NANOGEN INC
Form 10-K
March 30, 2004
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM 10-K

x ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2003

OR

¨ TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from _____ to _____

Commission File Number 000-23541

NANOGEN, INC.

(Exact name of Registrant as specified in its charter)

Delaware	**33-0489621**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
10398 Pacific Center Court, San Diego, CA	**92121**
(Address of principal executive offices)	(Zip code)

Registrant s telephone number, including area code: (858) 410-4600

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

NONE

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

Common Stock $0.001 par value

Preferred Stock Purchase Rights

(Title of Class)

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 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 __X__ NO _____

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (Section 229.405 of this chapter) is not contained herein, and will not 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-K or any amendment to this Form 10-K. x

Indicate by check mark whether the registrant is an accelerated filer (as defined in Rule 12b-2 of the Act).

YES _____ NO __X__

The aggregate market value of the voting stock held by non-affiliates of the registrant based upon the closing sale price of the common stock on June 30, 2003 (the last day of the registrant s most recently completed second fiscal quarter), as reported on the Nasdaq National Market was approximately $52,592,000. Shares of common stock held by each executive officer and director and by each person (including shares beneficially owned by Citigroup, Inc.) who own 10 percent or more of the outstanding common stock have been excluded in such calculation as such persons may be deemed to be affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

The number of shares outstanding of the registrant s common stock was 31,182,060 as of March 19, 2004.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant s definitive proxy statement for its annual meeting of stockholders to be held in 2004 are incorporated by reference in Part III of this Form 10-K.

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NANOGEN, INC.

FORM 10-K

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PART I

Item 1. Business

Forward Looking Statement

This Form 10-K includes forward-looking statements about our business and results of operations that are subject to risks and uncertainties that could cause our actual results to vary materially from those reflected in the forward-looking statements. Words such as believes, anticipates, plans, estimates, future, could, may, should, would, expect, envision, potentially, variations of such words and similar expres to identify such forward-looking statements. The forward-looking statements contained in this Form 10-K include, but are not limited to, statements about matters including the following: (i) the development of the markets and demand for our products and services; (ii) our product development plans, including the introduction of new products, and anticipated activities designed to pursue these plans, including collaborations and other corporate partnering arrangements; (iii) our ability to generate substantial revenues from sales of products and consumable cartridges and reagents and continuing revenues from reagent rental agreements; (iv) the ability of our product platform to affect the market and become an industry standard; (v) our ability to generate license and other fee revenue in the future; (vi) the amounts we invest in research and development activities in the future; (vii) future levels of operating expenses associated with our business; (viii) future levels of interest income; (ix) any amounts we may be able to realize from the liquidation of our investments, including our investments in short-term securities; (x) operating results of joint ventures, mergers, acquisitions and other corporate partnering arrangements; (xi) the amounts and timing of our contractual obligations and capital commitments and (xii) our future capital needs and our ability to fund those needs. Factors that could cause or contribute to these differences include those discussed under the caption Factors That May Affect Results and elsewhere in this Form 10-K. Readers are cautioned not to place undue reliance on these forward-looking statements that speak only as of the date hereof. We disclaim any intent or obligation to update these forward-looking statements.

Our internet address (presented as a textual reference only) is www.nanogen.com. We make available through our website, free of charge, our annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and amendments to these reports filed with or furnished to the SEC under Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, as soon as reasonably practicable after we file them with, or furnish them to, the SEC.

Overview

Molecular Diagnostics Market

Increased awareness of the role of genetics in regulating the functions of living organisms has generated a worldwide effort to identify and sequence genes and genomes of many organisms, including the estimated three billion nucleotide pairs of the human genome. In June 2000, the effort led by the Human Genome Project (sponsored by the Department of Energy and the National Institutes of Health) resulted in a first complete draft of the human genome sequence. While it is anticipated that many years of additional research will be required to understand the specific functions and roles in disease of each of these genes and their patterns of interaction, this research, commonly referred to as genomics, is leading to a new healthcare paradigm where disease is understood at the molecular level. It is believed that the use of genomics will lead to the introduction of new therapies, the development of targeted therapeutics and an abundance of new screening tests that will, in turn, shift the focus of medicine to proactive from reactive. Molecular diagnostic tools are integral to rendering genetic information accessible to researchers and clinicians.

The market for molecular diagnostics tools, assays and other products has been estimated in a report from SG Cowen to be approximately $1.2 billion in 2002 and is predicted to grow to over $3.0 billion in 2005. Of the $1.2 billion spent in 2002, the Company believes that approximately seventy-five percent (75%) was spent on infectious disease testing products for such diseases as Human Immune Deficiency Virus (HIV), Hepatitis C

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Virus (HCV), *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (GC) and the remaining twenty- five percent (25%) was spent on other products such as those used in genetic testing. As the molecular diagnostics market grows, we expect human genetic testing to represent an increasingly larger percentage of this annual amount.

The molecular diagnostics market currently primarily consists of customers in (1) research institutions such as universities, research hospitals, private companies and government institutions, (2) high complexity CLIA (Clinical Laboratory Improvements Act)-certified clinical diagnostics laboratories and (3) clinical diagnostics laboratories in hospitals, private companies and government clinics. Such customers are developing tests and assays to screen, predict, diagnose, treat or monitor individuals who have certain single nucleotide polymorphisms (SNPs), short tandem repeats (STRs), insertions, deletions or other genetic mutations that are correlated with various disease states. Research customers normally develop and perform assays that are designed to correlate various SNPs or other mutations with certain disease states. High complexity CLIA-certified laboratories, which are regulated under the federal CLIA rules, normally develop and validate their own home brew tests or they may run assays purchased from platform manufacturers or others to help physicians diagnose and treat patients. In the development and validation of a home brew test, a laboratory may utilize Analyte Specific Reagents (ASRs). ASRs are reagents manufactured under the Good Manufacturing Practices regulations and are subject to Food and Drug Administration (FDA) ASR regulations. As such, ASRs do not require the filing of a 510(k) or Pre Market Approval (PMA) application. Clinical diagnostic laboratories normally run clinical assays to help physicians diagnose and treat patients with various diseases and typically such assays require a 510(k) or PMA application prior to being offered for sale or distribution.

We believe that molecular diagnostics customers seek a versatile, accurate, simple and cost-effective platform technology on which to develop, validate and run simple and complex research and diagnostics tests and assays. While there are a number of platform technologies currently available to such molecular diagnostics customers, including those utilizing gel-based techniques such as Restriction Fragment Length Polymorphisms (RFLP), sequencing using capillary and gel-based techniques, dot-blot and glass slide based arrays, real-time PCR (polymerase chain reaction) methods and enzyme-based micro-well assays, it is our understanding that these technologies do not consistently meet the basic customer requirements. These platforms lack the versatility to perform both simple and complex assays. The molecular diagnostics customers also demand a technology platform that consistently provides results at a level approaching 100% accuracy. They also insist on operational simplicity, so that the laboratory technicians of any skill level may be used for its operation, and are seeking a cost-effective technology platform that will assist in optimizing capital and labor costs.

The healthcare industry is also evolving as a result of advances in molecular diagnostics. The Company believes that genetic testing will lead to a greater emphasis on predictive diagnoses rather than just symptomatic diagnoses and that healthcare and medicine will become more individualized and patient-focused. The Company believes that this will lead to a greater emphasis on the development of new drugs related to genetic characteristics and to prescribing practices based on a patient s own genetics. The development of predictive, patient-centered diagnosis is also leading to the development of new molecular diagnostic business models that reflect opportunities for companies to market and direct certain of their diagnostic products and services directly to consumers and to broaden the molecular diagnostics market to include a wider range of predictive healthcare products and services.

We believe that the technology used to develop human genetic testing could also be applied in the future to other markets such as food, water and animal testing among other fields.

The Company

Nanogen was founded on the vision of integrating multiple sciences to develop diagnostic products. Through advances in genomic and pharmaceutical research, we believed that diagnostics and therapeutics would become closely linked. Further, we believed that by using electronics, we could develop a highly accurate and flexible set

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of products that would facilitate the analysis of complex genetic relationships and the correlation to disease and therapies. This vision in turn led to the definition of the Company s mission: to become a leading provider of high quality innovative advanced diagnostic products and services to patients, providers and pharmaceutical companies.

Nanogen currently develops and commercializes molecular diagnostics products and tests for the gene-based testing market for sale primarily in the United States, Europe and the Pacific Rim. By integrating microelectronics and molecular biology into a core proprietary technology platform, the Company seeks to establish the unique, open-architecture design of its primary products, the NanoChip® Molecular Biology Workstation and the NanoChip® Cartridge (collectively, the NanoChip® System) as the standard platform for molecular identification and analysis. In furtherance of its mission to become a leading supplier of advanced diagnostics testing products, Nanogen is developing a broad menu of ASRs and other commercial applications for the NanoChip® System. The Company continually conducts research and development by itself and with third parties, to improve the NanoChip® System and to extend its technology to other applications such as biodefense, forensics, drug discovery and pharmacogenomics.

Nanogen believes that its technology platform provides a key advantage over conventional manual and mechanical platforms in that it provides an accurate, simple, versatile and cost-effective integrated microelectronic system that is capable of improving the quality of molecular diagnostic testing while reducing the overall cost of such testing. At the heart of Nanogen s technology is a silicon chip called the NanoChip® Electronic Microarray. Each Electronic Microarray has 100 microlocations or test sites upon which genetic tests can be conducted. DNA or RNA is moved and concentrated by controlling the electric current at each test site, improving accuracy, speed and flexibility. This electronic concentration of molecules greatly accelerates molecular binding at each test site. In addition, our technology allows the simultaneous analysis of multiple test results, or multiplexing, from a single sample. Current applications of the NanoChip® Electronic Microarray include SNPs, STRs, insertions, deletions and other mutation analyses.

The Company s current commercially available products include (1) the NanoChip® Molecular Biology Workstation, an automated, multi-purpose instrument primarily used for DNA-based analyses, (2) the NanoChip® Cartridge, which incorporates the NanoChip® Electronic Microarray and provides a flexible tool for the rapid identification and precise analysis of biological test samples containing charged molecules, (3) various ASRs for detection of gene mutations associated with diseases such as cystic fibrosis and (4) Nanogen s general purpose reagents and accessories used to facilitate assay and protocol development and validation on the NanoChip® Platform. The Company also has several other ASRs and applications of its proprietary technology under development. The Company provides technical support and field applications assistance to service and support its customers.

In February 2004, we announced that we had entered into a definitive agreement for the acquisition of SynX Pharma Inc., a point-of-care diagnostics company based in Ontario, Canada. SynX currently markets point-of-care diagnostic tests for myocardial infarction in Europe and Canada, and infectious diseases and drugs of abuse in Canada. SynX is preparing to commercialize a diagnostic product for congestive heart failure (CHF). We expect the acquisition will provide us with a pipeline of complementary products in order to expand our market share in the in vitro diagnostics market and augments our technology platform for developing advanced diagnostic products. Additional information regarding the SynX acquisition can be found in Part II, Item 7: Management s Discussion and Analysis of Financial Condition and Results of Operations.

Nanogen is a Delaware corporation and its stock is listed on the Nasdaq National Market under the symbol NGEN . Its corporate offices are located at 10398 Pacific Center Court, San Diego, California 92121. Our main telephone number is 858-410-4600.

Our Technology and Relevant Markets

Limitations of Current Molecular Diagnostic Assay Technologies

The initial technique for the analysis of genetic variations was hybridization, which was first developed in the 1970s. Hybridization relies on the principle that a unique piece of DNA will bind, or hybridize, most strongly to

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its exact complement. In hybridization, short synthetic segments of DNA, also known as probes, are used to locate and bind to their counterparts within a mixture of sample DNA or RNA. Hybridization is often performed using instrumentation that incorporates a detection medium that provides a signal to indicate whether the probe has hybridized to the sample DNA or RNA. However, initial hybridization techniques had several limitations. Even minute changes in testing conditions could dramatically affect the outcome of the hybridization reaction and, therefore, the reliability of test results.

Beginning in the 1980s, various techniques were invented with the objective of improving the reliability of hybridization. However, these methods did not generally provide a signal that was sufficient to be easily detectable. Therefore, in order to use these methods, it was necessary to first copy or amplify the segment of DNA or RNA to be analyzed using a technique known as polymerase chain reaction, or PCR. These initial techniques have significant limitations in meeting the need of molecular diagnostic customers, including:

Highly Complex Product Development Process: Conventional methods frequently require trial and error testing to validate tests or product designs. Therefore, with conventional technologies, the process of developing a test, or product, for analyzing a specific genetic variation is highly complex and cannot be automated easily.

Inaccuracy: Accuracy is essential to adequately detect and quantify genetic variations, which may involve the analysis of thousands of genetic variations per individual. Conventional methods can result in one or more data points in 10 being incorrect. These inaccuracies are magnified in tests for multiple variations.

Difficulty of Use: Many of the conventional analysis methods involve multiple technical steps requiring human intervention, which make the analysis difficult to perform and challenging to automate.

Lack of Flexibility: Many of the conventional analysis methods use a passive array in which what is done to one site on the array, must be done to all sites. This results in a lack of flexibility for the customer in using these technologies as they cannot mix different assays on a single array or may not fully utilize every site on the array.

Limited Clinical Viability: Because of the low degree of accuracy and difficulties associated with product development and use, conventional research methods have not been broadly applicable to clinical settings.

Beyond the limitations indicated above, in order to capture and expand the market for genetic analysis, one must provide cost-effective and highly reliable tests.

Despite recent advances in technology, many bioassays are too specialized or inflexible to be used throughout the various departments of a diagnostics or research laboratory. Current bioassay tools were designed for large scale data generation and the automation of repetitious tasks such as very high throughput discovery. In addition, many of these systems are not useful in molecular, protein, enzyme, cell biology, and forensics laboratories. These technologies fall primarily into three categories: high-density arrays; high throughput sequencing and SNP discovery tools; and gel-based methods. While these technologies each have certain advantages, they also have significant drawbacks that inhibit their broad applicability across the life sciences market and in particular in the molecular diagnostics market.

The Nanogen Microelectronic Solution

Today, clinical and research laboratories use a number of different platforms to perform a wide-range of different molecular tests. We are marketing the NanoChip® System based on our proprietary microelectronic technology. The Company believes that the NanoChip® System provides the following eight major advantages:

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Accuracy: Accuracy is critical in laboratory analysis. To date, the NanoChip® System has been shown to be exceptionally accurate when performing various genetic molecular analysis. Additionally, the NanoChip® System embodies the technology that allows multiplexing capability. This means that it allows two or more tests to be performed simultaneously, speeding results to the laboratory technician. This capability has been critical in developing the ASRs for use in detecting the 25 mutations associated with cystic fibrosis.

Simplicity. The NanoChip® System is fully automated and once programmed and validated by the customer, has simple point and click software. It allows the laboratory technician to load samples and easily modify parameters to facilitate minimal hands on time.

Versatility: One of the key attributes that positions the NanoChip® System as the platform for molecular diagnostics is its unique, open architecture. The flexible, addressable nature of the NanoChip® Cartridge enables assay development from a variety of sources. We believe this is particularly important to customers in an emerging and rapidly growing market like molecular diagnostics, where new markers are constantly being introduced. The ability of a molecular laboratory to respond quickly to customers who request a test for a new marker without having to procure a new platform is key to their success.

Profit Incentive: Nanogen s focus is to offer a compelling value proposition to end users by providing laboratories an alternative to sending out their tests to third party laboratories. With Nanogen products, these smaller laboratories should have the potential to earn additional profits by handling tests within their own facilities.

Fast Assay Design: Experimental design of tests and assays on the NanoChip® System is relatively straightforward. Our customers can develop, program and validate assays in their own laboratories, allowing for faster turnaround times (i.e., days versus weeks) for solutions to complex analyses.

Ease of use: Assays are easy to develop, validate and perform on our NanoChip® System. Our fully automated Loader allows the simultaneous programming and testing on up to four NanoChip® Cartridges. A loaded Cartridge is inserted and then analyzed on the Nanogen Reader. The NanoChip® System also includes proprietary software to automate testing operation. All test design and development must be validated by the end user prior to reporting any results. Data interpretation that is user defined is clear-cut and presented in a user-friendly format.

Throughput: The NanoChip® System s ability to program as many as 100 test sites per Cartridge (and up to four Cartridges per run) allows for higher throughput than is achievable with many competitive technologies. As testing volumes in molecular laboratories continue to grow, throughput is becoming increasingly important. We believe that the NanoChip® System is scalable to eventually utilize a Cartridge with 400 test sites at a time.

Cost effectiveness: The NanoChip® System has been designed to be a cost-effective solution for most molecular testing. The NanoChip® System s custom features allow users to employ their own reagents or Nanogen s ASRs in designing and validating assays for their specific purposes. Moreover, much of 2003 was dedicated to developing and marketing a menu of ASRs that many laboratories perform routinely. Walk-away automation conserves direct labor while improving the overall effectiveness of the laboratory operation. In addition, user definability allows important experiments to be done quickly, both accelerating the discovery process and simplifying the validation of important targets.

Nanogen s Core Technology

Nanogen s patented microelectronics-based technology uses the natural positive or negative charge of most biological molecules. Applying an electric current to individual test sites on the NanoChip® System enables rapid movement and concentration of the molecules. Nanogen s technology involves electronically addressing biotinylated DNA samples, hybridizing complementary DNA and applying stringency to remove nonspecifically bound DNA after hybridization. The NanoChip® System technology provides an open platform that allows customers to effectively develop, validate and run common assays as well as customize their own tests.

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The NanoChip® System can integrate in a single platform the following electronic operational features:

Electronic addressing

Electronic addressing involves placing charged molecules at specific test sites on a NanoChip® microarray. When a biotinylated sample solution is introduced onto the array, the negatively charged sample rapidly moves to the selected positively charged sites, where it is concentrated and bound to the streptavidin in the permeation layer. The array is then washed and another sample can be added. Site by site, row by row, an array of samples are assembled on the array. Such user-definable microchip arrays allow the customer to respond quickly to the ever evolving list of genes to be tested.

Electronic concentration and hybridization

In a standard SNP assay, following electronic addressing, red and green fluorescently-labeled reporter probes are used to discriminate between wildtype, heterozygote and mutant DNA. The ability of the NanoChip® technology to very specifically control binding of samples to reporters is a key feature of the platform.

Stringency control

Stringency control enables removal of unbound and nonspecifically-bound DNA quickly and easily after hybridization, providing quality control and ensuring that any bound pairs of DNA are truly complimentary. Nanogen s technology allows the customer to select electronic, thermal or chemical techniques, depending on the application, for precise, accurate stringency control. This provides extremely high discrimination and confidence in results.

Electronic multiplexing

The multiplexing feature is an extension of the open platform of the NanoChip® System. The customer may analyze multiple genes from a single test site (representing one sample) or from multiple test sites (representing different samples). The customer also has the ability to electronically address multiplexed amplicons to a single test site.

The ability to control individual test sites permits biochemically unrelated molecules to be used simultaneously on the same microchip array. Conventional DNA arrays do not have this feature all process steps must be performed on an entire array. Nanogen s microelectronic array technology delivers increased versatility over conventional methods.

Strand Displacement Amplification

Strand Displacement Amplification, or SDA, is a proprietary target amplification process whereby very low numbers of diagnostic targets in a test sample are enzymatically amplified to exponentially higher levels, greatly simplifying accurate detection of these targets. Because this process does not require thermal cycling, it is extremely fast, and complex instrumentation for thermal regulation is not required. We believe that SDA may be an important element in the development of sample-to-answer applications for our technology platform. We also believe that SDA may potentially provide our customers with operational benefits such as being easier to use as well as cost advantages due to the high cost of the most common amplification method. Although the current NanoChip® System does not utilize SDA, we expect to support SDA applications on future instruments.

Commercialization Strategy: Platformation™

What is happening today in molecular diagnostics closely mirrors the activities that occurred in clinical chemistry laboratories thirty years ago. The first clinical chemistry tests were done by hand they were time intensive and required great skill not unlike some of today s molecular diagnostic assays. Ultimately, the laboratory migrated from manual assays to automated accurate systems that could perform multiple assays simultaneously, increasing the reporting efficiency and reducing the time to a reportable result.

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Nanogen has focused on capturing the molecular diagnostics market by creating an open platform that we believe can automate laboratory testing. The process of consolidating various molecular tests onto one platform is what we have termed Platformation. The Company continually seeks to increase the installed base of the NanoChip® Systems and to establish our platform as a standard for the molecular diagnostics industry in order to reap the benefits of the higher margin profits on consumables such as the NanoChip® Cartridges, ASRs and other products. The NanoChip® System s open architecture facilitates development of molecular tests from multiple sources, driving the growth in assay development far beyond where Nanogen could take it on its own. The NanoChip® System could transform molecular diagnostics by, bringing to it the speed, efficiency and accuracy of a robust platform. As this market area grows and Nanogen s market share increases, the NanoChip® System could generate multiple revenue sources that will fuel next generation systems and the growth of the Company.

Nanogen s strategy to establish the NanoChip® System as the leading molecular diagnostics platform is five-fold.

Increase Installed Base of NanoChip® Systems

Our first strategy is to increase the installed base of the NanoChip® Molecular Biology Workstation in order to reap the benefits of the higher margin profits on consumables, such as the NanoChip® Cartridges, ASRs and other products. The Company has provided its customers with three main types of commercial transactions to obtain the NanoChip® System: outright sales, reagent rental agreements and/or cost per test agreements (collectively, reagent rentals) and development and strategic site agreements.

Nanogen typically sells its NanoChip® Systems directly to its customers through the Company s sales representatives in the U.S. or through distributors in Europe and other countries throughout the world. As of December 31, 2003, the Company had placed 100 NanoChip® Systems.

The sale of NanoChip® Systems is only one piece of the revenue stream. As is common with clinical instruments, the consumables form a substantial revenue segment. NanoChip® Cartridges and ASRs that are a part of each customer developed and validated assay will normally be ordered by customers to meet their testing demand. Nanogen anticipates demand to grow rapidly for certain ASRs, such as those for the detection of mutations in the CFTR gene that are associated with cystic fibrosis. While there may always be customers who wish to purchase the NanoChip® System outright, it is our belief that there will be many high complexity CLIA-certified clinical laboratories that will want to amortize the cost of the instrument over several years. These arrangements, called reagent rentals, have been the standard for the clinical instruments industry for the past 40 years, fueling the growth of industry leaders such as Beckman-Coulter, Abbott and Roche. Such agreements can span from three to five years and involve establishing a minimum monthly consumables ordering level. Based on that level and the term of the agreement, a premium is added to the cost of the consumables so that the total capital equipment cost of the NanoChip® System is recouped by the end of the agreement. The advantage of reagent rental agreements for Nanogen is that it locks in a minimum revenue flow over the term of each agreement after a validation period that normally runs from 60 to 120 days. Nanogen believes that many of its customers will increase their consumable ordering levels as new ASRs and ultimately FDA-cleared assays are made available.

The final type of agreement whereby a customer may use and eventually purchase a NanoChip® System, is a development or strategic site agreement. These agreements are normally with leading research organizations and laboratories or companies that could provide us with certain rights to commercialize the discoveries made using our system. These relationships have been focused on the discovery of the associations of specific genetic variations with major disease states, including cancer, hypertension, inflammation and cardiovascular disease. Nanogen installs a NanoChip® System at a customer site for a period ranging typically from six to twelve months during which time the customer can test the System by developing, validating and running certain assays on the System. For the use of the System during this period, the Customer typically assigns to Nanogen rights to improvements to the System and Nanogen and the customer agree on certain Nanogen rights to any assays

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developed or other intellectual property discovered thereon. Once the agreement period has terminated, the customer may then either return the System to the Company or purchase it through a sale or a reagent rental transaction.

Increase the Breadth of the ASR Menu on the NanoChip® System to further Penetrate the Clinical Diagnostics Market

The second strategy is to increase the breadth of the NanoChip® System s ASR menu for commercial applications. Each Nanogen ASR includes specific reagents that enable the customer to develop, validate and perform a molecular test that determines the presence or absence of certain gene mutations associated with certain disease states. As part of Nanogen s Platformationstrategy, the Company seeks to increase the number of commercially available ASRs that it provides its customers to increase the attractiveness of the NanoChip® System as well as to increase revenue from the sale of associated consumables.

During 2003, Nanogen introduced seven products, including five ASRs, which may be utilized by customers for development of tests that detect gene mutations associated with diseases such as cystic fibrosis, hereditary hemochomotosis, Canavan disease, beta thalasemia (in Europe) and Alzheimer s disease.

In the future, we intend to file with the FDA for clearance to market both the next generation of the NanoChip® System and certain of our products for clinical diagnostics. Nanogen is currently putting in place the internal procedures and groundwork necessary to submit such products for clearance. This may be a costly and time consuming process. FDA clearance will be essential to expanding our product offerings beyond CLIA certified laboratories.

Development and Introduction of Research Products

Our third strategy is to develop products that facilitate customers development and validation of their own home brew tests on the NanoChip® System. We provide research customers with most of the tools and reagents needed to develop and validate their own home brew tests on our system and take advantage of our open architecture. During 2003, Nanogen entered into a license agreement with Institut Pasteur and began development work on research reagents for the European market involving the detection of gene mutations associated with the diagnosis of hereditary deafness. We also intend to develop and commercialize other products for our research customers. While researchers want to use high throughput devices to discover genes and genetic mutations, they will want to explore the function and impact of these genes and mutations with a more accurate and targeted technology.

Improve the NanoChip® System and increase the depth of other applications of the NanoChip® Electronic Microarray technology.

Our fourth strategy is to continually improve the NanoChip® System through our engineering and advanced technology groups along with Hitachi, the manufacturer of the NanoChip® System. Initial improvements will be focused on cost reduction and throughput. In the long term, we would like to develop sample-to-answer systems which integrate otherwise time-consuming and labor-intensive sample preparation procedures onto a disposable cartridge. The availability of this lab-on-a-chip technology would fulfill a substantial unmet need in both commercial laboratory and academic research markets.

We also intend to continue the development of other technologies that may complement and improve the NanoChip® System, utilize the NanoChip® Electronic Microarray technology or are designed and developed by our employees or collaborators. Such products include those under development in the forensics, defense and pharmacogenomics arenas.

Continue to establish strategic collaborations in order to strengthen our product menu, penetrate new markets, obtain new intellectual property and enter the service market when appropriate.

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Our fifth strategy is to enter into collaborations to expand applications of our technology platform and to accelerate the commercialization of products in order to strengthen our product menu, penetrate new markets, obtain new intellectual property and enter the molecular diagnostics service provider market when appropriate.

During the third quarter of 2003, Nanogen entered into a collaboration agreement with Prodesse, Inc., a biotechnology company focused on developing reagents that can be used by CLIA-certified laboratories to develop assays to detect infectious pathogens. The collaboration agreement involves the development of automated, highly sensitive microarray-based products to detect a number of infectious disease agents, including influenza, pneumonia, adenovirus, herpes, West Nile Virus, and SARS. The Companies will integrate Prodesse s proprietary multiplex amplification technology with the automated NanoChip® platform and jointly develop and market gene-based testing products to clinical reference labs and health care providers.

We will pursue additional collaborations in various forms, including research and development agreements, licensing agreements and joint ventures.

Nanogen s Current Products

NanoChip® System s Components

The Company is seeking to establish the NanoChip® System as the standard platform for the detection of genetic mutations and to develop applications for future clinical use. Nanogen markets its NanoChip® Molecular Biology Workstation to research and molecular diagnostics laboratories.

The NanoChip® System consists of a consumable Cartridge containing a proprietary semiconductor microchip, the NanoChip® Electronic Microarray, a fully automated instrument and imbedded software that can be programmed by the end-user to control all aspects of microchip operations, processing, detection and reporting. The System has been designed so that once programmed, the end-user need only insert a consumable Cartridge into the instrument and all subsequent steps may be handled automatically under computer control.

The NanoChip® Cartridge

The consumable NanoChip® Cartridge consists of a proprietary semiconductor microchip with electrical and fluidic connections to the instrument. We expect that over time the consumable cartridge and microchip may be manufactured in high volumes at a low cost relative to many current technologies.

Semiconductor microchip

Our proprietary microchip (the NanoChip® Electronic Microarray) is designed and constructed using microlithography and semiconductor fabrication techniques. The NanoChip® Electronic Microarray is mounted within the consumable cartridge and is coated with a proprietary permeation layer. We have developed arrays of various sizes utilizing both passive and active CMOS microchips, as well as flip chip assembly technologies. Our current production of consumable cartridges employs 100 different test sites on a single NanoChip® Electronic Microarray. We are additionally developing a cartridge that employs 400 different test sites on a single NanoChip® Electronic Microarray for our next generation instrument.

Permeation layer

Our proprietary permeation layer, which is critical to the proper functioning of our System, is the reaction site of the microchip. The permeation layer isolates the biological materials from the electrochemical environment near the electrode surface and provides the chemistry necessary for attachment of the samples.

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Samples

Samples are electronically addressed to the desired microlocations and attached to the permeation layer. Because independent control can be applied at any test site on our microchip, different samples can be addressed on the same microchip, allowing multiple tests to be processed on the same Cartridge. Our open architecture approach allows the customer to address their specific samples onto a microchip to perform individualized analyses.

The NanoChip® Molecular Biology Workstation

Our fully integrated NanoChip® System consists of four major subsystems: (1) a freestanding microchip Loader to perform electronic addressing of blank microchips, (2) a highly sensitive, laser-based fluorescence scanner that detects molecular binding, (3) a fluid handling subsystem that controls test sample application and washing steps, ((2) and (3) are, collectively referred to as, the Reader), and (4) computer hardware and software that allow the operator to develop, validate and select protocols from a graphical user menu which controls all microchip operations, tabulates test results and prints test reports based upon user-defined inputs.

Microchip Loader

Our System includes a Cartridge/microchip Loader that will allow users to electronically address their own samples to selected test sites on up to four chips simultaneously. In addition, hybridization can be performed on the Loader or on the Reader. Multiple Loaders can operate concurrently under the control of one System.

Fluorescent array scanner

The fluorescent scanner component of the System uses optoelectronic technology to reduce instrument cost and size and eliminate the need for complicated array positioning mechanics. In its present configuration, the scanner is able to perform high sensitivity scans of arrays of 100 test sites in less than five minutes.

Fluidics

Within the fluorescent array scanner component of the System, the fluidics function automates the movement of the reagents and test sample onto the consumable Cartridge. The fluidic subassembly of the instrument includes a panel of precision syringe pumps, a cartridge-mounted sample assembly and fluidic connections between the instrument and the consumable Cartridge.

Computer hardware and software system

A multi-tasking operating system and microprocessor control all aspects of the systems operations, including bar-coded test selection, test operation, fluorescent signal detection and signal processing, calculation of assay results and report generation. The end-user must develop and validate the protocols used by the software as well as define the parameters used to calculate results and generate reports. Each of the individual array locations is separately controlled by the microprocessor. Fluorescent signals emanating from positive test sites are scanned, monitored and quantified.

NanoChip® Analysis Process

Cartridge

The electronic microchip is mounted within a plastic molded Cartridge. The bar-coded Cartridge is delivered in a ready-to-address format with no genetic sequences pre-attached.

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Electronic addressing

Users design, create and validate their own genetic tests on the microelectronic chip with our automated System. A 96 well or 384 well microtiter plate containing genetic sequences is placed in the Loader. The System then automatically electronically addresses the microchip with user-defined tests.

Hybridization and stringency

Users may add test samples to the Cartridge and insert the Cartridge into the Reader. The customer may then select to have the instrument automatically perform hybridization and the appropriate stringency control is selected by the user, chemical, thermal or electronic. The electronically enhanced process speeds and improves the genetic analysis, allowing single-base accuracy.

Simple-to-read output

Within minutes of inserting the bar-coded Cartridge for analysis, easy-to-read and easy-to-interpret output is available based upon user-defined inputs. Data can be automatically downloaded to network systems and to standard software spreadsheet packages. The entire electronic addressing and data output process can be completed rapidly, allowing users to accelerate their research process by creating new genetic tests based on previous experimental results.

Applications Manager Software (AMS)

Nanogen currently offers a separately priced software package designed to streamline routine or frequent testing for the same genetic markers (which must be validated by the customer). AMS enables users to run protocols they have written and validated for the NanoChip® System in a simplified, menu driven, point-and-click fashion. This supplemental software offers the ease of use required of those laboratories that run the same set of tests on a regular basis. It was designed in response to high complexity CLIA certified clinical laboratories that are frustrated by the research orientation of most of the currently available software. We believe that this software provides a significant competitive advantage for the NanoChip® System.

Analyte Specific Reagent (ASRs)

ASRs are the specific reagents that enable either research or high complexity CLIA certified laboratory customers to develop, validate and run certain SNP assays. Under the ASRs model, we sell not only NanoChip® Cartridges, but also the specific reagents that can be used to develop, validate and perform DNA-based tests.

We currently have five ASRs that are commercially available for (1) Factor II/Factor V multiplex launched in the first quarter 2003; (2) CFTR launched in the first quarter 2003; (3) HFE launched in the first quarter 2003; (4) ApoE launched in the second quarter 2003; and (5) ASPA launched in the second quarter of 2003. Below is a more detailed description of the ASRs:

Factor II/Factor V Multiplex ASRs

Nanogen offers ASRs for the detection of two genetic mutations associated with thrombosis: the G1691A mutation on the Factor V (Leiden) gene and the G20210A mutation on the Factor II (Prothrombin) gene. CLIA certified high complexity laboratories may use the reagents to create and validate laboratory developed tests for detection of these two mutations. Currently, Nanogen believes that it is the only provider of the Factor V (Leiden) and Factor II (Prothrombin) mutations in a multiplexed format.

Nanogen s Factor II/Factor V ASRs are multiplexed ASRs meaning that the customer can develop and validate multiple Factor II and Factor V gene mutations from a single test site (representing one sample) or from multiple test sites (representing different samples). The customer also has the ability to electronically address multiplexed

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amplicons to a single test site. The ability to control individual test sites permits biochemically unrelated molecules to be used simultaneously on the same microchip array. Conventional DNA arrays do not have this feature; all process steps must be performed on an entire array. Nanogen s Factor II/Factor V ASRs are a prime example of how our unique microelectronic array technology delivers increased versatility over conventional methods.

CFTR ASRs

Nanogen s CFTR ASRs enable the customer to develop and validate a test for the detection of the 25 CFTR mutations recommended by American College of Medical Genetics (ACMG)/American College of Obstetrics and Gynecology (ACOG) as part of a high complexity CLIA-certified laboratory homebrew assay.

In early 2003, we completed beta-site testing of our set of ASRs for use in developing and validating tests for the mutations in the CFTR gene, which are associated with cystic fibrosis, and commenced a controlled release of the product to market. Many people carry a single cystic fibrosis gene mutation, and they do not experience any significant health problems. In the general population, approximately 1 in 31 Americans carries the gene mutations. This is the reason ACOG announced that the Standard of Medical Care should include screening women contemplating pregnancy for cystic fibrosis. To meet the standard of medical care, a physician must at least offer screening to each woman contemplating pregnancy. If initial screening of the prospective mother is positive for the CFTR mutation, then further testing of the prospective father is warranted. When both parents are carriers, they have a 25% chance with every pregnancy of passing two copies of the defective gene to their child. The current recommendation from ACOG is for a 25-mutation screen. We believe that the ACOG recommendations may drive a significant increase in genetic testing for gene mutations associated with cystic fibrosis.

HFE ASRs

Nanogen offers ASRs for the development and validation of a test to detect the three mutations associated with hereditary hemochromatosis (HH). Hereditary hemochromatosis is an autosomal recessive disorder characterized by unusually high levels of iron in the blood due to polymorphisms in the HFE gene. Excess iron accumulates over a period of years in the patients major organ systems. Clinical indications of HH include type II diabetes (also known as bronze diabetes), heart disease, arthritis, and liver disease. Our reagents include oligonucleotides for the detection of nucleotides corresponding to the C282Y, H63D, and S65C mutations of the HFE gene. CLIA-certified high complexity laboratories may use the reagents to create and validate laboratory developed tests (LDT) for HFE. Currently, Nanogen s HFE ASRs are the only ASRs for use in developing and validating a test for the three mutations in the HFE gene.

ApoE ASRs

In 2002, Nanogen non-exclusively licensed rights to develop and commercialize ASRs relating to ApoE gene mutations linked to the detection of Alzheimer s disease. Nanogen s ApoE ASRs consist of various reagents that may be used by laboratories to develop and validate a test for the detection of ApoE4, the main Apolipoprotein E allele associated with increased risk for Alzheimer s disease. The Alzheimer s Association estimates that approximately 14 million Americans will develop the disease by 2050.

ASPA ASRs

During 2002, Nanogen entered into a non-exclusive license agreement with a third party that provided it with rights to develop ASRs for certain mutations in the ASPA gene associated with Canavan disease, a disease that has highest prevalence in the Ashkenazi Jewish community. This community has historically been very proactive in the United States in advocating that its members undergo genetic testing prior to having children. The ASPA mutation detection test is a key member of a panel of multiple tests frequently used in an Ashkenazi Jewish

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genetic disease screening panel. Cystic fibrosis also is a key part of this panel and Nanogen offers the ASRs to enable customers to develop and validate an assay to test for the specific mutations associated with cystic fibrosis. Strategically, the ASPA ASRs are important as they provide patent licensure to the end user which has historically been a challenge for individual laboratories to obtain.

Other Current Products

Assay ToolBox

The Nanogen Assay ToolBox is a collection of general purpose reagents and accessories used to facilitate assay and protocol development and validation on the NanoChip® platform. The Assay ToolBox components, together with oligos available from third party vendors, may be used to facilitate development and validation of laboratory developed tests by CLIA-certified high complexity laboratories or research laboratories. The unique, open-architecture of the NanoChip® Electronic Microarray and instrumentation enables researchers to define, select and build their own test panels. Customers may be required to obtain third party licenses to the specific gene mutations for the assays that they seek to develop or validate.

Beta Thalassemia Research Reagents

Nanogen, working with a company in Europe, developed a product for the detection of certain genes associated with beta thalassemia, a disease that is most prevalent in the Mediterranean regions of Europe. These research reagents have been initially marketed through the European company as an alternative method for testing beta thalassemia. Nanogen s research use only product for beta thalassemia consists of various reagents that can be used to detect mutations of the HBB gene, which is most commonly associated with beta thalassemia. Mutations in the HBB gene affect the production of hemoglobin, a protein in red blood cells that carries oxygen to tissues of the body. People whose hemoglobin does not produce enough beta protein have beta thalassemia, which can cause life-threatening anemia in children, for which there is no cure. The frequency of this mutation in the general population is about one in 300. However, people with Mediterranean (including North African), Middle Eastern or southeast Asian ancestry have a risk of about one in 30 for carrying this mutation, most likely related to the selective pressure from malaria. Beta thalassemia is an autosomal genetic disorder: if both parents have the HBB disease causing gene, each offspring has a one in four risk of being affected.

Products and Applications in Research and Development

We plan to further develop the NanoChip® System, integrating new features and broadening the applications of the currently marketed System, including enhancing chip design and simplifying instrument design. Our scientists will investigate new opportunities and develop and validate new protocols, ASRs and products for use on the NanoChip® System, while customers may create and validate new home brew assays by taking advantage of the flexible format of the System.

We also intend to pursue new opportunities utilizing electronics beyond the current microchip concept. For example, future technologies may include integration of sample processing and DNA amplification. The NanoChip® System may be designed to provide analysis of other charged molecules and antigen-antibody, enzyme substrate, cell-receptor, and cell-separation techniques. The NanoChip® System eventually may also become a portable lab on a chip for use in the field, away from the laboratory bench.

Below is a brief description of some of future products and applications currently in research and development at either the Company or with one of its collaborators.

Next Generation NanoChip® System

As part of the Nanogen Hitachi collaboration, we have been working on improvements to the current NanoChip® System and the development of a next generation NanoChip® System. We believe our next generation NanoChip® System should be more compact and less costly in order to access smaller hospital laboratories and other customers for molecular-based testing.

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Additional Potential ASRs and other Products

Infectious disease related products

We believe we have the potential to apply our technology in the field of infectious disease diagnostics to develop automated tests to replace the manual and time-intensive procedures used in hospitals and reference laboratories. The role of the clinical microbiology laboratory is to detect and identify disease causing microorganisms and to determine antibiotic sensitivity. To accomplish this task, colonies of microorganisms from patient specimens are grown, or cultured, in various growth media. Following colony growth, various direct and indirect techniques are utilized to determine the identity and, as required, the sensitivity of the microorganism to specific antibiotics. Using currently available technologies, the entire process may take days or weeks to complete. In the meantime, a patient requiring immediate therapy, must often be treated by the clinician based upon the best clinical facts available at that time. Upon receipt of the diagnostic analysis from the laboratory, the initial patient treatment protocol may need to be modified in order to treat the patient more effectively.

Current culture-based methods detect a single microorganism at one time. Because a particular infectious episode may be caused by one of many microorganisms or several microorganisms together, multiple tests may be required to determine the correct diagnosis. Single tube (one at a time) DNA probe diagnostics, which were first introduced to the marketplace in the mid-1980 s, have been unsuccessful in displacing culture based diagnostic tests in part due to their inability to identify several organisms simultaneously. Our technology addresses these shortcomings by allowing the simultaneous analysis of multiple microorganisms from a single patient sample. We believe our technology and integrated system may speed the time-to-result for diagnostic tests and offer our customers the opportunity to lower their costs and improve productivity by automating all or a significant portion of their labor-intensive testing.

In September 2003, we entered into a collaboration agreement with Prodesse, Inc. to develop automated, highly sensitive microarray products to detect a number of infectious disease agents, including influenza adenovirus, herpes, West Nile Virus, and SARS. The collaboration will integrate Prodesse s proprietary multiplex amplification technology with the automated NanoChip® and jointly develop and market gene-based testing products to health care and clinical reference labs.

Most infectious disease diagnostics are culture-based and labs often take a week or longer to produce results. Consequently, physicians frequently prescribe antibiotics or antivirals prior to determining the exact pathogen causing the infection. By combining Prodesse s pathogen detecting products with the NanoChip® Molecular Biology Workstation, the Company expects to be able to offer reagents for the development of an automated process for testing patient samples within hours, enabling physicians to obtain results and prescribe therapeutics in response to test results. The Company believes that this should help reduce inappropriate treatment with antibiotics, the overuse of which has resulted in an increase in antibiotic-resistant strains of bacteria and a decrease in the effectiveness of many commonly prescribed antibiotics.

Prodesse currently offers six different multiplex products that can be used to detect a total of 28 different pathogens, and it expects to release five more products with an additional 19 targets. The Company s technology amplifies the sequences for many different pathogens, simultaneously with virtually no lose of sensitivity and with no cross-reactivity, which is important for obtaining of precise test results.

ASRs for Genes related to epilepsy

In 2002, Nanogen entered into a development site agreement with Bionomics, an Australian company that provides for an option to the exclusive commercial rights for certain gene mutations believed to relate to epilepsy. This agreement was extended and modified in 2003. Bionomics is currently in the initial stage of validating its hypothesis and developing a test for these mutations. Since this research is in the early stage of development, no definitive time table has been set for the release of any of such ASRs. If ASRs or FDA cleared products are brought to market, Bionomics will market such products in Australia and New Zealand and Nanogen will market products to the remainder of the world.

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Advanced Technology and Research and Development

Besides the continued development of the NanoChip® System, ASRs and other similar products, we are currently conducting research and development into a number of other applications of our technology.

Developing Advanced Technologies, Nanotechnology and Point-of-Care Applications

In the long term, we plan to develop sample-to-answer systems which integrate otherwise time-consuming and labor-intensive sample preparation procedures on the disposable cartridge through the use of active microelectronics. The availability of this lab-on-a-chip technology would fulfill a substantial unmet need in both academic research and commercial sectors.

Biodefense

Nanogen began work on biodefense-related technology for the United States Government in 1995. The work has expanded to include three current government grants to support biowarfare detection efforts (one ongoing DARPA grant and two DUST grants).

Specific development efforts include a prototype portable field-based detection device and an integrated micro-laboratory and assay protocol to analyze simulated biowarfare targets. Also under development are assays aimed at detection of specific biowarfare agents and infectious diseases and a self-contained portable system capable of performing on-chip non-PCR amplification and detection of potential biowarfare threats.

Nanotechnology

As of December 31, 2003, Nanogen had been issued six key nanotechnology patents that relate to the electronic fabrication of micro and nanoscale devices. In May 2003, Nanogen received U.S. Patent No. 6,569,382 Method and Apparatus for the Electronic, Homogenous Assembly and Fabrication of Devices . The 382 patent relates to methods to integrate micro and nanoscale devices as light emitting diodes (LED) for displays, highly integrated biosensors and micromechanical devices, into higher order structures and devices. In November 2003, Nanogen received U.S. Patent No. 6,652,808 Methods for the Electronic Assembly and Fabrication of Devices . The 808 patent relates to a nanofabrication technology that combines an electric field assisted manufacturing platform and programmable self-assembling nanostructures (for example, DNA building blocks) for the fabrication of a wide range of unique higher-order nano and microscale devices, structures and materials.

Subsequently, in March 2004 the Company was issued another key nanotechnology patent, U.S. Patent No. 6,706,473, Systems and Devices for Photoelectrophoretic Transport and Hybridization of Oligonucleotides, by the U.S. Patent and Trademark Office. The 473 patent relates to new devices for nanofabrication that enable the photoelectric transport and positioning of self-assembling DNA nanostructures (and microstructures) on a semiconductor substrate material. These devices use directed light beams to create precise electric fields on the substrate material. Charged nanostructures (such as DNA derivatized nanoparticles) are transported to the electric field site where they become attached and can then lead to the further self-organization of higher-order nanoscale or microscale structures and devices.

Nanogen s proprietary nanotechnology may provide a technological foundation for the effective use of nanocomponents in many diverse applications. It is the current intention of Nanogen to realize value from our nanotechnology patents through use in biomedical applications or through licensing or partnering opportunities.

Forensics

STRs are the genetic sequences chosen by the U.S. government and various foreign governments to populate their national criminal identification databases. Some foreign researchers and governments are also beginning to examine certain SNPs to develop such databases. These databases are intended to provide nationwide tools for identifying repeat criminals by comparing a given piece of evidence or sample from a suspect with the sequences stored in the database. Currently, we have four overseas development sites working on forensic applications. We believe our NanoChip® System may be useful in human identity testing.

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Our research collaborations in the area of forensic applications include identity testing and have allowed us to further develop existing technology and explore new technology. Prior and current grants from the National Institute of Justice have involved sponsored research for forensic applications, such as the development of a portable system for human identification at the crime scene and the development of on-chip non-PCR amplification.

Nanogen Recognomics

Nanogen Recognomics, a joint venture of Nanogen and Aventis Pharma Deutchland, GmbH (formerly Aventis Research and Technologies), combines the NanoChip® technology and Aventis intellectual property and expertise in synthetic oligonucleotide chemistry and advanced molecular biology to develop new products and applications for the NanoChip® System. Besides assisting us in the development of ASRs for the detection of genes associated with Canavan disease, their research efforts have included genetic-based in vitro human detection, diagnostics, screening and monitoring applications, including research into novel oligonucleotide chemistries. The shareholders of Nanogen Recognomics have recently decided to convert Nanogen Recognomics into a non-operating holding company to attempt to commercialize its intellectual property through licensing and sale transactions.

Other Potential Applications

As the Human Genome Project opportunity and other public and private genetic sequencing efforts yield increasing amounts of genetic information, we believe that the demand for genetic predisposition testing will continue to grow. Because many important genetic diseases are ideally suited to diagnosis in multiplexed arrays, we believe that our technology platform could contribute significantly to the expansion of testing in this area. While our development efforts in this area with respect to specific genetic tests are still at an early stage, our core technology platform for other diagnostic applications may be well suited for these opportunities.

Pharmacogenomics

We believe that the ability of our technology to screen simultaneously for various DNA sequences and the ability to differentiate between SNPs has potentially wide applicability to the field of genetic testing in general and pharmacogenomics in particular. Pharmacogenomics is the science of individualizing therapy based on genetic differences among patients.

Our NanoChip® System may provide pharmaceutical and biotechnology companies with the ability to identify important genetic variations early in the drug development process. We believe our System may help stratify patients during clinical trials and identify those receiving the maximum benefit from treatment.

Collaborative Alliances

We intend to continue to enter into collaborations to expand applications of our technology platform and to accelerate the commercialization of products. We will pursue additional collaborations in various forms, including research and development agreements, licensing agreements and

joint ventures. These collaborations permit integration of the technology and resources of our partners with our technology, while allowing Nanogen to pursue diagnostics, drug discovery and genomics opportunities outside the scope of these collaborations.

We are currently involved in several material corporate collaborations. In July 2001, we formed a company with Aventis named Nanogen Recognomics GmbH. In January 2000, we entered into a manufacturing, development and distribution agreement with Hitachi, Ltd. In July 2000, we entered into an additional agreement with Hitachi, Ltd., Nissei Sangyo Co. Ltd. and Hitachi Instruments Service Co. Ltd. of Japan (collectively, Hitachi) to develop, manufacture and distribute additional potential products based on the parties proprietary technologies, potentially including, among other things, reduced-size instruments for genetic testing, integrated amplification and point-of-care detection. In July 2003 we entered into another manufacturing agreement with Hitachi relating to the manufacture of our next generation system.

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During the third quarter of 2003, Nanogen entered into a collaboration agreement with Prodesse, Inc., a biotechnology company focused on developing ASRs that can be used by CLIA certified laboratories to detect infectious pathogens. The Company believes that the products developed with Prodesse will enable physicians to immediately select and initiate appropriate therapy for patients.

Aventis/Nanogen Recognomics

In December 1997, we entered into a Letter Agreement with Aventis for an exclusive research and development collaboration relating to new drug discovery tools and immunodiagnostics research. In connection with the Letter Agreement, we entered into a definitive Collaborative Research and Development Agreement with an effective date of January 1, 1998. The term of this original collaboration agreement expired at the end of 2000. In September 1999 we entered into an additional collaboration agreement with Aventis that involved two new research and development programs focused on gene expression arrays and on an electronics-based high throughput screening system. We retain full commercialization rights for any products resulting from these new projects, while Aventis retains the right to use the technology for internal research and development. The September 1999 agreement expired at the end of 2001. We do not expect to receive additional funding for these projects.

In July 2001, we formed a company with Aventis named Nanogen Recognomics GmbH. This company was formed to allow us to benefit from the development of new technological advances for our platform while we are still focusing on our near-term goal of entry into molecular diagnostics. Nanogen Recognomics adds intellectual property and expertise in synthetic oligonucleotide chemistry and advanced molecular biology to Nanogen.

As described earlier herein, Nanogen Recognomics combines the NanoChip® technology and Aventis intellectual property and expertise in synthetic oligonucleotide chemistry and advanced molecular biology to develop new products and applications for the NanoChip® System. The shareholders of Nanogen Recognomics have recently decided to convert Nanogen Recognomics into a non-operating holding company to attempt to commercialize its intellectual property through licensing and sale transactions.

Hitachi

Manufacturing Agreements

In January 2000, the Company executed an agreement with Hitachi, Ltd., effective as of December 15, 1999, for the full-scale commercial manufacturing and distribution of the NanoChip® Molecular Biology Workstation in specified research markets. Hitachi, Ltd. s Instrument Group provides technology and technical support to aid in the manufacturing of the NanoChip® Molecular Biology Workstation s components.

Pursuant to the agreement, Hitachi, Ltd. has the right to be the sole distributor of NanoChip® Molecular Biology Workstations in Japan. Hitachi, Ltd. also has the non-exclusive right to distribute NanoChip® Cartridges in Japan. Under this arrangement, the Company receives a royalty for NanoChip® Molecular Biology Workstations sold by Hitachi, Ltd. in Japan. The Company retained the right to distribute, directly or through others, NanoChip® Molecular Biology Workstations outside of Japan. In addition, the Company manufactures NanoChip® Cartridges at its San Diego, California facility for distribution worldwide. The Company also retained the right to form other manufacturing and distribution agreements. Pursuant to our manufacturing agreement with Hitachi, the Company is required to provide annual purchase commitments to Hitachi for NanoChip® Workstations.

In June 2003, the Company entered into another manufacturing agreement with Hitachi for the manufacture of a new clinical instrument being developed under the collaborative research agreement (described below). Pursuant to the 2003 manufacturing agreement, Hitachi will manufacture the new clinical instrument, when development is completed, exclusively for the Company for worldwide distribution. Once production instruments are received by the Company, the Company is required to meet certain annual purchase commitments for the new instrument.

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Research Collaboration Agreement

In July 2000, the Company executed a ten-year agreement with Hitachi, Ltd., Nissei Sangyo Co. Ltd. and Hitachi Instruments Service Co. Ltd. of Japan (collectively, Hitachi) to develop, manufacture and distribute additional potential products based on the parties proprietary technologies, potentially including, among other things, reduced-size instruments for genetic testing, integrated amplification and point-of-care detection. The agreement provides that the parties will jointly determine which projects to prioritize over the term of the agreement. The agreement may be terminated before its expiration by either party, subject to certain restrictions. Pursuant to the terms of the agreement, Hitachi and the Company each may contribute, toward the research and development efforts of the Company, up to $28.5 million in cash over the ten-year period. At a minimum, the Company is required to contribute on an annual basis funding for its own general technology development in an amount equal to or greater than payments made by Hitachi. In addition, the Company is liable to repay to Hitachi fifty percent of all funding provided by Hitachi over an indefinite period of time. Repayment amounts are determined as a percentage of the Company s gross NanoChip® Cartridge sales until the liability is paid in full. Furthermore, Hitachi made an equity investment in the Company by purchasing 74,590 shares of the Company s common stock worth approximately $2.0 million pursuant to a private sale by the Company based on a per share price of $26.813 (the fair market value as of the signing date of the Hitachi agreement). Hitachi has the right to be the exclusive distributor of collaboration products in Japan and, based upon the attainment of minimum sales targets to be mutually agreed upon, in other Asian countries. The Company retains the exclusive right to distribute collaboration products outside of these countries.

In August 2003, the Company received written notice from Hitachi to exercise its right to terminate the collaborative research agreement in accordance with the terms of the agreement. Hitachi s exercise of its right to terminate this agreement does not accelerate the repayment due Hitachi for the fifty percent of Hitachi provided funding. Neither Nanogen nor Hitachi has terminated any of the other agreements between the companies. Based on joint discussions, Nanogen and Hitachi have determined to focus their joint efforts on the development and manufacture of a new clinical instrument. Nanogen and Hitachi will continue to be jointly responsible for development of the new clinical instrument. Hitachi is responsible for world-wide manufacturing of the instrument. Nanogen is responsible for development of assays and for marketing and sales except in Japan.

Service Agreement

In November 2003, the Company entered into an amendment to an agreement with Hitachi signed in October 2000 for the service by Hitachi of the NanoChip® Molecular Biology Workstations in the United States after sale or placement by the Company with the Company s customers. The agreement modified the agreed-upon amount the Company pays to Hitachi for annual service for each Workstation covered under the agreement.

Government Grants

In 2003, we continued work under a number of biodefense-related technology grants for the United States Government. The work has expanded to include three current government grants to support biowarfare detection efforts (one ongoing DARPA grant and two DUST grants) In the latter part of 2002, we received an additional $1.7 million grant from the National Institute of Justice (NIJ) to continue an earlier NIJ grant for the development of a forensics detection system for the identification of certain relevant SNPs and STRs and we received a grant from the National Institute of Health for $162,000 for the development of a sample preparation system for the detection of certain biological agents.

Specific development efforts include a prototype portable field-based detection device and an integrated micro-laboratory and assay protocol to analyze simulated biowarfare targets. Also under development are assays aimed at detection of specific biowarfare agents and infectious

diseases and a self-contained portable system capable of performing on-chip non-PCR amplification and detection of potential biowarfare threats.

Also, in 2003, we received Phase II and Phase III grants totaling approximately $858,000 from the National Institutes of Health to develop on-chip SDA amplification techniques.

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We believe that the actions we are taking to develop our product platform for use in molecular diagnostics are directly portable and complementary to what we are doing in the biowarfare arena for the U.S. Army and for the NIH. As a result, we believe that our government and commercial programs complement one another.

Proprietary Technology and Patents

As of December 31, 2003, we have 58 issued U.S. patents and 42 foreign patents and a number of pending patent applications filed in the U.S. and abroad. In addition to pursuing patents and patent applications relating to our platform technology, we have and may enter into other license arrangements to obtain rights to third-party intellectual property where appropriate.

Our, or our licensors patent applications may not be issued. Issued patents may not be found valid if challenged. In addition, intellectual property rights licensed by us may not be successfully integrated into commercial products. Others may independently develop similar technologies or duplicate any technology developed by us. Because of the extensive time required for development, testing, and regulatory review of a potential product, it is possible that, before any of our products can be commercialized, any related patent may expire or remain in existence for only a short period following commercialization, thus reducing any advantage of the patent, which could adversely affect our ability to protect future product development and, consequently, our business, financial condition and results of operations.

We seek to protect our inventions through filing U.S. patents and foreign counterpart applications in selected other countries. Because patent applications in the U.S. are maintained in secrecy for at least eighteen months after the applications are filed and since publication of discoveries in the scientific or patent literature often lags behind actual discoveries, we cannot be certain that we were the first to make the inventions covered by each of our issued or pending patent applications or that we were the first to file for protection of inventions set forth in such patent applications. Our planned or potential products may be covered by third-party patents or other intellectual property rights, in which case continued development and marketing of the products would require a license. Required licenses may not be available to us on commercially acceptable terms, if at all. If we do not obtain these licenses, we could encounter delays in product introductions while we attempt to design around the patents, or could find that the development, manufacture or sale of products requiring these licenses is foreclosed.

We are aware of U.S. and European patents and patent applications owned by Oxford Gene Technology (OGT). We have opposed one allowed European Patent that had broad claims to array technology for analyzing a predetermined polynucleotide sequence. OGT s position with respect to the opposed patent is that the claims relate to what it terms the diagnostic mode. Those claims have now been narrowed before the Opposition Division to the point that, if these claims remain final before the European Patent Office, we believe they would not be infringed by our technology. In the Oral Proceedings before the Opposition Division on November 13, 14, and 15, 2001, the Division determined that the claims language must be limited to arrays with smooth, impermeable surfaces. The case is currently on appeal. If the decision of the Opposition Division is successfully appealed by OGT and the original claims are reinstated, or if an application relating to arrays issued in another country with claims as broad as the original European patent, we could be subject to infringement accusations that could delay or preclude sales of some or all of our anticipated diagnostic products.

In addition to the patent litigation described in Item 3 herein, other litigation may be necessary to defend against or assert claims of infringement, to enforce patents issued to us, to protect trade secrets or know-how owned by us or to determine the scope and validity of the proprietary rights of others. In addition, interference proceedings declared by the U.S. Patent and Trademark Office may be necessary to determine the priority of inventions with respect to our patent applications. Litigation or interference proceedings could result in substantial costs to and diversion of our effort, and could have a material adverse effect on our business, financial condition, and results of operations. Any such efforts may not be successful.

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We may rely on trade secrets to protect our technology. Trade secrets are difficult to protect. We seek to protect our proprietary technology and processes by confidentiality agreements with our employees and certain consultants and contractors. These agreements may be breached, we may not have adequate remedies for any breach and our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our employees or our consultants or contractors use intellectual property owned by others in their work for us, disputes may also arise as to the rights in related or resulting know-how and inventions.

Manufacturing

In January 2000, we formed a collaboration with Hitachi for the manufacture of our NanoChip® Molecular Biology Workstation instruments. In July 2000, we executed a ten-year agreement with Hitachi, Ltd., Nissei Sangyo Co. Ltd. and Hitachi Instruments Service Co. Ltd. of Japan to develop, manufacture and distribute products based on the parties proprietary technologies. For the manufacture of the NanoChip® Cartridge, we perform many of the proprietary assembly steps in-house. In June 2003, the Company entered into another manufacturing agreement with Hitachi for the manufacture of a new clinical instrument being developed under the collaborative research agreement (described below). Pursuant to the 2003 manufacturing agreement, Hitachi will manufacture the new clinical instrument, when development is completed, exclusively for the Company for worldwide distribution. Once production instruments are received by the Company, the Company is required to meet certain annual purchase commitments for the new instrument. We believe our technology allows for large-scale microchip production at a relatively low cost. We believe that the implementation of this scalability and low cost will help promote the rapid acceptance of our proprietary semiconductor-based platform technology as an industry standard. However, achieving these efficiencies will require substantial commercial volumes and there can be no assurance we will be successful in generating sufficient demand to scale up manufacturing capacity to levels that will allow our products to be priced competitively.

Sales and Marketing

We began commercializing the NanoChip® Molecular Biology Workstation during the latter part of 2000. Since then, we have built a commercial structure that allows us to sell directly in certain markets, while selling through distributors and partners in other markets. We began selling our first ASRs in 2002.

Our commercial organization includes direct sales representatives and sales management, customer support personnel, field support personnel and marketing. We began selling our product in 2000 to customers in the United States, Canada, Mexico and several European countries. To support the commercial efforts in Europe, in August 2000 we established Nanogen Europe B.V., a company with limited liability, in The Netherlands. This wholly-owned subsidiary operates as our primary European sales and marketing office. Hitachi s distribution company, Hitachi High Technologies, began distributing our product in Japan during the latter part of 2000 as well. In January 2004, we entered into a distribution agreement with Transgenomic Inc. for distribution of our products in certain European countries. We expect to augment our commercial selling process by adding additional distributor partners in other countries. In San Diego, we support world-wide field activities with a customer applications laboratory. This laboratory is used to assist in early customer demonstrations, protocol development and system and applications training.

Competition

As we develop applications of our technology, we expect to encounter intense competition from a number of companies that offer products competing in our targeted applications. The molecular diagnostic test market, in particular, is highly competitive, and we expect the intensity of competition to increase. We anticipate that our competitors will include health care companies that manufacture laboratory-based tests and

analyzers, diagnostic and pharmaceutical companies, as well as companies developing drug discovery technologies. To the extent we are successful in developing products in these areas, we will face competition from established and development-stage companies both in the United States and abroad.

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In many instances, our competitors have substantially greater financial, technical, research, and other resources and larger, more established marketing, sales, distribution and service organizations than we. Moreover, competitors may offer broader product lines and have greater name recognition than we, and may offer discounts as a competitive tactic. In addition, several development stage companies are making or developing products that compete with our potential products. There can be no assurance that our competitors will not succeed in developing or marketing technologies or products that are more effective or commercially attractive than our potential products, or that would render our technologies and products obsolete. Also, we may not have the financial resources, technical expertise or marketing, distribution or support capabilities to compete successfully in the future. Our success will depend in large part on our ability to maintain a competitive position with respect to our technologies. Rapid technological development by others may also result in competing products or technologies.

Government Regulation

Currently our NanoChip® System is marketed for the detection of known sequences in the U.S. and primarily distributed for research use in Europe. The ASRs under development and commercially available are manufactured and distributed in the U.S. pursuant to 21CFR 864.4020 (which delineates the Class II and III ASRs, and otherwise exempts from the 510(k)/PMA requirements ASRs distributed to (1) *in vitro* diagnostic manufacturers or (2) organizations that use the reagents to make tests for purposes other than providing diagnostic information to patients and practitioners) and 21 C.F.R. § 809.30 (which places limitations on the distribution, labeling, advertising, and promotion of ASRs). Future short term plans include distribution of these reagents for research use in Europe with eventual CE marking of the next generation system under the European IVDMDD regulations.

For our initial commercial markets, the biomedical research market and the high complexity CLIA certified laboratory market, we may not need FDA or other regulatory clearances for our NanoChip® System and certain ASRs prior to marketing. The FDA has recently communicated, however, that certain microarray devices that qualify as ASRs by regulation, may nonetheless lose their Class I, 510(k)-exempt status by operation of other provisions of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 360(1)) and FDA regulations (21 C.F.R. § 864.9), i.e., if the microarray is intended for a use which is of substantial importance in preventing impairment of human health or it presents a potential unreasonable risk of illness or injury. It is unclear what the impact of these FDA communications and determinations will be on Nanogen and its current and future products. We have not applied for FDA or other regulatory clearances with respect to any of our products under development. We anticipate, however, that the manufacturing, labeling, distribution and marketing of some or all of the diagnostic products we may develop and seek to commercialize in the future will be subject to regulation in the U.S. and in other countries. In addition to clinical diagnostic markets, we also may pursue forensic, agricultural, environmental, laboratory and industrial applications for our products which may be subject to different government regulation. Aspects of our manufacturing and marketing activities may also be subject to federal, state and local regulation by various governmental authorities.

In the U.S., the FDA regulates, as medical devices, most diagnostic tests and *in vitro* reagents that are marketed as finished test kits and equipment. Pursuant to the Federal Food, Drug, and Cosmetic Act, and the regulations promulgated thereunder, the FDA regulates the preclinical and clinical testing, design, manufacture, labeling, distribution and promotion of medical devices. We will not be able to commence marketing or commercial sales in the U.S. of our new medical devices that require pre-market authorization until we receive clearance or approval from the FDA, which can be a lengthy, expensive, and uncertain process. Noncompliance with applicable requirements can result in, among other things, Warning Letters, administrative or judicially imposed sanctions such as injunctions, civil penalties, recall or seizure of products, total or partial suspension of production, failure of the government to grant premarket clearance (510(k)) or premarket approval (PMA) for devices, withdrawal of marketing clearances or approvals, or criminal prosecution.

In the U.S., medical devices are generally classified into one of three classes (i.e., Class I, II or III) on the basis of the controls deemed necessary by the FDA to reasonably ensure the safety and effectiveness of the product.

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Generally, Class I devices are subject to general controls (e.g., labeling, postmarket controls, Medical Device Reporting and adherence to Quality System Regulations, or QSR). Generally, Class II devices are subject to general and special controls (e.g., performance standards, premarket notification and postmarket surveillance). Generally, Class III devices are new technology or high-risk devices which must receive premarket approval by the FDA to ensure their safety and effectiveness (e.g., life-sustaining, life-supporting, and implantable devices or new devices which have been found not to be substantially equivalent to legally marketed devices). Before a device can be introduced in the market, the manufacturer must generally obtain FDA clearance of a 510(k) notification or approval of a PMA application. Our products will vary significantly in the degree of regulatory approvals required. We believe that certain of our products labeled for research, genomics, drug discovery and industrial applications may not require regulatory approvals or clearance. Some *in vitro* diagnostic products will require 510(k) clearances, while other diagnostic and genetic testing products will require PMA approvals.

A 510(k) clearance will generally only be granted if the information submitted to the FDA establishes that the device is substantially equivalent to a legally marketed predicate device. For any devices that are cleared through the 510(k) process, significant modifications or enhancements in the design or intended use that could significantly affect safety or effectiveness will require new 510(k) submissions. It generally takes at least three to six months or more from submission to obtain 510(k) premarket clearance, but the process may take longer if FDA requests more data or research. The FDA may determine that we must adhere to the more costly, lengthy, and burdensome PMA approval process for our potential products.

The Premarket Approval (PMA) application process is more expensive, burdensome, and lengthy than the 510(k) clearance process. A PMA must establish the safety and effectiveness of the device to the FDA s satisfaction, which typically requires extensive data, including but not limited to, technical, preclinical, clinical trials, manufacturing and labeling to demonstrate the safety and effectiveness of the device. Although clinical investigations of most devices are subject to the investigational device exemption requirements, clinical investigations of non significant risk *in vitro* diagnostic tests, such as certain of our products and products under development, are exempt from the investigational device exemption (IDE) requirements, including the need to obtain the FDA s prior approval. We believe certain of our diagnostics are non significant risk devices because the testing is noninvasive, does not require an invasive sampling procedure that presents a significant risk, does not introduce energy into the subject, and is not used as a diagnostic procedure without confirmation by another medically established test or procedure. To fall within this exemption to the IDE requirement, the *in vitro* diagnostic tests must be labeled for research use only or investigational use only, and distribution and due diligence controls must be established by the company to assure that IVDs distributed for research or clinical investigation are used only for those purposes.

After a PMA is accepted for filing, the FDA begins its review of the submitted information, which generally takes between one and two years. During this review period, the FDA may request additional information or clarification of information already provided, as well as conduct a pre-approval inspection of the manufacturing facility. If we are not in compliance with Quality System Regulations (QSRs) applicable to manufacturing, we will not receive PMA approval. Also during the review period, an advisory panel of experts from outside the FDA will be convened to review and evaluate the application and provide recommendations to the FDA as to the approvability of the device. Significant modifications to the design, labeling or manufacturing process of a PMA-approved device may require approval by the FDA of a PMA supplement. We may not be able to obtain necessary approvals on a timely basis, if at all, and delays in obtaining or failure to obtain such approvals, the loss of previously obtained approvals, or failure to comply with existing or future regulatory requirements could have a material adverse effect on our business, financial condition and results of operations.

Manufacturers of medical devices marketed in the U.S. are required to adhere to the QSR requirements (formerly Good Manufacturing Practices), which include testing, control and documentation requirements. Manufacturers must also comply with Medical Device Reporting requirements that a manufacturer report to the FDA any incident in which its product may have caused or contributed to a death or serious injury, or in which its product malfunctioned and would be likely to cause or contribute to a death or serious injury upon recurrence.

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Medical device labeling and promotional activities are subject to scrutiny by the FDA and, in many circumstances, by the Federal Trade Commission. FDA enforcement policy prohibits the marketing of unapproved devices or marketing approved medical devices for unapproved uses.

We may become subject to routine inspection by the FDA and certain state agencies for compliance with QSR requirements, medical device reporting requirements and other applicable regulations (and state equivalent requirements). The QSR requirements include design controls for which there is a relatively high cost of compliance. We may incur significant costs to comply with laws and regulations in the future and these laws and regulations may have a material adverse effect upon our business, financial condition and results of operation.

Any of our customers using our potential future diagnostic devices for clinical use in the U.S. may be regulated under the Clinical Laboratory Improvement Act of 1988 (CLIA). CLIA is intended to ensure the quality and reliability of clinical laboratories in the U.S. by mandating specific standards in the areas of personnel qualification, administration, participation in proficiency testing, patient test management, quality control, quality assurance and inspections. The regulations promulgated under CLIA establish three levels of diagnostic tests (waived, moderately complex and highly complex), and the standards applicable to a clinical laboratory depend on the level of the tests it performs. CLIA requirements may prevent some clinical laboratories from using our diagnostic products. Therefore, CLIA regulations and future administrative interpretations of CLIA may have a material adverse impact on us by limiting the potential market for our products.

There can be no assurance that new legislation will not impose additional costs or lengthen review times for our products.

Additionally, should we develop food pathogen products, they will be subject to the regulations of various domestic and foreign government agencies which regulate food safety and food adulteration, including the U.S. Department of Agriculture.

Employees

As of December 31, 2003, we had 136 full-time employees and 1 part-time employee, of whom 21 hold Ph.D. degrees and 14 hold other advanced degrees. Approximately 47 are involved in research and development, 45 in operations, manufacturing and quality assurance, 23 in sales and marketing, and 22 in finance, legal and other administrative functions. Our success will depend in large part upon our ability to attract and retain employees. We face competition in this regard from other companies, research and academic institutions, government entities and other organizations. None of our employees are covered by a collective bargaining agreement.

Factors That May Affect Results

If our products are not successfully developed or commercialized, we could be forced to curtail or cease operations.

We are at an early stage of development. As of December 31, 2003, we had only a limited product offering that includes our NanoChip® System (which consists of our NanoChip® Molecular Biology Workstation and NanoChip® Cartridge), NanoChip® Cartridge, five ASRs, Assay Toolbox and a product available only in Europe solely for research use for beta thalasemia. All of our other platforms and ASRs and other potential

products are under development. Our NanoChip® System, ASRs or our other products may not be successfully developed or commercialized on a timely basis, or at all. If we are unable, for technological or other reasons, to complete the development, introduction or scale-up of manufacturing of our new products, or if our products do not achieve a significant level of market acceptance, we would be forced to curtail or cease operations.

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As of December 31, 2003 we have placed a total of 100 NanoChip® Systems. This includes instruments we have placed at various customer sites under development or strategic site agreements whereby title of the NanoChip® Molecular Biology Workstation did not pass to the customer and therefore no revenue was recognized.

We are also party to transactions known as reagent rentals and cost-per-test agreements. Under these types of transactions, we place a Workstation at a customer site with no upfront cost to the customer. The value of the instrument is typically recaptured through a contracted stream of future reagent sales, sold at a premium to cover the cost of the system. Many of our reagent rentals and cost-per-test agreements entered into as of December 31, 2003 require customer acceptance of our CFTR ASRs as a pre-condition to the customer s commitment to purchase the instrument. Our CFTR ASRs may be utilized by customers to develop and validate tests for the detection of mutations in the CFTR gene associated with cystic fibrosis. These reagent rentals and cost-per-test agreements might have an adverse impact on our short-term instrument sales revenue and cash flow as the revenues and cash received under these agreements are over the life of the contract, as reagents are shipped to the customer. Our success will depend upon our ability to continue to overcome significant technological challenges and successfully introduce our products into the marketplace. A number of applications envisioned by us may require significant enhancements to our basic technology platform. There can be no assurance that we can successfully develop such enhancements.

Lack of market acceptance of our technology would harm us.

Although we have developed a number of products as discussed above, we may not be able to further develop these products or to develop other commercially viable products. Even if we develop a product, it may not be accepted in the marketplace. If we are unable to achieve market acceptance, we will not be able to generate sufficient product revenue to become profitable. We may also be forced to carry greater inventories of our products for longer periods than we may have anticipated. If we are unable to sell the inventory of our products in a timely fashion and at anticipated price levels, we may not become profitable. In addition, we may have to take accounting charges and reduce the value of our product inventory to its net realizable value. In September 2003 we took an accounting charge of $829,000 to reduce product inventory to its estimated net realizable value. If actual future demand or market conditions are less favorable than those projected by us, additional inventory write-downs may be required. Market acceptance will depend on many factors, including our ability to:

convince prospective strategic partners and customers that our technology is an attractive alternative to other technologies;

manufacture products in sufficient quantities with acceptable quality and at an acceptable cost; and

sell, place and service sufficient quantities of our products.

In addition, our technology platform could be harmed by limited funding available for product and technology acquisitions by our customers, internal obstacles to customer approvals of purchases of our products and market conditions in general.

Commercialization of some of our potential products depends on collaborations with others. If our collaborators are not successful or if we are unable to find collaborators in the future, we may not be able to develop these products.

Our strategy for the research, development and commercialization of some of our products requires us to enter into contractual arrangements with corporate collaborators, joint venture partners, licensors, licensees and others. Our success depends in part upon the performance by these collaboration partners and potential collaboration partners of their responsibilities under these arrangements. Some collaborators may not

perform their obligations as we expect, and we may not derive any revenue or other benefits from these arrangements. We do not know whether our collaborations will successfully develop and market any products under our respective agreements. Moreover, some of our collaborators are also researching competing technologies targeted by our collaborative programs.

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In August 2003, Hitachi, Ltd. exercised its right to terminate the research collaboration agreement it has with us. The agreement is scheduled to terminate during the second quarter of 2004. Until the agreement terminates, we and Hitachi expect to continue to work on the development of a new clinical instrument. Our manufacturing and distribution agreements with Hitachi remain in place. In June 2001, we formed a new company, Nanogen Recognomics GmbH, with Aventis Research and Technologies & Co. KG, in which we own 60% of the stock of Nanogen Recognomics and Aventis R&T owns the remaining 40%. Nanogen Recognomics seeks to combine our NanoChip® technology and Aventis R&T s intellectual property and expertise in synthetic oligonucleotide chemistry and advanced molecular biology to develop new products and applications for the NanoChip® System. In February 2004, the shareholders of Nanogen Recognomics decided to convert Nanogen Recognomics into a non-operating holding company to attempt to commercialize its intellectual property through licensing and sales transactions.

We may be unsuccessful in entering into other collaborative arrangements to develop and commercialize our products. In addition, disputes may arise over ownership rights to intellectual property, know-how or technologies developed with our collaborators.

We have a history of net losses. We expect to continue to incur net losses and we may not achieve or maintain profitability.

Since our inception, we have incurred cumulative net losses which, as of December 31, 2003, total approximately $176.3 million. Moreover, our negative cash flow and losses from operations will continue for the foreseeable future. We may never generate sufficient product revenue to become profitable. We also expect to have quarter-to-quarter fluctuations in revenues, expenses and losses, which fluctuations could be significant. The amount and timing of product revenue recognition and cash flow may depend on whether potential customers for the NanoChip® System choose to enter into sales, reagent rentals, cost-per-test or development site transactions.

To develop and sell our products successfully, we may need to increase our spending levels in research and development, as well as in selling, marketing and administration. We may have to incur these increased spending levels before knowing whether our products can be sold successfully.

We will need additional capital in the future. If additional capital is not available, we may have to curtail or cease operations.

We will need to raise more money to continue the research and development necessary to further develop our current products to bring our products to market and to further our manufacturing and marketing capabilities. We may seek additional funds through public and private stock offerings, arrangements with corporate partners, borrowings under lease lines of credit or other sources. If we cannot raise more money, we will have to reduce our capital expenditures, scale back our development of new products, reduce our workforce and seek to license to others products or technologies that we otherwise would seek to commercialize ourselves. The amount of money we will need will depend on many factors, including among others:

- the progress of our research and development programs;
- the commercial arrangements we may establish;
- the time and costs involved in:

scaling up our manufacturing capabilities;

meeting regulatory requirements, including meeting necessary Quality System Regulations or QSRs and obtaining necessary regulatory clearances or approvals;

filing, prosecuting, defending and enforcing patent claims and litigation; and

the scope and results of our future clinical trials, if any.

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Additional capital may not be available on terms acceptable to us, or at all. Any additional equity financing would likely be dilutive to stockholders, and debt financing, if available, may include restrictive covenants and require significant collateral.

Competing technologies may adversely affect us.

We expect to encounter intense competition from a number of companies that offer products in our targeted application areas. We anticipate that our competitors in these areas will include:

- health care and other companies that manufacture laboratory-based tests and analyzers;
- diagnostic and pharmaceutical companies;
- companies developing drug discovery technologies; and
- companies developing molecular diagnostic tests.

If we are successful in developing products in these areas, we will face competition from established companies and numerous development-stage companies that continually enter these markets. In many instances, our competitors have substantially greater financial, technical, research and other resources and larger, more established marketing, sales, distribution and service organizations than us. Moreover, these competitors may offer broader product lines and have greater name recognition than us and may offer discounts as a competitive tactic.

In addition, several development-stage companies are currently making or developing products that compete with or will compete with our potential products. Our competitors may succeed in developing, obtaining approval from the U.S. Food and Drug Administration or marketing technologies or products that are more effective or commercially attractive than our current or potential products or that render our technologies and current or potential products obsolete.

As these companies develop their technologies, they may develop proprietary positions that may prevent us from successfully commercializing products.

Also, we may not have the financial resources, technical expertise or marketing, distribution or support capabilities to compete successfully in the future.

The uncertainty of patent and proprietary technology protection may adversely affect us.

Our success will depend in part on obtaining and maintaining meaningful patent protection on our inventions, technologies and discoveries. Our ability to compete effectively will depend on our ability to develop and maintain proprietary aspects of our technology, and to operate without infringing the proprietary rights of others, or to obtain rights to third-party proprietary rights, if necessary. Our pending patent applications may not result in the issuance of patents. Our patent applications may not have priority over others applications, and even if issued, our patents may not offer protection against competitors with similar technologies. Any patents issued to us may be challenged, invalidated or circumvented, and the rights created thereunder may not afford us a competitive advantage.

We also rely upon trade secrets, technical know-how and continuing inventions to develop and maintain our competitive position. Others may independently develop substantially equivalent proprietary information and techniques or otherwise gain access to our trade secrets or disclose our technology and we may not be able to meaningfully protect our trade secrets, or be capable of protecting our rights to our trade secrets. We seek to protect our technology and patents, in part, by confidentiality agreements with our employees and contractors. Our employees may breach their existing Proprietary Information, Inventions, and Dispute Resolution Agreements and these agreements may not protect our intellectual property. This could have a material adverse effect on us.

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Our products could infringe on the intellectual property rights of others, which may subject us to future litigation and cause us to be unable to license technology from third parties.

Our commercial success also depends in part on us neither infringing valid, enforceable patents or proprietary rights of third parties, nor breaching any licenses that may relate to our technologies and products. We are aware of other third-party patents that may relate to our technology. It is possible that we may unintentionally infringe these patents or other patents or proprietary rights of third parties. We may in the future receive notices claiming infringement from third parties as well as invitations to take licenses under third-party patents. Any legal action against us or our collaborative partners claiming damages and seeking to enjoin commercial activities relating to our products and processes affected by third-party rights may require us or our collaborative partners to obtain licenses in order to continue to manufacture or market the affected products and processes. In addition, these actions may subject us to potential liability for damages. We or our collaborative partners may not prevail in an action and any license required under a patent may not be made available on commercially acceptable terms, or at all.

There are many U.S. and foreign patents and patent applications held by third parties in our areas of interest, and we believe that there may be significant other litigation in the industry regarding patent and other intellectual property rights. Additional litigation could result in substantial costs and the diversion of management s efforts regardless of the result of the litigation. Additionally, the defense and prosecution of interference proceedings before the U.S. Patent and Trademark Office, or USPTO, and related administrative proceedings would result in substantial expense to us and significant diversion of effort by our technical and management personnel. We may in the future become subject to USPTO interference proceedings to determine the priority of inventions. In addition, laws of some foreign countries do not protect intellectual property to the same extent as do laws in the U.S., which may subject us to additional difficulties in protecting our intellectual property in those countries.

We are aware of U.S. and European patents and patent applications owned by Oxford Gene Technologies. We have opposed one allowed European patent that had broad claims to array technology for analyzing a predetermined polynucleotide sequence. Oxford Gene s position with respect to the opposed patent is that the claims relate to what it terms the diagnostic mode. Those claims have now been narrowed before the Opposition Division of the European Patent Office to the point that, if these claims remain final before the European Patent Office, we believe they would not be infringed by our technology. In the oral proceedings before the Opposition Division on November 13, 14, and 15, 2001, the Division determined that the claims language must be limited to arrays with smooth, impermeable surfaces. The case is currently on appeal. If the decision of the Opposition Division is successfully appealed by Oxford Gene and the original claims are reinstated, or if an application relating to arrays is issued in another country with claims as broad as the original European patent, we could be subject to infringement accusations that could delay or preclude sales of some or all of our anticipated diagnostic products.

We may continue to be involved in intellectual property litigation that may be costly, time-consuming and may impact our competitive position.

In December 2002, Oxford Gene Technologies filed a complaint against us in the United States District Court for the District of Delaware claiming that we infringe U.S. Patent No. 6,054,270 entitled Analytical Polynucleotide Sequences. In April 2003, we filed an answer to the complaint that denied that we infringe this patent. In October 2003, we entered into a settlement agreement with Oxford Gene Technologies pursuant to which the lawsuit was dismissed by Oxford Gene Technology without prejudice. If the litigation were to be reinitiated, significant attorneys costs and fees could result. Although it is our position that Oxford Gene s assertions of infringement have no merit, neither the outcome of any further litigation nor the amount and range of potential fees can be assessed. No assurances can be given that we would prevail in any future lawsuits or that we could successfully defend ourselves against any future claims.

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The regulatory approval process is expensive, time consuming, uncertain and may prevent us from obtaining required approvals for the commercialization of our products.

The manufacturing, labeling, distribution and marketing of any diagnostic products we may develop will be subject to regulation in the U.S. and other countries. These regulations could subject us to several problems such as:

failure to obtain necessary regulatory approvals or clearances for our products on a timely basis, or at all;

delays in receipt of or failure to receive approvals or clearances;

the loss of previously received approvals or clearances;

limitations on intended uses imposed as a condition of approvals or clearances; or

failure to comply with existing or future regulatory requirements.

In the U.S., the Food and Drug Administration, or FDA, regulates as medical devices most test systems, kits and reagents that are marketed for human *in vitro* diagnostic use. Pursuant to the Federal Food, Drug, and Cosmetic Act, the FDA regulates the preclinical and clinical testing, design, safety, effectiveness, manufacture, labeling, distribution and promotion of medical devices. We will not be able to commence marketing or commercial sales in the U.S. of these products until we receive an exemption, clearance or approval from the FDA, which can be a lengthy, expensive and uncertain process. We have not applied for FDA or other regulatory approvals with respect to any of our current products or products under development. We may experience difficulties that could delay or prevent the successful development, introduction and marketing of proposed products. Regulatory clearance or approval of any proposed products may not be granted by the FDA or foreign regulatory authorities on a timely basis, if at all. Noncompliance with applicable FDA requirements can result in:

criminal prosecution, civil penalties, other administrative sanctions or judicially imposed sanctions, such as injunctions;

recall or seizure of products;

total or partial suspension of production; and

failure of the government to grant premarket clearance or premarket approval for devices or withdrawal of marketing clearances or approvals once granted.

The FDA also has the authority to request the recall, repair, replacement or refund of the cost of any regulated device that may eventually be manufactured or distributed by us. Any devices manufactured or distributed by us pursuant to FDA clearance or approvals are subject to thorough and continuing regulation by the FDA and certain state agencies, including the California Department of Health Services.

Our dependence on suppliers for materials could impair our ability to manufacture our products.

Outside vendors provide key components and raw materials used by us and Hitachi in the manufacture of our products. Although we believe that alternative sources for these components and raw materials are available, any supply interruption in a limited or sole source component or raw material would harm our and Hitachi s ability to manufacture our products until a new source of supply is identified and qualified, including qualification under applicable FDA regulations. In addition, an uncorrected defect or supplier s variation in a component or raw material, either unknown to us or Hitachi or incompatible with our or Hitachi s manufacturing processes, could harm our or Hitachi s ability to manufacture products. We or Hitachi may not be able to find a sufficient alternative supplier in a reasonable time period, or on commercially reasonable terms, if at all. If we or Hitachi fail to obtain a supplier for the manufacture of components of our potential products, we may be forced to curtail or cease operations.

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If we are unable to manufacture products on a commercial scale, our business may suffer.

Hitachi manufactures our NanoChip® System, and we manufacture our NanoChip® Cartridges, our ASRs and most of our other products. We and Hitachi rely on subcontractors to manufacture the limited quantities of microchips and other components we require for use by and sale to our customers, as well as for internal and collaborative purposes. Manufacturing, supply and quality control problems may arise as we or Hitachi either alone, together or with subcontractors, attempt to further scale up manufacturing procedures or to manufacture new products. We or Hitachi may not be able to scale-up in a timely manner or at a commercially reasonable cost. Problems could lead to delays or pose a threat to the ultimate commercialization of our products and cause us to fail.

We or Hitachi or any of our contract manufacturers could encounter manufacturing difficulties, including those relating to:

- the ability to scale up manufacturing capacity;
- production yields;
- quality control and assurance; or
- shortages of components or qualified personnel.

Our manufacturing facilities and those of Hitachi and any other of our contract manufacturers are or will be subject to periodic regulatory inspections by the FDA and other federal, state and international regulatory agencies and these facilities are or may become subject to Quality System Regulation, or QSR, requirements of the FDA. If we, Hitachi or our third-party manufacturers, fail to maintain facilities in accordance with QSR regulations, other international quality standards or other regulatory requirements, then the manufacture process could be suspended or terminated which would harm us.

Lead times for obtaining materials and components for our products and the manufacturing and introduction of our products may vary significantly which could lead to excess inventory levels as well as shortages of critical components and products if our supply and demand forecasts are inaccurate.

We anticipate that our products, including our ASRs and most of our other products will be manufactured and introduced by us and third parties, if any, based on forecasted demand and that we will seek to purchase components and materials in anticipation of the actual receipt of purchase orders from our customers. Lead times for materials and components to be included in our products vary significantly and may depend on factors such as the business practices of each specific supplier and the terms of the particular contracts, as well as the overall market demand for such materials and components at any given time. Also, we often rely on our own and third party forecasted demand for various products and the accuracy of such forecasts may depend on a number of factors, including but not limited to, government reports and recommendations for certain genetic testing, regulatory burdens, competitive products, the nature and effectiveness of our products, the timing and extent of the introduction of our products into the marketplace and other factors. If the forecasts are inaccurate, we could experience fluctuations in excess inventory of our products, or shortages of critical components or products, either of which could cause our business to suffer.

We currently rely on one manufacturer of our Workstation and for certain future generations of the Workstation and other hardware products, and only we manufacture our NanoChip® Cartridges, and our ASRs and most of our other products, which may delay the manufacture and shipment of our products to customers.

We have signed an exclusive manufacturing agreement with Hitachi to manufacture our NanoChip® Workstation and agreements to exclusively manufacture certain of our other second generation Workstations and other hardware products to be developed, subject to certain terms and conditions in each agreement. We have

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retained exclusive rights pursuant to each agreement to manufacture the NanoChip® Cartridges. Pursuant to the manufacturing agreements and the collaboration agreement, each party is obligated to provide the other with certain notice periods if such party determines to curtail or terminate the manufacturing relationship. Nevertheless, while alternative manufacturers of our Workstation and other products currently exist, a lengthy process would be required to negotiate and begin work under a manufacturing agreement with a new manufacturer which could disrupt our manufacturing process and harm our business.

The number of our sales and marketing employees may not result in corresponding numbers of sales or placements of the NanoChip® System or sale of ASRs or other Nanogen products.

As of December 31, 2003, we had 30 total employees in our worldwide sales and marketing group. In July 2000, we incorporated a subsidiary, Nanogen Europe B.V. in The Netherlands as our European sales office. As of December 31, 2003, this office employed 7 European-based sales executives and support personnel in Germany and The Netherlands.

Developing, training and monitoring this sales and marketing force has required and will further require capital and time expenditures by us and certain of our employees. The size of our sales and marketing force may not result in corresponding numbers of sales or placements of the NanoChip® System nor increased product revenues associated with such sales or placements or our ASRs or other products. We may be required to increase or decrease the size of this sales and marketing force as deemed necessary and such increases or decreases in staff will require additional capital and time expenditures by us and our employees.

Failure to expand our international sales as we intend would reduce our ability to become profitable.

We expect that a portion of our sales will be made outside the United States. A successful international effort will require us to develop relationships with international customers and partners. We may not be able to identify, attract or retain suitable international customers and distribution partners. As a result, we may be unsuccessful in our international expansion efforts. Furthermore, expansion into international markets will require us to continue to establish and expand foreign sales and marketing efforts, hire additional sales and marketing personnel and maintain good relations with our foreign customers and distribution partners.

International operations involve a number of risks not typically present in domestic operations, including:

- currency fluctuation risks;
- changes in regulatory requirements;
- costs and risks of deploying the NanoChip® System, ASRs and other products in foreign countries;
- licenses, tariffs and other trade barriers;

political and economic instability, including the war on terrorism;

difficulties in staffing and managing foreign offices;

costs and difficulties in establishing and maintaining foreign distribution partnerships;

potentially adverse tax consequences; and

the burden of complying with a wide variety of complex foreign laws and treaties.

Our international sales and marketing efforts will also be subject to the risks associated with the imposition of legislation and regulations relating to the import or export of high technology products. We cannot predict whether tariffs or restrictions upon the importation or exportation of our products will be implemented by the United States or other countries.

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We may lose money when we exchange foreign currency received from international sales into U.S. dollars. A portion of our business is expected to be conducted in currencies other than the U.S. dollar. We recognize foreign currency gains or losses arising from our operations in the period incurred. As a result, currency fluctuations between the U.S. dollar and the currencies in which we do business will cause foreign currency transaction gains and losses. We cannot predict the effects of exchange rate fluctuations upon our future operating results because of the number of currencies involved, the variability of currency exposure and the potential volatility of currency exchange rates. We currently do not engage in foreign exchange hedging transactions to manage our foreign currency exposure.

We may have significant product liability exposure.

We face an inherent business risk of exposure to product liability and other claims in the event that our technologies or products are alleged to have caused harm. These risks are inherent in the testing, manufacturing and marketing of our products. Any product liability claim brought against us could be expensive to defend and could result in a diversion of management s attention from our core business. A successful product liability claim or series of claims could have an adverse effect on our business, financial condition and results of operations.

If we lose our key personnel or are unable to attract and retain additional personnel, we may not be able to pursue collaborations or develop our own products.

We are highly dependent on the principal members of our scientific, manufacturing, marketing, administrative, management and executive personnel, the loss of whose services might significantly delay or prevent the achievement of our objectives. We face competition from other companies, academic institutions, government entities and other organizations in attracting and retaining personnel. For the year ended December 31, 2003, the turnover rate at all levels at Nanogen was 25%. For the years ended December 31, 2002 and 2001 the turnover rates at Nanogen were 29% and 31%, respectively. Turnover at these rates may, and if they continue, will adversely affect us.

The turnover rates above exclude the impact of reductions in workforce. In April 2003, we reduced our workforce by approximately 20% and incurred a severance charge of approximately $500,000 in the second quarter. Also, in October 2002, we reduced our workforce by approximately 10% and incurred severance charges of approximately $290,000 during the fourth quarter of fiscal 2002. Continued layoffs could have an adverse effect on us.

Health care reform and restrictions on reimbursement may limit our returns on potential products.

Our ability to earn sufficient returns on our products will depend in part on the extent to which reimbursement for our products and related treatments will be available from:

- government health administration authorities;
- private health coverage insurers;

managed care organizations; and

other organizations.

If appropriate reimbursement cannot be obtained, we could be prevented from successfully commercializing our potential products.

There are efforts by governmental and third party payors to contain or reduce the costs of health care through various means. We expect that there will continue to be a number of legislative proposals to implement government controls. The announcement of proposals or reforms could impair our ability to raise capital. The adoption of proposals or reforms could impair our business.

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Additionally, third party payors are increasingly challenging the price of medical products and services. If purchasers or users of our products are not able to obtain adequate reimbursement for the cost of using our products, they may forego or reduce their use. Significant uncertainty exists as to the reim