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PROSPECTUS SUPPLEMENT NO. 3
(To Prospectus Dated August 12, 2004)

Manhattan Pharmaceuticals, Inc.

21,229,163 Shares
Common Stock

The information contained in this prospectus supplement amends and updates our prospectus dated August 12, 2004, as supplemented by Prospectus Supplement No. 1 dated August 16, 2004 and Prospectus Supplement No. 2 dated November 15, 2004 (collectively, the "Prospectus"), and should be read in conjunction therewith. Please keep this Prospectus Supplement with your Prospectus for future reference.

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

The date of this Prospectus Supplement is January 6, 2005

Changes in Management

Manhattan Pharmaceuticals, Inc. and Leonard Firestone, M.D., the Company's president and chief executive officer, determined not to extend Dr. Firestone's employment with us. The terms of Dr. Firestone's January 2004 employment agreement with us provided that, unless renewed or extended, the agreement would expire January 2, 2005. Accordingly, effective as of January 3, 2005, Dr. Firestone is no longer an officer of, or is otherwise employed by, our company. However, we and Dr. Firestone are contemplating entering into an agreement pursuant to which Dr. Firestone will provide consulting services to us as we transition to a new chief executive officer and completes our proposed acquisition of Tarpan Therapeutics, Inc. (as described below). In addition, Dr. Firestone's January 2004 employment agreement provided that he would be deemed to have resigned from our Board of Directors in the event his employment with the Company ended. Accordingly, as of January 3, 2005, Dr. Firestone has also resigned from our Board of Directors.

Letter of Intent to Acquire Tarpan Therapeutics, Inc.

On January 5, 2005, we announced that we had entered into a letter of intent to acquire Tarpan Therapeutics, Inc., a privately-held, New York-based pharmaceutical company developing dermatological therapeutics, in an all stock transaction. In connection with the proposed transaction, Tarpan will merge with a wholly-owned subsidiary of our company, resulting in Tarpan becoming our wholly-owned subsidiary. In exchange for all of the outstanding shares of Tarpan's stock, we will issue a number of shares of our common stock such that the Tarpan shareholders will own approximately 20 percent of our outstanding fully-diluted shares of common stock.

Assuming the completion of the transaction, we will acquire the rights to develop and market Tarpan's primary product candidate, known as PTH (1-34), which is a peptide believed to be a regulator of epidermal cell growth and differentiation. It is currently under development as a topical treatment for psoriasis and additional dermatological indications. Psoriasis affects more than 4 million Americans and approximately 1-3% of the world population with total treatment costs estimated to exceed $4 billion annually. Our existing lead product, Oleoyl estrone, in development for the treatment of obesity, is expected to begin Phase I clinical trials in the first quarter of 2005. Our other candidate, Propofol Lingual Spray, in development for pre-procedural sedation, continues to pursue accelerated FDA approval under a 505(b)2 "bioequivalence" regulatory pathway.

Pursuant to the proposed terms of the merger, Douglas Abel, currently the President and CEO of Tarpan, will be appointed Chief Executive Officer of our Company, overseeing all of our operations and the clinical development of all three product candidates. Prior to becoming President and CEO of Tarpan, Mr. Abel served as Vice President of the Dermatology Business Unit at Biogen Idec, Inc. from October 2001 to November 2004 and as Director/Senior Director, Dermatology Marketing at Biogen Idec from August 2000 to October 2001. Prior to joining Biogen Idec, Mr. Abel was employed by Allergan, Inc. from 1987 until August 2000, serving in a number of positions in sales and marketing at that company's Dermatology, Ophthalmology and Neurology business, including Director of Marketing for BOTOX® from January 2000 to August 2000.

Researchers, led by Michael Holick, MD, PhD, Professor of Medicine, Physiology, and Biophysics at Boston University Medical Center, recently reported positive results from a U.S. Phase I/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. Assuming we successfully complete the proposed acquisition of Tarpan, we will obtain 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, which Tarpan licenses from IGI, Inc., based in Buena Park, New Jersey, and we intend to initiate additional clinical activities with PTH (1-34) in 2005.