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NEOPROBE CORP
Form 424B3
April 05, 2005

Filed Pursuant to Rule 424(b)(3)
Registration No. 333-110858

PROSPECTUS SUPPLEMENT

Number 1

to

First Amended Prospectus, dated January 18, 2005,

of

NEOPROBE CORPORATION

21,817,257 Shares of Common Stock

This Prospectus Supplement relates to the sale of up to 21,817,257 shares of Neoprobe Corporation common stock (the "Shares"). The Shares are being registered to permit public secondary trading of the shares that are being offered by the selling shareholders named in the prospectus. We are not selling any of the Shares in this offering and therefore will not receive any proceeds from this offering.

This Prospectus Supplement No. 1 includes the attached Annual Report on Form 10-KSB (the "Form 10-KSB") of Neoprobe Corporation (the "Company"), for the year ended December 31, 2004, filed by the Company with the Securities and Exchange Commission on March 31, 2005. The exhibits to the Form 10-KSB are not included with this Prospectus Supplement No. 1 and are not incorporated by reference herein.

Our common stock is traded on the Over-the-Counter Bulletin Board under the symbol "NEOP."

NEITHER THE SECURITIES AND EXCHANGE COMMISSION NOR ANY STATE SECURITIES COMMISSION HAS APPROVED OR DISAPPROVED OF THESE SECURITIES OR PASSED UPON THE ACCURACY OR ADEQUACY OF THIS PROSPECTUS SUPPLEMENT. ANY REPRESENTATION TO THE CONTRARY IS A CRIMINAL OFFENSE.

The date of this Prospectus Supplement No. 1 is April 5, 2005.

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

FORM 10-KSB

(Mark One)

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

For the fiscal year ended: December 31, 2004

OR

TRANSITION REPORT UNDER SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT

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OF 1934

For the transition period from _____ to _____.

Commission file number: 0-26520

NEOPROBE CORPORATION

(Name of Small Business Issuer in Its Charter)

Delaware

31-1080091

(State or Other Jurisdiction of
Incorporation or Organization)

(I.R.S. Employer
Identification No.)

425 Metro Place North, Suite 300, Dublin, Ohio

43017-1367

(Address of Principal Executive Offices)

(Zip Code)

Issuer's telephone number, including area code: (614) 793-7500
Securities registered pursuant to Section 12(b) of the Act: None
Securities registered pursuant to Section 12(g) of the Act:

Common Stock, par value \$.001 per share

(Title of Class)

Rights to Purchase Series A Junior Participating Preferred Stock

(Title of Class)

Check whether the Registrant: (1) filed all reports required to be filed by Section 13 or 15(d) of the Exchange Act during the past 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days.

Yes No

Check if there is no disclosure of delinquent filers pursuant to Item 405 of Regulation S-B 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 \$5,952,640.

The aggregate market value of shares of common stock held by non-affiliates of the registrant on March 15, 2005 was \$25,571,506.

The number of shares of common stock outstanding on March 15, 2005 was 58,586,008.

Transitional Small Business Disclosure Format (check one): Yes No

DOCUMENTS INCORPORATED BY REFERENCE

None.

PART I

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Item 1. Description of Business

Development of the Business

Neoprobe Corporation (Neoprobe, the company or we) is a biomedical company that develops and commercializes innovative biomedical products that enhance patient care and improve patient outcome by meeting the critical intraoperative diagnostic information needs of physicians and therapeutic treatment needs of patients. We were originally incorporated in Ohio in 1983 and reincorporated in Delaware in 1988. Our executive offices are located at 425 Metro Place North, Suite 300, Dublin, Ohio 43017. Our telephone number is (614) 793-7500.

From our inception through 1998, we devoted substantially all of our efforts and resources to the research and clinical development of radiopharmaceutical and medical device technologies related to the intraoperative diagnosis and treatment of cancers including our proprietary radioimmunoguided surgery (RIGS(R)) technology. At that point, an evaluation of the status of the regulatory pathway for our RIGS products coupled with our limited financial resources caused us to suspend development activities related to our radiopharmaceutical business and to retrench our organization to focus on our medical device business. After achieving profitability in 2000 following this retrenchment, we set out on a strategy to expand our medical device portfolio outside the cancer field. In December 2001, we took a major step in executing this strategy with the acquisition of Biosonix Ltd., a private Israeli company limited by shares, which we subsequently renamed Cardiosonix Ltd. (Cardiosonix).

Cardiosonix is developing and commercializing the Quantix(R) line of blood flow measurement devices for a variety of diagnostic and surgical applications in the cardiac and vascular management arena. The decision to expand beyond our product focus on oncology was based on our belief that the Cardiosonix products would diversify the markets we address. We believe the Cardiosonix product line has great market potential and a path of market adoption similar to our gamma detection devices, but one that also has significant operational synergies in the development, regulation and manufacture to that of our existing gamma devices. Our foray into blood flow measurement devices has not been without its disappointments. The version of the Quantix/ORTM product that was originally launched failed to meet initial user expectations. During 2004, we focused significant effort on redesigning certain aspects of the device, primarily the probe and software, and during 2005 have re-launched an enhanced system that we believe will address the blood flow measurement needs of the user.

In addition, although our strategic focus expanded to include cardiac and vascular blood flow management, we continued to look for other avenues to reinvigorate our radiopharmaceutical development. During 2004, our efforts resulted in a number of positive events that caused us to take steps to re-activate development of our radiopharmaceutical and therapeutic initiatives. As a result, we now have two of our radiopharmaceutical products, LymphoseekTM and RIGScan(R) CR, on the verge of entering Phase III clinical trials and have recently formed a new subsidiary, CIRA Biosciences, Inc. (CIRA Bio), to evaluate the current market opportunities for our activated cellular therapy (ACT) technology. Our unique virtual business model combines revenue generation from medical devices with the capital infusions we received in 2004 to allow us to fund Lymphoseek development while we look for a development partner to assist us in the final clinical and commercial development for RIGScan CR and to evaluate the commercial opportunities for ACT.

Our Technology

Gamma Detection Devices

Through 2004, substantially all of our revenue has been generated from the sale

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of a line of gamma radiation detection devices and related products used by surgeons in the diagnosis and treatment of cancer and related diseases. Our currently-marketed line of gamma detection devices has been cleared by the U.S. Food and Drug Administration (FDA) and other international regulatory agencies for marketing and commercial distribution throughout most major global markets.

2

Our patented gamma detection device systems consist of hand-held detector probes and a control unit. The critical detection component is a highly radiosensitive crystal contained in the tip of the probe that relays a signal through a preamplifier to the control unit to produce both a digital readout and an audible signal. The detector element fits into a housing approximately the size of a pocket flashlight. The neo2000(R) Gamma Detection System, originally released in 1998, is the third generation of our gamma detection systems. The neo2000 is designed as a platform for future growth of our instrument business. The neo2000 is software upgradeable and is designed to support future surgical targeting probes without the necessity of costly remanufacture. Since 1998, we have developed and released three major software upgrades for customer units designed to improve the utility of the system and/or offer the users additional features.

Surgeons are using our gamma detection devices in a surgical application referred to as sentinel lymph node biopsy (SLNB) or intraoperative lymphatic mapping (lymphatic mapping or ILM). ILM helps trace the lymphatic patterns in a cancer patient to evaluate potential tumor drainage and cancer spread in lymphatic tissue. The technique does not detect cancer; rather it helps surgeons identify the lymph node(s) to which a tumor is likely to drain and spread. The lymph node(s), sometimes referred to as the "sentinel" node(s), may provide critical information about the stage of a patient's disease. ILM begins when a patient is injected at the site of the main tumor with a commercially available radioactive tracing agent. The agent is intended to follow the same lymphatic flow as the cancer would if it had metastasized. The surgeon may then track the agent's path with a hand-held gamma-radiation-detection probe, thus following the potential avenues of metastases and identifying lymph nodes to be biopsied for evaluation and determination of cancer spread.

Numerous clinical studies, involving a total of nearly two thousand patients and published in peer-reviewed medical journals such as Oncology (January 1999) and The Journal of The American College of Surgeons (December 2000), have indicated ILM is approximately 97% accurate in predicting the presence or absence of disease spread in melanoma and breast cancers. Consequently, it is estimated that more than 80% of breast cancer patients who would otherwise have undergone full axillary lymph node dissections (ALND), involving the removal of as many as 20 - 30 lymph nodes, might be spared this radical surgical procedure if the sentinel node was found to be free of cancer. Surgeons practicing ILM have found that our gamma-detection probes are well suited to the procedure.

Hundreds of articles have been published in recent years in peer-reviewed journals on the topics of sentinel lymph node biopsy and ILM. Furthermore, a number of thought leaders and cancer treatment institutions have recognized and embraced the technology as standard of care for melanoma and, in some cases, for breast cancer. Our marketing partner continues to see strong sales, especially for use in breast cancer treatment. Lymphatic mapping in breast cancer is the subject of national and international clinical trials, including studies sponsored by the U.S. Department of Defense, the National Cancer Institute (NCI) and the American College of Surgeons. Although we have been selling gamma detection devices for use in surgical oncology for over seven years, we believe many surgeons in the U.S. and the rest of the world have delayed adoption of lymphatic mapping pending the outcome of these important trials. We believe that once data from these trials are published; there will be an additional demand

for our devices. We continue to monitor these trials and to work with our marketing partners and thought leaders in the surgical community to set up and support training courses internationally for lymphatic mapping. We also believe, based on an estimate of the total number of operating rooms in medical centers that are capable of performing the types of procedures in which our gamma devices are used, that roughly half of the potential global market for devices such as ours remains untapped. Courses showcasing our instruments continue to be held at many nationally and internationally renowned cancer-specializing and teaching institutions. These courses appear to be positively impacting the adoption of lymphatic mapping, albeit not as rapidly as we would like to see.

3

In addition to lymphatic mapping, surgeons are investigating the use of our device for other gamma guided surgery applications, such as evaluating the thyroid function, in determining the state of disease in patients with vulvar and penile cancers, and in SLNB in prostate, gastric and non-small cell lung cancers. Expanding the application of ILM beyond the current primary uses in the treatment of breast cancer and melanoma is the primary focus of our strategy regarding our gamma guided surgery products. To support that expansion, we continue to work with our marketing and distribution partners to develop additional software-based enhancements to the neo2000 platform as well as new probes such as the laparoscopic probe introduced in 2002 that supports the minimally invasive emphasis in today's practice of surgery. To that end, our goals for our gamma device business for 2005 center around introducing additional improvements to our neo2000 system and working with our marketing partners to further penetrate the breast care market and identify ways to expand the application of ILM to other indications beyond breast cancer and melanoma. We also believe that our development of Lymphoseek could be an integral step in helping expand the application of ILM.

Blood Flow Measurement Devices

Accurate blood flow measurement is essential for a variety of clinical needs, including:

- o real-time monitoring;
- o intra-operative quantification;
- o non-invasive diagnostics; and
- o evaluation of cardiac function.

Currently, the medical community has no simple, immediate, real-time means to quantify the adequacy of organ perfusion, that is, the direct measurement of blood flow into the organ. Devices do exist that visually show perfusion of a target organ. We are unaware, however, of any device that provides an accurate, real-time measurement of blood flow in as many applications without having to isolate target vessels or conduct other invasive procedures.

In addition, blood flow velocity measurements are often confused with volume blood flow. These two variables, however, are normally different parameters that respond differently to pathological conditions and provide different data. Blood flow velocity is used primarily for determining the existence of a stenosis (narrowing or obstruction) in the vascular surgery setting, while the applications of blood flow volume have potential impact across a much broader range of medical disciplines.

Cardiosonix is developing and commercializing the Quantix line of products that employ a unique and proprietary technology that allows for measurement of blood flow volume, velocity and several other hemodynamic parameters that permit the real-time assessment of conduit hemodynamic status.

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The Quantix technology utilizes a special application of the Doppler method through simultaneous projection of a combination of narrow beams with a known angle between them. Thus, based on trigonometric and Doppler considerations, the angle of insonation can be obtained, resulting in accurate, angle-independent blood flow velocity measurements that do not require the use of complicated, expensive imaging systems. In order to obtain high-resolution velocity profiles, the Quantix devices use a multi-gated pulse wave Doppler beam. With this method, specific sample volumes along the ultrasound beam can be separately evaluated, and the application of a flow/no flow criterion can be made. The Cardiosonix technology applies a special use of digital Doppler technology, which with the digital signal processing power of the system allows hundreds of sample volumes to be sampled and processed simultaneously, thus providing high resolution velocity profiles for both angle and vascular diameter calculations, and subsequently volume blood flow measurements. At present, Cardiosonix has two products in the early stages of commercialization designed to provide blood flow measurement and cardiac output information to physicians in cardiac/vascular surgery and neurosurgery. The technology also has the potential to be applied in other healthcare settings where measurement of blood flow may be beneficial.

4

Quantix/NDTM is designed to allow neurosurgeons and neurologists, as well as intensive care unit or emergency room physicians, to non-invasively measure carotid artery blood flow in a simple, real-time manner. Quantix/ND consists of a control unit and an ultrasound probe that obtains signals directly from the carotid artery in a non-invasive manner. Quantix/ND is designed primarily for use in monitoring head trauma patients in neuro-intensive care units and emergency rooms. Periodic blood flow measurements minimize the risk of brain impairment. We are unaware of any measurement system on the market today that provides real-time, bedside, non-invasive, continuous, direct and accurate measurements of a complete suite of hemodynamic parameters including blood flow. Other modalities that do monitor capabilities of the brain are significantly more invasive, expose the patient to incremental risk or are inherently complicated, offering only indirect estimation of perfusion conditions. Some medical devices use an estimated measurement of blood flow velocity to create an index of blood flow but do not account for instantaneous changes in the vascular cross-sectional area. In most competing devices, the angle of insonation of the device to the vessel is also critical to the measurement and often may affect the user's ability to consistently and accurately measure the patient's blood flow. The Quantix/ND device, as well as its predecessor device, the FlowGuard™, has received CE mark regulatory clearance for marketing in the European Union (EU) as well as FDA 510(k) clearance for marketing in the United States.

Quantix/OR is designed to permit cardiovascular surgeons and assisting physicians to obtain intraoperative volume blood flow readings in various targeted blood vessels within seconds. The system consists of an insonation angle-independent ultrasound probe and digital numerical displays of blood flow rate. Thus, the surgeon obtains immediate, real-time and quantitative readings while focused on the target vessel. Quantifying blood flow can be very beneficial during anastomotic or other bypass graft procedures to determine adequate blood flow. While measurement is advisable whenever a blood vessel is exposed and manipulated intra-operatively, generally this is not the current practice.

Ultimately, in practice, the surgeon generally resorts to using his eyes and fingers in a process called finger palpation to qualitatively assess vessel flow. The Quantix/OR offers the surgeon immediate and simple quantitative assessment of blood flow in multiple blood vessels and grafts. The primary advantage of finger palpation is that it is fast and simple; the disadvantages are that it requires a good deal of experience, it is difficult to perform in vessels embedded in tissue, it can become difficult to interpret in large

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vessels, and it permits only a very qualitative and subjective assessment. A significant partial occlusion (or even a total occlusion) will result in significant vessel "distention" and strong palpations that may mislead the surgeon. Rather than rely on such a subjective clinical practice, which is highly experience-dependent, the Quantix/OR is designed to allow the surgeon to rely on more quantifiable and objective information. We believe that Quantix/OR represents a significant improvement over existing technologies to directly measure blood flow intraoperatively. Other technologies that attempt to measure intraoperative blood flow directly are generally more invasive and are impractical when multiple vessel measurements are required. As a result, the majority of surgeons generally resort to finger palpation to qualitatively, rather than quantitatively, measure vessel perfusion.

The initial physician and distributor evaluation of the flagship product, the Quantix/OR, during 2004 indicated a number of design deficiencies that needed to be corrected before further commercial distribution of the product was advisable. The development activities for the Quantix/OR over the last year have therefore involved modification of the user interface software functions and a redesign of the Quantix/OR probe ergonomics to enhance system performance, improve ease of measurement and expand physician acceptance of the system. With completion of the initial development activities for Quantix/OR, we submitted a special 510(k) application to FDA for clearance to market the revised Quantix/OR system in the United States and we received this marketing clearance in early February 2005. In addition, revisions to the technical file in Europe have been completed to permit us to begin delivery of the improved Quantix/OR system in Europe as new flexible probes are received from our contract manufacturer.

Our strategy related to Cardiosonix products for 2005 continues to emphasize the three primary objectives we have established for the Quantix product line:

- o to promote and expand the clinical evaluation of the Quantix/ND and Quantix/OR with thought leaders in the neurosurgical, cardiovascular and vascular surgery arenas;
- o to secure and train additional marketing and distribution partners for key global markets for the Quantix/ND and Quantix/OR devices; and

5

- o to achieve commercial sales of Cardiosonix' Quantix products beyond demonstration unit sales that would demonstrate the initial market acceptance of the products.

We cannot assure you, however, that any of Cardiosonix' products will achieve market acceptance. See also Risk Factors.

Lymphoseek

Our gamma detection devices are primarily capital in nature; as such, they generate revenue only on the initial sale. To complement the one-time revenue stream related to capital products, we are working on developing recurring revenue or "procedural" products that would generate revenue based on each procedure in which they were used. The product we are working on with the most near-term potential in this area involves an exclusive worldwide license agreement with the University of California, San Diego (UCSD) for a proprietary compound we refer to as Lymphoseek. If proven effective and cleared for commercial sale, Lymphoseek would be the first radiopharmaceutical specifically designed and labeled for the targeting of lymphatic tissue.

Neoprobe and UCSD completed the initial pre-clinical evaluations of Lymphoseek in 2001. Since that time, UCSD has initiated four Phase I clinical trials

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involving Lymphoseek. The status of these trials is listed below:

Indication -----	Number of Patients	Status -----
Breast (peritumoral injection)	24	Completed
Melanoma	24	Completed
Breast (intradermal injection, next day surgery)	60	Ongoing
Prostate	60	Ongoing

These Phase I studies have been supported, including being substantially funded through research grants, by a number of organizations such as the Susan G. Komen Breast Cancer Research Foundation, the American Cancer Society (ACS) and the NCI. Research data from these clinical evaluations of Lymphoseek have been presented at recent meetings of the Society of Nuclear Medicine, the Society of Surgical Oncology and the World Sentinel Node Congress.

In November 2003 we met with the Interagency Council on Biomedical Imaging in Oncology (Interagency Council), an organization representing FDA, the NCI and the Centers for Medicare and Medicaid Services to discuss the regulatory approval process and to determine the objectives for the next clinical trial involving Lymphoseek. During 2004, we prepared and submitted a draft clinical protocol to FDA for a pivotal trial to support the marketing clearance of Lymphoseek. FDA has accepted our investigational new drug (IND) submission for Lymphoseek. With the establishment of the corporate IND, responsibility for the clinical and commercial development of Lymphoseek has been officially transferred from UCSD to Neoprobe. Neoprobe has therefore assumed clinical responsibility for the development of Lymphoseek from UCSD. FDA has provided guidance that they would prefer to have Lymphoseek evaluated in a multi-center clinical study to confirm the clinical findings observed by the UCSD researchers to be followed by a confirmation Phase III study that would be initiated with the final cGMP material. Neoprobe intends to commence enrollment in this multi-institutional study as soon as the appropriate regulatory and institutional review board clearances are received. The study will be conducted at some of the nation's leading cancer treatment institutions. FDA guidelines also require Neoprobe to complete some additional preclinical activities prior to the initiation of the multi-center trials. Neoprobe has initiated this preclinical work in parallel to its other development activities and intends to submit an IND amendment prior to the initiation of the multi-center studies. We cannot assure you, however, that this product will achieve regulatory approval, or if approved, that it will achieve market acceptance. See also Risk Factors.

6

RIGS

From inception until 1998, Neoprobe devoted significant efforts and resources to the development of its proprietary RIGS technology. The RIGS system combines a patented hand-held gamma radiation detection probe, proprietary radiolabeled cancer-specific targeting agents, and patented surgical methods to provide surgeons with real-time information to locate tumor deposits not detectable by conventional methods, and to assist in more thorough removal of the cancer. The RIGS system is designed to assist the surgeon in the more thorough removal of the cancer, thereby leading to improved surgical treatment of the patient. The targeting agents used in the RIGS process are monoclonal antibodies, labeled with a radioactive isotope that emits low energy gamma rays. The device used is a very sensitive radiation detection instrument that is capable of detecting small amounts of radiation bound to the targeting agent. Before surgery, a cancer patient is injected with one of the targeting agents which circulates

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throughout the patient's body and binds specifically to cancer cell antigens or receptors. Concentrations of the targeting agent are then located during surgery by Neoprobe's gamma-detection device, which emits an audible tone to direct the surgeon to targeted tissue.

RIGScan CR is an intraoperative agent consisting of a radiolabeled murine monoclonal antibody (MAB CC49). The radiolabel used is ¹²⁵I, a 27 - 35 KeV emitting isotope. The MAB used in RIGScan CR is the CC49 MAB developed by the NCI and licensed to Neoprobe by the National Institutes of Health (NIH). The CC49 MAB is produced from a murine cell line generated by the fusion of splenic lymphocytes from mice immunized with tumor-associated glycoprotein-72 (TAG-72) with non-immunoglobulin secreting P3-NS-1-Ag4 myeloma cells. The CC49 MAB localizes or binds to TAG-72 and shows a strong reactivity with both LS-174T colon cancer extract and to a breast cancer extract.

RIGScan CR is the biologic component for the RIGS system to be used in patients with colon or rectal cancer. The RIGS system was conceived to be a diagnostic aid in the intraoperative detection of clinically occult disease. RIGScan CR is intended to be used in conjunction with other diagnostic methods, for the detection of the extent and location of tumor in patients with colorectal cancer. The detection of clinically occult tumor provides the surgeon with a more accurate assessment of the extent of disease, and therefore may impact the surgical and therapeutic management of the patient. Clinical trials suggest that RIGScan CR provides additional information outside that provided by standard diagnostic modalities (including surgical exploration) that may aid in patient management. Specifically, RIGScan CR used as a component of the RIGS system confirms the location of surgically suspicious metastases, evaluates the margins of surgical resection, and detects occult tumor in perihepatic (portal and celiac axis) lymph nodes.

Neoprobe conducted two Phase III studies, NEO2-13 and NEO2-14, of RIGScan CR in patients with primary and metastatic colorectal cancer, respectively. Both studies were multi-institutional involving cancer treatment institutions in the United States, Israel, and Europe. The primary endpoint of both studies was to demonstrate that RIGScan CR detected pathology-confirmed disease that had been undetected by traditional preoperative (i.e., CT Scans) or intraoperative (i.e., surgeon's visual observations and palpation) means. That is, the trials were intended to show that the use of RIGScan CR assisted the surgeon in the detection of occult tumor. In 1996, Neoprobe submitted applications to the European Agency for the Evaluation of Medicinal Products (EMEA) and FDA for marketing approval of RIGScan CR for the detection of metastatic colorectal cancer.

Clinical study NEO2-14, which was submitted to FDA in the RIGScan CR Biologic License Application (BLA), enrolled 151 colorectal cancer patients with either suspected metastatic primary colorectal disease or recurrent colorectal disease. During FDA's review of the BLA, 109 of the enrolled patients were determined to be evaluable patients. Clinical study NEO2-13 was conducted in 287 enrolled patients with primary colorectal disease. The primary end-point for clinical study NEO2-13 was the identification of occult tumor.

NEO2-14 was the pivotal study submitted with Neoprobe's referenced BLA. Two additional studies evaluating patients with either primary or metastatic colorectal disease, NEO2-11 (a multi-center study) and NEO2-18 (a single institution study), were included in the BLA and provided supportive proof of concept (i.e., localization and occult tumor detection) and safety data. A study summary report for NEO2-13 was submitted under the BLA; however, FDA undertook no formal review of the study.

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Following review of our applications, we received requests for further information from FDA and from the European Committee for Proprietary Medicinal Products on behalf of the EMEA. Both FDA and EMEA acknowledged that our studies met the diagnostic endpoint of the Phase III clinical study, which was to provide incremental information to the surgeon regarding the location of hidden tumor. However, both agencies wanted to know how the finding of additional tumor provided clinical benefit that altered patient management or outcome for patients with metastatic colorectal cancer. In a series of conversations with FDA the product claims were narrowed to the intraoperative detection of hepatic and perihepatic disease in patients with advanced colorectal cancer and patients with recurrent colorectal cancer.

FDA determined during its review of the BLA that the clinical studies of RIGScan CR needed to demonstrate clinical utility in addition to identifying additional pathology confirmed disease. In discussions between Neoprobe and the agency, an FDA driven post hoc analysis plan was developed to limit the evaluation of RIGScan CR to patients with hepatic and perihepatic disease with known metastasis to the liver. Findings of "occult" disease and subsequent changes in patient management (i.e., abandoning otherwise risky hepatic resections) in this limited population would serve as a measure of patient benefit. FDA's analysis of the patients enrolled in NEO2-14 matching the limited criteria was evaluated with a determination to confirm the surgical resection abandonment outcome. The number of evaluable patients in this redefined patient population was deemed too small by the agency and the lack of pre-stated protocol guidance precluded consistent sets of management changes given similar occult findings. The number of evaluable patients for any measure of clinical utility, therefore, was too small to meet relevant licensing requirements and FDA ultimately issued a not approvable letter for the BLA on December 22, 1997, describing certain clinical and manufacturing deficiencies. Neoprobe also withdrew its application to the EMEA in November 1997.

We developed a clinical response plan for both agencies during the first half of 1998. However, following our analysis of the regulatory pathways for approval that existed at that time, we determined that we did not have sufficient financial resources to conduct the additional studies requested and sought to identify others with an interest in continuing the development process.

In recent years, we have obtained access to survival analyses of patients treated with RIGScan CR which have been prepared by third parties, indicating that RIGScan CR may be predictive of, or actually contribute to, a positive outcome when measuring survival of the patients that participated in our original BLA studies. The data or its possible significance was unknown at the time of the BLA review given the limited maturity of the follow-up experience. The data includes publication by some of the primary investigators involved in the Phase III RIGS trials who have independently conducted survival follow-up analyses to their own institution's RIGS trial patients with apparently favorable results relating to the long-term survival prognosis of patients who were treated with RIGS. In addition, we have recently learned that FDA has held the BLA originally filed with FDA in 1996 open. Based primarily on these pieces of information, we requested a meeting with FDA to discuss the possible next steps for evaluating the survival related to our previous Phase III clinical trials as well as the possible submission of this data, if acceptable, as a prospective analysis in response to questions originally asked by FDA in response to our original BLA. This meeting with FDA took place in April 2004.

The April 2004 meeting with FDA was an important event in the re-activation of the RIGS program. The meeting was very helpful from a number of aspects: we confirmed that the RIGS BLA remains active and open. We believe this will improve both the cost effectiveness and timeliness of future regulatory submissions for RIGScan CR. Additionally, FDA preliminarily confirmed that the BLA may be applicable to the general colorectal population; and not just the recurrent colorectal market as applied for in 1996. Applicability to a general

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colorectal population could result in a greater market potential for the product than if applicable to just the recurrent population. During the meeting, FDA indicated that it would consider possible diagnostic and prognostic indications for RIGScan CR and that survival data from one of our earlier Phase III studies could be supportive of a prognostic indication. Our initial submission included a proposed clinical trial design with objectives to demonstrate both diagnostic and prognostic/therapeutic endpoints.

8

In October 2004, Neoprobe received a response from FDA that the prognostic/therapeutic trial design appeared to meet their guidelines, but they requested additional information concerning the diagnostic clinical objective. FDA's response to our clinical submission included an invitation for Neoprobe to seek a special protocol assessment (SPA) of its proposed Phase III study. Neoprobe intends to seek a SPA review of the complete Phase III package including the clinical protocol, training materials and data collection forms later this year. In concert with our meetings with FDA, we met with representatives of the European regulatory body, the EMEA, to seek guidance for the RIGScan CR program in Europe. The guidance from the EMEA was consistent with the input from FDA with the additional recommendation that any future clinical studies be conducted with the humanized version of the RIGScan CR antibody. It is possible that the regulatory pathway may continue to evolve as we seek to reach a consensus with the regulatory agencies on the reactivation of the BLA for RIGScan CR.

In addition, the RIGScan CR biologic drug has not been produced for several years and we believe it is likely we would have to perform some additional work related to ensuring the drug cell line is still viable and submit this data to FDA for their evaluation before approval could be considered. We have initiated discussions with established biologic manufacturing organizations to determine the costs and timelines associated with the production of commercial quantities of the CC49 antibody. In addition, we will need to establish radiolabeling capabilities for the CC49 antibody in order to meet the regulatory needs for the RIGScan CR product.

In parallel with our discussions with the regulatory authorities, we have discussed the clinical and regulatory strategy for RIGScan CR with reimbursement consultants who provided us with valuable input regarding the potential target pricing for a RIGScan product. Our consultants have advised us that if we proceed with our original plans to seek an earlier conditional clearance for the potential diagnostic indications for RIGScan CR, followed by clearance for the prognostic/therapeutic indication we might significantly limit the ultimate potential price for the prognostic/therapeutic product. However, since we have announced that it is our intention to develop RIGScan CR in cooperation with a development partner, we intend to make the decision on which indications to seek clearance for jointly.

We are encouraged by the recent developments regarding RIGS. We believe we would need to obtain additional funding and/or secure a development partner in order to carry out all the activities necessary for commercialization. We do not have any agreements in place or pending with third parties that would ensure the continued development of the RIGS process and the completion of the survival analysis proposed to FDA at the April 2004 meeting. In addition, even if we are able to make such arrangements on satisfactory terms, we believe that the time required for continued development, regulatory approval and commercialization of a RIGS product would likely be a minimum of five years before we receive any significant product-related royalties or revenues. However, we cannot assure you that we will be able to complete definitive agreements with a development partner for the RIGS technology and do not know if a partner will be obtained on a timely basis on terms acceptable to us, or at all. We also cannot assure you

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that FDA or the EMEA will clear our RIGS products for marketing or that any such products will be successfully introduced or achieve market acceptance. See also Risk Factors.

Activated Cellular Therapy

During the late 1990's, through various research collaborations, we performed early stage research on another technology platform, ACT, based on work originally done in conjunction with the RIGS technology. ACT is intended to boost the patient's own immune system by removing lymph nodes identified during surgery and then, in a cell processing technique, activating and expanding "helper" T-cells found in the nodes. Within 10 to 14 days, the patient's own immune cells, activated and numbering more than 20 billion, are infused into the patient in an attempt to trigger a more effective immune response to the cancer.

9

In the course of our research into ACT performed with RIGS, we learned that these lymph node lymphocytes containing helper T-cells could be activated and expanded to treat viral and autoimmune disease afflicted patients as well as oncology patients. We have seen promising efficacy of this technology demonstrated from six Phase I clinical trials covering the oncology, viral and autoimmune applications.

In early 2005, we formed a new subsidiary, CIRA Bio, to explore the development of ACT. Neoprobe owns approximately 90% of the outstanding shares of CIRA Bio with the remaining shares being held by the principals of a private holding company, CIRA LLC. In conjunction with the formation of CIRA Bio, an amended technology license agreement also was executed with The Ohio State University Research Foundation (OSURF) from whom both Neoprobe and CIRA LLC had originally licensed or optioned the various cellular therapy technologies. As a result of the cross-license agreements, CIRA Bio has the development and commercialization rights to three issued U.S. patents that cover the oncology and autoimmune applications of its technology. In addition, CIRA Bio has licenses to several pending patent applications.

CIRA Bio has engaged the Battelle Memorial Institute to complete a technology and manufacturing process assessment of the cellular therapy approach. In addition, a scientific advisory group is being formed to develop a clinical and regulatory approach for the CIRA Bio technology. Following the completion of these assessments and the formation of a commercialization strategy, CIRA Bio intends to raise the necessary capital to move this technology platform forward. The means by which this funding is obtained will likely dilute Neoprobe's ownership interest in CIRA Bio; however, we believe that moving forward such a promising technology will only yield positive results for the Neoprobe shareholders and the patients who could benefit from these treatments. However, we do not know if we will be successful in obtaining additional funding, on terms acceptable to us, or at all.

In addition, although the prospects for ACT may be improved depending on the outcome of a decision to renew development efforts for RIGS, we currently do not intend to fund any significant ACT-related research and development beyond the evaluation work to be performed in 2005. We cannot assure you that any ACT products will be successfully developed, tested or licensed, or that any such products will gain market acceptance. See also Risk Factors.

Market Overviews

The medical device marketplace is a fast growing market. Medical Device & Diagnostic Industry magazine reports an annual medical device and diagnostic market of \$75 billion in the U.S. and \$169 billion internationally.

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Cancer Market Overview

Cancer is the second leading cause of death in the U.S. and Western Europe and is responsible for over half a million deaths annually in the U.S. alone. The NIH estimates the overall annual costs for cancer (the primary focus of our products) for the U.S. in the year 2004 at \$189.8 billion: \$69.4 billion for direct medical costs, \$16.9 billion for indirect morbidity, and \$103.5 billion for indirect mortality. Our line of gamma detection systems is currently used primarily in the application of ILM in breast cancer and melanoma which, according the ACS, are expected to account for 16% and 4%, respectively, of new cancer cases in the U.S. in 2004.

The NIH has estimated that breast cancer will annually affect approximately 500,000 women in North America, Western Europe, and other major economic markets. Breast cancer is the second leading cause of death from cancer among all women in the U.S. According to the ACS, over 211,000 new cases of invasive breast cancer are expected to be diagnosed and approximately 41,000 women are expected to die from the disease during 2005 in the U.S. alone. The incidence of breast cancer increases with age, rising from about 100 cases per 100,000 women at age 40 to about 400 cases per 100,000 women at age 65. Thus, we believe that the significant aging of the population, combined with improved education and awareness of breast cancer and diagnostic methods, will lead to an increased number of breast cancer surgical diagnostic procedures.

10

Approximately 80% of the patients diagnosed with breast cancer undergo a lymph node dissection (either ALND or SLNB) to determine if the disease has spread. While many breast cancer patients are treated in large cancer centers or university hospitals, regional and/or community hospitals currently treat the majority of breast cancer patients. Over 10,000 hospitals are located in the markets targeted for our gamma detection ILM products. While we are aware of no published statistics on the number of institutions that are currently using gamma detection devices in ILM, we believe that approximately fifty percent of the total potential global market for gamma detecting devices remains to be penetrated at this time. However, if the potential of Lymphoseek as a radioactive tracing agent is ultimately realized, it has the potential to address not only the current breast and melanoma markets on a procedural basis, but also to assist in the clinical evaluation and staging of solid tumor cancers and expanding ILM to additional indications, such as gastric, non-small cell lung and other solid tumor cancers.

We estimate the total market potential for Lymphoseek, if ultimately approved for all of these indications, could exceed \$200 million. However, we cannot assure you that Lymphoseek will be cleared to market, or if cleared to market, that it will achieve the prices or sales we have estimated.

The ACS estimates that over 145,000 new incidences of colon and rectum cancers will occur in the U.S. in 2005. Based on an assumed recurrence rate of 40%, this would translate into total potential surgical procedures of over 200,000 annually in the U.S. alone. We believe the number of procedures in other markets of the world to be approximately two times the estimated U.S. market. As a result, we believe the total potential global market for RIGScan CR could, depending on the reimbursement allowed for RIGScan CR, be in excess of \$2 billion annually. However, we cannot assure you that RIGScan CR will be cleared to market, or if cleared to market, that it will receive the reimbursement or achieve the level of sales we have currently estimated.

Blood Flow Measurement Market Overview

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Cardiovascular disease is the number one killer of men and women in the U.S. and in a majority of countries in the rest of the world that track such statistics. In the U.S. alone, the Centers for Disease Control (CDC) estimated that there were over 80 million physician office visits and over 6.8 million outpatient department visits in 2002 with a primary diagnosis of cardiovascular disease. The CDC registered over 6.8 million inpatient cardiovascular procedures in the U.S. during 2002 that directly involve cardiovascular circulation. We, as well as our competitors and other industry analysts, generally estimate the rest of the world's incidence of such modalities at roughly twice U.S. estimates.

The American Heart Association estimates the total cost of cardiovascular diseases and stroke in the United States will exceed \$393.5 billion in 2005. A substantial portion of these expenditures is expected to be for non-invasive image and intravascular examination. We are focused on two distinct markets within the hospital setting for Cardiosonix' products:

- o non-invasive diagnostics (Quantix/ND); and,
- o intraoperative assessment (Quantix/OR).

It is estimated that there are approximately 1 million vascular and cardiovascular procedures performed in the U.S. that could benefit from qualitative blood flow measurement. Based on these estimates, information obtained from industry sources and data published by our competitors and other medical device companies, we estimate the worldwide total of target procedures to be approximately two times the U.S. totals.

11

Based on the above number of procedures, assuming we are able to achieve market prices that are comparable to what our competitors are achieving (estimated at averaging \$20,000 per system or \$130 per procedural use), we believe the worldwide market potential for blood flow measurement products in the niches which our products address to be more than \$1.5 billion. We believe that gaining even a modest share of this market would result in significant annual revenues for our company. We cannot assure you, however, that Cardiosonix products will achieve market acceptance and generate the level of sales or prices anticipated.

Marketing and Distribution

Gamma Detection Devices

We began marketing the current generation of our gamma detection systems, the neo2000, in October 1998. Since October of 1999, our gamma detection systems have been marketed and distributed throughout most of the world through Ethicon Endo-Surgery, Inc. (EES), a Johnson and Johnson company. In Japan, however, we market our products through a pre-existing relationship with Century Medical, Inc. (CMI).

The heart of the neo2000 system is a control unit that is software-upgradeable, permitting product enhancements without costly remanufacturing. Since the original launch of the neo2000 system, we have introduced an enhanced version of our 14mm reusable probe optimized for lymphatic mapping procedures and a laparoscopic probe intended for certain minimally invasive procedures. We have also developed three major software version upgrades for the system that have been made available for sale to customers. We intend to continue developing additional ILM-related probes and instrument products in cooperation with EES to maintain our leadership position in the ILM field.

Physician training is critical to the use and adoption of ILM products by surgeons and other medical professionals. Our company and our marketing partners have established relationships with leaders in the ILM surgical community and

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have established and supported training courses internationally for lymphatic mapping. We intend to continue to work with our partners to expand the number of ILM training courses available to surgeons.

We entered into our current distribution agreement with EES effective October 1, 1999 for an initial five-year term with options to extend for two successive two-year terms. In March 2004 EES exercised their option for the first of the two-year term extensions, thus extending the term of our current agreement through December 31, 2006. Under this agreement, we manufacture and sell our ILM products almost exclusively to EES, who distributes the products globally (except for Japan). EES agreed to purchase minimum quantities of our products over the first three years of the five-year original term of the agreement and to reimburse us for certain research and development costs during the first three years and a portion of our warranty costs. EES' minimum purchase and reimbursement commitments were satisfied during 2002. EES has no ongoing purchase or reimbursement commitments to us other than the rolling four-month binding purchase commitment for gamma detection devices as outlined in the distribution agreement. Our agreement with EES also contains certain termination provisions and licenses to our intellectual property that take effect only in the event we fail to supply product, or for other reasons such as a change of control. See also Risk Factors.

Gamma Detection Radiopharmaceuticals

We have not established a marketing or distribution channel for either RIGScan CR or Lymphoseek. We anticipate initiating such discussions as we move forward with the clinical development. We have had initial discussions with parties who may be interested in marketing and distribution of these products; however, such discussions to date have been preliminary in nature and have not resulted in any definitive arrangements at this time. We have engaged a third party business development firm to assist us in identifying a potential development and commercialization partner for our RIGS technology; however, at this time, we have not extended the scope of this firm's engagement to include identifying a partner for Lymphoseek as we intend to manage development and at least the initial stages of commercialization internally. We cannot assure you that we will be able to secure marketing and distribution partners for RIGS or Lymphoseek, or if secured, that such arrangements will result in significant sales of either product.

12

Blood Flow Measurement Devices

Both of our blood flow measurement devices, the Quantix/ND and Quantix/OR have received marketing clearance in the in the U.S. and the EU and certain other global markets. Our goal is to ensure sales and distribution coverage through third parties of substantially all of the U.S. and EU and selective markets in the rest of the world. To that end, we have put in place a master distributor arrangement covering the major markets in the EU and are working with a number of independent sales organizations to ensure coverage of major markets within the U.S. In addition, we have distribution arrangements in place covering major portions of the Pacific Rim and Central and South America.

The initial negative response to the original Quantix/OR system strained many of our distributor relationships; however, we are heartened by the distributor response to the changes and improvements we have made to the Quantix/OR system. Despite the difficulties we have encountered, our underlying belief in the market need for a reliable system to measure blood flow has not been dampened. We continue to believe strongly in the blood flow market and believe the recently completed changes to our Quantix/OR system will lead to the successful launch of a competitive product in early 2005.

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We reintroduced the Quantix/OR to the European surgical community at the Germanic Surgical Congress in Hamburg in February 2005 and we expect to introduce the product to the North American surgical community at the American Association of the Thoracic Surgeons (AATS) meeting in San Francisco in early April.

In addition to the development activities on the Quantix/OR, the first multi-center data from the correlation of CBF measurement with accepted clinical events was presented at the International Conference on Xenon CT-CBF and Related CBF Techniques in Bordeaux, France in June 2004. The presentation of the clinical evaluations of the Quantix/ND has set the stage for the broader adoption of the technology in the monitoring of patients with neuro-trauma and other neurology situations

We anticipate spending a significant amount of time and effort through during 2005 to penetrate the end-user market. We will need to complete the training of our distributors and independent sales agents and work through them with thought leaders in the cardiac and neurosurgical fields to gain penetration at the end-user level. We anticipate placing some additional blood flow systems with industry thought leaders to obtain critical pre-commercialization feedback; however, we plan to continue working with the thought leaders already identified to promote publication in support of more widespread market launch. To date, we have placed a small number of devices with thought leaders in the U.S. and EU to support clinical investigations by their institutions. We are also investigating different sales models that include both capital sales and per-use or lease-type transactions. We expect the sales model will evolve over the initial months of sales. The market education process we envision will likely take some time to develop in the manner we desire. In addition, the sales cycle for capital medical devices such as our blood flow products is typically a four to six month cycle. As such, significant end customer sales, if they occur, will likely lag the signing of distribution arrangements.

Manufacturing

Gamma Detection Devices

We rely on independent contract manufacturers, some of which are single-source suppliers, for the manufacture of the principal components of our current line of gamma detection system products. See also Risk Factors. We have devoted significant resources to develop production capability for our gamma detection systems at qualified contract manufacturers. Production of the neo2000 control unit, the 14mm probe and the 11mm laparoscopic probe involve the manufacture of components by a combination of subcontractors, including but not limited to eV Products, a division of II-VI Corporation (eV), and TriVirix International, Inc. (TriVirix). Currently, we have manufacturing and supply agreements with eV for the production of crystal modules used in the detector probes and for the manufacture of the 14mm probe, 11mm laparoscopic probe and the neo2000 control unit at TriVirix. We also purchase certain accessories for our line of gamma detection systems from other qualified manufacturers.

In December 1997, we entered into a supply agreement with eV for the supply of certain crystals and associated electronics to be used in the manufacture of our proprietary line of hand-held gamma detection probes. The original term of the agreement expired on December 31, 2002, but was automatically extended through December 31, 2005; however, the agreement is no longer exclusive for the last three years. eV supplies 100% of the crystals used in our products. While eV is not the only potential supplier of such crystals, any prolonged interruption of this source could restrict the availability of our probe products, which would

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adversely affect our operating results.

In February 2004, we executed a Product Supply Agreement with TriVirix for the manufacture of the neo2000, 14mm probe and 11mm laparoscopic probe. We have completed the transfer of the manufacturing for the neo2000 and 14mm probes to TriVirix. TriVirix began providing 14mm probes during February and the neo2000 control unit during March 2004 for shipment to EES.

We cannot assure you that we will be able to maintain agreements with our subcontractors on terms acceptable to us, or that our subcontractors will be able to meet our production requirements on a timely basis, at the required levels of performance and quality. In the event that any of our subcontractors is unable or unwilling to meet our production requirements, we cannot assure you that an alternate source of supply could be established without significant interruption in product supply or without significant adverse impact to product availability or cost. Any significant supply interruption or yield problems that we or our subcontractors experience would have a material adverse effect on our ability to manufacture our products and, therefore, a material adverse effect on our business, financial condition, and results of operations until a new source of supply is qualified. See also Risk Factors.

Gamma Detection Radiopharmaceuticals

In preparation for the commencement of multi-center clinical evaluation of Lymphoseek, Neoprobe evaluated potential drug manufacturing organizations and initiated the transfer of manufacturing protocols developed at UCSD to the selected contract manufacturing organization. Neoprobe has selected Reliable Biopharmaceuticals (Reliable) to produce the chemical compound that is then labeled at hospital or regional commercial radiopharmacies with Tc99m to become Lymphoseek. Reliable has completed an initial production lot of the unlabeled compound that compares favorably to the material produced by UCSD. Reliable has also been recently favorably inspected by FDA and they will be responsible for the manufacturing section development of our NDA for Lymphoseek. At this point, our agreement with Reliable covers only product to be used in the Phase III clinical trial for Lymphoseek. Further commercial supply and distribution agreements have yet to be negotiated with Reliable. We cannot assure you that we will be successful in reaching an agreement with Reliable on terms satisfactory to us or at all.

In preparation for the initiation of the next phase of clinical evaluation of RIGScan CR, we have initiated discussions with potential biologic manufacturers and radiolabeling organizations. We have held discussions with parties who may assist in the manufacturing validation and radiolabeling of the RIGScan product; however, we have not yet finalized agreements with these entities. We anticipate finalizing these discussions in the near future to accommodate the planned commencement of RIGScan CR clinical trials. We cannot assure you that we will be successful in securing and/or maintaining the necessary biologic, product and/or radiolabeling capabilities. See also Risk Factors.

Blood Flow Measurement Devices

The Quantix blood flow measurement devices distributed to date have been manufactured by our subsidiary, Cardiosonix Ltd., located in Ra'anana Israel. We intend to transfer the manufacture of Cardiosonix' Quantix product line to contract manufacturers in 2005; however, we are currently in the process of finalizing negotiations on this matter with the Office of the Chief Scientist in Israel. See also Risk Factors. In February 2004, we executed a Product Supply Agreement for the assembly of the blood flow control units with TriVirix; however, we are working with TriVirix to maintain some level of component sourcing from Israel that will satisfy our royalty requirements to the Israeli government. We expect assembly of the Quantix control units at TriVirix to start during the first half of 2005. We currently purchase ultrasound transducer

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modules and probe subassemblies from Vermon S.A. (Vermon) of France under purchase orders. The ultrasound probe assemblies are then completed by Technical Services for Electronics, Inc. (TSE), also under purchase orders. We are in the process of evaluating subcontractors to manufacture the other accessories associated with the Quantix product line.

14

We cannot assure you that we will be able to finalize supply and service agreements with Vermon, TSE or other subcontractors for the Quantix products, that we will be able to maintain our agreement with TriVirix, or that our subcontractors will be able to meet our production requirements on a timely basis, at the required levels of performance and quality. In the event that any of our subcontractors is unable or unwilling to meet our production requirements, we cannot assure you that an alternate source of supply could be established without significant interruption in product supply or without significant adverse impact to product availability or cost. Any significant supply interruption or yield problems that we or our subcontractors experience would have a material adverse effect on our ability to manufacture our products and, therefore, a material adverse effect on our business, financial condition, and results of operations until a new source of supply is qualified. See also Risk Factors.

In addition, we determined that development of the Quantix line had progressed to the point where we did not need the number of development staff we had in order to support the final development phases and to support our commercialization efforts. As such, we reduced employment at our Cardiosonix subsidiary during the fourth quarter of 2003. We have entered into new employment arrangements with certain key personnel in Israel in order to continue to provide limited developmental and commercial support for the Quantix products.

Competition

We face competition from medical product and biotechnology companies, as well as from universities and other non-profit research organizations in the field of cancer diagnostics and treatment. Many emerging medical product companies have corporate partnership arrangements with large, established companies to support the research, development, and commercialization of products that may be competitive with our products. In addition, a number of large established companies are developing proprietary technologies or have enhanced their capabilities by entering into arrangements with or acquiring companies with technologies applicable to the detection or treatment of cancer and the measurement of blood flow. Many of our existing or potential competitors have substantially greater financial, research and development, regulatory, marketing, and production resources than we have. Other companies may develop and introduce products and processes competitive with or superior to those of ours. See also Risk Factors.

For our products, an important factor in competition is the timing of market introduction of our products or those of our competitors' products. Accordingly, the relative speed with which we can develop products, complete the regulatory clearance processes and supply commercial quantities of the products to the market is an important competitive factor. We expect that competition among products cleared for marketing will be based on, among other things, product efficacy, safety, reliability, availability, price, and patent position.

Gamma Detection Devices

With the emergence of ILM, a number of companies have begun to market gamma radiation detection instruments. Most of the competitive products have been

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designed from an industrial or nuclear medicine perspective rather than being developed initially for surgical use. We compete with products produced by Care Wise Medical Products Corporation, Pol.Hi.Tech. Srl, Silicon Instruments GmbH and other companies. GE Healthcare has recently entered the gamma detection market through an arrangement with Intra-Medical Imaging LLC. The effects of their entry into the market cannot be predicted at this time.

It is often difficult to glean accurate competitive information within the lymphatic mapping field, primarily because most of our competitors are either subsidiaries or divisions of a large corporation (i.e., Tyco Healthcare) or privately held corporations, whose sales revenue or volume data is, therefore, not readily available or determinable. In addition, lymphatic mapping does not currently have a separate reimbursement code in most healthcare systems. As such, determining trends in the actual number of procedures being performed is difficult. We believe, based on our understanding of EES' success rate in competitive bid situations, that our market share has remained relatively constant or increased slightly in light of changes in the competitive landscape over the past few years. As we have discussed, we believe that current sales levels indicate that some prospective customers may be waiting on the results of important international clinical trials prior to adoption the ILM procedure and purchasing a gamma detection device. We expect the results from these trials, when announced, will likely have a positive impact on sales volumes. We believe our intellectual property portfolio will be a barrier to competitive products; however, we cannot assure you that competitive products will not be developed, be successful in eroding our market share or affect the prices we receive for our gamma detection devices. See also Risk Factors.

15

Gamma Detection Radiopharmaceuticals

We do not believe there are any directly competitive intraoperative diagnostic radiopharmaceuticals with RIGScan CR that would be used intraoperatively in the colorectal cancer application that RIGScan CR is initially targeted for. There are other radiopharmaceuticals that are used as preoperative imaging agents; however, we are unaware of any that could be used as a real-time diagnostic aid during surgery such as RIGScan CR.

Surgeons who practice the lymphatic mapping procedure that Lymphoseek is intended for currently use other radiopharmaceuticals such as sulphur-colloid compound in the U.S. and other colloid compounds in other markets. However, these drugs are being used "off-label" (i.e., they are not specifically indicated for use as a lymphatic targeting agent). As such, we believe that Lymphoseek, if ultimately approved, would be the first drug specifically labeled for use as a lymphatic tissue targeting agent.

Blood Flow Measurement Devices

There are several technologies on the market that measure or claim to measure indices of blood flow. These products can be categorized as devices that measure blood flow directly and devices that only obtain an estimation of flow conditions.

Direct Blood Flow Measurement Devices

- o Transit Time Ultrasound (TT) Flowmetry is the leading modality in the operating room today. TT systems monitor blood flow invasively, and are restricted to isolated vessels. They require probe adaptation to the vessel size, and do not provide additional vascular parameters. The technology requires the operator to encircle the blood vessel with a probe that includes two ultrasound transmitters/receivers on one side, and a

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mirror reflector on the opposite side of the vessel. By measuring the transit time of the ultrasound beam in the upstream and downstream directions, volume blood flow estimates can be evaluated.

- o Electromagnetic Flowmeters (EMF) are probably the oldest modality to quantify blood flow (other than timed collection). These devices monitor blood flow invasively, are impractical for multiple readings on different vessels, require precise sizing of probes to blood vessels, and do not provide additional hemodynamic parameters. The technology requires the operator to encircle the blood vessel with an electromagnetic probe. The probe generates an electromagnetic field, and the voltage measured due to the blood flow is translated into volume flow estimates. In practice, however, this technology is generally considered outdated.
- o Doppler technology has been around for several decades, and is being widely used in non-invasive vascular diagnostics. Duplex ultrasound systems have the potential to measure blood flow non-invasively. Duplex systems are designed for imaging the anatomical severity of pathology. This method is technician-dependent, cumbersome, inaccurate and does not offer monitoring capabilities. However, plain Doppler systems provide only blood flow velocity rather than volume flow.

16

Indirect Blood Flow Measurement Devices

- o Cardiac Output (CO) Monitors include various means to monitor CO such as Thermal Dilution, Bio Impedance, and the Fick Method. These methods are either invasive or indirect in their measurement. Thermal Dilution, primarily through pulmonary artery catheterization, is the standard of care today for cardiac output measurements. This technology is not applicable to other intraoperative blood flow applications. The patient is injected with cold saline at a fixed temperature, and a temperature-sensitive transducer that is placed at the site of interest (usually the pulmonary artery) measures the time to return to baseline temperature, which is proportional to the blood flow rate. There are many limitations to this technology, including the relatively large inaccuracies of cardiac output measurements, the fact that it is not truly real-time, and the fact that this method is highly invasive, and is being linked to increased morbidity and mortality (JAMA, Connors et al., 1996).
- o Computed Tomography, Magnetic Resonance Imaging and Single Photon Emission Computed Tomography techniques show target organ perfusion, but lack the ability to monitor or to provide real-time information. They are technician-dependent, impractical for bedside usage and very expensive.
- o Laser Doppler Flowmeters monitor skin blood flow non-invasively. They are applicable only to superficial and tiny vessels and do not provide additional hemodynamic parameters.
- o Transcranial Doppler (TCD) monitors cerebral blood velocity rather than direct blood flow. TCD is non-invasive and provides continuous measurement of blood flow velocity in the vessels of the brain. TCD is technician-dependent and cannot be used on every patient.
- o Plethysmography indirectly measures an index of blood flow and is limited primarily to limb assessment. Measurement depends upon many factors and output is accordingly inaccurate.
- o Jugular Bulb Saturation measures the efficiency of oxygen use by the brain. It is invasive, and provides global results.

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- o NIRS is a non-invasive method utilizing near infrared spectroscopy to provide regional perfusion in the brain.

Potentially Competitive Blood Flow Measurement Devices

Cardiosonix products are designed to address blood flow measurement across a variety of clinical and surgical settings, and there are a number of companies already in the marketplace that offer products related to blood flow measurement. However, most of these products do not directly compete with Cardiosonix products. The companies that do offer potentially competitive products are, for the most part, smaller, privately held companies, with which we believe we can effectively compete. Indeed, due to our belief in the technical superiority of our products, we believe the existence of competitors will help to educate the marketplace regarding the importance of blood flow measurement. As we have discussed, adoption of blood flow monitoring devices for the measurement of hemodynamic status will likely take an involved education process as it often involves a change in clinical or surgical management. While there is not a clear leader in these markets, the following companies compete most directly with Cardiosonix:

- o Intraoperative applications: Transonic Systems, Inc., Medi-Stim AS (TT), and Carolina Medical, Inc. (EMF).
- o Neurosurgery applications: HADECO, Hayashi Denki Co., Ltd. (Doppler based), DWL Elektronische Systeme GmbH and Nicolet Biomedical (TCD).

17

Patents and Proprietary Rights

We regard the establishment of a strong intellectual property position in our technology as an integral part of the development process. We attempt to protect our proprietary technologies through patents and intellectual property positions, in the United States as well as major foreign markets. Specifically, twenty instrument patents have been issued in the United States as well as major foreign markets protect our ILM technology.

Cardiosonix has also applied for patent coverage for the key elements of its Doppler blood flow technology in the EU and the U.S. The first of the two patents covering Cardiosonix technology was issued in the U.S. in January 2003 and claims for the second patent have been allowed. Two patents have been filed in the EU and the claims of one patent have been allowed and the claims of the second patent are in the late stage of review by the relevant governing bodies.

Lymphoseek is also the subject of patent applications in the United States and certain major foreign markets. The patent applications are held by UCSD and licensed exclusively to Neoprobe for lymphatic tissue imaging and detection. The first composition of matter patent covering Lymphoseek was issued in the U.S. in June 2002. The claims of the composition of matter patent covering Lymphoseek have been allowed in the EU and the composition of matter patent is being prosecuted in Japan.

We continue to maintain proprietary protection for the products related to RIGS and ACT in major global markets such as the U.S. and the EU, which although not currently integral to our near-term business plans, may be important to a potential RIGS or ACT development partner. The original methodology aspects of our RIGS technology are claimed in the United States in U.S. Patent No. 4,782,840, which expires in August 2005. However, Neoprobe has recently gained access to additional methodology applications related to our RIGS technology that are covered by patents that provide additional patent coverage through

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2018, unless extended. In addition to the RIGS methodology patents, composition of matter patents have been issued in the U.S. and EU that cover the antibodies used in clinical studies. The most recent of these patents issued in 2004.

The activated cellular therapy technology of CIRA Bio is the subject of issued patents in the United States to which Neoprobe has license rights. European patent statutes do not permit patent coverage for treatment technologies such as CIRA Bio's. The oncology applications of CIRA Bio's treatment approach are covered by patents with expiration dates of 2018 and 2020, unless extended. The autoimmune applications are covered by an issued patent with an expiration date of 2018, unless extended. The viral applications are the subject of patent applications and other aspects of the CIRA Bio technology that are in the process of being reviewed by the United States patent office.

The patent position of biotechnology and medical device firms, including our company, generally is highly uncertain and may involve complex legal and factual questions. Potential competitors may have filed applications for, or may have been issued patents, or may obtain additional patents and proprietary rights relating to products or processes in the same area of technology as that used by our company. The scope and validity of these patents and applications, the extent to which we may be required to obtain licenses thereunder or under other proprietary rights, and the cost and availability of licenses are uncertain. We cannot assure you that our patent applications will result in additional patents being issued or that any of our patents will afford protection against competitors with similar technology; nor can we assure you that any of our patents will not be designed around by others or that others will not obtain patents that we would need to license or design around. See also Risk Factors.

We also rely upon unpatented trade secrets. We cannot assure you that others will not independently develop substantially equivalent proprietary information and techniques, or otherwise gain access to our trade secrets, or disclose such technology, or that we can meaningfully protect our rights to our unpatented trade secrets.

We require our employees, consultants, advisers, and suppliers to execute a confidentiality agreement upon the commencement of an employment, consulting or manufacturing relationship with us. The agreement provides that all confidential information developed by or made known to the individual during the course of the relationship will be kept confidential and not disclosed to third parties except in specified circumstances. In the case of employees, the agreements provide that all inventions conceived by the individual will be the exclusive property of our company. We cannot assure you, however, that these agreements will provide meaningful protection for our trade secrets in the event of an unauthorized use or disclosure of such information.

18

Government Regulation

Most aspects of our business are subject to some degree of government regulation in the countries in which we conduct our operations. As a developer, manufacturer and marketer of medical products, we are subject to extensive regulation by, among other governmental entities, FDA and the corresponding state, local and foreign regulatory bodies in jurisdictions in which our products are sold. These regulations govern the introduction of new products, the observance of certain standards with respect to the manufacture, safety, efficacy and labeling of such products, the maintenance of certain records, the tracking of such products and other matters.

Failure to comply with applicable federal, state, local or foreign laws or regulations could subject us to enforcement action, including product seizures, recalls, withdrawal of marketing clearances, and civil and criminal penalties,

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any one or more of which could have a material adverse effect on our business. We believe that we are in substantial compliance with such governmental regulations. However, federal, state, local and foreign laws and regulations regarding the manufacture and sale of medical devices are subject to future changes. We cannot assure you that such changes will not have a material adverse effect on our company.

For some products, and in some countries, government regulation is significant and, in general, there is a trend toward more stringent regulation. In recent years, FDA and certain foreign regulatory bodies have pursued a more rigorous enforcement program to ensure that regulated businesses, like ours, comply with applicable laws and regulations. We devote significant time, effort and expense addressing the extensive governmental regulatory requirements applicable to our business. To date, we have not received any notifications or warning letters from FDA or any other regulatory bodies of alleged deficiencies in our compliance with the relevant requirements, nor have we recalled or issued safety alerts on any of our products. However, we cannot assure you that a warning letter, recall or safety alert, if it occurred, would not have a material adverse effect on our company.

In the early to mid 1990s, the review time by FDA to clear medical products for commercial release lengthened and the number of marketing clearances decreased. In response to public and congressional concern, FDA Modernization Act of 1997 (the 1997 Act) was adopted with the intent of bringing better definition to the clearance process for new medical products. While FDA review times have improved since passage of the 1997 Act, we cannot assure you that FDA review process will not continue to delay our company's introduction of new products in the U.S. in the future. In addition, many foreign countries have adopted more stringent regulatory requirements that also have added to the delays and uncertainties associated with the release of new products, as well as the clinical and regulatory costs of supporting such releases. It is possible that delays in receipt of, or failure to receive, any necessary clearance for our new product offerings could have a material adverse effect on our business, financial condition or results of operations.

While we are unable to predict the extent to which our business may be affected by future regulatory developments, we believe that our substantial experience dealing with governmental regulatory requirements and restrictions on our operations throughout the world, and our development of new and improved products, should enable us to compete effectively within this environment.

Gamma Detection and Blood Flow Measurement Devices

As a manufacturer of medical devices sold in various global markets, we are required to manufacture the devices under quality system regulations (QSR) and maintain appropriate technical files and quality records. Our medical devices are regulated in the United States by FDA. Our medical devices are regulated in the EU according to the Medical Device Directive (93/42/EEC). Under this regulation, we must obtain CE Mark status for all products exported to the EU.

Our initial generation gamma detection instruments received 510(k) marketing clearance from FDA in December 1986 with modified versions receiving similar clearances in 1992 through 1997. In 1998, FDA reclassified "nuclear uptake detectors" as being exempt from the 510(k) process. We believe the neo2000 device is exempt from the 510(k) process because it is substantially equivalent to previously cleared predecessor devices. We obtained the CE Mark for the neo2000 device in January 1999, and therefore, must continue to manufacture the devices under a quality system compliant to the requirements of ISO 9001/EN 46001 and maintain appropriate technical files. We maintain a license to import our gamma devices into Canada, and therefore must continue to manufacture the devices under a quality system compliant to the requirements of ISO 13485 and CMDCAS.

Cardiosonix has received 510(k) and CE mark clearance to market the Quantix/ND device in the U.S. and EU for non-invasive applications. The Quantix/OR has also received CE Mark clearance to market in the EU and 510(k) clearance in the U.S. Our distribution partners in certain foreign markets other than the EU are seeking marketing clearances, as required, for both the Quantix/ND and Quantix/OR.

Gamma Detection Radiopharmaceuticals (Lymphoseek and RIGScan)

Our radiolabeled targeting agents and biologic products, if developed, would require a regulatory license to market by FDA and by comparable agencies in foreign countries. The process of obtaining regulatory licenses and approvals is costly and time consuming, and we have encountered significant impediments and delays related to our previously proposed biologic products.

The process of completing pre-clinical and clinical testing, manufacturing validation and submission of a marketing application to the appropriate regulatory bodies usually takes a number of years and requires the expenditure of substantial resources, and we cannot assure you that any approval will be granted on a timely basis, if at all. Additionally, the length of time it takes for the various regulatory bodies to evaluate an application for marketing approval varies considerably, as does the amount of preclinical and clinical data required to demonstrate the safety and efficacy of a specific product. The regulatory bodies may require additional clinical studies that may take several years to perform. The length of the review period may vary widely depending upon the nature and indications of the proposed product and whether the regulatory body has any further questions or requests any additional data. Also, the regulatory bodies will likely require post-marketing reporting and surveillance programs to monitor the side effects of the products. We cannot assure you that any of our potential drug or biologic products will be approved by the regulatory bodies or approved on a timely or accelerated basis, or that any approvals received will not subsequently be revoked or modified.

In addition to regulations enforced by FDA, the manufacture, distribution, and use of radioactive targeting agents, if developed, are also subject to regulation by the Nuclear Regulatory Commission (NRC), the Department of Transportation and other federal, state, and local government authorities. We, or our manufacturer of the radiolabeled antibodies, must obtain a specific license from the NRC to manufacture and distribute radiolabeled antibodies, as well as comply with all applicable regulations. We must also comply with Department of Transportation regulations on the labeling and packaging requirements for shipment of radiolabeled antibodies to licensed clinics, and must comply with federal, state, and local governmental laws regarding the disposal of radioactive waste. We cannot assure you that we will be able to obtain all necessary licenses and permits and be able to comply with all applicable laws. The failure to obtain such licenses and permits or to comply with applicable laws would have a materially adverse effect on our business, financial condition, and results of operations.

Employees

As of March 15, 2005, we had 21 full-time employees, including those of our subsidiary, Cardiosonix. We consider our relations with our employees to be good.

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Risk Factors

An investment in our common stock is highly speculative, involves a high degree of risk, and should be made only by investors who can afford a complete loss. You should carefully consider the following risk factors, together with the other information in this prospectus, including our financial statements and the related notes, before you decide to buy our common stock. Our most significant risks and uncertainties are described below; however, they are not the only risks we face. If any of the following risks actually occur, our business, financial condition, or results of operations could be materially adversely affected, the trading of our common stock could decline, and you may lose all or part of your investment therein.

We have suffered significant operating losses for several years in our history and we may not be able to again achieve profitability.

We had an accumulated deficit of approximately \$126 million as of December 31, 2004. Although we were profitable in 2000 and in 2001, we incurred substantial losses in the years prior to that, and in 2002 through 2004. The deficit resulted because we expended more money in the course of researching, developing and enhancing our technology and products and establishing our marketing and administrative organizations than we generated in revenues. We expect to continue to incur significant operating expenses in the foreseeable future, primarily related to the completion of development and commercialization of the Cardiosonix product line but also potentially related to RIGS and Lymphoseek. As a result, we are sustaining substantial operating and net losses, and it is possible that we will never be able to sustain or develop the revenue levels necessary to again attain profitability.

Our products and product candidates may not achieve the broad market acceptance they need in order to be a commercial success.

Widespread use of our gamma detection devices is currently limited to a surgical procedure (ILM) used in the treatment and diagnosis of two primary types of cancer: melanoma and breast cancer. The success of our gamma detection devices greatly depends on the medical community's ongoing adoption of ILM, and on our devices for use in ILM as a reliable, safe and cost effective alternative to current treatments and procedures. The adoption rate for ILM appears to be leveling off and may not meet our growth expectations. Although we continue to believe that ILM has significant advantages over other currently competing procedures, broad-based clinical adoption of ILM will likely not occur until after the completion of ongoing international trials related to breast cancer. Even if the results of these trials are positive, we cannot assure you that ILM will attain rapid and widespread acceptance. Our efforts and those of our marketing and distribution partners may not result in significant demand for our products, and the current demand for our products may decline.

Our future success now also greatly depends on the success of the Cardiosonix product line. Cardiosonix' products are just beginning to be marketed commercially. The market for these products is in an early stage of development and may never fully develop as we expect. The long-term commercial success of the Cardiosonix product line will require widespread acceptance of our products as safe, efficient and cost-effective. Widespread acceptance would represent a significant change in medical practice patterns. Other cardiac monitoring procedures, such as pulmonary artery catheterization, are generally accepted in the medical community and have a long standard of use. It is possible that the Cardiosonix product line will never achieve the broad market acceptance necessary to become a commercial success.

Our radiopharmaceutical product candidates are still in the process of development, and even if we are successful in commercializing them, we cannot assure you that they will obtain significant market acceptance.

Clinical trials for our radiopharmaceutical product candidates will be lengthy and expensive and their outcome is uncertain.

Before obtaining regulatory approval for the commercial sale of any product candidates, we must demonstrate through preclinical testing and clinical trials that our product candidates are safe and effective for use in humans. Conducting clinical trials is a time consuming, expensive and uncertain process and may take years to complete. Our most advanced product candidates, Lymphoseek and RIGScan CR are preparing to enter the Phase III stage of clinical trials. Historically, the results from preclinical testing and early clinical trials have often not been predictive of results obtained in later clinical trials. Frequently, drugs that have shown promising results in preclinical or early clinical trials subsequently fail to establish sufficient safety and efficacy data necessary to obtain regulatory approval. At any time during the clinical trials, we, our collaborative partners or FDA might delay or halt any clinical trials for our product candidates for various reasons, including:

- o ineffectiveness of the product candidate;
- o discovery of unacceptable toxicities or side effects;
- o development of disease resistance or other physiological factors;
- o delays in patient enrollment; or
- o other reasons that are internal to the businesses of our potential collaborative partners, which reasons they may not share with us.

The results of the clinical trials may fail to demonstrate the safety or effectiveness of our product candidates to the extent necessary to obtain regulatory approval or such that commercialization of our product candidates is worthwhile. Any failure or substantial delay in successfully completing clinical trials and obtaining regulatory approval for our product candidates could severely harm our business.

If we fail to obtain collaborative partners, or those we obtain fail to perform their obligations or discontinue clinical trials for particular product candidates, our ability to develop and market potential products could be severely limited.

Our strategy for the development and commercialization of our product candidates depends, in large part, upon the formation of collaborative arrangements. Collaborations may allow us to:

- o generate cash flow and revenue;
- o offset some of the costs associated with our internal research and development, preclinical testing, clinical trials and manufacturing;
- o seek and obtain regulatory approvals faster than we could on our own; and,
- o successfully commercialize existing and future product candidates.

We do not currently have collaborative agreements covering Lymphoseek or RIGScan CR. We cannot assure you that we will be successful in securing collaborative partners, or that we will be able to negotiate acceptable terms for such arrangements. The development, regulatory approval and commercialization of our product candidates will depend substantially on the efforts of collaborative partners, and if we fail to secure or maintain successful collaborative arrangements, or if our partners fail to perform their obligations, our development, regulatory, manufacturing and marketing activities may be delayed, scaled back or suspended.

We rely on third parties for the worldwide marketing and distribution of our

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gamma detection and blood flow measurement devices, who may not be successful in selling our products.

We currently distribute our gamma detection devices in most global markets through two partners who are solely responsible for marketing and distributing these products. The partners assume direct responsibility for business risks related to credit, currency exchange, foreign tax laws or tariff and trade regulation. Our blood flow products are marketed and sold in the U.S. and a number of foreign markets through other distribution partners specific to those markets. Further, our Quantix line of blood flow products has only recently been introduced, and we have only limited experience in marketing or selling these devices. While we believe that our distribution partners intend to continue to aggressively market our products, we cannot assure you that the distribution partners will succeed in marketing our products on a global basis. We may not be able to maintain satisfactory arrangements with our marketing and distribution partners, who may not devote adequate resources to selling our products. If this happens, we may not be able to successfully market our products, which would decrease our revenues.

22

Our radiopharmaceutical product candidates are subject to extensive government regulations and we may not be able to obtain necessary regulatory approvals.

We may not receive the regulatory approvals necessary to commercialize our Lymphoseek and RIGScan product candidates, which could cause our business to be severely harmed. Our product candidates are subject to extensive and rigorous government regulation. FDA regulates, among other things, the development, testing, manufacture, safety, record-keeping, labeling, storage, approval, advertising, promotion, sale and distribution of pharmaceutical products. If our potential products are marketed abroad, they will also be subject to extensive regulation by foreign governments. None of our product candidates has been approved for sale in the United States or any foreign market. The regulatory review and approval process, which includes preclinical studies and clinical trials of each product candidate, is lengthy, complex, expensive and uncertain. Securing FDA approval requires the submission of extensive preclinical and clinical data and supporting information to FDA for each indication to establish the product candidate's safety and efficacy. Data obtained from preclinical and clinical trials are susceptible to varying interpretation, which may delay, limit or prevent regulatory approval. The approval process may take many years to complete and may involve ongoing requirements for post-marketing studies. In light of the limited regulatory history of monoclonal antibody-based therapeutics, regulatory approvals for our products may not be obtained without lengthy delays, if at all. Any FDA or other regulatory approvals of our product candidates, once obtained, may be withdrawn. The effect of government regulation may be to:

- o delay marketing of potential products for a considerable period of time;
- o limit the indicated uses for which potential products may be marketed;
- o impose costly requirements on our activities; and
- o provide competitive advantage to other pharmaceutical and biotechnology companies.

We may encounter delays or rejections in the regulatory approval process because of additional government regulation from future legislation or administrative action or changes in FDA policy during the period of product development, clinical trials and FDA regulatory review. Failure to comply with applicable FDA or other applicable regulatory requirements may result in criminal prosecution, civil penalties, recall or seizure of products, total or partial suspension of production or injunction, as well as other regulatory action against our product

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candidates or us. Outside the United States, our ability to market a product is contingent upon receiving clearances from the appropriate regulatory authorities. This foreign regulatory approval process includes similar risks to those associated with FDA approval process.

Our radiopharmaceutical product candidates will remain subject to ongoing regulatory review even if they receive marketing approval. If we fail to comply with continuing regulations, we could lose these approvals and the sale of our products could be suspended.

Even if we receive regulatory approval to market a particular product candidate, the approval could be conditioned on us conducting additional costly post-approval studies or could limit the indicated uses included in our labeling. Moreover, the product may later cause adverse effects that limit or prevent its widespread use, force us to withdraw it from the market or impede or delay our ability to obtain regulatory approvals in additional countries. In addition, the manufacturer of the product and its facilities will continue to be subject to FDA review and periodic inspections to ensure adherence to applicable regulations. After receiving marketing approval, the manufacturing, labeling, packaging, adverse event reporting, storage, advertising, promotion and record keeping related to the product will remain subject to extensive regulatory requirements. We may be slow to adapt, or we may never adapt, to changes in existing regulatory requirements or adoption of new regulatory requirements.

23

If we fail to comply with the regulatory requirements of FDA and other applicable U.S. and foreign regulatory authorities or previously unknown problems with our products, manufacturers or manufacturing processes are discovered, we could be subject to administrative or judicially imposed sanctions, including:

- o restrictions on the products, manufacturers or manufacturing processes;
- o warning letters;
- o civil or criminal penalties;
- o fines;
- o injunctions;
- o product seizures or detentions;
- o import bans;
- o voluntary or mandatory product recalls and publicity requirements;
- o suspension or withdrawal of regulatory approvals;
- o total or partial suspension of production; and
- o refusal to approve pending applications for marketing approval of new drugs or supplements to approved applications.

Our existing products are highly regulated and we could face severe problems if we do not comply with all regulatory requirements in the global markets in which these products are sold.

FDA regulates our gamma detection and blood flow products in the United States. Foreign countries also subject these products to varying government regulations. In addition, these regulatory authorities may impose limitations on the use of our products. FDA enforcement policy strictly prohibits the marketing of FDA cleared medical devices for unapproved uses. Within the European Union, our products are required to display the CE Mark in order to be sold. We have obtained FDA clearance to market and European certification to display the CE Mark on our current line of gamma detection systems and on two blood flow products, the Quantix/ND and Quantix/OR. We may not be able to obtain clearance to market for any new products in a timely manner, or at all. Failure to comply with these and other current and emerging regulatory requirements in the global markets in which our products are sold could result in, among other things,

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warning letters, fines, injunctions, civil penalties, recall or seizure of products, total or partial suspension of production, refusal of the government to grant pre-market clearance for devices, withdrawal of clearances, and criminal prosecution.

We rely on third parties to manufacture our products and our business will suffer if they do not perform.

We rely on independent contract manufacturers for the manufacture of our current line of gamma detection systems and for our Quantix line of blood flow monitoring products. Our business will suffer if our contract manufacturers have production delays or quality problems. Furthermore, medical device manufacturers are subject to the QSR regulations of FDA, international quality standards, and other regulatory requirements. If our contractors do not operate in accordance with regulatory requirements and quality standards, our business will suffer. We use or rely on components and services used in our devices that are provided by sole source suppliers. The qualification of additional or replacement vendors is time consuming and costly. If a sole source supplier has significant problems supplying our products, our sales and revenues will be hurt until we find a new source of supply. In addition, our distribution agreement with EES for gamma devices contains failure to supply provisions, which, if triggered, could have a significant negative impact on our business.

We may be unable to establish the pharmaceutical manufacturing capabilities necessary to develop and commercialize our potential products.

We do not have our own manufacturing facility for the manufacture of the radiopharmaceutical compounds necessary for clinical testing or commercial sale. We intend to rely in part on third-party contract manufacturers to produce sufficiently large quantities of drug materials that are and will be needed for clinical trials and commercialization of our potential products. Third-party manufacturers may not be able to meet our needs with respect to timing, quantity or quality of materials. If we are unable to contract for a sufficient supply of needed materials on acceptable terms, or if we should encounter delays or difficulties in our relationships with manufacturers, our clinical trials may be delayed, thereby delaying the submission of product candidates for regulatory approval and the market introduction and subsequent commercialization of our potential products. Any such delays may lower our revenues and potential profitability.

24

We may develop our manufacturing capacity in part by expanding our current facilities or building new facilities. Either of these activities would require substantial additional funds and we would need to hire and train significant numbers of employees to staff these facilities. We may not be able to develop manufacturing facilities that are sufficient to produce drug materials for clinical trials or commercial use. We and any third-party manufacturers that we may use must continually adhere to current Good Manufacturing Practices regulations enforced by FDA through its facilities inspection program. If our facilities or the facilities of third-party manufacturers cannot pass a pre-approval plant inspection, FDA will not grant approval to our product candidates. In complying with these regulations and foreign regulatory requirements, we and any of our third-party manufacturers will be obligated to expend time, money and effort on production, record-keeping and quality control to assure that our potential products meet applicable specifications and other requirements. If we or any third-party manufacturer with whom we may contract fail to maintain regulatory compliance, we or the third party may be subject to fines and/or manufacturing operations may be suspended.

Unfavorable pricing regulations, third-party reimbursement practices or

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healthcare reform initiatives applicable to our products and product candidates could limit our potential product revenue.

The regulations governing drug pricing and reimbursement vary widely from country to country. Some countries require approval of the sale price of a drug before it can be marketed and, in many of these countries, the pricing review period begins only after approval is granted. In some countries, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. Although we monitor these regulations, our product candidates are currently in the development stage and we will not be able to assess the impact of price regulations for at least several years. As a result, we may obtain regulatory approval for a product in a particular country, but then be subject to price regulations that may delay the commercial launch of the product and may negatively impact the revenues we are able to derive from sales in that country.

The healthcare industry is undergoing fundamental changes resulting from political, economic and regulatory influences. In the United States, comprehensive programs have been proposed that seek to increase access to healthcare for the uninsured, control the escalation of healthcare expenditures within the economy and use healthcare reimbursement policies to balance the federal budget.

We expect that Congress and state legislatures will continue to review and assess healthcare proposals, and public debate of these issues will likely continue. We cannot predict which, if any, of such reform proposals will be adopted and when they might be adopted. Other countries also are considering healthcare reform. Significant changes in healthcare systems could have a substantial impact on the manner in which we conduct our business and could require us to revise our strategies.

We may have difficulty raising additional capital, which could deprive us of necessary resources.

We expect to continue to devote significant capital resources to fund research and development and to maintain existing and secure new manufacturing capacity. In order to support the initiatives envisioned in our business plan, we may need to raise additional funds through the sale of assets, public or private debt or equity financing, collaborative relationships or other arrangements. Our ability to raise additional financing depends on many factors beyond our control, including the state of capital markets, the market price of our common stock and the development or prospects for development of competitive technology by others. Because our common stock is not listed on a major stock market, many investors may not be willing or allowed to purchase it or may demand steep discounts. Sufficient additional financing may not be available to us or may be available only on terms that would result in further dilution to the current owners of our common stock. At current market prices, the limited number of shares we have available to sell severely limits our ability to use equity as a method of raising capital. If we are unable to raise additional funds when we need them, we may have to severely curtail our operations.

25

The sale of the shares of common stock acquired in private placements could cause the price of our common stock to decline.

During 2003 and 2004, we completed several financings in which we issued common stock, convertible notes, warrants and other securities convertible into common stock to certain private investors and as required under the terms of those transactions, we filed registration statements with the United States Securities and Exchange Commission (SEC) under which the investors may resell common stock

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acquired in these transactions, as well as common stock acquired on the exercise of the warrants and convertible securities held by them, to the public. We have also filed a registration statement covering the resale of common stock issued to former stockholders of Cardiosonix in connection with our acquisition of that business.

The selling stockholders under these registration statements may sell none, some or all of the shares of common stock acquired from us, as well as common stock acquired on the exercise of the warrants and convertible securities held by them. We have no way of knowing whether the selling stockholders will sell the shares covered by these registration statements. Depending upon market liquidity at the time, a sale of shares covered by these registration statements at any given time could cause the trading price of our common stock to decline. The sale of a substantial number of shares of our common stock under this prospectus, or anticipation of such sales, could make it more difficult for us to sell equity or equity-related securities in the future at a time and at a price that we might otherwise wish to effect sales.

We may lose out to larger and better-established competitors.

The medical device and biotechnology industries are intensely competitive. Some of our competitors have significantly greater financial, technical, manufacturing, marketing and distribution resources as well as greater experience in the medical device industry than we have. The particular medical conditions our product lines address can also be addressed by other medical devices, procedures or drugs. Many of these alternatives are widely accepted by physicians and have a long history of use. Physicians may use our competitors' products and/or our products may not be competitive with other technologies. If these things happen, our sales and revenues will decline. In addition, our current and potential competitors may establish cooperative relationships with large medical equipment companies to gain access to greater research and development or marketing resources. Competition may result in price reductions, reduced gross margins and loss of market share.

Our products may be displaced by newer technology.

The medical device and biotechnology industries are undergoing rapid and significant technological change. Third parties may succeed in developing or marketing technologies and products that are more effective than those developed or marketed by us, or that would make our technology and products obsolete or non-competitive. Additionally, researchers could develop new surgical procedures and medications that replace or reduce the importance of the procedures that use our products. Accordingly, our success will depend, in part, on our ability to respond quickly to medical and technological changes through the development and introduction of new products. We may not have the resources to do this. If our products become obsolete and our efforts to develop new products do not result in any commercially successful products, our sales and revenues will decline.

Our intellectual property may not have or provide sufficient legal protections against infringement or loss of trade secrets.

Our success depends, in part, on our ability to secure and maintain patent protection, to preserve our trade secrets, and to operate without infringing on the patents of third parties. While we seek to protect our proprietary positions by filing United States and foreign patent applications for our important inventions and improvements, domestic and foreign patent offices may not issue these patents. Third parties may challenge, invalidate, or circumvent our patents or patent applications in the future. Competitors, many of which have significantly more resources than we have and have made substantial investments in competing technologies, may apply for and obtain patents that will prevent, limit, or interfere with our ability to make, use, or sell our products either in the United States or abroad.

In the United States, patent applications are secret until patents issue, and in foreign countries, patent applications are secret for a time after filing. Publications of discoveries tend to significantly lag the actual discoveries and the filing of related patent applications. Third parties may have already filed applications for patents for products or processes that will make our products obsolete or will limit our patents or invalidate our patent applications.

We typically require our employees, consultants, advisers and suppliers to execute confidentiality and assignment of invention agreements in connection with their employment, consulting, advisory, or supply relationships with us. They may breach these agreements and we may not obtain an adequate remedy for breach. Further, third parties may gain access to our trade secrets or independently develop or acquire the same or equivalent information.

Agencies of the United States government conducted some of the research activities that led to the development of antibody technology that some of our proposed antibody-based surgical cancer detection products use. When the United States government participates in research activities, it retains rights that include the right to use the technology for governmental purposes under a royalty-free license, as well as rights to use and disclose technical data that could preclude us from asserting trade secret rights in that data and software.

The government grants Cardiosonix has received for research and development expenditures restrict our ability to manufacture blood flow monitoring products and transfer technologies outside of Israel and require us to satisfy specified conditions. If we fail to satisfy these conditions, we may be required to refund grants previously received together with interest and penalties, and may be subject to criminal charges.

Cardiosonix received grants from the government of Israel through the Office of the Chief Scientist (OCS) of the Ministry of Industry and Trade for the financing of a portion of its research and development expenditures associated with our blood flow monitoring products. From 1998 to 2001, Cardiosonix received grants totaling \$775,000 from the OCS. The terms of the OCS grants may affect our efforts to transfer manufacturing of products developed using these grants outside of Israel without special approvals. The OCS issued a letter to Neoprobe in December 2001, prior to the acquisition of Cardiosonix, consenting to the transfer of manufacturing as long as Neoprobe consented to the terms of the OCS statutes under Israeli law. As a result of our efforts to transfer a significant portion of the manufacture of our blood flow products out of Israel, we will likely be required to pay an increased amount of royalties, which may be up to 300% of the grant amount, depending on the manufacturing volume that is performed outside of Israel. This may impair our ability to effectively outsource manufacturing or engage in similar arrangements for those products or technologies. In addition, if we fail to comply with any of the conditions imposed by the OCS, we may be required to refund any grants previously received together with interest and penalties, and may be subject to criminal charges. In recent years, the government of Israel has accelerated the rate of repayment of OCS grants related to other grantees and may further accelerate them in the future.

We could be damaged by product liability claims.

Our products are used or intended to be used in various clinical or surgical procedures. If one of our products malfunctions or a physician misuses it and injury results to a patient or operator, the injured party could assert a product liability claim against our company. We currently have product liability insurance with a \$10 million per occurrence limit, which we believe is adequate

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for our current activities. However, we may not be able to continue to obtain insurance at a reasonable cost. Furthermore, insurance may not be sufficient to cover all of the liabilities resulting from a product liability claim, and we might not have sufficient funds available to pay any claims over the limits of our insurance. Because personal injury claims based on product liability in a medical setting may be very large, an underinsured or an uninsured claim could financially damage our company.

27

We may have trouble attracting and retaining qualified personnel and our business may suffer if we do not.

Our business has experienced developments the past two years that have resulted in several significant changes in our strategy and business plan, including the shifting of resources to support our current product initiatives and downsizings to what we consider to be the minimal support structure necessary to operate a publicly traded company. Our management will need to remain flexible to support our business model over the next few years. However, losing members of the Neoprobe management team could have an adverse effect on our operations. Our success depends on our ability to attract and retain technical and management personnel with expertise and experience in the medical device business. The competition for qualified personnel in the medical device industry is intense and we may not be successful in hiring or retaining the requisite personnel. If we are unable to attract and retain qualified technical and management personnel, we will suffer diminished chances of future success.

Our secured indebtedness imposes significant restrictions on us, and a default could cause us to cease operations.

All of our material assets, except the intellectual property associated with our Lymphoseek and RIGS products under development, have been pledged as collateral for the \$8.1 million in principal amount of our 8% Series A Convertible Notes due December 12, 2008 (the Notes). In addition to the security interest in our assets, the Notes carry substantial covenants that impose significant requirements on us, including, among others, requirements that:

- o we pay all principal, interest and other charges on the Notes when due;
- o we use the proceeds from the sale of the Notes only for permitted purposes, such as Lymphoseek development and general corporate purposes;
- o we nominate and recommend for election as a director a person designated by the holders of the Notes;
- o we keep reserved out of our authorized shares of common stock sufficient shares to satisfy our obligation to issue shares on conversion of the Notes and the exercise of the warrants issued in connection with the sale of the Notes;
- o we achieve annual revenues on a consolidated basis of at least \$5.4 million in 2005, \$6.5 million in 2006, and \$9.0 million in each year thereafter;
- o we maintain minimum cash balances of \$4.5 million at the end of the first six months of 2005, \$4.0 million at the end of the second six months of 2005, and \$3.5 million at the end of each six-month period thereafter; and
- o we indemnify the purchasers of the Notes against certain liabilities.

Additionally, with certain exceptions, the Notes prohibit us from:

- o amending our organizational or governing agreements and documents, entering into any merger or consolidation, dissolving the company or liquidating its assets, or acquiring all or any substantial part of the

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- business or assets of any other person;
- o engaging in transactions with any affiliate;
- o entering into any agreement inconsistent with our obligations under the Notes and related agreements;
- o incurring any indebtedness, capital leases, or contingent obligations outside the ordinary course of business;
- o granting or permitting liens against or security interests in our assets;
- o making any material dispositions of our assets outside the ordinary course of business;
- o declaring or paying any dividends or making any other restricted payments; or
- o making any loans to or investments in other persons outside of the ordinary course of business.

28

Our ability to comply with these provisions may be affected by changes in our business condition or results of our operations, or other events beyond our control. The breach of any of these covenants would result in a default under the Notes, permitting the holders of the Notes to accelerate their maturity and to sell the assets securing them. Such actions by the holders of the Notes could cause us to cease operations or seek bankruptcy protection.

Our common stock is traded over the counter, which may deprive stockholders of the full value of their shares.

Our common stock is quoted via the National Association of Securities Dealers' Over The Counter Bulletin Board (OTCBB). As such, our common stock may have fewer market makers, lower trading volumes and larger spreads between bid and asked prices than securities listed on an exchange such as the New York Stock Exchange or the NASDAQ Stock Market. These factors may result in higher price volatility and less market liquidity for the common stock.

A low market price may severely limit the potential market for our common stock.

Our common stock is currently trading at a price substantially below \$5.00 per share, subjecting trading in the stock to certain SEC rules requiring additional disclosures by broker-dealers. These rules generally apply to any non-NASDAQ equity security that has a market price share of less than \$5.00 per share, subject to certain exceptions (a "penny stock"). Such rules require the delivery, prior to any penny stock transaction, of a disclosure schedule explaining the penny stock market and the risks associated therewith and impose various sales practice requirements on broker-dealers who sell penny stocks to persons other than established customers and institutional or wealthy investors. For these types of transactions, the broker-dealer must make a special suitability determination for the purchaser and have received the purchaser's written consent to the transaction prior to the sale. The broker-dealer also must disclose the commissions payable to the broker-dealer, current bid and offer quotations for the penny stock and, if the broker-dealer is the sole market maker, the broker-dealer must disclose this fact and the broker-dealer's presumed control over the market. Such information must be provided to the customer orally or in writing before or with the written confirmation of trade sent to the customer. Monthly statements must be sent disclosing recent price information for the penny stock held in the account and information on the limited market in penny stocks. The additional burdens imposed upon broker-dealers by such requirements could discourage broke