedures that are not particularly painful, but which require the patient to remain still for the best technical result.

Novadel's delivery systems (both patented and patent-pending) are lingual sprays, enabling drug absorption through the oral mucosa and more rapid absorption into the bloodstream than presently available oral delivery systems. NovaDel refers to its delivery system as Immediate-Immediate Release (I2R™) because its delivery system is designed to provide therapeutic benefits within minutes of administration. We are working with NovaDel to develop, manufacture and commercialize the licensed product, having jointly announced commencement of a development program for lingual spray propofol in June 2003.

In July 2004, we released the results of the first human trial for our proprietary lingual spray formulation of propofol. The study, which took place in the United Kingdom, was a single-center, randomized, double-blind, placebo-controlled dose-escalating study of propofol lingual spray in twelve healthy adult volunteers. The primary objectives were to compare the safety and tolerability of three dose levels of the propofol spray to a single intravenous bolus low dose of propofol, as well as to determine the respective pharmacokinetic profiles and relative bioavailability of the three escalating doses.

No serious adverse events, nor dose-dependent changes in vital signs, occurred in any group. The mean time to maximum blood concentration of propofol following spray was approximately 30 min across all doses. Propofol was detectable in blood as early as 4 minutes following spray administration. The mean maximum blood concentrations plateaued at the highest of the three doses tested, and the mean bioavailability of the current spray formulation was up to 18% of that of the intravenous formulation.

In January 2005, the FDA accepted our IND for the initiation of the human clinical trials in the United States required for FDA approval of Propofol Lingual Spray (Propofol LS). We continue to pursue FDA approval of Propofol LS under 505(b)2 regulatory pathway. Section 505(b)2 of the U.S. Food, Drug & Cosmetic Act allows the FDA to approve a drug on the basis of existing data in the scientific literature or data used by the FDA in the approval of other drugs. Accordingly, the FDA has indicated to us that we will be able to utilize Section 505(b)2 to proceed directly to a pivotal Phase III trial for lingual spray propofol following completion of Phase 1 trials. We are actively planning the next steps of the clinical development process for Propofol LS, meeting with scientific advisors and Novadel regarding formulation, reviewing existing data, developing trial design, and evaluating plans to re-enter the clinic in mid-2005. See also "Management's Discussion and Analysis of Financial Condition and Results of Operations - Liquidity and Capital Resources - Research and Development Projects - Lingual Spray Propofol.

Although we have the sole right and obligation to develop and commercialize lingual spray propofol on a worldwide basis, NovaDel has undertaken to perform certain development activities on our behalf. NovaDel's responsibilities include formulation development, formulation stability testing, formulation analytic method development and testing and manufacture of clinical trial material for the pre-clinical and early clinical development. We will oversee pre-clinical testing, as necessary, and have responsibility for overall product development and product management. In addition, we will design and oversee clinical trials and be responsible for regulatory filings and meetings. The license agreement provides that these development activities are to be performed under the supervision of a development committee, which is comprised of an equal number of appointees of us and NovaDel. Within 30 days of the end of each calendar quarter in which any agreed-upon development activities are to be performed, each of us and NovaDel are to provide a written progress report to the development committee, which should describe the activities that have been performed and evaluate the work performed in relation to the goals of the development plan and budget. Currently, a proprietary formulation has been prepared and is undergoing one, two, three and six month stability tests, as well as specification analysis. The NovaDel license agreement also provides that NovaDel will manufacture and supply us with lingual spray propofol for use in clinical development and for commercial purposes pursuant to a manufacturing agreement to be entered into between us and NovaDel.

Market and Competition

According to estimates, the market for prescription anti-obesity drugs is approximately \$10 billion, or equal to that of diabetes. It is estimated that 61 percent of Americans are overweight and that 26 percent are obese. According to the National Institute of Health's estimate, direct costs for the treatment of obesity in 1988 were in excess of \$45 billion and accounted for nearly 8 percent of the total national cost of health care in the United States. By 1999, direct costs for the treatment of obesity had reached \$102.2 billion dollars. Meridia® and Xenical®, two currently approved anti-obesity medications, together accounted for approximately \$800 million in sales in 2001. We believe that the disease currently lacks a treatment that is safe and effective for most patient groups, and that oleoyl-estrone has the potential to meet the needs of this market.

To date, Midazolam (now a generic), which is delivered both intravenously and orally, has dominated the preprocedural sedation market, posting sales of \$536 million in 1999. However, serious adverse events are reported in midazolam's package insert, including respiratory depression, airway obstruction, oxygen desaturation, apnea and even respiratory arrest. In contrast, at the doses being developed by us, we believe that Propofol Lingual Spray may offer a safer, noninvasively administered alternative to midazolam. Propofol's rapid onset profile will allow clinicians to more accurately time its peak effects during procedures, as well as to determine the precise concentration needed for desired levels of sedation.

Competition in the pharmaceutical industry, and the anti-obesity drug market in particular, is intensely competitive. In addition to Abbott Laboratories, Inc. and Roche Holdings AG, the makers of Meridia® and Xenical®, respectively, some of the largest drug companies in the world have anti-obesity drugs currently in development, including GlaxoSmithKline PLC, Johnson & Johnson, Inc., Bristol-Myers Squibb Company, Regeneron Pharmaceutical, Inc., Phytopharm, PLC, Amgen, Inc. These companies are all substantially larger and more established than we are and have significantly greater financial and other resources than we do.

Intellectual Property and License Agreements

Our goal is to obtain, maintain and enforce patent protection for our products, formulations, processes, methods and other proprietary technologies, preserve our trade secrets, and operate without infringing on the proprietary rights of other parties, both in the United States and in other countries. Our policy is to actively seek to obtain, where appropriate, the broadest intellectual property protection possible for our product candidates, proprietary information and proprietary technology through a combination of contractual arrangements and patents, both in the U.S. and elsewhere in the world.

We also depend upon the skills, knowledge and experience of our scientific and technical personnel, as well as that of our advisors, consultants and other contractors, none of which is patentable. To help protect our proprietary know-how which is not patentable, and for inventions for which patents may be difficult to enforce, we rely on trade secret protection and confidentiality agreements to protect our interests. To this end, we require all employees, consultants, advisors and other contractors to enter into confidentiality agreements which prohibit the disclosure of confidential information and, where applicable, require disclosure and assignment to us of the ideas, developments, discoveries and inventions important to our business.

Oleoyl-estrone License Agreement

We currently have worldwide, exclusive license rights to the U.S. and foreign patents and patent applications regarding oleoyl-estrone and its use for the treatment of human disease:

1. US Patent No. 5,798,348 entitled “Fatty-acid monesters of estrogens for the treatment of obesity and/or overweight.” M. Alemany, Inventor. Application filed, October 30, 1996. Patent issued August 25, 1998. This patent expires on October 30, 2016.
2. European Patent No. 771.817 entitled “Oleate monoesters of estrogens for the treatment of obesity and/or overweight.” M. Alemany, Inventor. Application filed, October 28, 1996. Patent issued March 26, 2003. This patent expires on October 28, 2016.
3. Spanish Patent Application No. ES 200100785 entitled “Fatty-acid monoesters of estrogens acting as anti-diabetic and hypolipidemia agents.” M. Alemany Lamana, Francisco Javier Remesar Betiloch, and Jose Antonio Fernandez Lopez, Inventors. Application filed March 28, 2001, European Patent Application No. EP1380300A1, filed March 25, 2002, and Canadian Patent Application No. 2441890, filed March 25, 2002.

The U.S. and European patents have numerous, detailed, and specific claims for both the composition of oleoyl-estrone, and its method of use for weight loss. Our rights to these patents are subject to the terms of a February 2002 license agreement between us and Oleoylestrone Developments. The license agreement provides us with an exclusive, worldwide right to the intellectual property covered by the license agreement, including the right to grant sublicenses. Our success in developing oleoyl-estrone depends on our ability to maintain and enforce the patents relating to oleoyl-estrone.

In consideration for the license, we paid an initial license fee of \$175,000. The license agreement provides for further cash payments of \$9,250,000 in the aggregate, payable as follows: \$250,000 payable upon treatment of the first patient in a Phase I clinical trial under an IND sponsored by us; \$250,000 upon treatment of the first patient in a Phase II clinical trial; \$750,000 upon the first successful completion of a Phase II clinical trial; \$2,000,000 upon the first successful completion of a Phase III clinical trial; and \$6,000,000 upon the first final approval of a New Drug Application (“NDA”) for oleoyl-estrone by the FDA. The license agreement does not require us to make any royalty payments.

Subject to earlier termination as described below, the term of the license expires on the last to expire patent right licensed under the agreement, which is currently October 2016. Oleoylestrone Developments has the right to terminate the license agreement sooner, subject to certain requirements to provide us advance notice, in the event we become bankrupt or similar proceedings are initiated, fail to make the required milestone payments required under the agreement or otherwise materially breach the license agreement. We have the right to terminate the license agreement for any reason upon written notice.

Propofol LS License Agreement

Pursuant to the NovaDel license agreement, we have an exclusive, worldwide license to NovaDel’s proprietary lingual spray technology to deliver propofol for preprocedural sedation prior to diagnostic, therapeutic or endoscopic procedures. Our rights under the NovaDel License include license rights to the following patents held by NovaDel:

1. U.S. Patent No. 5,955,098, entitled "Buccal Non Polar Spray or Capsule." H.A. Dugger, III, Inventor. Application filed April 12, 1996. Patent issued September 21, 1999. This patent expires April 12, 2016.
2. U.S. Patent No. 6,110,486, entitled "Buccal Polar Spray or Capsule." H.A. Dugger, III, Inventor. Application filed November 25, 1998. Patent issued August 29, 2000. This patent expires April 12, 2016.
3. European Patent No. 0904055 entitled "Buccal, Non-Polar Spray or Capsule." H.A. Dugger, III, Inventor. Application filed, February 21, 1997. Patent issued April 16, 2003. This patent expires February 21, 2017.
4. U.S. Patent Application No. 10/834815 entitled "Buccal, Polar and Non-Polar Sprays Containing Propofol." H.A. Dugger and M.A. El-Shafy, Inventors. Application filed April 27, 2004.

These issued patents have numerous, detailed, and specific claims relating to the formulation for lingual spray applications and their method of use. We have the right to use the technology in connection with one application - delivering propofol. Our success in developing lingual spray propofol depends substantially on the maintenance and enforcement of NovaDel's patents covering its proprietary spray technology. In consideration for our rights under the NovaDel license agreement, we paid NovaDel an initial license fee of \$500,000 upon the completion of our \$10 million private placement of Series A Convertible Preferred Stock in November 2003. In addition, the license agreement requires us to make certain milestone payments as follows: \$1,000,000 payable following the date that the first IND for lingual spray propofol is accepted for review by the FDA; \$1,000,000 following the date that the first European Marketing Application is accepted for review by any European Union country; \$2,000,000 following the date when the first filed NDA for lingual spray propofol is approved by the FDA; \$2,000,000 following the date when the first filed European Marketing Application for lingual spray propofol is approved by a European Union country; \$1,000,000 following the date on which an application for commercial approval of lingual spray propofol is approved by the appropriate regulatory authority in each of Australia, Canada, Japan and South Africa; and \$50,000 following the date on which an application for commercial approval for lingual spray propofol is approved in any other country (other than the U.S. or a member of the European Union). In addition, we are obligated to pay NovaDel an annual royalty based on a fixed rate of net sales of licensed products, or if greater, the annual royalty is based on our net profits from the sale of licensed products at a rate that is twice the net sales rate.

Subject to certain requirements to provide us with notice and an opportunity to cure, NovaDel may terminate the license agreement in the event we (1) become subject to a bankruptcy or similar proceeding that is not dismissed within 60 days, (2) default in our obligation to make a required payment under the license agreement, or (3) otherwise materially breach the license agreement. The license agreement also provided that NovaDel could terminate the license agreement in the event we did not raise \$5 million in financing on or before March 31, 2004; however, we satisfied that condition in November 2003 in connection with the \$10 million private placement of our Series A Convertible Preferred Stock. We may terminate the license agreement for any reason upon 90 days' notice to NovaDel.

Manufacturing

We do not have any manufacturing capabilities. We have been in contact with several contract "Good Manufacturing Process" (GMP) manufacturers for the supply of both oleoyl-estrone and lingual spray propofol that will be necessary to conduct Phase I human clinical trials. A method has been identified for synthesizing oleoyl-estrone, and can be done through simple reactions that produce the substance at above 99 percent purity. We believe that the production of oleoyl-estrone will involve one contract manufacturer for clinical trials. Bids are being received from multiple providers, so that provider redundancy can be maintained during product launch.

Government Regulation

The research, development, testing, manufacture, labeling, promotion, advertising, distribution, and marketing, among other things, of our products are extensively regulated by governmental authorities in the United States and other countries. In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or the “FDCA,” and its implementing regulations. Failure to comply with the applicable U.S. requirements may subject us to administrative or judicial sanctions, such as FDA refusal to approve pending NDAs, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, and/or criminal prosecution.

Drug Approval Process. None of our drugs may be marketed in the U.S. until the drug has received FDA approval. The steps required before a drug may be marketed in the U.S. include:

- preclinical laboratory tests, animal studies, and formulation studies,
- submission to the FDA of an IND for human clinical testing, which must become effective before human clinical trials may begin,
- adequate and well-controlled human clinical trials to establish the safety and efficacy of the drug for each indication,
 - submission to the FDA of an NDA,
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the drug is produced to assess compliance with current good manufacturing practices, or “cGMPs,” and
 - FDA review and approval of the NDA.

Preclinical tests include laboratory evaluation of product chemistry, toxicity, and formulation, as well as animal studies. The conduct of the preclinical tests and formulation of the compounds for testing must comply with federal regulations and requirements. The results of the preclinical tests, together with manufacturing information and analytical data, are submitted to the FDA as part of an IND, which must become effective before human clinical trials may begin. An IND will automatically become effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions about issues such as the conduct of the trials as outlined in the IND. In such a case, the IND sponsor and the FDA must resolve any outstanding FDA concerns or questions before clinical trials can proceed. We cannot be sure that submission of an IND will result in the FDA allowing clinical trials to begin.

Clinical trials involve the administration of the investigational drug to human subjects under the supervision of qualified investigators. Clinical trials are conducted under protocols detailing the objectives of the study, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated. Each protocol must be submitted to the FDA as part of the IND.

Clinical trials typically are conducted in three sequential phases, but the phases may overlap. The study protocol and informed consent information for study subjects in clinical trials must also be approved by an Institutional Review Board for each institution where the trials will be conducted. Study subjects must sign an informed consent form before participating in a clinical trial. Phase I usually involves the initial introduction of the investigational drug into people to evaluate its short-term safety, dosage tolerance, metabolism, pharmacokinetics and pharmacologic actions, and, if possible, to gain an early indication of its effectiveness. Phase II usually involves trials in a limited patient population to (i) evaluate dosage tolerance and appropriate dosage; (ii) identify possible adverse effects and safety risks; and (iii) evaluate preliminarily the efficacy of the drug for specific indications. Phase III trials usually further evaluate clinical efficacy and test further for safety by using the drug in its final form in an expanded patient population. There can be no assurance that phase I, phase II, or phase III testing will be completed successfully within any specified period of time, if at all. Furthermore, the Company or the FDA may suspend clinical trials at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk.

The FDCA permits FDA and the IND sponsor to agree in writing on the design and size of clinical studies intended to form the primary basis of an effectiveness claim in an NDA application. This process is known as Special Protocol Assessment, or SPA. These agreements may not be changed after the clinical studies begin, except in limited circumstances.

Assuming successful completion of the required clinical testing, the results of the preclinical studies and of the clinical studies, together with other detailed information, including information on the manufacture and composition of the drug, are submitted to the FDA in the form of an NDA requesting approval to market the product for one or more indications. The testing and approval process requires substantial time, effort, and financial resources. The agencies review the application and may deem it to be inadequate to support the registration and we cannot be sure that any approval will be granted on a timely basis, if at all. The FDA may also refer the application to the appropriate advisory committee, typically a panel of clinicians, for review, evaluation and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendations of the advisory committee.

The FDA has various programs, including fast track, priority review, and accelerated approval, that are intended to expedite or simplify the process for reviewing drugs, and/or provide for approval on the basis surrogate endpoints. Generally, drugs that may be eligible for one or more of these programs are those for serious or life-threatening conditions, those with the potential to address unmet medical needs, and those that provide meaningful benefit over existing treatments. We cannot be sure that any of our drugs will qualify for any of these programs, or that, if a drug does qualify, that the review time will be reduced.

Section 505(b)2 of the FDCA allows the FDA to approve a follow-on drug on the basis of data in the scientific literature or data used by FDA in the approval of other drugs. This procedure potentially makes it easier for generic drug manufacturers to obtain rapid approval of new forms of drugs based on proprietary data of the original drug manufacturer.

Before approving an NDA, the FDA usually will inspect the facility or the facilities at which the drug is manufactured, and will not approve the product unless cGMP compliance is satisfactory. If the FDA evaluates the NDA and the manufacturing facilities as acceptable, the FDA may issue an approval letter, or in some cases, an approvable letter followed by an approval letter. Both letters usually contain a number of conditions that must be met in order to secure final approval of the NDA. When and if those conditions have been met to the FDA's satisfaction, the FDA will issue an approval letter. The approval letter authorizes commercial marketing of the drug for specific indications. As a condition of NDA approval, the FDA may require postmarketing testing and surveillance to monitor the drug's safety or efficacy, or impose other conditions.

After approval, certain changes to the approved product, such as adding new indications, making certain manufacturing changes, or making certain additional labeling claims, are subject to further FDA review and approval. Before we can market our product candidates for additional indications, we must obtain additional approvals from FDA. Obtaining approval for a new indication generally requires that additional clinical studies be conducted. We cannot be sure that any additional approval for new indications for any product candidate will be approved on a timely basis, or at all.

Post-Approval Requirements. Often times, even after a drug has been approved by the FDA for sale, the FDA may require that certain post-approval requirements be satisfied, including the conduct of additional clinical studies. If such post-approval conditions are not satisfied, the FDA may withdraw its approval of the drug. In addition, holders of an approved NDA are required to: (i) report certain adverse reactions to the FDA, (ii) comply with certain requirements concerning advertising and promotional labeling for their products, and (iii) continue to have quality control and manufacturing procedures conform to cGMP after approval. The FDA periodically inspects the sponsor's records related to safety reporting and/or manufacturing facilities; this latter effort includes assessment of compliance with cGMP. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance. We intend to use third party manufacturers to produce our products in clinical and commercial quantities, and future FDA inspections may identify compliance issues at the facilities of our contract manufacturers that may disrupt production or distribution, or require substantial resources to correct. In addition, discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved NDA, including withdrawal of the product from the market.

Orphan Drug. The FDA may grant orphan drug designation to drugs intended to treat a "rare disease or condition," which generally is a disease or condition that affects fewer than 200,000 individuals in the United States. Orphan drug designation must be requested before submitting an NDA. If the FDA grants orphan drug designation, which it may not, the identity of the therapeutic agent and its potential orphan use are publicly disclosed by the FDA. Orphan drug designation does not convey an advantage in, or shorten the duration of, the review and approval process. If a product which has an orphan drug designation subsequently receives the first FDA approval for the indication for which it has such designation, the product is entitled to orphan exclusivity, meaning that the FDA may not approve any other applications to market the same drug for the same indication, except in certain very limited circumstances, for a period of seven years. Orphan drug designation does not prevent competitors from developing or marketing different drugs for that indication.

Non-United States Regulation. Before our products can be marketed outside of the United States, they are subject to regulatory approval similar to that required in the United States, although the requirements governing the conduct of clinical trials, including additional clinical trials that may be required, product licensing, pricing and reimbursement vary widely from country to country. No action can be taken to market any product in a country until an appropriate application has been approved by the regulatory authorities in that country. The current approval process varies from country to country, and the time spent in gaining approval varies from that required for FDA approval. In certain countries, the sales price of a product must also be approved. The pricing review period often begins after market approval is granted. Even if a product is approved by a regulatory authority, satisfactory prices may not be approved for such product.

In Europe, marketing authorizations may be submitted at a centralized, a decentralized or national level. The centralized procedure is mandatory for the approval of biotechnology products and provides for the grant of a single marketing authorization that is valid in all EU members states. As of January 1995, a mutual recognition procedure is available at the request of the applicant for all medicinal products that are not subject to the centralized procedure. There can be no assurance that the chosen regulatory strategy will secure regulatory approvals on a timely basis or at all.

Tarpan Product Candidate

Pending a planned merger with Tarpan Therapeutics, Inc., Manhattan Pharmaceuticals, Inc. will have a third biomedical technology under development:

- PTH (1-34), a peptide believed to be a regulator of epidermal cell growth and differentiation currently under development as a topical treatment for psoriasis and additional dermatological indications.

To date, researchers, led by Michael Holick, MD, PhD, Professor of Medicine, Physiology, and Biophysics at Boston University Medical Center, recently reported positive results from a US Phase I and II clinical trial evaluating the safety and efficacy of PTH (1-34) as a topical treatment for psoriasis. This double-blinded, controlled trial in 15 patients comparing PTH (1-34) formulated in the Novasome® Technology versus the Novasome® vehicle alone showed PTH (1-34) to be a potentially safe and effective treatment for plaque psoriasis. Following 8 weeks of treatment, the application of PTH (1-34) resulted in complete clearing of the treated lesion in 60% of patients and partial clearing in 85% of patients. Additionally, there was a statistically significant improvement in the global severity score. Ten patients continued into an open label extension study in which the Psoriasis Area and Severity Index (PASI) was measured; PASI improvement across all 10 patients achieved statistically significant improvement compared to baseline. No patients experienced any significant adverse events.

Due to the high response rate seen in psoriasis patients in the initial trial PTH (1-34) may have an important clinical advantage over current topical psoriasis treatments. Following the acquisition, Manhattan intends to initiate additional clinical activities with PTH (1-34) in 2005. Through the transaction with Tarpan, Manhattan obtains rights to issued and pending patents for all topical uses of PTH (1-34) as well as access to the Novasome® technology and patents for these applications. Novasome® is a registered trademark of IGI, Inc., Buena Park, NJ.

Market and Competition

The efficacy and safety profile of PTH (1-34) will potentially make it an attractive alternative to existing topical treatments, photo therapies and systemic treatments such as methotrexate and biologics for the treatment of psoriasis. We intend to achieve market share as a monotherapy at the expense of existing and established products to be used in combination with currently available therapies. Some of PTH (1-34)'s competitors would include, but are not limited to over-the-counter, or "OTC," and prescription topical treatments, Dovonex, phototherapies, laser treatment, methotrexate, cyclosporine, Johnson & Johnson (Remicade), Amgen (Enbrel), BiogenIdec (Amevive) and Genentech (Raptiva).

Topical treatments include numerous OTC ointments that help to reduce inflammation, soothe skin and enhance the efficacy of other therapies. Additionally, steroids are prescribed as an adjunct therapy for pain and anti-inflammation. One of the most frequently prescribed topical treatments is Calcipotriene (Dovonex), which is an active vitamin D3 analogue. Approximately 60% of patients show some response to Dovonex in the first few months of treatment, however, 60% of these become resistant to treatment in 6-12 months. Dovonex achieved \$700 million in sales in its first two years after launch but sales have not declined to \$130 million due to high incidence of resistance.

There are two main types of phototherapy, Ultra-violet A, or "UVA" and Ultra-violet B, or "UVB." UVA penetrates deeper into the skin but requires the use of photo-sensitizing agent and carries a higher risk of skin cancer. UVB, on the other hand, is 1,000 times more powerful than UVA in producing sunburn. UV treatments are often combined with other treatments such as topicals and methotrexate. Phototherapy treatments have been shown to clear the disease and induce remission but they require frequent doctor visits, making treatment expensive and inconvenient.