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Limited Liability Company

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BIOSITE DIAGNOSTICS INCORPORATED

(BSTE)

December 18, 1998 (98-104)
Basic Report

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Price: $7 29/32 ($3 9/16–$17 3/4)
Fiscal Year Ends: December

Fiscal Year	Earnings Per Share	Price/Earnings Ratio
1997	$0.09	87.9x
1998E	$(0.12)	NM
1999E	$0.01	NM
2000E	$0.31	25.5x
2001E	$0.67	11.8x

Earnings Per Share Growth		Return on Equity	
1996-1998E	NM	1998E	NM
Long-term	40%	2000E	6%

Net Debt/Total Cap. (September 1998):	8.4%	Dividend:	None
Book Value Per Share (September 1998):	$4.25	Common Shares:	13 million
Insider Ownership:	30%	Market Value:	$105 million
Sales (1998E):	$34.1 million		

Investment Opinion: Strong Buy

Biosite is one of the leading companies providing rapid in-vitro diagnostic assays to hospitals and other clinical sites. Its lead product—Triage® Drugs of Abuse—designed to test for the most commonly abused illicit and prescription drugs, currently is used by 45% of the hospitals in the United States. In addition to this product line, Biosite recently has launched two new, high-potential product lines. The first, Triage® Cardiac, is intended to better determine if a patient has had a heart attack, and the second, the Triage® Micro product lines, comprising Triage® C. difficile and Triage® Parasite Panel, are products to identify gastrointestinal infections. We estimate the worldwide market potential for all three of Biosite's product lines is $1.5 billion, with $730 million in the United States. While Biosite's easy-to-use products produce diagnostic results in about 15 minutes, the products have accuracy similar to or better than that achieved by the larger, mainstream laboratory equipment found in hospitals and commercial laboratories. The Triage products are designed to attain high gross margins relative to other in-vitro diagnostic products—70%-80% for Biosite, versus a 44% industry average. On the basis of the strong revenue and earnings growth we expect, as well as Biosite's solid, expanding franchise and capabilities, and the current stock valuation, we strongly recommend purchase of this stock.

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Summary of Investment Recommendation

Biosite is one of the leading companies supplying rapid assays to the $20 billion in-vitro diagnostic (IVD) market. In-vitro diagnostics are medical tests that use samples taken from the human body, for example blood or urine tests. Biosite currently maintains a presence in 45% of U.S. acute care hospitals with its Triage® Drugs of Abuse (DOA) panel. This panel comprises seven or eight tests for different drugs on one disposable test device. Additionally, the gross margin for this product line is high for an IVD, averaging almost 80%. Biosite's success with its Triage® DOA products has required the company to identify additional markets and product lines to resume its historically exceptional growth profile. We believe that the necessary products and infrastructure are now in place to capture the market opportunities. These include Triage® Cardiac, quantitative cardiac markers to diagnose heart attacks; and Triage® Micro, tests for identifying gastrointestinal diseases. With these additional product lines, Biosite once again is positioned to increase earnings per share at greater than 40% per year. In light of this projected EPS growth rate and the current valuation, we believe that Biosite is an excellent investment opportunity.

Our investment recommendation for Biosite is based on the following three key factors.

- The company is pursuing large and attractive markets potentially valued at $1.5 billion worldwide, in which we believe it is well positioned to succeed.

- Capitalizing on these opportunities should enable Biosite to increase earnings per share by at least 40% per year for the foreseeable future.

- We believe that the company currently is undervalued on the basis of a variety of valuation metrics, including our 2000 estimated price-to-earnings ratio of 26.

Biosite is pursuing large and attractive markets in which we believe it is well-positioned to succeed.

Large and attractive markets. Biosite is pursuing three large and attractive markets: 1) drugs of abuse (DOA) testing, predominantly in hospital emergency departments (EDs); 2) cardiac enzyme markers to triage chest pain and diagnose heart attacks; and 3) easy-to-use microbiology tests for gastrointestinal infections. The current potential market for DOA testing is $360 million in the United States and $580 million globally. The market for cardiac markers currently is $150 million worldwide, and we expect it to grow at almost 40% annually to reach $720 million by 2003. Lastly, the current market for relevant microbiology tests is worth $200 million worldwide. The DOA testing market in EDs is attractive because rapid information regarding a patient's illicit-drug status is crucial for effective treatment. Likewise, time also is critical in diagnosing heart attacks with cardiac markers and beginning the proper treatment, because for every hour without treatment, mortality increases 1%. In addition, reducing the amount of time in the hospital for a patient with chest pain who is *not* having a heart attack should save significant amounts of money. Lastly, there is a substantial, unmet need in hospital microbiology departments for an easy-to-use, rapid test to properly and quickly identify the various infectious agents that could cause gastrointestinal disease.

Biosite is well-positioned. We believe that the company is well positioned to profitably participate in these and other potentially attractive markets for three tangible reasons.

- *Excellent products.* Biosite has excellent products, in our view, that we believe are accurate; easy-to-use; provide the optimized panel of tests (e.g., the Triage® cardiac system tests for a panel of the three most clinically relevant analytes); afford the most beneficial information (qualitative or quantitative); use automatic internal controls; and are convenient sizes.

- *DOA franchise*. Entry into the cardiac-enzyme and microbiology-testing markets is supported by linkages to Biosite's strong DOA franchise, which is used in 45% of U.S. hospitals, through its current position in EDs; its established qualitative platform; and Fisher Scientific, its U.S. sales partner's position in both emergency and microbiology departments.

- *Flexible technologies.* We believe the technologies that the company possesses permit excellent flexibility to serve these and other possible markets. Biosite has the ability to provide either qualitative or quantitative rapid assays using whole blood, urine, or stool; to quickly turn around new generations of high-quality antibodies, a key raw material; and to develop new assays at low cost, as well as to produce products with a low cost of goods.

Superior company management. On the intangible side, we believe that Biosite has a superior management team that can take advantage of the company's potential opportunities and well-placed position. First, management has proven itself with its historical success in penetrating the DOA market with Triage® DOA. Second, the management team has excellent personal backgrounds that should further propel the company's success. Third, the management has, in our opinion, developed relationships with highly qualified sales partners such as Fisher Scientific in the United States and Shield Diagnostics in the United Kingdom. Lastly, the senior management team has shown what we believe to be keen strategic thinking in the way it has pursued its opportunities. Three noteworthy examples are: 1) its understanding of hospital decision processes, politics, and incentives, which led management to work first and always with a hospital's central laboratory in placing its systems; making the central lab an integral part of the ongoing process and not going around it straight to the using department, as competitors often try to do; 2) selecting the platform—qualitative or quantitative—that makes the most clinical, but not necessarily obvious, sense; and 3) reacquiring the European distribution rights for Biosite's products from Merck KGaA to align with more-aggressive and -appropriate sales partners.

Biosite's earnings per share should grow at greater than 40% annually for at least the next five years.

We estimate that the company should achieve greater than 40% annual earnings per share growth. This increase fundamentally is driven by revenue growth due to the Triage® Cardiac and Micro product lines. We estimate that Triage® Cardiac revenue will grow from $800,000 in 1998 to $9 million in 2000, and we believe that it will continue to grow almost 90% compounded annually from 2000 to 2003. Likewise, we estimate that Triage® Micro should increase from $630,000 in 1998 to $7 million in 2000, and continue to grow 30% compounded annually from 2000 to 2003. We estimate that the overall gross margin will decline to slightly more than 60% during the current launch phase of the new product lines, but expect it to rebound to almost 70% by the end of 1999. Operating expenses should decline as a percentage of sales as both selling, general, and administrative expenses and research-and-development spending is leveraged over greater revenue, with estimates of SG&A at 36% and R&D at 26% by 2000, versus 44% and 35%, respectively, in 1998. Additionally, legal expenses should decline from $4 million in 1998 to a negligible amount in 2000, as an agreement likely will be reached with Spectral through already-ongoing discussions, and as the Dade-Behring suit is resolved through either trial, motions, or negotiation. The tax rate should increase as Biosite again shows positive earnings, reducing the effective rate reduction from research tax credits as those earnings accelerate. We estimate that the combined tax rate for 2000 will be about 33%, versus an expected tax benefit in 1998 and 1999.

The company currently appears undervalued on the basis of a variety of valuation metrics.

We believe that the company currently is undervalued compared with comparable stocks. Although its estimated 2000 price-to-earnings ratio of 26 is above the 19 average for this sector, comparison of Biosite's P/E ratio to forecast growth, as well as other measures,

indicate that it is undervalued. Analysis of forward growth rates show Biosite's 40% estimated growth rate appears not to be incorporated into its price when compared with the *limited* number of other companies for which data is available (the average P/E multiple for this *limited* group is 28, with an average growth rate 24%). Price relative to revenue per share places the company in the lower half of the rapid diagnostic comparables, while it has the second-highest revenue per share of this group. Stock price relative to cash per share also reveals Biosite's favorable position, at 39% versus a group average of 23%. Lastly, Biosite's high gross margins place it at the top of the diagnostic universe, which averages 44%. Overall, we would expect Biosite to trade at least 35 times our 2000 EPS estimate and likely be valued at 40-50 times.

Risks

Patent litigation. At present, the company is a defendant in two significant lawsuits alleging that it infringed patents. As with medical devices, patent litigation is not uncommon in the IVD market, with most issues resolved through license fees or royalty payments. For cardiac markers, Spectral Diagnostics is alleging that the company infringed its patent for the simultaneous use of at least three cardiac enzymes to assess whether chest pain is cardiac in origin, and for distinguishing between unstable angina and heart attack. Biosite currently is in negotiations with Spectral that likely will lead to an agreement that would not affect the company's financial or market prospects substantially. Spectral has a substantial incentive to opt to receive a license fee or royalty payments from Biosite, rather than see its patent potentially invalidated due to notable claims of prior art or publication. In addition, by coming to terms with Biosite, Spectral likely strengthens its case to enforce its patent against others. For DOA, Dade-Behring is alleging infringement of a patent that expires in August 2000. If the company continues to incur sizable litigation expenses or loses the lawsuit, financials would be adversely affected by an estimated of $5 million to $10 million. We believe that the risk is low and manageable due to the near-term patent expiration. Also, the suit involves a specific matter of fact of whether the fluid flow, used in the Biosite Triage® DOA device works in the same manner as that claimed in the Dade-Behring patent; Biosite management specifically states that it does not.

First mover (placement speed). The market for diagnosing chest pain appears to be moving toward protocols that favor using test panels of cardiac markers. While this poses a great opportunity for Biosite, it also creates the risk associated with not being the first system placed in a facility. When a system is placed in a facility, at least three barriers to entry arise. First, once the capital expense occurs, a new system will have to justify an additional capital expense or incur the cost of trading out the old system. Second, all IVDs have certain test characteristics (such as the range of normal values) that then become the standard. Consequently, to make a change, the physicians and laboratory personnel must relearn these characteristics—for example, What are normal, versus abnormal, values? Lastly, the various protocols for handling the information will be developed around the first system placed, such as: Are qualitative or quantitative results used? What are the cutoff values for quantitative tests? When should confirmatory testing be done? The most important way that Biosite will try to mitigate these issues is to place its products as quickly as possible, help develop the protocols that drive selection, and develop high-quality, well-designed products that can overcome the barriers in cases where competitive systems already are placed.

Successful Company History

Biosite is a 10-year-old in-vitro diagnostic firm that has shown considerable success with its original strategy and first product line—the Triage® Drugs of Abuse (DOA) rapid assay. The company was formed in 1988, began commercial sales of its Triage® Drugs of Abuse (DOA) product line in 1992, achieved profitability in 1994, and in that same year also began the process of developing its next wave of growth opportunities—the Triage® Cardiac and Micro product lines. In February 1997, the company completed its initial public offering. A detailed history of Biosite is found in table 1.

Table 1
Biosite Diagnostics Incorporated
Timeline

1988	Founded
October 1991	510K received for Triage® DOA
November 1991	Entered into distribution agreement with Curtin Matheson Scientific (CMS), a subsidiary of Fisher Scientific
1992	Initiated commercial sales of Triage® DOA
July 1992	Entered international distribution agreement with Merck for Triage® DOA
1993	Scale-up of Triage® DOA, Development of Triage® Cardiac
June 1994	Collaborative agreement with Merck for the development of Triage® Cardiac Triage® DOA Plus TCA Launched
September 1994	Entered development and production agreement with LRE for the Carelink meter (Triage® Cardiac).
February 1995	Entered into development, supply, and distribution agreement with Arkray KDK, Japan for Triage® Cardiac
September 1995	Entered license agreement with Novartis for the development of NeoralCheck®
March 1996	510K received for improved DOA
March 1996	510K received for DOA + TCA
September 1996	Settlement of patent infringement suit with Abbott ($5.5 Million)
February 1997	Initial public offering
March 1997	Enters licensing agreement with Scios for the development of a diagnostic for congestive heart failure utilizing B-type Natriuretic Peptide (BNP)
March 1997	Enters licensing agreement with Xoma for the development of a new point-of-care diagnostic for sepsis, or endotoxemia utilizing Lipopolysaccharide Binding Protein (LBP)
October 1997	510K for Triage® Cardiac Panel received
January 1998	510K for Triage® Cardiac Controls received
January 1998	510K for Triage® Cardiac Meter received
March 1998	510K for Triage® C.difficile received
March 1998	Launch of both Triage® Cardiac and Triage® C.difficile
October 1998	510K for Triage® Parasite received

Source: Biosite; Center for Device and Radiological Health (CDRH); William Blair & Company, L.L.C. analysis

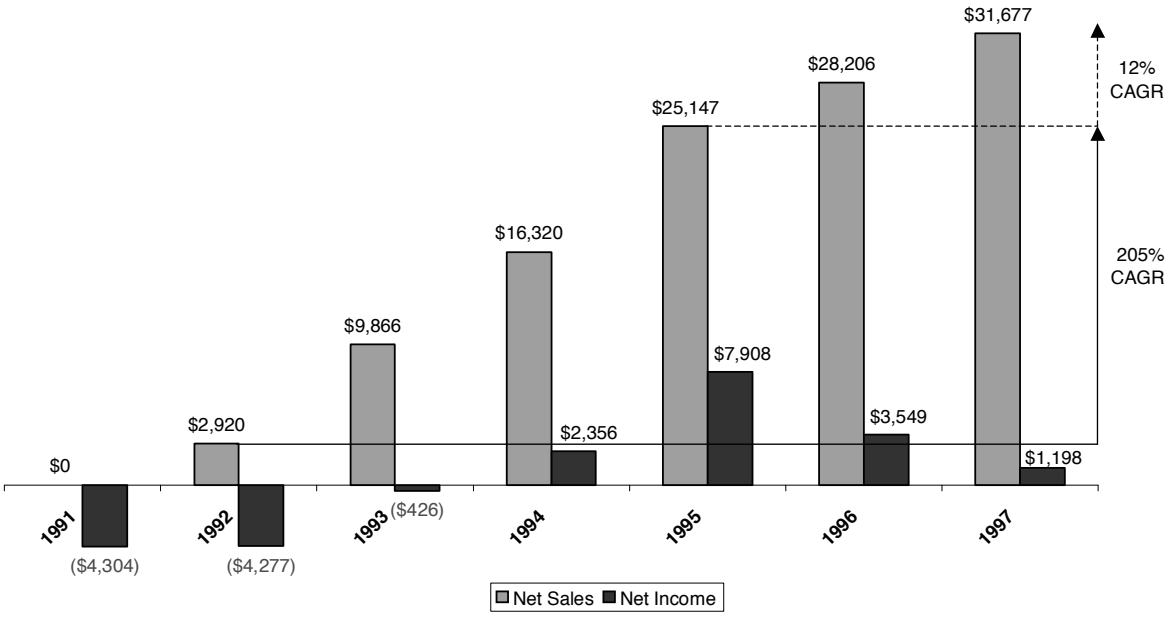
The company has its roots in one of the early monoclonal antibody start-ups, Hybritech. All three of the original founders of Biosite—Kim Blickenstaff, Gunars Valkirs, and Ken Buechler—came from Hybritech. Kleiner Perkins Caufield & Byers, one of the backers of Genentech, funded the launch of Hybritech, and subsequently, Biosite. Ted Greene, who was president of Hybritech when it went public, and when it was later acquired, also was

one of Biosite's venture investors. While at Hybritech, Mr. Valkirs was the primary inventor of the ICON system that became one of the standard methods for pregnancy testing in doctors' offices. Eli Lilly bought Hybritech in 1985 for $300 million, and in 1988, Kim Blickenstaff left Hybritech to form Biosite with Messrs. Valkirs and Buechler.

Triage® DOA Success

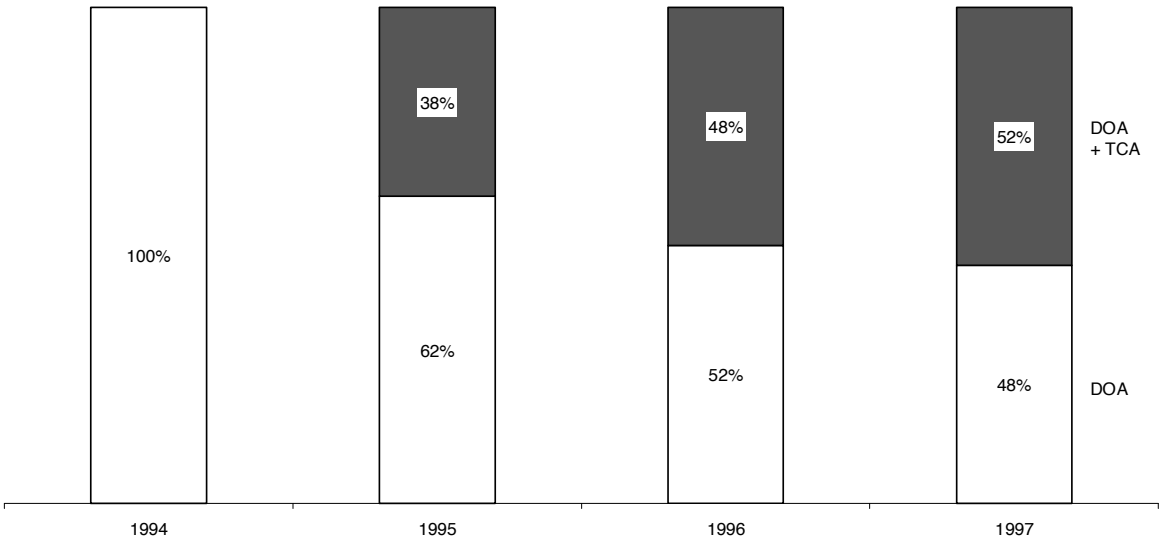
The Triage® DOA product line has been very successful. It was commercially launched in 1992 and achieved almost $3 million in sales its first year. As shown in figure 1, from 1992 to 1995, Triage® DOA sales grew at a compounded annual growth rate of more than 200%, from $2.9 million to $25.1 million, resulting in a 30% market share for rapid DOA assays. By 1997, the product was being used in more than 45% of hospitals, and more than 6.4 million panels had been sold cumulatively worldwide. Hospital or end-user sales were $47 million, with Biosite receiving almost $32 million of revenue after the distributor margin. To sell Triage® DOA, the company entered into agreements with Curtin Matheson Scientific (CMS), a subsidiary of Fisher Scientific, in 1991 to distribute the product in the United States, and with Merck KGaA in 1992 to distribute the product to most of the rest of the world. In February 1995, Biosite launched its product-line extension, the Triage® DOA Plus TCA (Tricyclic Antidepressant) Panel, the first urine-based immunoassay for TCA. It carried a 20% higher price and quickly grew to make up one-third of total company sales in 1995 and almost one-half of sales in 1996. It now is the predominant DOA product, as shown in figure 2, on the next page.

Figure 1
Biosite Diagnostics Incorporated
Annual Sales and Net Income
($ in thousands)



Source: Biosite financials; William Blair & Company, L.L.C. estimates

Figure 2
Biosite Diagnostics Incorporated
DOA Product Line Extension

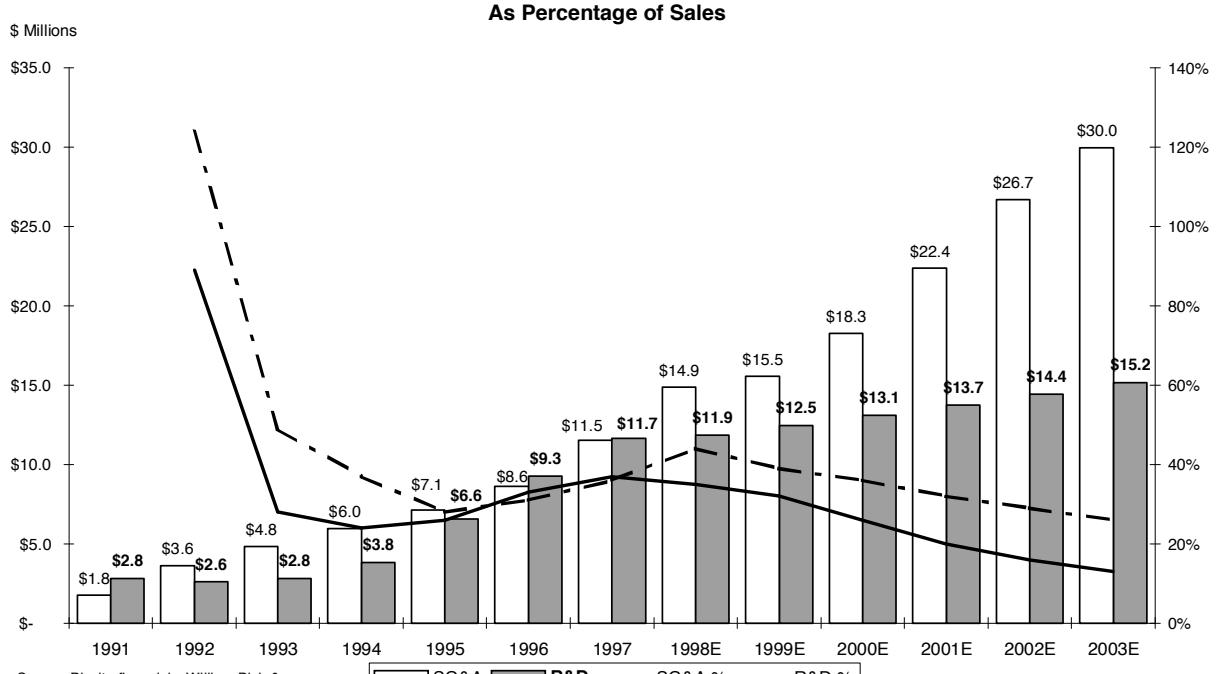


Source: Biosite financials; William Blair & Company, L.L.C. estimates

From a revenue growth perspective, Biosite could have been considered a victim of its own success. As shown in figure 1, while sales grew more than 200% compounded annually from 1992 to 1995, they only rose 12% compounded annually from 1995 to 1997. This lower growth predominantly was the result of rapidly penetrating almost 50% of the U.S. market for DOA.

By 1994, Biosite began to reinvest in new growth platforms and research and development, as shown in figure 3. This increase in R&D spending as a percentage of sales continued from its low of 24% in 1994 through to its peak of 37% in 1997. In dollar terms, R&D grew from $3.8 million in 1994 to $11.7 million in 1997. Had the company chosen not to pursue its continued aggressive growth strategy, we believe that R&D would have declined to no more than 15% of sales. In addition to R&D, the company continued to increase investment in SG&A spending to capture incremental share and prepare the market for the new product lines. SG&A expense bottomed at 28% in 1995 and rose to what we believe is a peak of 45% in 1998. In this case, the company could have maintained its SG&A comfortably at the 1995 level if not for its pursuit of growth. We estimate that as Biosite's revenues rise, it eventually should be able to achieve combined operating expenses of 45%, R&D expenses of about 15%, and SG&A of about 30%, and still be able to develop new growth opportunities.

Figure 3
Biosite Diagnostics Incorporated
Annual R&D and SG&A
As Percentage of Sales



Source: Biosite financials; William Blair & Company, L.L.C. estimates

Development of Quantitative Triage® Meter Platform

In contrast to the qualitative Triage® DOA platform, the new Triage® Cardiac required a quantitative meter system. In 1994, Biosite entered into an agreement with LRE Relais + Elektronik GmbH (LRE) to develop a portable, photometric meter to be used in conjunction with the cardiac assays to be developed by Biosite. The two companies also entered into an agreement for LRE to be the exclusive supplier of these meters once they were developed. Part of the development work also was funded by Merck KGaA and Arkray KDK. KDK helped fund the development in exchange for exclusive distribution rights in Japan and certain other countries in Asia, the Middle East, and Pacific Islands. These marketing partners later could be allowed to purchase the meters directly from LRE if this were more advantageous to Biosite. LRE and Biosite subsequently successfully designed the Triage® Cardiac meter system with what we believe are superior performance characteristics. This quantitative meter system now can be used as a platform for additional, appropriate growth opportunities, such as NeoralCheck®, Triage® BNP, and Triage® LBP. Both the Triage® Cardiac system performance and additional growth opportunities are discussed later in this report, in the section titled “Biosite Well Positioned.”

FDA Approval of New Product Lines

Thus far, Biosite has been successful in getting regulatory approvals from the Food and Drug Administration (FDA). As shown in table 2, within the past year, the company has achieved the five necessary 510(k) clearances needed to launch its new product lines. For Triage® Cardiac, Biosite required and received clearance for all the necessary parts of a quantitative system—the meter, the reagents, and the controls. Additionally, it received FDA clearance to market in the United States both qualitative Triage® Micro products—Triage® C. difficile and Triage® Parasite.

Table 2
Biosite Diagnostics Incorporated
Recent FDA Approvals

October 1991	510K received for Triage® DOA
February 1996	510K received for Triage® Intervention
March 15, 1996	510K received for improved Triage® DOA
March 16, 1996	510K received for Triage® DOA + TCA
October 6, 1997	510K for Triage® Cardiac Panel received*
January 8, 1998	510K for Triage® Cardiac Controls received*
January 13, 1998	510K for Triage® Cardiac Meter received*
March 20, 1998	510K for Triage® C. difficile received
October 6, 1998	510K for Triage® Parasite received

* For quantitative system, separate 510K clearance needed for reagents, meter, and controls

Source: Biosite; Center for Devices and Radiological Health (CDRH); William Blair & Company, L.L.C. analysis

Attractive Markets for Selective Rapid In Vitro Diagnostic Assays

Biosite currently is pursuing three IVD markets. The first is drugs of abuse (DOA), where the company already has substantial sales and where rapid assays led by Biosite already have been significantly penetrated. Second is the market for cardiac enzymes. These are used to triage patients entering emergency rooms with chest pain who might have had heart attacks, or acute myocardial infarctions (AMI). This market has substantial potential for both underlying growth and penetration of rapid assays. Third is the microbiology market related to gastrointestinal infectious diseases. These are caused by the opportunistic microorganism Clostridium difficile (*C. difficile*), parasites, or enteric bacteria. This testing market already exists, but with little to no penetration of rapid assays, providing an excellent growth opportunity. These markets combined have a worldwide market potential of $1.5 billion.

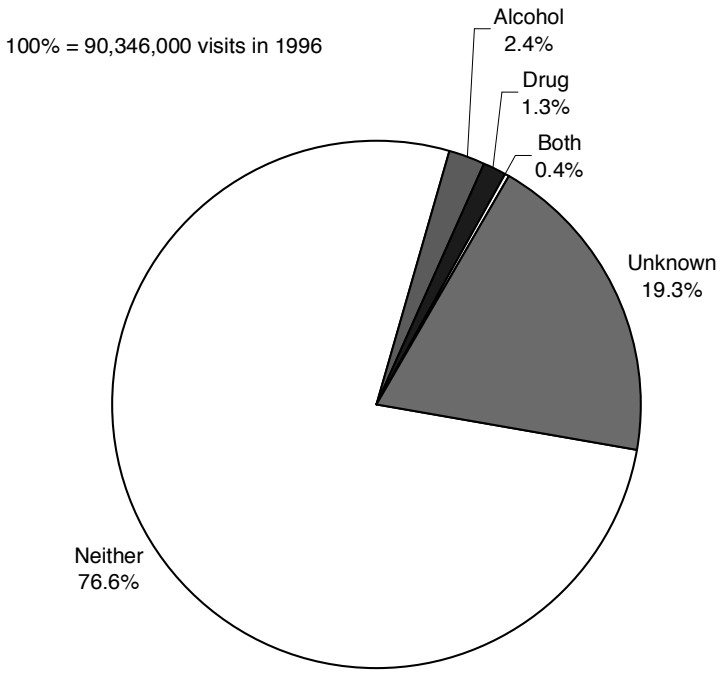
DOA Market Is Large and Stable

The estimated global market for DOA testing in 1998 is approximately $580 million, with revenues in the United States accounting for $360 million, or about 60%. Rapid assays account for about one-third of this U.S. market, or about $100 million. As this percentage reflects, DOA testing predominantly is a U.S. phenomenon. These revenue figures translate into 38 million tests performed in the United States in 1998. We anticipate that this large market will experience little growth as unit growth is mitigated by price decreases.

The DOA market can be divided into two segments—medical and nonmedical testing. Medical testing consists of emergency-department (ED) testing and neonatal testing. ED testing is conducted in cases where use of illicit substances is suspected. As shown in figure 4, 4% of the 90 million annual visits to EDs are directly related to drug or alcohol abuse. To identify that 4%, all patients for whom drug use is suspected must be screened by using an IVD test. The presence of such substances may interfere with or determine the course of

therapy administered by the attending physician. Tests for DOA also may be used to ensure accurate diagnosis of psychiatric disorders, as well as cardiovascular problems—one symptom of illicit drug use is chest pain. In the ED, the cost associated with the immediate (STAT) results that are made possible and simple by rapid assays are well justified.

Figure 4
Biosite Diagnostics Incorporated
Potential DOA-related ED Visits



Source: Center for Disease Control; William Blair & Company, L.L.C. estimates

Each year, 7% of newborns are born to mothers who abuse drugs. Screening for illegal substances in the blood of both mother and child could lead to timely intervention, possibly curbing long-term effects attributed to prenatal drug abuse, as well as decreasing the $360 million annual cost of treating exposed infants.

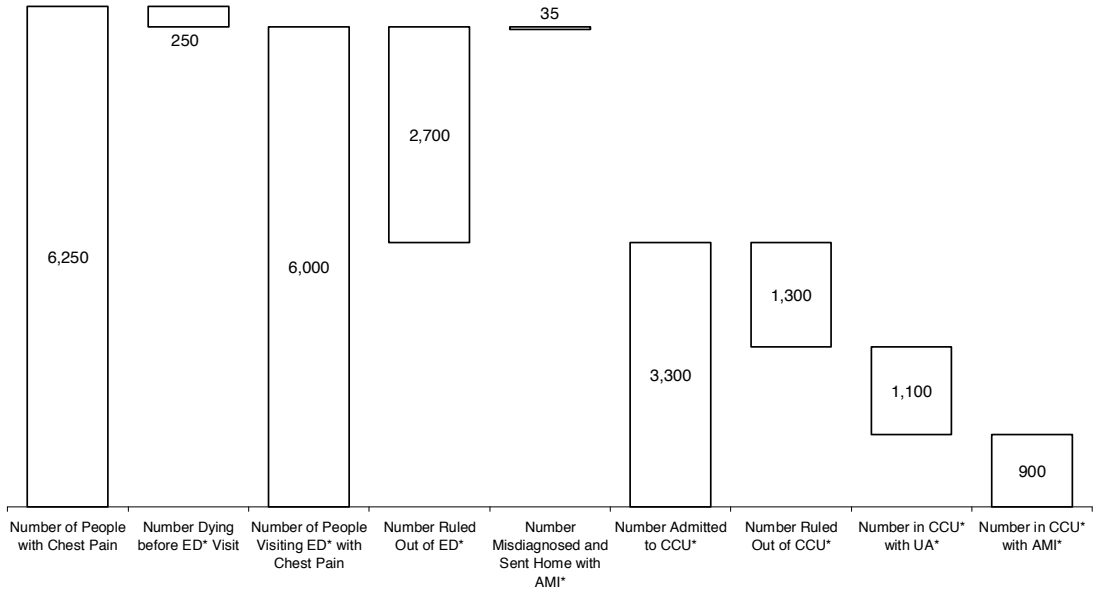
Nonmedical testing comprises workplace screening, as well as tests conducted in drug rehabilitation centers and within the criminal justice system. In 1991, the American Management Association found that 63% of firms conducted some type of workplace drug testing. By 1997, it was estimated that more than 75% of new hires were tested for illicit drug use. In 1997, 5% of employees tested positive for drugs, down from 18.1% in 1987. Workplace testing most often is conducted offsite at commercial labs, allowing employers to avoid the cost of maintaining onsite facilities and personnel. As discussed further in appendix B, rapid assays are often justified in this market as well, to avoid chain of custody issues and to not unnecessarily postpone hiring the 95% of employees who do *not* test positive.

The cardiac-marker market has significant potential, and rapid assay acceptance should grow quickly.

Myoglobin (Mb), CK-MB, and the Troponins are cell proteins frequently used as markers for cardiac dysfunction. These proteins are released into the bloodstream from damaged heart tissue following a heart attack, and their measurement in blood samples from patients arriving in the ED provides *reliable indicators of a recent heart attack*. They are used in conjunction with an electrocardiogram (EKG), which alone only identifies about 40%-70% of AMIs. The use of these cardiac enzyme markers—predominantly CK-MB alone—constitutes a $150 million global market in 1998, with $100 million in the United States. We estimate that the total global market potential for rapid assays of cardiac markers is approximately $720 million. We estimate that the cardiac-marker market will grow at an annual rate of almost 40%.

Better diagnosis of heart attack, or acute myocardial infarction (AMI), through expanded use of cardiac markers appears justified. More than 6 million individuals come to the ED with complaints of chest pain each year. While about 2.5 million are admitted into critical care units to rule out AMI, only 900,000 patients are diagnosed with AMI—less than 40%—as shown in figure 5. The American College of Cardiology estimates that the annual cost of AMI rule-out is $6 billion. The cost of misdiagnosis also is high. Approximately 34,000 patients are misdiagnosed as not having AMI and are sent home; the mortality among those wrongly diagnosed is 25%. This group of patients constitutes 20% of the malpractice litigation filed against EDs. With the aging of the U.S. population, the losses and costs associated with AMI likely will increase. Appendix B explores chest pain and AMI in detail.

Figure 5
Biosite Diagnostics Incorporated
Presentation of Chest Pain in the United States
(Thousands of patients)



* ED - Emergency Department; AMI - Acute Myocardial Infarction; CCU - Cardiac or Critical Care Unit; UA - Unstable Angina
Source: American Heart Association; American College of Cardiology; American College of Emergency Medicine; NCHS; Wilkerson Group; William Blair & Company, L.L.C. estimates

Due to the time-sensitive nature of AMI diagnosis, the longer treatment is withheld, the greater the extent of myocardial damage, or vice versa, the greater the incurred cost of keeping non-AMI patients in the hospital. Additionally, expensive thrombolytic therapies that often carry adverse side-effects have been shown to greatly improve patient outcome if delivered in time, highlighting the critical nature of this information and the need for a rapid diagnostic platform to deliver it.

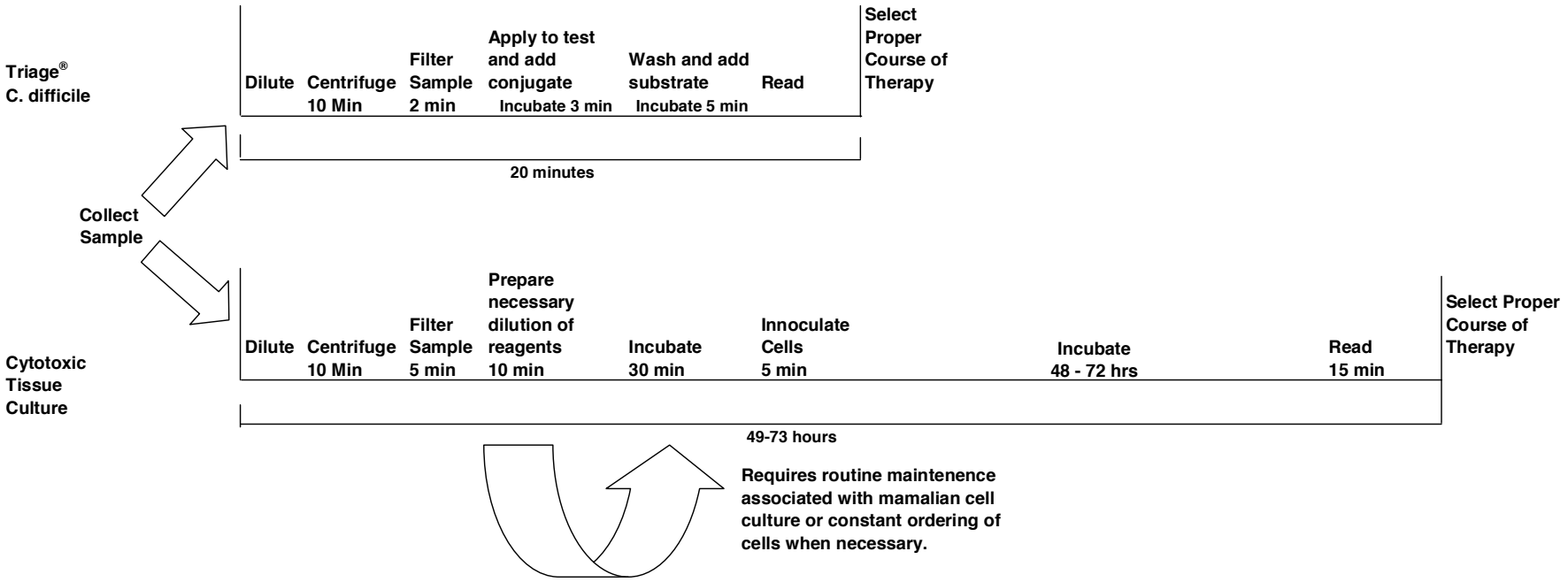
Integrated into the ED's protocol for AMI, blood-test panels of cardiac markers performed serially on each patient serve as indicators of AMI allowing for more-accurate rule-in/rule-out criteria. Diagnostics algorithms, discussed in appendix B, are under development to define these criteria concretely. These algorithms would promote the serial testing of cardiac-marker panels. The American College of Cardiology estimates that instituting more-precise protocols for triaging patients would result in an estimated total savings in the United States of $3 billion-$6 billion and several thousand lives. The rapid and accurate delivery of this information allows doctors to make qualified decisions quickly, enhancing overall care quality.

The microbiology testing market already is large and growing modestly, ripe for penetration of rapid assays.

Gastrointestinal disorders caused by microbes wreak havoc unknown to most people. The FDA estimates that the total annual cost of infectious intestinal diseases amounts to $23 billion. Despite this incredibly high morbidity, we believe that the microbiology testing market is still underserved. Identifying two disease-causing agents reveals large markets served by dated technology. Clostridium difficile is the leading cause of hospital-acquired (nosocomial) infectious diarrhea, requiring 3 million tests annually in the United States. Waterborne parasites such as *Cryptosporidium parvum, Giardia lamblia,* and *Entamoeba histolytica* have caused massive infectious outbreaks across the United States, and an untold number of amoebic dysentery cases, requiring more than 1 million tests annually in the United States. Combined, these tests represent a worldwide market potential of $200 million. Appendix B offers a detailed discussion of these parasites.

Of the 10 million-plus tests performed worldwide annually, the majority of diagnoses are based upon either labor-intensive, microscopic examination of stool samples or time-intensive (48-72 hours) cytotoxin tests. Because each organism necessitates a different treatment, identification of the specific microorganism is mandatory. In addition, the earlier identification occurs, the earlier the proper treatment is started, lowering cost and improving outcomes. It also is important to note that the future incidence and severity of nosocomial infections can be tempered with timely intervention and use of antibiotics only when warranted. Historic overuse of antibiotics has contributed to an increase in the number of antibiotic-resistant organisms. Lastly, labor cost-savings also should be realized. These points make it clear that a rapid, easy-to-use diagnostic solution is needed. Figure 6, on the next page, illustrates the significant improvement in the diagnostic process possible when using rapid assays instead of the current labor-intensive, inaccurate method.

Figure 6
Biosite Diagnostics Incorporated
Comparison of Microbiology Process



Source: Triage® C. difficile package inserts; industry interviews; William Blair & Company, L.L.C. estimates

Triage® Product Lines Very Competitive

The Triage® product line covers a full range of disease categories, as shown in table 3. Demonstrated by the success of Triage® DOA, Biosite's offerings incorporate a host of features that make them extremely competitive versus products from other diagnostics manufacturers, including high levels of ease of use, accuracy, and speed, as well as internal controls and small size. In addition, Biosite has designed products with the appropriate panels of tests and type of information provided, whether qualitative or quantitative.

Table 3
Biosite Diagnostics Incorporated
Current Product Line

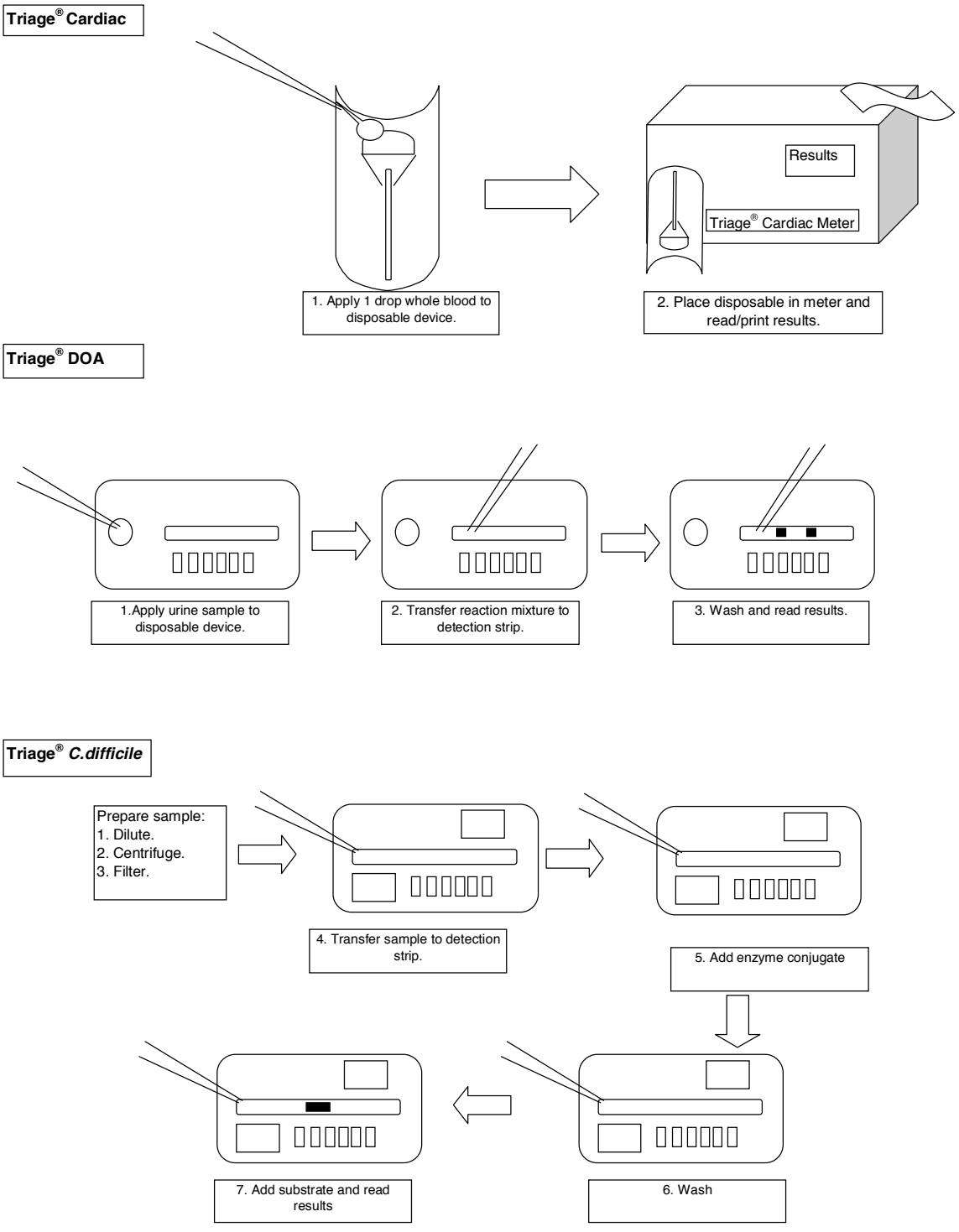
Biosite Diagnostic Product	Disease Category	Common Diseases	Worldwide Potential End-User Market Size ($ millions)
Triage® DOA Triage® DOA + TCA	Drugs of abuse testing	Overdose Chest Pain	580
Triage® Cardiac Triage	Cardiovascular disease	Heart Attack	720
Triage® C. difficile	Gastrointestinal	Diarrhea Collitis	200
Triage® Parasite	Parasitology	Gastrointestinal Distress	
Under Development			
Triage® Enteric	Gastrointestinal	Food Poisoning	200
NeoralCheck®	Organ transplantation	Immune system suppression	125
Triage® LBP	Infectious diseases	Sepsis Edotoxemia	50-100
Triage® BNP	Cardiovascular disease	Congestive Heart Failure	500 – 1,700

Source: Biosite; Wilkerson Group; Roche; Dade-Berhinh; Spectral Diagnostics; Meridian Diagnostics; Novartis; XOMA; CDC; NCHS; AHA; ACEP; William Blair & Company, L.L.C. estimates

Ease of Use

Biosite's Triage® line is extremely easy to use. Procedures allow tests to yield results in a few, simple steps, depending on the panel, as shown in figure 7, on the next page. This contrasts with the competitive platforms being replaced that involve complicated, timed, and multistep procedures. For example, in microbiology testing for gastrointestinal pathogens, the standard processes take 48-72 hours to yield useful results. Sample handling also is greatly simplified. Biosite's tests do not involve the traditional array of test tubes found in other diagnostic products. Whole blood, urine, or stool samples are loaded directly onto single-use devices using a syringe or eyedropper. Internal microfluidics control the sample volume, as well as all of the timing. Additionally, internal controls incorporated into each Biosite test eliminate the need to run separate positive and negative controls along with the experimental sample. For typical tests, controls must be run *every time* a batch of a specific type of test is performed.

Figure 7
Biosite Diagnostics Incorporated
Biosite Product Ease of Use



Source: Biosite; William Blair & Company L.L.C. analysis

Using Triage® Cardiac as an example, whole blood is taken from the sample vial and applied directly to the disposable cartridge. Internal mechanisms enable Triage® Cardiac to use whole blood samples, as opposed to most other systems that often require that the blood be transported for processing, then be physically or chemically treated, complicating the handling process and increasing turnaround time by as much as six times (e.g., 20 minutes total time to results versus 2 hours). For the Triage® Cardiac system, the cartridge is placed in the meter, 15 minutes elapse, and a definitive, quantitative reading for all three cardiac markers is delivered. In contrast, the Stratus® CS, a competing whole-blood system from Dade-Behring, requires the user to place a special cap on the sample vial, load the sample vial into the machine, load a disposable rotor in the machine, load up to three different test packs into the machine, and then press "Run." The Stratus® CS will yield results in 15 minutes for a single marker, but running the entire 3-marker panel requires 23 minutes.

Incredible Accuracy, Combined With Speed

In our opinion, Biosite's products are extremely accurate and give care providers applicable information in 10-15 minutes. The immunodiagnostic-based technology used by Biosite offers levels of specificity and sensitivity unparalleled by other traditional methods. This is in contrast with most other rapid assays that compromise accuracy for ease of use and speed. (For a discussion on specificity and sensitivity as it relates to medical diagnostics, see appendix A.) Competitive products also may be immunodiagnostic-based, yet when compared, the Triage® line clearly appears to be more accurate. This is shown in the case of both the *C. difficile* tests currently on the market in table 4, the various cardiac marker diagnostics available, as shown in table 5 and parasite testing shown in table 6. Accuracy is a function both of test system design, as well as the particular antibodies used. As such, once a product is developed, it is difficult to improve its accuracy without developing a new generation of system or new antibodies, both of which are time consuming and costly.

Table 4
Biosite Diagnostics Incorporated
***C.difficile* Immunoassay Comparison**

Company	Product	% Sensitivity	% Specificity
Biosite	Triage® C.difficile	98	99.7
Meridian	Cytclone A+B	86	99
TechLab	Tox A/B	86	100
Bartels	Cytotoxic tissue culture	75	100

Source: Biosite; ASCP; William Blair & Company, L.L.C. estimates

Table 5
Biosite Diagnostics Incorporated
Cardiac Marker Diagnostic Efficiencies

Company	Test	Marker	% Sensitivity*	% Specificity*
Biosite	**Triage® Cardiac**	cTnI	98	100
Biosite	**Triage® Cardiac**	CK-Mb	95	91
Biosite	**Triage® Cardiac**	Mb	81	92
Abbott	**AxSYM**	cTnI	83.3	94.3
Dade	**Stratus**	cTnI	83.3	98.9
First Medical	**Alpha Dx**	cTnI	93	94
First Medical	**Alpha Dx**	CK-Mb	90	90
First Medical	**Alpha Dx**	Mb	71	83

* Peak concentrations in CCU at time of presentation
Source: American Associaton of Clinical Chemistry;
William Blair & Company, L.L.C. estimates

Table 6
Biosite Diagnostics Incorporated
Parasite Immunoassay Comparison

Test Method	Parasite	% Sensitivity	% Specificity
Biosite Triage® Parasite	Giardia	95	88
Biosite Triage® Parasite	Entamoeba	91	85
Biosite Triage® Parasite	Cryptosporidium	91	98
Microscopic Examination	Giardia, Entamoeba, Cryptosporidium	62	NA

Source: Biosite; William Blair & Company, L.L.C. estimates

Internal Controls Simplify Testing

Biosite's products incorporate internal controls into each single-use device. Positive and negative controls greatly simplify the testing procedure, eliminating many external-control samples that typically have to be run with each test to ensure accurate results. In addition to simplifying the procedure, these internal controls can save costs by eliminating the additional reagents, labor, and time needed to run external controls. These controls also satisfy the various quality-control requirements that often have to be run to be compliant with the various federal and state regulations, as discussed further in appendix C.

Small Size Adds to Convenience

Each member of the Triage® product line is small. The Triage® DOA, *C. difficile,* and Parasite panels are self-contained, disposable devices—each the size of a credit card. Incorporated into each of these tiny packages may be up to eight analytes, plus two controls. This allows for the simultaneous testing of up to eight substances in one test. Results are relayed visually, yielding a yes/no answer.

Triage® Cardiac actually is two components—a single, disposable cartridge, and a fluorescent meter the size of a small answering machine. Up to six analytes may be detected and quantified simultaneously. The meter's small footprint allows it to be placed either directly in the ED or in central labs that often are cluttered with equipment. Competing machines are large desktop models that rob precious space in already cramped quarters. Quantitative results can be read directly off the Biosite meter, printed, or transferred into a computer file for use with Biosite patient-management software or other information systems already in place in the hospital.

Another important aspect of the convenient size is the subsequent price afforded to customers. The list price of the Triage® Cardiac meter is $3,500 compared to the almost 10 times greater list price of $30,000 for the competing, and much larger, Stratus CS system from Dade-Behring.

Appropriate Panels Enhance Utility and Acceptance

Biosite has chosen to include tests in the Triage® panel assays that maximize the usable information delivered to the caregiver. Tests are grouped into panels that make the most sense for the triaging situation. In the case of Triage® Parasite, the three most likely causative agents of severe gastric distress—Cryptosporidium, Entamoeba histolytica, and Giardia—are ruled in or out with a single sample.

The Triage® DOA Panel has been modified to offer five-, seven- and, eight-panel tests. The ExpressTest® five-panel test had been created to cater to the growing workplace-testing market. The eight-panel test was modified to include Tricyclic Antidepressants (TCA), which previously required separate tests. The additions of Triage® DOA+TCA and ExpressTest® demonstrate the ability to modify the Panel platform to satisfy shifting market needs and expand the market opportunity.

Tests also may be grouped to cater to doctors' opinions of proper treatment protocols. The discovery of the Troponin I, a more definitive marker of myocardial death, offers doctors more accurate information that has significant prognostic value 30 days post presentation to the ED of future cardiovascular events. Yet, doctors and hospitals may use various combinations of the three cardiac markers. Biosite has included all three markers (MB, CK-MB, and Troponin I) into Triage® Cardiac to satisfy the needs of these doctors. The three-marker panel also fits into the current reimbursement scheme, allowing hospitals to test for and receive payment for these three markers.

Choice of Platform Allows for Most Appropriate Information

Biosite has two product platforms from which it can develop and manufacture products—the Triage® Panel and the Triage® Meter. To echo previous discussions of these products, the Panels offer rapid, qualitative (yes/no) diagnostic answers in simple, self-contained and single-use credit card-sized devices, while the Meter provides rapid, quantitative results. In some situations, a qualitative answer might serve to diagnose correctly, such as the use of illicit drugs. In other instances, where the diagnostic takes on more of a monitoring function, quantitative answers might be preferred. Such is the case in the triaging of AMI, where changes in cardiac markers over time are used to rule in or rule out patients suspected of having suffered a heart attack. NeoralCheck®, a product currently under development, uses the Meter platform to monitor the concentration of the drug Cyclosporin in organ-transplant patients. With two platforms, Biosite is better able to serve the medical community compared to competitors offering a single platform.

Targeted Cardiac and Microbiology Markets Linked to DOA Success

Biosite's excellent record with Triage® DOA should enable the company to successfully launch its three new products—Triage® Cardiac, Triage® C. difficile, and Triage® Parasite. Biosite's Triage® DOA currently is used in 45% of U.S. hospitals, representing 35% of sales and 30% of units sold to perform rapid assays. We believe that the penetration of the DOA market with an industry-leading product has provided the company with a superior understanding of the triaging processes (patient sorting and disposition) and culture in which these tests are conducted. Central laboratories control the flow of diagnostic information in hospitals, even in settings where point-of-care testing has been instituted. By targeting the central lab as the key customer for its diagnostic products, Biosite has been able to develop relationships with both customers and distributors that should foster the growth of the Triage® franchise.

With recent surveys indicating 90% of labs have undergone some form of consolidation in the last 5 years, and 64% of labs experiencing staff cuts, central-lab managers are under pressure to improve operations, improve turnaround time, and reduce costs. Biosite's products offer solutions to these issues. Biosite's Triage® Cardiac, Triage® C. difficile, and Triage® Parasite are products designed as replacements for tests currently conducted in central lab environments. They present users with very simple procedures, followed by rapid and highly accurate results. This should be of no surprise to lab personnel familiar with Triage® DOA, since this high-quality product already delivers the promised improvements. The leveraging of existing relationships and customers' positive experience with the Triage® DOA line should allow Biosite to generate sales of its two new product lines.

Triage® Micro Uses Same Proven Qualitative Platform as Triage® DOA

The new microbiology product line is based on the proven platform technology used in the popular Triage® DOA Panel line. These credit-card-sized immunoassays afford users many advantages over current methods of microbiology testing. As previously illustrated in figures 6 and 7, only a few steps are required to get results from this platform, greatly reducing the turnaround time, while reducing lab personnel's exposure to patient stool samples at the same time. As an immunoassay, the Triage® Micro line offers unparalleled accuracy. Table 4 illustrates the diagnostic characteristics of the Triage® C. difficile compared to similar immunoassay-based products. This data is striking considering the fact that cytotoxic tissue culture, the gold standard for *C. difficile* testing, may miss up to 25% of true positives, even in the hands of a skilled lab technician.

Like the Triage® DOA line, the Triage® Micro products are capable of measuring the presence of multiple analytes, allowing a single panel to test for various potential symptom causes. This feature gives lab personnel the ability to extract as much information as possible from a single sample. Using the Triage® C. difficile as an example again, a single test determines not only the presence of *C. difficile,* but also determines if the strain of bacteria present is the disease-causing agent. The Triage® Panel line also incorporates internal controls that ensure the integrity of the information while eliminating extra steps and measures. Lastly, easy-to-read results eliminate guesswork from the process. We expect these features to encourage labs to conduct once difficult and time-consuming tests onsite, holding much promise for future Biosite tests.

Fisher Salesforce Has Good Access to Emergency, Central Laboratory, and Microbiology Departments

Fisher Scientific, one of the world's leading distributors of research-related products, has been the distributor of Biosite's products in the United States since 1991. Fisher's largest source of revenue is the scientific research supply market, estimated to be $5 billion in 1997. The second-largest revenue source for Fisher is the U.S. clinical laboratory testing market, estimated to be approximately $31 billion in 1998. The clinical equipment and supply submarket, the area that encompasses Biosite's product offerings, was estimated to be a $6 billion subset. Offering more than 245,000 products, Fisher readily takes care of the needs of its customers and offers numerous methods through which to do business with them, including direct sales, catalogue sales, and Web-based procurement.

Fisher's overall customer service organization consists of more than 2,000 technically trained representatives; the direct salesforce comprises 1,000 account representatives. More specifically, 180 representatives from Fisher's Curtin Matheson Scientific division are responsible for the sale of Biosite's product line to hospitals and commercial labs in the United States. These salespeople actively call on the different lab areas within the hospital, including the central, STAT, and microbiology labs. These representatives report directly to one of the 25 Biosite direct salespeople distributed across the country. With a combined sales effort of 210 people, which includes 3 regional managers and 2 national account representatives, Biosite is poised to penetrate EDs and microbiology labs with its recently expanded product line.

Flexible Technologies Offer Excellent Platforms for Growth

Biosite's collection of flexible technologies should provide new product opportunities and fuel growth into the future. A combination of two rapid platforms, the ability to use three quite different sample types, a unique antibody development and production method, low costs of goods, and low development costs for new tests should allow the company to reaccelerate its historically strong performance.

Rapid Qualitative and Quantitative Platforms Provide Foundation to Exploit Unserved Markets

Biosite actively is developing new diagnostic tests based on both the panel and meter platforms to fully leverage its competitive advantage in R&D, as well as build upon the high-quality reputation that its products carry in the marketplace.

Based on the qualitative Panel platform, the Triage® Enteric Panel currently is under development. It is designed to test for the presence of a group of bacteria (members of the Enteric family) that are responsible for gastrointestinitis, or "food poisoning." Triage® Enteric will test for disease-causing agents like salmonella, shigella, campylobacter, and the infamous E. coli 0157:H7. With more than 6 million cases of food-born disease each year and more than 3.5 million time-consuming stool cultures conducted for these cases in the United States, the market for a rapid diagnostic for this area is long overdue. Globally, we estimate that a market exists for 4 million of these tests (the current number of tests are higher than would be necessary using Triage® due to the need to repeat unsuccessful cultures), translating into a potential $100 million markets in both the United States and the rest of the world.

The meter platform provides quantitative results that allow monitoring of the amount of substances in the body over time. Biosite had identified and put into development three diagnostic tests that seek to take advantage of the monitoring ability of the meter platform—NeoralCheck®, Triage® LBP, and Triage® BNP.

NeoralCheck® is being developed jointly by Biosite and Novartis. Organ-transplant patients are required to take the drug Cyclosporin, an immune-system suppressor that prevents organ rejection. Cyclosporin, sold by Novartis, with a generic drug recently introduced by Sangstat, is dosed variably to maintain a concentration of the drug known as the patient's "therapeutic window." The therapeutic window is defined as the level of drug that allows sufficient suppression of the immune system while not exceeding a level in which it becomes toxic. Medication noncompliance is a frequent problem among transplant patients, ranging from 5%-47% of that population. Inconvenient dosing and complex regimens are reasons often cited for noncompliance. This noncompliance greatly reduces the success rate and life expectancy of transplant recipients. Antibodies licensed from Novartis will allow for the development of an assay to monitor the concentration of cyclosporin in the patient's blood easily. This system should allow patients to keep themselves within the therapeutic window, aiding medical compliance. With more than 20,000 transplants performed in the United States alone, and with more than 300,000 surviving transplant patients worldwide, there appears to be an ample opportunity to serve another ripe market. We estimate that the total United States/European market for these tests is estimated at 5 million tests annually, a $125 million market.

Triage® LBP also is under development using the flexible Meter platform. Triage® LBP is intended to measure levels of circulating lipopolysaccharide binding protein (LBP) to detect sepsis prior to septic shock—a life-threatening condition. LBP is released in response to infections of the blood by the bacteria that cause sepsis or endotoxemia. Sepsis is characterized by an inflammatory reaction, causing widespread blood-vessel damage. If left unchecked, this damage could lead to toxic septic shock, organ failure, gangrene, and possibly death. Such a diagnostic tool would enable doctors to discern endotoxin-related cases from those of other diseases with similar symptoms. New treatments for sepsis under development by biotechnology companies have not proved successful, and a powerful diagnostic may provide the key missing component to success. The necessary technologies and patents for the development of Triage® LBP have been licensed from XOMA Corporation.

Lastly, Triage® BNP is being developed as a diagnostic for congestive heart failure (CHF). Elevated levels of B-type natriuretic peptide (BNP) have been implicated as an indicator of CHF in both symptomatic and asymptomatic patients. Quantitative measures of circulating BNP should enable physicians to better diagnose CHF and provide the proper interventional therapy. Biosite has licensed technology and patents from Scios, Inc. for the development of this assay. Other licensees include Abbott Laboratories, Bayer AG, and Shionogi & Co.

Technologies Applicable to Three Sample Sources

Biosite's technologies can be used for the testing of analytes from three sample sources—whole blood, urine, and stool. This allows the company to leverage its platforms to relevant analytes regardless of the specimen's source. To illustrate, the Triage® DOA uses a urine sample to test for illicit drugs, while the Triage® C. difficile, based on the same platform as Triage® DOA, uses a stool sample to test for the presence of the disease-causing bacteria *Clostridium difficile*. Lastly, Triage® Cardiac uses whole blood.

Phage-display Technology Allows for Rapid Assay Development

Immunodiagnostic companies can be judged by the efficiency with which they generate stable and specific antibodies, which is a difficult and costly process. Traditional methods use hybridoma cells for the development and production of specific antibodies, as discussed in appendix A. This process is expensive and time-consuming—taking up to a year—and often ends in frustration. Biosite has implemented a group of technologies collectively known as phage display for antibody development and production. This new process allows the development of antibodies for a fraction of the cost and in one-tenth of the time associated with the old hybridoma method. Phage display's efficiency, coupled with "Directed Evolution" technologies licensed from Ixsys, allow scientists at Biosite to refine antibodies easily, yielding products of higher specificity and quality. With this core competency, Biosite is able to capitalize on opportunities as they arise. It also allows the company to license inferior antibodies and quickly improve them for use in new products.

Robust Technology Coupled With Efficient Manufacturing Equals Low Cost

Biosite's flexible, robust technology platforms have allowed it to maintain COGS and new-product development costs that are well below IVD industry standards. Efficient antibody-production techniques using the phage-display technique allows Biosite to produce gram quantities for hundreds of dollars, versus competitors who pay thousands using less-efficient methods. The company's focus on streamlining manufacturing processes has yielded a 2% scrap rate for its current Triage® DOA product line. Applying the Panel and Meter platforms to many applications will let Biosite maintain a minimum number of manufacturing lines, further reducing costs. Development costs for both of Biosite's platforms are extremely low. The company estimates that the Triage® DOA Panel platform cost $5 million to initially develop, while the Triage® Cardiac Meter platform cost $20 million. Expansion of the product line on current platforms is estimated to cost between $3 million-$5 million, with an additional $500,000 to file and receive the proper FDA approval.

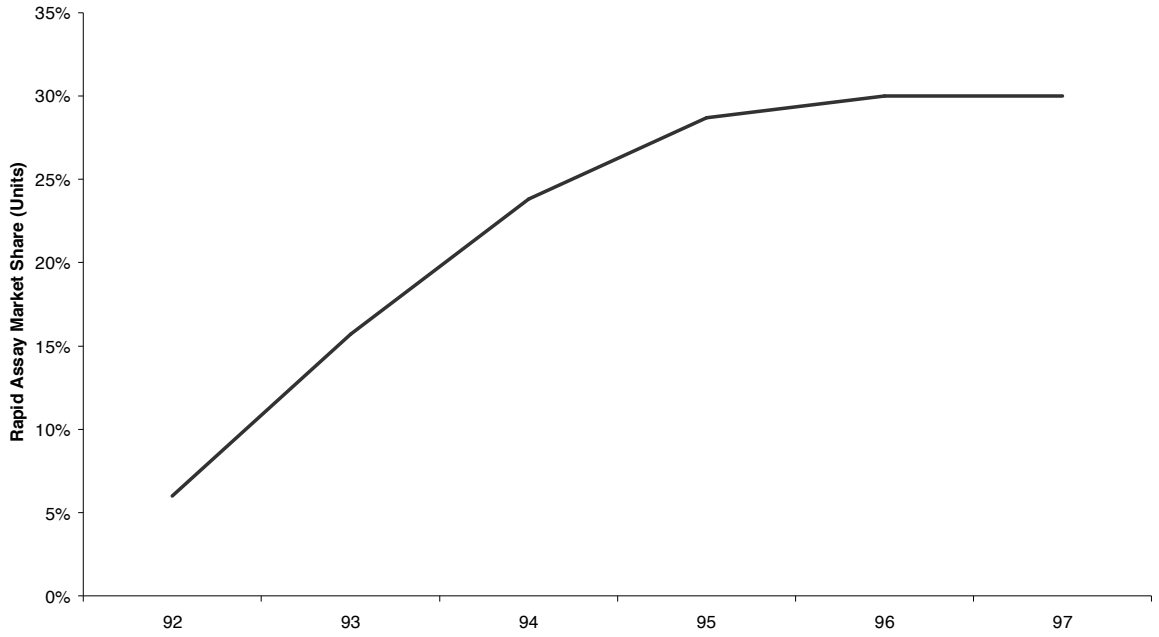
Superior Company Management

Biosite possesses a senior management team that not only has demonstrated the ability to create and sell successful products, but also has the necessary foresight to cultivate future growth opportunities. The team has a successful record with Biosite—as proven through the Triage® DOA achievements—as well as notable accomplishments with its members' previous employers. In addition, the team has associated itself with high-caliber sales-and-distribution partners. Lastly, we believe that the team has shown the high-quality strategic thinking necessary to be successful in its chosen markets.

Successful Triage® DOA Record

Biosite commenced sales of Triage® DOA in 1992. As shown in figure 8, Biosite quickly expanded an initial market share from 6% of rapid-assay units sold in the United States in 1992 to 30% of all units sold in 1997. This translates into 35% of the dollars spent on rapid DOA testing kits and placements in 45% of hospitals. In 1995, the Triage® DOA product line was expanded to include the higher-priced Triage® DOA+TCA. The addition of a convenient test to Tricyclic antidepressants further expanded the utility of Biosite's tests. Triage® DOA+TCA quickly accounted for 38% of the revenue mix, reaching 50% in 1997. An additional five-drug test, the ExpressTest®, was added to expand the reach of the Triage® DOA franchise into the growing workplace-screening market.

Figure 8
Biosite Diagnostics Incorporated
Triage® DOA Market Penetration



Source: Biosite; William Blair & Company, L.L.C. estimates

Strong Senior Management Team

Biosite's current senior management brings together a wealth of successful experience in the in vitro diagnostics industry. As mentioned, the company's founders, CEO Kim Blickenstaff, Vice President of Research and Development Gunars Valkirs, and Vice President of Research Ken Buechler all came from Hybritech, one of the early monoclonal antibody biotechnology companies from the 1980s. Mr. Valkirs was the primary inventor of Hybritech's ICON technology, which quickly became a standard method of pregnancy screening in doctors' offices. In 1986, Hybritech was acquired for by pharmaceutical giant Eli Lilly for $300 million and later was sold to Beckman Coulter. In 1988, Messrs. Blickenstaff, Buechler, and Valkirs left Hybritech to start Biosite.

In addition, other members of senior management possess a great deal of experience as well. Thomas Watlington, senior vice president, joined Biosite after 14 years at Boehringer Mannheim Corporation, now part of Roche Holding AG. At Boehringer, he was vice president of marketing for the diabetes care business unit that supplies rapid assays for the home monitoring of blood glucose. Chief Financial Officer Christopher Twomey joined Biosite in 1990 after a 9-year tenure at Ernst & Young as an audit manager. Nicholas Stiso, vice president of operations since 1989, comes to Biosite from Syntex Medical Diagnostics

(now part of Dade-Behring), where he was manufacturing director for a line of quantitative therapeutic drug assays. Christopher Hibberd, Biosite's head of business development, brings Biosite experience in value-creating strategies acquired from time at the Boston Consulting Group and as a development engineer at Albright & Wilson Americas, an international chemical and engineering concern. Charles Patrick, Biosite's vice president of sales and marketing rounds out the management team with experience from Abbott Laboratories, where he was a manager for their abused-drugs business.

High-caliber Sales Partners

Biosite's 30 person-strong direct salesforce is complemented by several strong partners. Table 7 explains Biosite's key relationships. Biosite began its successful relationship with Fisher Scientific in 1991. As a world-leading distributor of research products to the $30 billion U.S. market for clinical laboratory, Fisher has been a powerful ally. Fisher's 180 representatives assigned to selling the Triage® product line report to the company's direct salesforce and have enabled wide dissemination of Biosite's products across the United States, exemplified by the fact that 45% of treatment sites use Triage® DOA. Partners Merck KGaA in Europe and ARKRAY KDK in Japan have generated increasing international sales (9% in 1997). These partners also have helped fund the development of the Triage® Cardiac in exchange for distribution rights, thereby decreasing Biosite's R&D expenditures.

Table 7
Biosite Diagnostics Incorporated
Alliances

Date	Partner	Nature	Financial Payments
11/91	Curtin Matheson Scientific (as of 1995 a division of Fisher Scientific)	Distribution of products in the United States	NA
7/92	Merck kGaA	Distribution agreement for certain countries in Europe, Latin America, Asia, the Middle East, and Africa	NA
9/94	Merck kGaA	Collaborative agreement for the development and distribution of Triage® Cardiac	40% of development costs, as well as European regulatory costs
9/94	LRE Relais + Elektronik GmbH	Triage® Cardiac Meter development and manufacturing	Biosite to pay up to $1.9 million for the development
2/95	ARKRAY KDK	Development and distribution agreement for Triage® Cardiac in Japan	$2 million for development
9/95	Novartis	Two licensing agreements for the development of NeoralCheck®	$1.5 million investment in Biosite
3/97	Xoma	Licensed LBP for sepsis diagnosis	NA
3/97	Scios	Licensed cardiac hormone BNP for CHF diagnosis	NA

Source: Biosite; William Blair & Company, L.L.C. estimates

Revision of Biosite's European sales-and-distribution strategy due to a change in Merck KGaA's market focus has led the company to amicably reacquire distribution rights from Merck KGaA and form agreements with a list of aggressive new partners (listed in table 8). Of particular note is Biosite's new U.K. partner, Shield Diagnostics. An established diagnostics

development and distribution company, Shield has a core portfolio of more than 60 products in 230 kits. Shield is particularly well-suited for the distribution of Triage® Cardiac since it currently is developing the Afecta (Activated Factor XIIa) test, a predisposition test for cardiovascular disease.

Table 8
Biosite Diagnostics Incorporated
Worldwide Sales Distribution

Country	Distribution Partner	Sales Reps	Start Date
United States	Fisher Scientific	180	November-91
Germany	Viva Diagnostika	7	November-98
France	Biomedical Diagnostics S.A.	10	November-99
United Kingdom	Shield Diagnostics	12	December-98
Italy	*		
Spain	*		
Japan	ARKRAY KDK Corp.		March-95
Rest Of World (R.O.W.)			

* By end of 1998

Source: Company reports; William Blair & Company, L.L.C. analysis

The competition appears to be in a quandary as to how to establish successful distribution channels for its products. While Biosite has been able to establish successful partnerships and expand its direct effort from the start, others have vacillated between distribution strategies. Spectral Diagnostics, a developer of a qualitative cardiac-marker diagnostic that competes with Triage® Cardiac, initially entered into a distribution agreement for the United States with Baxter Diagnostics. Baxter sold its diagnostics business to Dade International, who was responsible for the disappointing launch of Spectral's products in 1995. Dade soon terminated its agreement with Spectral, leading the company to form a subsidiary, CarePoint Cardiac Corporation, for distribution of tests to the United States. As another example, Roche chose to stop pursuing selling and distributing its Frontline® DOA rapid assays itself in the United States. Instead, Roche sold off the U.S. rights while keeping those outside the United States, even though it predominantly is a U.S. market.

Strategic Thinking Leads to Growth

Biosite's senior management team has demonstrated by several actions that early strategic thinking leads to future profitable growth opportunities and competitive flexibility. The team has recognized the need for growth and has developed additional product platforms to maintain it; the team has assessed complex buying processes and correctly pursued pivotal customers and influencers; and it has reacquired its European distribution rights to pursue that market more aggressively.

Platform development to fuel growth. Upon launch, Biosite's Triage® DOA panel was a success, with sales growing at a compounded annual growth rate of 200% from 1992 to 1995. However, sales grew only 12% compounded annually from 1995 to 1997, as the overall market growth slowed and Biosite's share gains were more hard-fought. Rather than resting on its laurels, Biosite initiated the development of Triage® Cardiac in 1994, when the company recognized early that it might fall victim to its own success. It began work on a quantitative meter platform that could be used to monitor changes in analytes over time, adding a new dimension of functionality to Biosite's product line. This new quantitative platform, a complement to the existing qualitative platform used in the drugs of abuse and microbiology products, would provide new growth opportunities in the form of Triage® Cardiac, NeoralCheck®, Triage® LBP, and Triage® BNP.

Central lab as key customer. Although the need of point-of-care testing (POCT) is theoretically accepted, one should understand the great paradigm shift that must occur to make such testing feasible. Biosite clearly recognized these issues. Early investments to determine the critical adoption process have led the company to focus on the hospital central lab as its primary customer. It is this understanding that has allowed Biosite to succeed in the sale of Triage® DOA. Importantly, Biosite's products are designed to fit into the workflow of either the central lab or POCT environment. Thus, as the eventual switch to POCT occurs, the company's products also will be able to make the switch.

Reacquisition of European sales rights. Biosite reacquired its European distribution rights from Merck KGaA in for $3.3 million in the fourth quarter of 1997. The reacquisition has allowed Biosite to revise its European strategy. Planning to considerably expand the European market, Biosite has chosen aggressive new European partners that will sell the entire Triage® product line. We estimate that the annual European market for Biosite's current line of products is $660 million. The new partners and their respective territories are listed in table 8.

Forty-percent Long-term EPS Growth Forecast

We estimate that Biosite's earnings per share will grow at more than 40% per year over the next 3-5 years. This EPS growth should be driven primarily by increasing revenue, supported by high margins and declining expenses as a percentage of sales. In addition, both the balance sheet and cash flow should support this growth, even as they also strengthen. Tables 8 through 11 contain our financial models, including quarterly and annual income statements, annual product-line revenue forecasts, annual balance sheets, and annual cash flow statements. Below is a more-detailed discussion of both these models and the financial drivers in the context of forecast EPS growth.

Revenue Growth Should Accelerate to More Than 30%

We believe that revenue growth again should accelerate for Biosite as new products penetrate the market. As shown in figure 9, on the next page, we expect revenue growth to increase from an estimated 8% in 1998 to 16% in 1999, 30% in 2000, and 36% in 2001. Even without more new product lines already in development, the company should be able to sustain revenue growth greater than 20% through at least 2003.

Biosite's revenue growth is being driven by its introduction of the new product lines, Triage® Cardiac and Triage® Micro. As shown in table 9, on page 28, we expect combined sales of the new product lines to grow from an estimated $1.4 million in 1998 to $16.2 million in 2000. Furthermore, we foresee sales of these products to be $74.4 million five years from now, in 2003. If events unfold as we anticipate, figure 10, on the next page, illustrates that by 2003, these products will make up about 65% of Biosite's sales. Through this period, we forecast that Triage® DOA revenues will be almost flat, as it already has such a large share of the U.S. market, which is the dominant market worldwide.

Because Triage® Cardiac clearly is the most important driver of revenue growth in our forecast, we have included a copy of our instrument-placement model in table 10, on page 30. As the table shows, we estimate that Biosite will have a total of 220 instruments placed by the end of 1999 and 558 by the end of 2000. These will have used, on average, about 22 kits per placement in 1999 and 28 kits per placement in 2000. We believe that by 2003, the company will have almost 1,500 placements, and the average annual kit usage per placement will be 79. There are 25 quantitative test panels per kit, so this equates to almost 2000 cardiac-marker panels per placement.

Figure 9
Biosite Diagnostics Incorporated
Annual Revenues and Growth Rate
($ in millions)

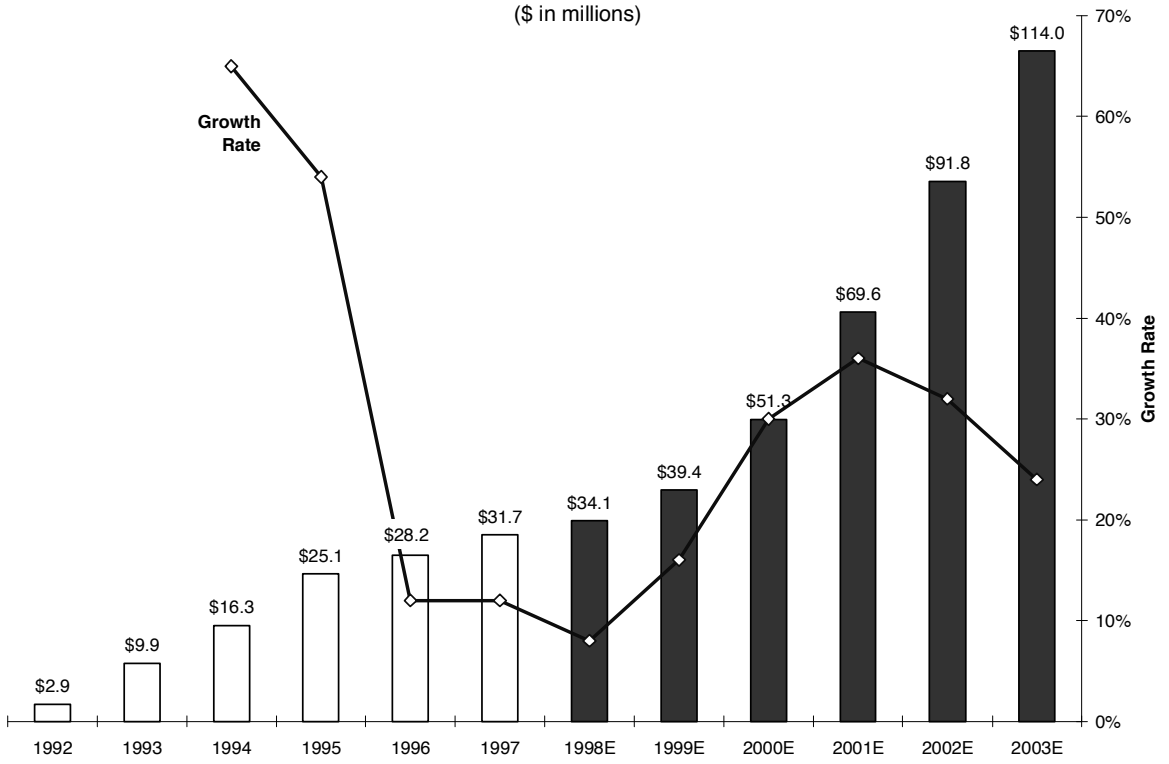


Figure 10
Biosite Diagnostics Incorporated
Revenue MIx

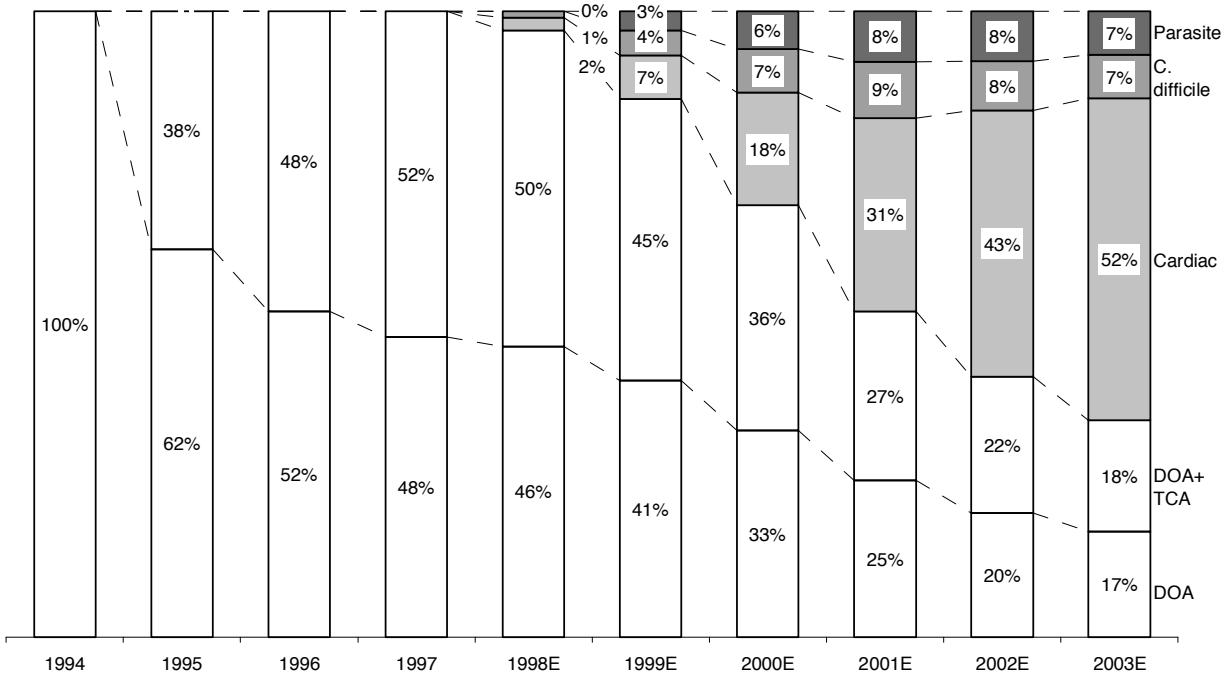


Table 9
Biosite Diagnostics Incorporated
Product Line Analysis

Annual sales

(In Thousands)		1992	1993	1994	1995	1996	1997	1998 E	1999 E	2000 E	2001 E	2002 E	2003 E
Triage® Panels													
	DOA	$ 2,920	$ 9,866	$ 16,320	$ 15,591	$ 14,667	$ 15,205	$ 15,664	$ 16,210	$ 16,868	$ 17,553	$ 18,265	$ 19,007
	DOA+TCA				$ 9,556	$ 13,539	$ 16,472	$ 16,970	$ 17,560	$ 18,273	$ 19,015	$ 19,787	$ 20,591
	C.difficile							$ 482	$ 1,583	$ 3,818	$ 5,947	$ 7,082	$ 7,893
	Parasite							$ 150	$ 1,193	$ 3,229	$ 5,404	$ 6,977	$ 7,628
Triage® Meter	Cardiac							$ 802	$ 2,875	$ 9,123	$ 21,646	$ 39,720	$ 58,922
Total Sales		$ 2,920	$ 9,866	$ 16,320	$ 25,147	$ 28,206	$ 31,677	$ 34,068	$ 39,420	$ 51,310	$ 69,565	$ 91,831	$ 114,041

Annual Growth

		1992	1993	1994	1995	1996	1997	1998 E	1999 E	2000 E	2001 E	2002 E	2003 E
Triage® Panels													
	DOA Total		238%	65%	54%	12%	12%	3%	3%	4%	4%	4%	4%
	DOA		238%	65%	-4%	-6%	4%	3%	3%	4%	4%	4%	4%
	DOA+TCA					42%	22%	3%	3%	4%	4%	4%	4%
	C.difficile								228%	141%	56%	19%	11%
	Parasite								695%	171%	67%	29%	9%
Triage® Meter	Cardiac								259%	217%	137%	83%	48%
Total Sales			238%	65%	54%	12%	12%	8%	16%	30%	36%	32%	24%

% of Sales

		1992	1993	1994	1995	1996	1997	1998 E	1999 E	2000 E	2001 E	2002 E	2003 E
	DOA Total	100%	100%	100%	100%	100%	100%	96%	86%	68%	53%	41%	35%
	Micro Total	0%	0%	0%	0%	0%	0%	2%	7%	14%	16%	15%	14%
	Cardiac Total	0%	0%	0%	0%	0%	0%	2%	7%	18%	31%	43%	52%
	Total	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%

Cost of Goods

		1992	1993	1994	1995	1996	1997	1998 E	1999 E	2000 E	2001 E	2002 E	2003 E
	DOA Total	55%	33%	27%	22%	21%	22%	22%	21%	20%	19%	19%	19%
	Micro Total							235%	96%	43%	34%	29%	26%
	Cardiac Total							288%	128%	66%	48%	37%	30%
	Total	55%	33%	27%	22%	21%	22%	32%	34%	31%	31%	28%	26%

Source: Company financials; William Blair & Company, L.L.C. estimates

Placement assumptions. We estimate that cardiac-marker panels will eventually be used in about 4,000 hospitals in the United States, generating about 12 million tests annually. Furthermore, on the basis of analysis of other IVDs, we believe that this penetration will occur over approximately six years, and at the end of that time Biosite will have almost a 20% market share, or placement in almost 1,000 hospitals. While the market in the rest of the world will eventually be larger than the United States, we estimate that it will be only about half the size during our forecast period, and thus account for only about one-third of Biosite's sales.

Reagent assumptions. When a system is first placed, we estimate that approximately 100 patients are tested over 3 months on both the new system as well as on the existing system or using the existing protocol. After this, we believe that it will take 1 1/2 years for the hospital to fully adopt the new testing protocol in its ED, and 3 years for all of the doctors practicing at the hospital to adopt the protocol. This means that it will take 1 1/2 years to fully realize the initial panel used to screen and a triage patients (one-half of the test volume) and 3 years for all relevant doctors to routinely order the follow-up, serial tests at around 6 and 12 hours after the patient enters the ED (the other half of the test volume)—see appendix B. Lastly, we believe that the laboratory will run parallel testing for about six months, including the three-month initial trial.

Gross Margins Should Remain High

Efficient manufacturing processes and careful use of sophisticated technologies has allowed Biosite to maintain gross margins that are substantially above the industry average of 44%. Historically, gross margins for Triage® DOA, and consequently Biosite as a whole, were almost 80%. However, as the new product lines are being introduced, this overall gross margin is being depressed. This is due to three factors: low cumulative production volume of the new products; substantially higher scrap rates for the new quantitative Triage® Cardiac production than those experienced for the qualitative production lines used to make Triage® DOA and Triage® Micro; and low gross margins associated with the meter. As figure 11, on page 31, illustrates, we believe that the gross margins will decline to a low of 66% in 1999—still much greater than the industry average—increasing back to about 74% by 2003 as Biosite moves down the learning curve, leverages raw material purchases and adds automation in appropriate steps. As production volume of both new product lines increases, the cost of goods will decline. In addition, we expect Biosite to continue to improve the production process used to make the quantitative products, significantly reducing the scrap and rework. Thus far, the company has made reductions from more than 50% to less than 25%, and hopes to achieve the 2% scrap it receives with the qualitative line used to make Triage® DOA. Finally, while meter gross margins likely will improve only modestly as the installed base of meters and kit usage per meter increases (see table 11), the effect of the meters on gross margins will decline considerably.

Operating Leverage Should Lead to a 33% Lower Expense Ratio from 1998 to 2000

We expected Biosite to realize a decline in operating expenses from 90% in 1998 to 61% in 2000. As shown in figures 2 and 12, SG&A expenses as a percentage of sales have increased rapidly in the past few years (with an estimated peak of 44% in 1998) as the company prepared itself for the launch of its new products. This should reverse itself in 1999 as new product sales increase, leading to 39% in 1999 and 36% in 2000. There still is about $1.0 million-$1.5 million needed over the next few years for FDA trials of the new quantitative assays in the pipeline such as NeoralCheck®, or else expenses would improve even faster. There should be even more leverage in R&D. We expect this to grow slowly, as the nominal dollars already are high, and development of the quantitative platform essentially is complete. In addition, R&D costs associated with the start-up of the new products will be mostly completed by year end 1998. Consequently, R&D only should grow from an estimated $11.9 million in 1998 to $13.1 million in 2000, or from 35% of sales to 26% of sales. Both SG&A and R&D expenses are expected to decline as a percentage of sales through 2003.

Table 10
Biosite Diagnostics Incorporated
Triage® Cardiac Sales Model

Quarterly	1998E 4Q98	1999E 1Q99	2Q99	3Q99	4Q99	2000E 1Q00	2Q00	3Q00	4Q00	2001E 1Q01	2Q01	3Q01	4Q01	2002E 1Q02	2Q02	3Q02	4Q02	2003E 1Q03	2Q03	3Q03	4Q03
United States																					
Meters Placed	10	15	20	27	35	47	62	83	110	88	70	56	45	42	39	36	34	30	26	23	20
Cumulative Installations	85	100	120	147	182	229	291	374	484	572	642	698	743	785	824	860	894	924	950	973	993
Number of Kits*	265	600	913	1,293	1,756	2,263	2,767	3,631	4,630	5,713	7,246	9,054	10,652	12,309	13,928	15,467	16,962	18,447	19,956	21,521	23,149
Average Kits / Installed Meter	3.1	6.0	7.6	8.8	9.6	9.9	9.5	9.7	9.6	10.0	11.3	13.0	14.3	15.7	16.9	18.0	19.0	20.0	21.0	22.1	23.3
ROW																					
Meters Placed	-	-	-	13	25	5	8	10	14	18	24	31	42	55	44	35	28	23	21	20	18
Cumulative Installations	-	-	-	13	38	43	50	60	74	91	115	146	187	242	286	321	349	372	393	412	430
Number of Kits	-	-	-	44	133	300	456	647	878	1,131	1,383	1,816	2,315	2,857	3,623	4,527	5,326	6,154	6,964	7,733	8,481
Average Kits / Installed Meter				3.5	3.5	7.1	9.1	10.8	11.9	12.4	12.1	12.5	12.4	11.8	12.7	14.1	15.3	16.6	17.7	18.8	19.7
Total																					
Meters Placed	10	15	20	40	60	52	70	93	124	106	94	87	87	97	83	71	62	53	47	43	38
Cumulative Installations	85	100	120	160	220	272	341	434	558	663	757	844	930	1,027	1,110	1,181	1,243	1,296	1,343	1,385	1,423
Number of Kits	265	600	913	1,337	1,888	2,563	3,223	4,278	5,507	6,844	8,629	10,870	12,967	15,165	17,551	19,994	22,288	24,601	26,920	29,254	31,630
Average Kits / Installed Meter	3.1	6.0	7.6	8.4	8.6	9.4	9.5	9.9	9.9	10.3	11.4	12.9	13.9	14.8	15.8	16.9	17.9	19.0	20.1	21.1	22.2
Annually																					
United States																					
Meters Placed					97				302				259				151				99
Cumulative Installations					182				484				743				894				993
Number of Kits					4,561				#####				32,665				58,665				83,073
Average Kits / Installed Meter					25.1				27.5				44.0				65.6				83.7
ROW																					
Meters Placed					38				36				114				162				81
Cumulative Installations					38				74				187				349				430
Number of Kits					177				2,281				6,645				16,333				29,333
Average Kits / Installed Meter					4.7				31.0				35.5				46.8				68.2
Total																					
Meters Placed					135				338				373				313				180
Cumulative Installations					220				558				930				1,243				1,423
Number of Kits					4,738				#####				39,310				74,998				112,405
Average Kits / Installed Meter					21.6				27.9				42.3				60.3				79.0

* Each kit contains 25 tests, with each test consisting of a 3 marker panel.

Source: William Blair & Company, L.L.C. estimates

Figure 11
Biosite Diagnostics Incorporated
Gross Margins

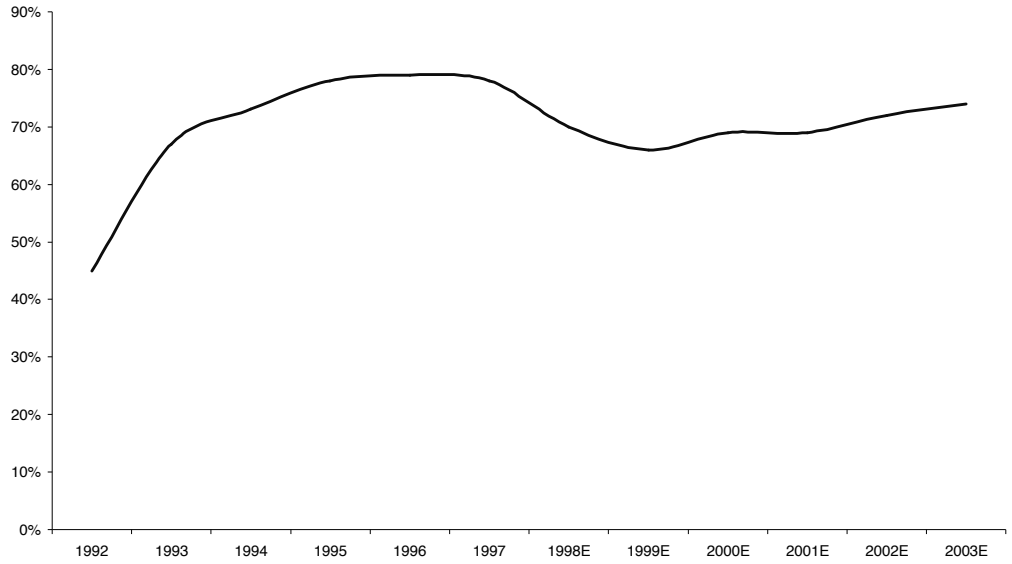
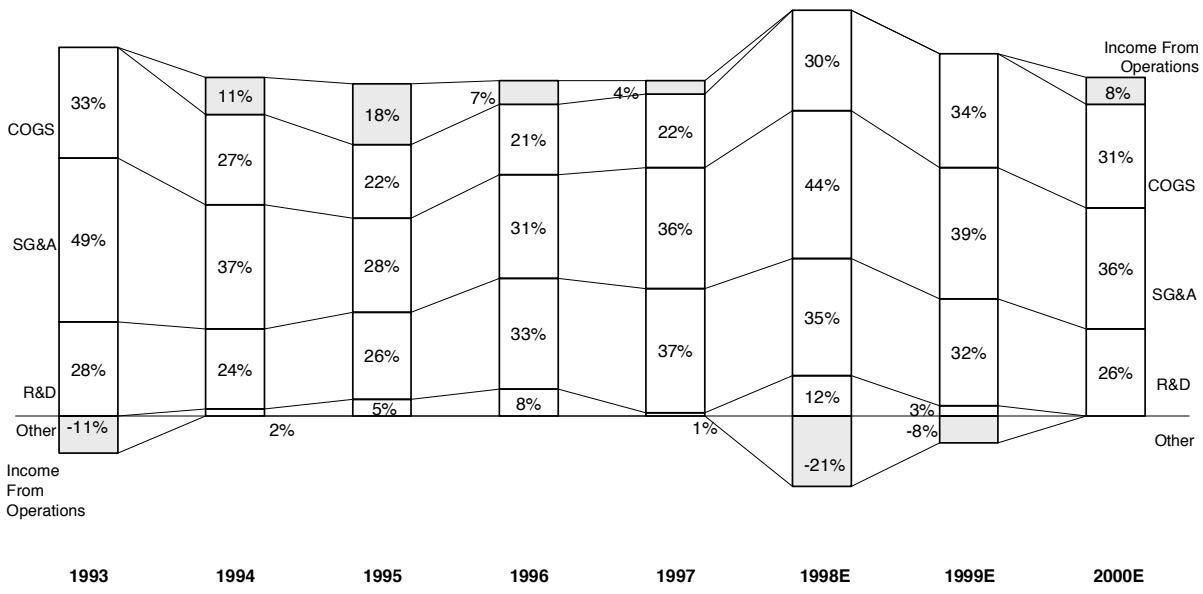


Figure 12
Biosite Diagnostics Incorporated
COGS and Operating Expense



Source: Biosite financials; William Blair & Company, L.L.C. estimates

Legal Expenses Should Decline Considerably

We anticipate that Biosite's legal expenses will drop significantly as progress is made in its two legal conflicts. The suit against Biosite by Spectral Diagnostics over patent issues surrounding the Triage® Cardiac has entered settlement negotiations, and management expects resolution. Litigation with Dade-Behring also has slowed. A trial date for summary judgement for a case surrounding the Triage® DOA product has been pushed out into the second half of 1999. This not only delays any related legal expenses but also brings the case closer to the expiration of the patent being disputed. We estimate that Biosite will

spend $1.2 million in 1999 and a negligible amount after that. The possible range of 1999 expenses is about $200,000 to $2 million, depending on the eventual resolution of the two cases.

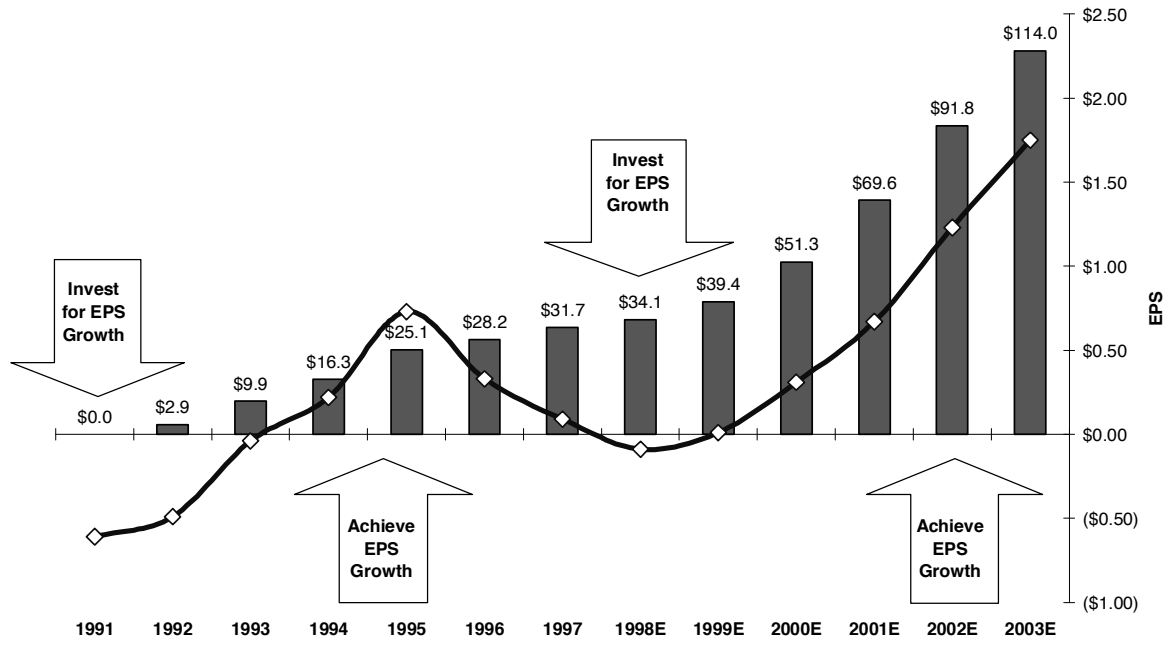
Tax Rates Should Increase Significantly Due to Increasing Profit

As Biosite again returns to healthy profitability, it will begin to incur higher taxes. Thus, we still expect a net tax benefit in 1999, but a tax rate of 33% in 2000. By 2003, we expect the effective tax rate to be 40%. A mitigating factor that should help is the various R&D tax credits the company currently is permitted. If these are not renewed over time, the tax rate would rise more quickly than our estimates, up to a maximum of 41%.

Per-share Earnings Should Grow Substantially After the Company Again Breaks Even in the First Half of 1999

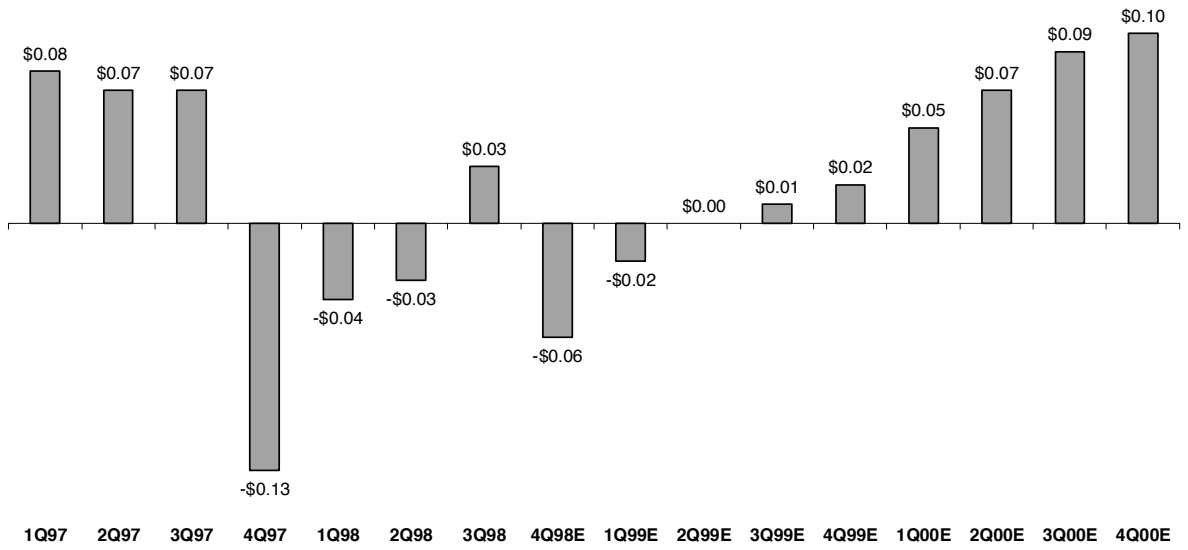
We expect that the net result of revenue growth and improvements in expenses should be a reacceleration of EPS growth for Biosite. Figure 13 provides the overview of this effect from 1991 through 2003, with figure 14 detailing the next few quarters through 2000. As shown in these figures, we estimate that EPS will grow at high double- and triple-digit rates, settling in at about 40% growth in 2003.

Figure 13
Biosite Diagnostics Incorporated
Annual Revenue and EPS
(sales in millions of dollars; EPS in dollars)



Source: Biosite financials; William Blair & Company, L.L.C. estimates

Figure 14
Biosite Diagnostics Incorporated
Quarterly EPS
($ Per Share)



Source: Biosite financials; William Blair & Company, L.L.C. estimates

Balance Sheet and Cash Flow Should Support Revenue and Earnings Growth

Both the balance sheet and cash flow should support this EPS growth because they also should strengthen. Only about 8% of the company's total capitalization is made up of debt; it maintains almost $38 million in cash, equating to about 57% of total capitalization and almost $3 per share in cash. While Biosite will use an estimated $700,000 in operating cash in 1998 and $3 million net of investment, we estimate that it will generate about $200,000 from operations in 1999, and more than $4 million in 2000. These equate to a use of about $3 million in 1999 net of investment and $2 million in 2000. Preliminary estimates show the company generating more than $20 million in cash from operations in 2003, resulting in a positive $10 million, net of investing activities. (See tables 11-13 on the following pages.)

Attractive Valuation Today

We believe that Biosite shares are undervalued. Our valuation exercises involved the analysis of 44 publicly traded in-vitro diagnostic companies. This group was divided into five sectors: Rapid Diagnostics, Lab Diagnostics, Cytology, Molecular Diagnostics, and Miscellaneous, with Biosite fitting into Rapid Diagnostics. Table 14 provides data on the entire group. Lack of sufficient coverage of this group, and consequently, the lack of reliable First Call earnings estimates, has led us to expand our analysis beyond EPS multiples and growth rates. In addition to these traditional measures, we analyzed price relative to revenues and cash per share, as well as gross margins as a measure of sustained earnings potential.

Table 11

Biosite Diagnostics Incorporated

Income Statement

(Dollars in Thousands)	1997 Mar-97	Jun-97	Sep-97	Dec-97	1997	1998 Mar-98	Jun-98	Sep-98	E Dec-98	1998	1999 E Mar-99	Jun-99	Sep-99	Dec-99	1999	2000 E Mar-00	Jun-00	Sep-00	Dec-00	2000 E	2001 E
Net Sales	$7,533	$7,797	$8,079	$8,268	$31,677	$7,884	$8,711	$8,753	$8,720	$34,067	$9,137	$9,574	$10,030	$10,678	$39,420	$11,485	$12,271	$13,224	$14,329	$51,310	$ 69,565
COGS	1,624	1,613	1,693	1,996	6,926	1,755	2,342	3,038	3,710	10,845	3,457	3,277	3,228	3,347	13,309	3,495	3,780	4,146	4,556	15,977	21,330
Gross Margin	5,909	6,184	6,386	6,272	24,751	6,129	6,369	5,715	5,010	23,223	5,680	6,298	6,802	7,332	26,111	7,990	8,491	9,079	9,774	35,333	48,235
SG&A	2,303	2,768	3,037	3,441	11,549	3,951	3,599	3,750	3,575	14,876	3,746	3,827	3,909	4,058	15,541	4,255	4,433	4,658	4,921	18,267	22,376
R&D	2,738	2,681	3,022	3,221	11,662	2,965	2,974	2,896	3,041	11,875	3,113	3,122	3,041	3,193	12,468	3,269	3,278	3,193	3,352	13,092	13,746
Other (Legal, ETC)	0	0	0	331	331	849	1,154	1,335	700	4,038	200	200	400	400	1,200	0	0	0	0	-	-
Total Operating Expense	5,041	5,449	6,059	6,993	23,542	7,765	7,726	7,981	7,316	30,788	7,059	7,150	7,350	7,650	29,209	7,524	7,711	7,850	8,273	31,359	36,122
Income From Operations	868	735	327	(721)	1,209	(1,636)	(1,357)	(2,267)	(2,305)	(7,566)	(1,379)	(852)	(548)	(319)	(3,098)	466	779	1,228	1,501	3,974	12,113
Interest and Other Income	324	554	631	1,926	3,435	612	577	576	560	2,325	559	557	556	557	2,229	560	567	576	585	2,288	2,501
Contract Revenue	336	244	198	(3,364)	(3,364)	300	471	1,910	0	2,680	200	0	100	0	300	0	0	0	0	-	-
Non-operating Income (Expense)	660	798	829	(1,438)	71	912	1,048	2,485	560	5,005	759	557	656	557	2,529	560	567	576	585	2,288	2,501
Earnings Before Income Taxes	1,528	1,533	1,156	(2,937)	1,280	(724)	(309.7)	219	(1,745)	(2,561)	(621)	(295)	108	239	(569)	1,027	1,347	1,804	2,085	6,262	14,614
Provision (Benefit) for Income Taxes	535	547	266	(1,266)	82	(224)	64	(236)	(591)	(987)	(380)	(246)	(81)	(27)	(733)	296	427	615	730	2,068	5,492
Net Income	993	986	890	(1,671)	1,198	(500)	(374)	455	(1,155)	(1,574)	(241)	(49)	189	266	164	731	919	1,189	1,355	4,195	9,123
Net Income Per Share Diluted	0.08	0.07	0.07	-0.13	0.09	-0.04	-0.03	0.03	-0.09	(0.12)	-0.02	0.00	0.01	0.02	0.01	0.05	0.07	0.09	0.10	0.31	0.67
Weighted Average Shares Outstanding	11,886	13,439	13,454	12,820	13,081	12,906	12,938	13,514	13,537	13,224	13,560	13,583	13,606	13,629	13,595	13,652	13,676	13,699	13,722	13,687	13,711
Year-over-year Growth																					
Net Sales	21%	15%	11%	4%	12%	5%	12%	8%	5%	7.5%	16%	10%	15%	22%	16%	26%	28%	32%	34%	30%	36%
100% Income Statement	**1997**					**1998**			**E**	**E**		**1999 E**									
	Mar-97	**Jun-97**	**Sep-97**	**Dec-97**	**1997**	**Mar-98**	**Jun-98**	**Sep-98**	**Dec-98**	**1998 E**	**Mar-99**	**Jun-99**	**Sep-99**	**Dec-99**	**1999 E**	**Mar-00**	**Jun-00**	**Sep-00**	**Dec-00**	**2000 E**	**2001 E**
Net Sales	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100%	100.0%	100.0%	100.0%	100.0%	100%	100.0%	100.0%	100.0%	100.0%	100%	100%
COGS	21.6%	20.7%	21.0%	24.1%	21.9%	22.3%	26.9%	34.7%	42.5%	32%	37.8%	34.2%	32.2%	31.3%	34%	30.4%	30.8%	31.3%	31.8%	31%	31%
Gross Margin	78.4%	79.3%	79.0%	75.9%	78.1%	77.7%	73.1%	65.3%	57.5%	68%	62.2%	65.8%	67.8%	68.7%	66%	69.6%	69.2%	68.7%	68.2%	69%	69%
SG&A	30.6%	35.5%	37.6%	41.6%	36.5%	50.1%	41.3%	42.8%	41.0%	44%	41.0%	40.0%	39.0%	38.0%	39%	37.1%	36.1%	35.2%	34.3%	36%	32%
R&D	36.3%	34.4%	37.4%	39.0%	36.8%	37.6%	34.1%	33.1%	34.9%	35%	34.1%	32.6%	30.3%	29.9%	32%	28.5%	26.7%	24.1%	23.4%	26%	20%
Other (Legal, ETC)	0.0%	0.0%	0.0%	4.0%	1.0%	10.8%	13.2%	15.3%	8.0%	12%	2.2%	2.1%	4.0%	3.7%	3%	0.0%	0.0%	0.0%	0.0%	0%	0%
Total Operating Expense	66.9%	69.9%	75.0%	84.6%	74.3%	98.5%	88.7%	91.2%	83.9%	90%	77.3%	74.7%	73.3%	71.6%	74%	65.5%	62.8%	59.4%	57.7%	61%	52%
Income From Operations	11.5%	9.4%	4.0%	-8.7%	3.8%	-20.8%	-15.6%	-25.9%	-26.4%	-22%	-15.1%	-8.9%	-5.5%	-3.0%	-8%	4.1%	6.4%	9.3%	10.5%	8%	17%
Interest and Other Income	4.3%	7.1%	7.8%	23.3%	10.8%	7.8%	6.6%	6.6%	6.4%	7%	6.1%	5.8%	5.5%	5.2%	6%	4.9%	4.6%	4.4%	4.1%	4%	4%
Contract Revenue	4.5%	3.1%	2.5%	-40.7%	-10.6%	3.8%	5.4%	21.8%	0.0%	8%	2.2%	0.0%	1.0%	0.0%	1%	0.0%	0.0%	0.0%	0.0%	0%	0%
Non-operating Income (Expense)	8.8%	10.2%	10.3%	-17.4%	0.2%	11.6%	12.0%	28.4%	6.4%	15%	8.3%	5.8%	6.5%	5.2%	6%	4.9%	4.6%	4.4%	4.1%	4%	4%
Earnings Before Income Taxes	20.3%	19.7%	14.3%	-35.5%	4.0%	-9.2%	-3.6%	2.5%	-20.0%	-8%	-6.8%	-3.1%	1.1%	2.2%	-1%	8.9%	11.0%	13.6%	14.6%	12%	21%
Provision (Benefit) for Income Taxes	35.0%	35.7%	23.0%	43.1%	6.4%	30.9%	-20.7%	-107.9%	33.8%	39%	61.1%	83.3%	-74.3%	-11.4%	129%	28.8%	31.7%	34.1%	35.0%	33%	38%
Net Income	13.2%	12.6%	11.0%	-20.2%	3.8%	-6.3%	-4.3%	5.2%	-13.2%	-5%	-2.6%	-0.5%	1.9%	2.5%	0%	6.4%	7.5%	9.0%	9.5%	8%	13%

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Table 12

Biosite Diagnostics Incorporated

Balance Sheet

	1997				1998			E	1999 E				2000 E				2001 E
	Mar-97	Jun-97	Sep-97	Dec-97	Mar-98	Jun-98	Sep-98	Dec-98	Mar-99	Jun-99	Sep-99	Dec-99	Mar-00	Jun-00	Sep-00	Dec-00	Dec-01
Assets																	
Current assets:																	
Cash and Cash Equivalents	$8,239,426	$6,605,888	$4,826,814	$2,330,274	$2,309,304	$2,217,679	$1,508,932	$1,417,803	$973,064	$845,616	$625,219	$646,082	$701,334	$1,233,706	$1,483,070	$2,098,517	$7,040,374
Marketable Securities	31,613,890	33,809,653	36,467,874	36,927,167	38,380,817	36,343,070	35,895,172	35,859,277	36,217,870	36,181,652	36,543,468	36,506,925	36,871,994	36,835,122	37,203,473	37,166,270	37,837,523
Accounts Receivable	4,266,890	5,599,326	5,784,255	5,282,500	5,467,095	7,080,522	5,799,675	6,191,257	6,487,359	6,797,749	7,121,457	7,581,660	8,154,651	8,712,303	9,389,204	10,173,864	13,863,840
Receivable from Stockholder	1,335,524	1,077,404	1,277,934	648,664	3,085,213												
Inventory	1,884,549	1,954,772	2,219,544	2,169,896	3,914,959	3,484,871	3,910,785	4,822,522	4,494,611	4,259,684	4,196,944	4,350,654	4,543,816	4,914,454	5,389,347	5,922,239	7,584,441
Deferred Income Taxes				2,310,000													
Prepaid Expenses and Other Current Assets	2,463,511	2,298,769	2,730,881	1,367,348	3,914,959	4,025,015	3,663,841	3,292,094	3,176,621	3,217,326	3,307,443	3,442,716	3,385,832	3,470,058	3,532,666	3,722,885	4,310,827
Total current assets	49,803,790	51,345,812	53,307,302	$ 51,035,849	53,157,388	53,151,157	50,778,405	51,582,952	51,349,525	51,302,027	51,794,531	52,528,037	53,657,627	55,165,643	56,997,760	59,083,774	70,637,005
Net PP&E	4,751,756	6,363,750	7,065,738	7,216,983	7,716,890	7,589,363	7,504,123	7,586,470	7,949,299	8,329,636	8,726,292	9,290,204	9,992,319	10,675,639	11,505,081	12,466,566	16,988,085
Deferred Income Taxes				338,000													
Patents and License Rights	4,179,674	4,031,417	3,879,103	3,720,035	3,567,226	3,487,063	6,467,463	6,338,114	6,211,351	6,087,124	5,965,382	5,846,074	5,729,153	5,614,570	5,502,278	5,392,233	4,973,624
Deposits and Other Assets	2,241,306	1,110,277	1,088,048	1,000,341	852,587	395,964	1,119,368	1,085,787	1,053,213	1,021,617	990,968	961,239	932,402	904,430	877,297	850,978	753,365
Total Assets	60,976,526	62,851,256	65,340,191	63,311,208	65,294,091	64,623,547	65,869,359	66,593,322	66,563,389	66,740,404	67,477,174	68,625,554	70,311,501	72,360,282	74,882,416	77,793,551	93,352,079
Liabilities and Equity																	
Current Liabilities																	
Accounts Payable	1,127,667	1,123,203	1,260,680	1,420,969	3,023,328	2,322,617	2,880,765	3,524,150	3,284,524	3,112,846	3,066,997	3,179,324	3,320,481	3,591,332	3,938,369	4,327,790	5,542,476
Accrued Salaries and Other	916,093	1,051,797	1,840,589	1,107,476	1,083,695	1,195,508	1,960,359	1,463,153	1,411,832	1,429,923	1,469,975	1,530,096	1,504,814	1,542,248	1,570,074	1,654,615	1,915,923
Accrued Contract Payable	751,544	630,283	630,283	563,812	563,812	324,779	205,928	181,217	159,471								
Current Portion of Long-term Obligations	1,397,912	1,366,155	1,379,837	1,332,200	1,424,629	1,531,915	1,565,048	1,648,095	1,726,917	1,809,542	1,895,712	2,018,217	2,170,745	2,319,191	2,499,380	2,708,254	3,690,515
Total Current Liabilities	4,193,216	4,171,438	5,111,389	4,424,457	6,095,464	5,734,819	6,612,100	6,816,615	6,582,743	6,352,311	6,432,684	6,727,637	6,996,040	7,452,770	8,007,822	8,690,659	11,148,914
Longterm Commitments and Contingencies	2,671,320	3,233,590	3,803,521	3,796,975	4,024,352	4,048,700	3,905,243	5,493,650	5,756,389	6,031,805	6,319,039	6,727,389	7,235,817	7,730,635	8,331,265	9,027,513	12,301,717
Total Liabilities	6,864,536	7,405,028	8,914,910	8,221,432	10,119,816	9,783,519	10,517,343	12,310,265	12,339,132	12,384,116	12,751,723	13,455,025	14,231,857	15,183,405	16,339,088	17,718,172	23,450,631
Stockholders' Equity:																	
Convertible Preferred Stock																	
Common Stock	127,317	127,933	128,103	128,647	129,329	129,882	129,333	129,527	129,721	129,916	130,111	130,306	130,501	130,697	130,893	131,090	131,878
Additional Paid-in Capital	53,086,734	53,339,879	53,369,398	53,684,302	54,261,713	54,622,347	54,190,557	54,353,129	54,516,188	54,679,737	54,843,776	55,008,307	55,173,332	55,338,852	55,504,869	55,671,383	56,342,452
Unrealized net gain (loss) on marketable securities	(84,903)	(17,248)	15,578	5,658	(14,516)	(3,638)	98,249										
Deferred Compensation	(400,284)	(372,921)	(345,258)	(317,595)	(290,534)	(263,171)	(235,508)	(214,312)	(195,024)	(177,472)	(161,500)	(146,965)	(133,738)	(121,701)	(110,748)	(100,781)	(69,110)
Retained Earnings (Deficit)	1,383,126	2,368,585	3,257,460	1,588,764	1,088,283	714,608	1,169,385	14,713	(226,628)	(275,892)	(86,936)	178,880	909,548	1,829,029	3,018,315	4,373,687	13,496,229
Total Stockholders' Equity	54,111,990	55,446,228	56,425,281	55,089,776	55,174,275	55,200,028	55,352,016	54,283,056	54,224,257	54,356,288	54,725,451	55,170,528	56,079,644	57,176,877	58,543,329	60,075,379	69,901,448
Total Liabilities and Equity	60,976,526	62,851,256	65,340,191	63,311,208	65,294,091	64,623,547	65,869,359	66,593,322	66,563,389	66,740,404	67,477,174	68,625,554	70,311,501	72,360,282	74,882,416	77,793,551	93,352,079

Table 13
Biosite Diagnostics Incorporated
Statement of Cash Flows

	1996	1997	1998E	1999E	2000E	2001E
Cash from Operating Activities						
Net Income	$ 3,548,973	$ 1,198,117	$ (1,574,051)	$ 164,167	$ 4,194,807	$ 9,122,542
Reconciliation of Net Income to Net Cash						
Depreciation and Amortization	2,417,816	2,738,230	366,880	1,618,547	3,017,544	4,295,443
Amortization of Deferred Compensation	11,665	109,750	103,283	67,348	46,184	31,670
Deferred Income Taxes	110,000	(931,000)	2,648,000	0	0	0
Changes in Operating Assets and Liabilities						
Accounts Receivable	(806,317)	(674,428)	(908,757)	(1,390,404)	(2,592,204)	(3,689,975)
Receivable from Stockholders	(728,535)	220,871	648,664	0	0	0
Inventory	(43,056)	(437,716)	(2,652,626)	471,868	(1,571,585)	(1,662,202)
Prepaid Expenses and Other Current Assets	(257,486)	(688,659)	(1,924,746)	(150,622)	(280,169)	(587,943)
Accounts Payable	191,581	452,995	2,103,181	(344,826)	1,148,466	1,214,686
Accrued Liabilities	(1,462,967)	(860,205)	(26,919)	(114,274)	124,519	261,308
Deferred Revenue from Stockholders	(615,282)	0	0	0	0	0
Net Cash Provided by Operating Activities	2,366,392	1,127,955	(1,217,090)	321,804	4,087,563	8,985,529
Cash from Investing Activities						
Net Sale (Purchase) of Marketable Securities	3,364,707	(28,607,483)	1,062,232	(647,648)	(659,345)	(671,253)
Purchase of Property, Equipment and Leasehold Improvements	(1,967,143)	(5,221,969)	(736,367)	(3,322,281)	(6,193,906)	(8,816,962)
Patents, License Rights Deposits and Other Assets	(4,929,555)	1,108,389	(2,703,525)	616,587	564,103	516,222
Net Cash Provided by Investing Activities	(3,531,991)	(32,721,063)	(2,377,659)	(3,353,342)	(6,289,149)	(8,971,993)
Financing Activities						
Net Proceeds (Payments)	412,832	1,864,158	2,012,571	1,603,860	2,990,162	4,256,465
Proceeds from Issuance of Stock	86,225	30,449,363	669,707	655,957	663,860	671,857
Net Cash Provided by Financing Activities	499,057	32,313,521	2,682,277	2,259,817	3,654,021	4,928,322
Increase in Cash and Cash Equivalents	(666,542)	720,413	(912,472)	(771,721)	1,452,436	4,941,857
Cash and Cash Equivalents at Beginning of Period	2,276,403	1,609,861	2,330,274	1,417,802	646,081	2,098,517
Cash and Cash Equivalents at End of Period	1,609,861	2,330,274	1,417,802	646,081	2,098,517	7,040,375

Forecast 2000 P/E Ratio Versus Growth

Currently trading at 26 times our EPS estimate for 2000, Biosite appears fairly valued when compared to the average P/E ratio of 19 for the 12 companies in the diagnostics comparison with 2000 earnings estimates available, as shown in figure 15. However, as shown in figure 16, analysis of available First Call data for forward growth estimates relative to 2000 P/E ratios reveals that Biosite appears rather undervalued when compared to the four companies for which the necessary data was available (Beckman Coulter, Diagnostic Products, IGEN, and I-STAT). Biosite's 40% forward growth rate does not seem be factored into current valuations. Given the limited comparable data available, we would expect Biosite to have a P/E ratio of 35-60 times, on the basis of our regression analysis, with our estimate in the 40-50 range.

Price Relative to Revenue and Cash Per Share

Within the rapid diagnostics sector, Biosite's price relative to revenue per share of 3.1 places the company in the lower half of the group, well below the average of 59, although in line with the median of 4, as shown in figure 17. This contrasts sharply with sales per share measures (also shown in figure 17). Analysis of sales per share reveals Biosite's sales per share of $2.56 places it second among this group of 12 companies. This contrast is particularly noteworthy given Biosite's gross margins, as discussed below.

Measuring cash per share relative to share price across the broad in vitro diagnostic universe provides another metric of Biosite's potential value. Thirty-nine-percent cash per share relative to share price, as shown in figure 18, positions Biosite in the top 10% of the universe, fourth out of 31 companies analyzed. This also contrasts with an average of 23% cash per share relative to share price for the group. In addition to mitigating potential risk, the cash position and cash per share should obviate the need for outside capital, thus likely precluding future significant dilution.

Table 14
Biosite Diagnostics Incorporated
Comparable Company Valuation Analysis

TICKER SYMBOL	COMPANY NAME	Price 12/16/98	Market Cap ($ Millions)	REVENUE 1997	R&D 1997	NET INCOME 1997	AVG. SHARES	CASH AND EQUIVALENTS 1997	Gross Margin	Cash/ Share	Sales/ Share	Price Per Sales/ Share	98 EPS	99 EPS	00 EPS	00 P/E
Rapid																
BMRA	BIOMERICA, INC.	1.31	5.22	9,376	554	141	3,952	2,175	42%	0.55	2.37	0.55	NA	NA	NA	NA
BSTE	BIOSITE DIAGNOSTICS INC.	7.84	100.91	31,677	11,662	1,198	12,371	39,257	78%	3.17	2.56	3.06	NM	NM	0.31	25.30
CALY	CALYPTE BIOMEDICAL CORP.	2.88	37.95	376	3,685	(7,794)	11,028	10,820	-513%	0.98	0.03	84.32	-0.61	-0.2	0.4	7.19
CVDI	CARDIOVASCULAR DIAGNOSTICS	5.50	37.13	7,618	2,573	(4,679)	6,722	5,885	19%	0.88	1.13	4.85	-0.49	-0.32	NA	NA
CMTR	CHEMTRAK INC.	0.03	0.07	6,402	1,897	(5,195)	2,583	1,114	44%	0.43	2.48	0.01	NA	NA	NA	NA
CTEC	CHOLESTECH CORP.	2.94	33.49	21,664	2,224	1,988	11,289	14,751	51%	1.31	1.92	1.53	0.15	0.37	NA	NA
DMED	DIAMETRICS MEDICAL, INC.	4.44	92.70	10,434	7,232	(21,037)	18,666	11,760	-12%	0.63	0.56	7.94	-0.8	-0.37	NA	NA
NTEG	INTEG INC.	1.50	14.05	-	7,832	(11,564)	9,305	21,777	NA	2.34	-	NA	-1.3	-1.02	NA	NA
STAT	I-STAT CORP.	6.00	79.22	37,840	6,721	(16,973)	14,498	32,914	18%	2.27	2.61	2.30	-1.21	-0.33	0.17	35.29
KITS	MERIDIAN DIAGNOSTICS, INC.	6.25	89.78	35,229	1,502	5,982	14,342	21,736	65%	1.52	2.46	2.54	0.34	0.42	NA	NA
OPSI	OPTICAL SENSORS INC.	1.44	12.08	141	4,975	(11,333)	8,375	17,101	-1457%	2.04	0.02	85.38	-1.45	-1.05	-0.4	-3.59
QQQQ	QUANTECH LTD.	1.75	4.49	81	2,115	(3,925)	2,366	719	NA	0.30	0.03	51.12	NA	NA	NA	NA
QDEL	QUIDEL CORP.	2.06	48.98	49,479	7,940	1,110	23,649	9,720	51%	0.41	2.09	0.99	0.15	0.27	NA	NA
DIAGF	SPECTRAL DIAGNOSTICS	1.44	14.04	739	4,409	(8,148)	8,210	17,430	72%	2.12	0.09	15.97	NA	NA	NA	NA
SPRX	SPECTRX, INC.	5.81	45.04	901	3,428	(5,726)	4,528	12,449	NA	2.75	0.20	29.21	-0.78	-0.09	0.85	6.84
TCPI	TECHNICAL CHEMICALS & PRODUCT	1.72	17.21	6,194	2,726	(4,489)	9,992	7,337	45%	0.73	0.62	2.77	-0.71	NA	NA	NA
ZMTX	ZYMETX, INC.	4.13	27.38	10	1,098	(2,676)	1,430	1,821	80%	1.27	0.01	589.88	NA	NA	NA	NA
Molecular																
AFFX	AFFYMETRIX, INC.	25.00	569.68	19,765	28,168	(22,526)	22,644	71,573	77%	3.16	0.87	28.64	-1.08	-0.93	0.16	156.25
HYSQ	HYSEQ, INC.	4.63	58.89	6,199	9,430	(6,537)	7,589	57,134	NA	7.53	0.82	5.66	-1.17	-0.38	0.23	20.11
VYSI	VYSIS INC.	6.00	6.43	18,233	10,136	(16,876)	1,062	669	60%	0.63	17.17	0.35	-1.66	-0.5	0.97	6.19
Miscellaneous																
BASI	BIOANALYTICAL SYSTEMS, INC.	4.00	8.99	14,923	1,568	684	3,101	161	58%	0.05	4.81	0.83	0.07	0.2	NA	NA
EPTO	EPITOPE, INC.	4.94	66.43	9,360	4,157	(4,081)	13,404	9,076	62%	0.68	0.70	7.07	NA	NA	NA	NA
HGN	HEMAGEN DIAGNOSTICS, INC.	0.97	7.61	12,991	1,072	405	7,677	1,025	41%	0.13	1.69	NA	NA	NA	NA	NA
HYBD	HYCOR BIOMEDICAL, INC.	1.28	9.17	19,289	2,889	(4,254)	7,134	2,305	52%	0.32	2.70	0.47	NA	NA	NA	NA
IGEN	IGEN INTERNATIONAL INC.	27.00	412.05	13,433	11,615	(11,830)	15,116	23,123	NA	1.53	0.89	30.38	-0.82	-0.25	0.54	50.00
BLUD	IMMUCOR, INC.	9.00	72.71	39,790	971	2,069	8,095	15,816	54%	1.95	4.92	1.83	NA	NA	NA	NA
MTRA	METRA BIOSYSTEMS, INC.	0.75	9.52	6,725	5,670	(13,127)	12,610	30,585	41%	2.43	0.53	1.41	NA	NA	NA	NA
OSTX	OSTEX INTERNATIONAL, INC.	0.47	5.95	4,108	4,470	(2,264)	12,574	18,965	78%	1.51	0.33	1.43	NA	NA	NA	NA
PBMI	PACIFIC BIOMETRICS INC.	0.50	1.86	2,789	1,087	(1,577)	3,082	3,890	39%	1.26	0.90	0.55	NA	NA	NA	NA
SALV	SALIVA DIAGNOSTOC SYS INC	0.70	2.05	1,422	665	(6,612)	2,489	271	0%	0.11	0.57	1.23	NA	NA	NA	NA
Lab Dx																
ABAX	ABAXIS, INC.	2.00	24.38	12,187	1,635	(4,353)	11,920	5,897	14%	0.49	1.02	1.96	NA	NA	NA	NA
BEC	BECKMAN COULTER, INC.	49.50	1,366.20	1,198,000	405,600	(264,400)	27,600	33,500	49%	1.21	43.41	1.14	1.48	3.68	4.25	11.65
BIO A	BIO-RAD LABORATORIES, INC.	22.19	275.76	426,914	46,138	16,364	12,260	10,843	56%	0.88	34.82	0.64	2.1	2.15	NA	NA
DP	DIAGNOSTIC PRODUCTS CORP.	26.88	368.64	186,264	19,710	18,248	13,641	20,372	55%	1.49	13.65	1.97	1.5	1.8	2.15	12.50
Cytology																
ACMI	ACCUMED INTERNATIONAL, INC.	1.63	6.15	19,110	8,897	(16,919)	3,675	470	38%	0.13	5.20	0.31	NA	NA	NA	NA
AICX	APPLIED IMAGING CORP.	1.75	13.42	13,134	7,381	(7,512)	7,324	8,378	52%	1.14	1.79	0.98	NA	NA	NA	NA
ACYT	AUTOCYTE INC.	4.19	52.36	2,668	4,462	(10,985)	6,903	28,655	27%	4.15	0.39	10.83	-0.74	-1.02	NA	NA
CVSN	CHROMAVISION MEDICAL SYSTEMS	5.50	94.46	44	3,565	(6,344)	13,456	12,926	NA	0.96	0.00	NA	-0.44	-0.19	NA	NA
IMII	INTELLIGENT MEDICAL IMAGING	0.56	6.20	3,770	5,023	(11,729)	10,952	7,083	12%	0.65	0.34	1.63	NA	NA	NA	NA
NPTH	NEOPATH, INC.	5.75	82.74	10,824	14,249	(23,597)	14,197	28,719	56%	2.02	0.76	7.54	-1.58	-1.08	NA	NA
NSIX	NEUROMEDICAL SYSTEMS, INC.	0.28	8.73	9,374	8,362	(36,581)	30,928	45,936	-29%	1.49	0.30	0.93	NA	NA	NA	NA
VMSI	VENTANA MEDICAL SYSTEMS, INC.	17.75	235.13	32,153	3,050	(372)	12,778	18,902	65%	1.48	2.52	7.05	0.36	0.86	1.15	15.43

Source: Moody's; SEDAR; Maxxess; William Blair & Company, L.L.C. estimates

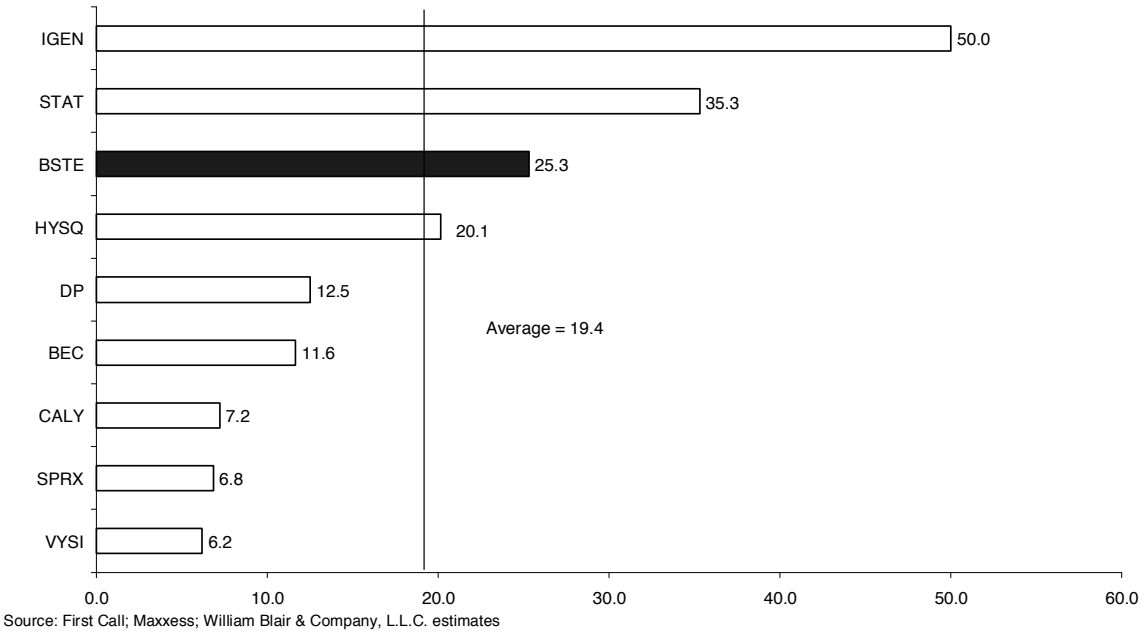
Gross Margins

Gross margins are a final measure of value within the universe of diagnostic companies. As shown in figure 19, Biosite's 1997 gross margin of 78% placed it second in the diagnostic universe, while the average was 44%. With an estimated 1998 gross margin of 68% due to the launch of its two new product lines, Biosite would still be ranked fifth among the 34 companies examined.

In summary, it appears that Biosite is possibly well-undervalued relative to its competitors when comparing its estimated 2000 P/E ratio to its long-term growth rate forecast of 40%, as well as intrinsic measures of business and potential performance such stock price relative to revenue and cash per share and gross margins.

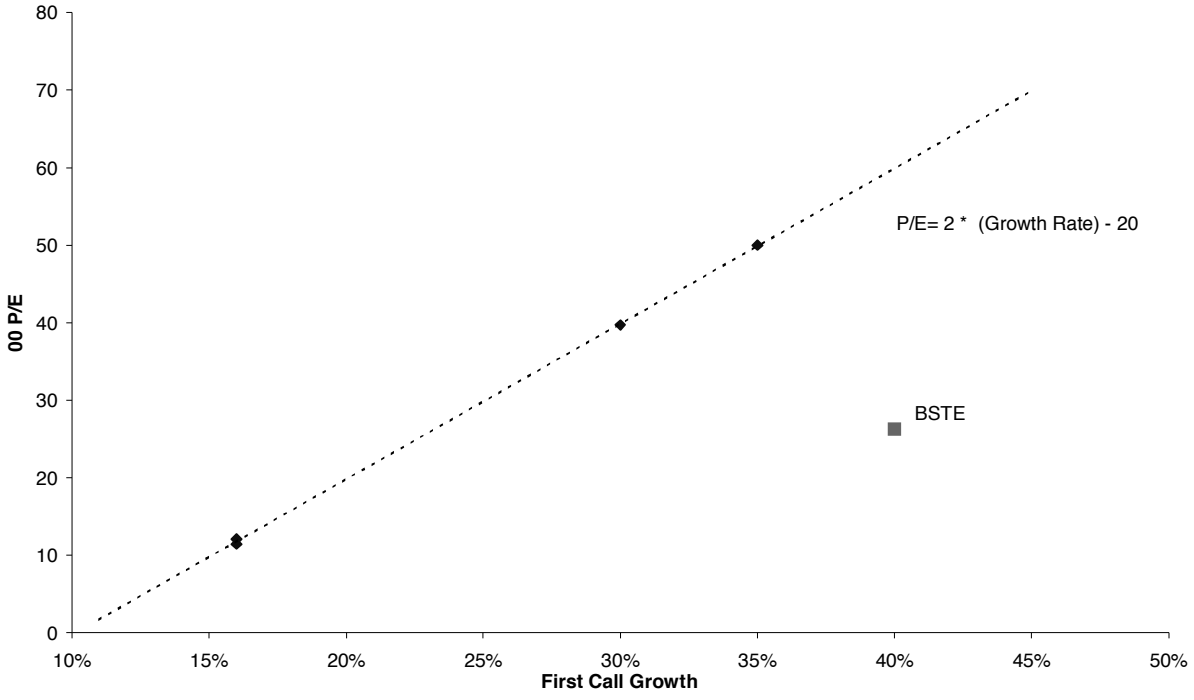
Additional information is available upon request.

Figure 15
Biosite Diagnostics Incorporated
Estimated 2000 P/E Ratio Comparison



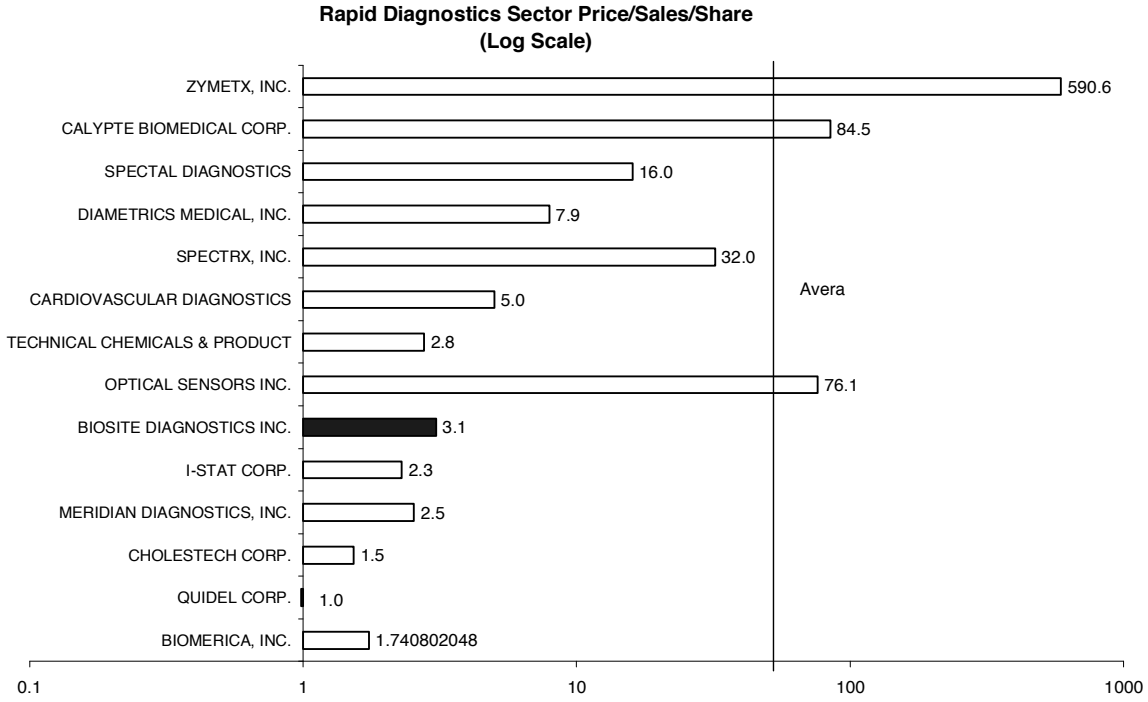
Source: First Call; Maxxess; William Blair & Company, L.L.C. estimates

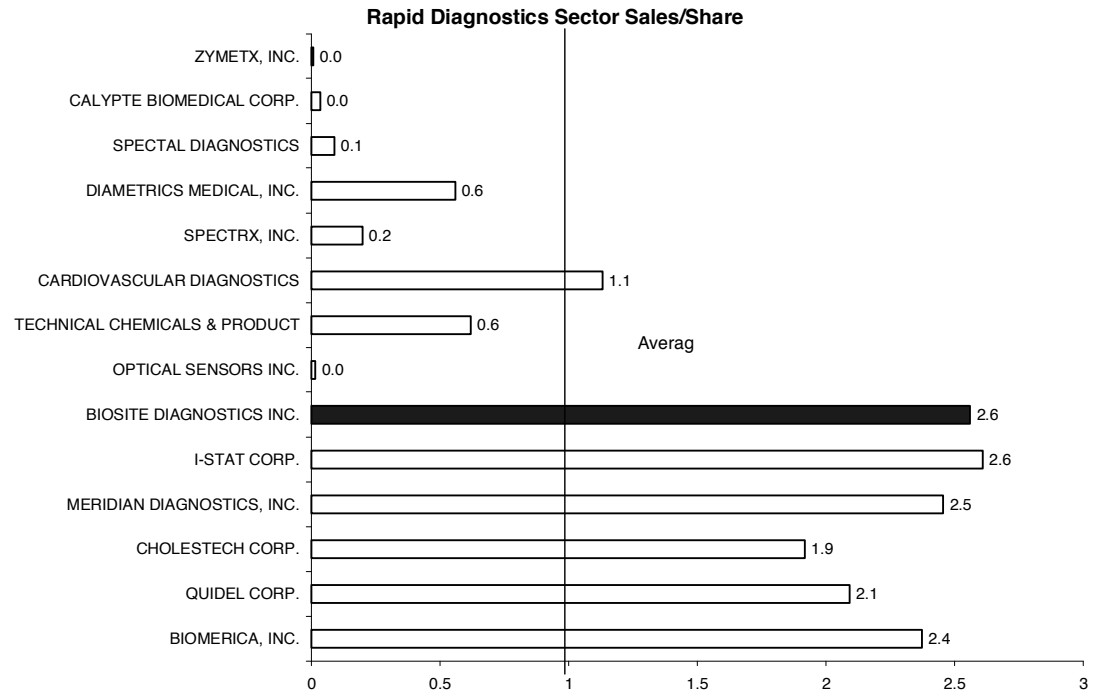
Figure 16
Biosite Diagnostics Incorporated
Estimated 2000 P/E Ratio Versus First Call Growth Estimates



Source: First Call; Maxess; William Blair & Company, L.L.C. estimates

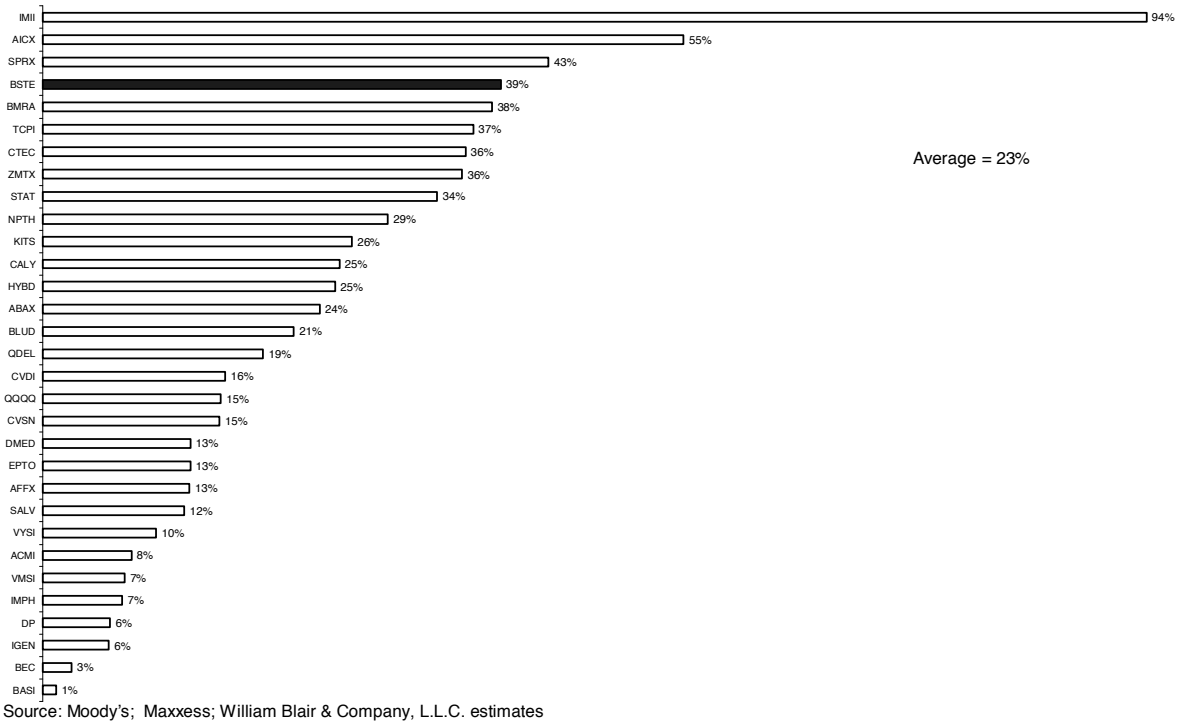
Figure 17
Biosite Diagnostics Incorporated





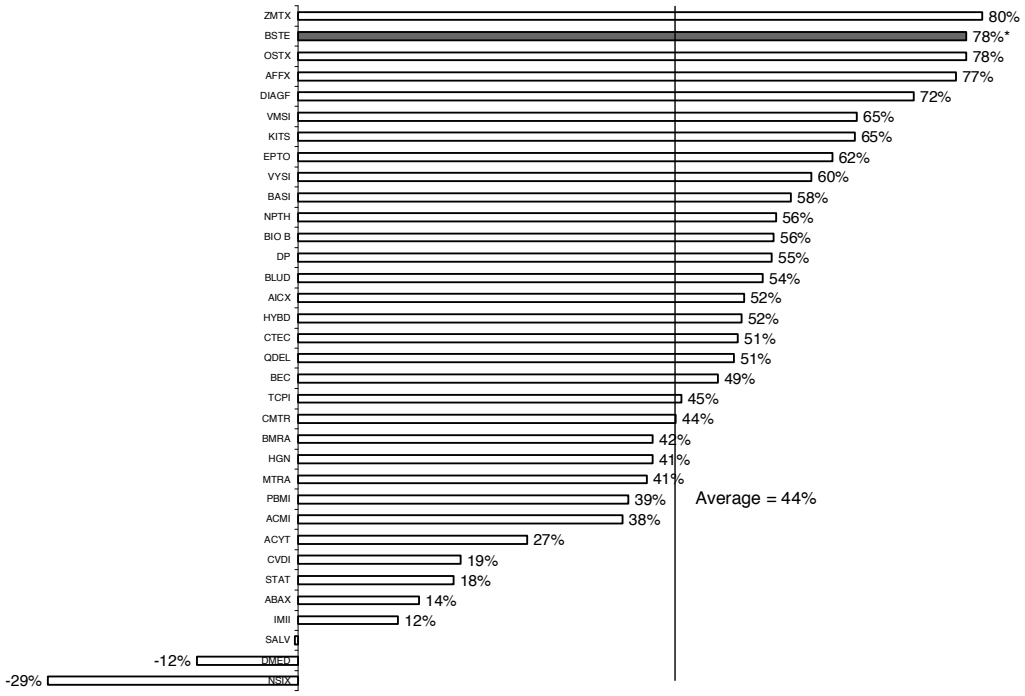
Source: Moody's; SEDAR; Maxxess; William Blair & Company, L.L.C. estimates

Figure 18
Biosite Diagnostics Incorporated
Cash Per Share / Price



Source: Moody's; Maxxess; William Blair & Company, L.L.C. estimates

Figure 19
Biosite Diagnostics Incorporated
Diagnostic Universe 1997 Gross Margins*



* 1998 gross margin for BSTE estimated at 68%
Source: Moody's; SEDAR; Maxxess; William Blair & Company, L.L.C. estimates

DJIA:	8875.82
S&P 500:	1179.96
NASDAQ:	2043.89

William Blair & Company, L.L.C. maintains a market in the common shares of Biosite Diagnostics Incorporated.

The prices of the common stock of other public companies mentioned in this report follow:

Abbott Laboratories	$47 3/4
Eli Lilly and Company	$89 1/2
Fisher Scientific	$17 15/16
Genentech	$72 9/16
Johnson & Johnson	$80 1/8
Novartis	$97 1/4
Roche Holdings	$120 1/2
Scios, Inc.	$7 5/8
XOMA Corporation	$3 1/8

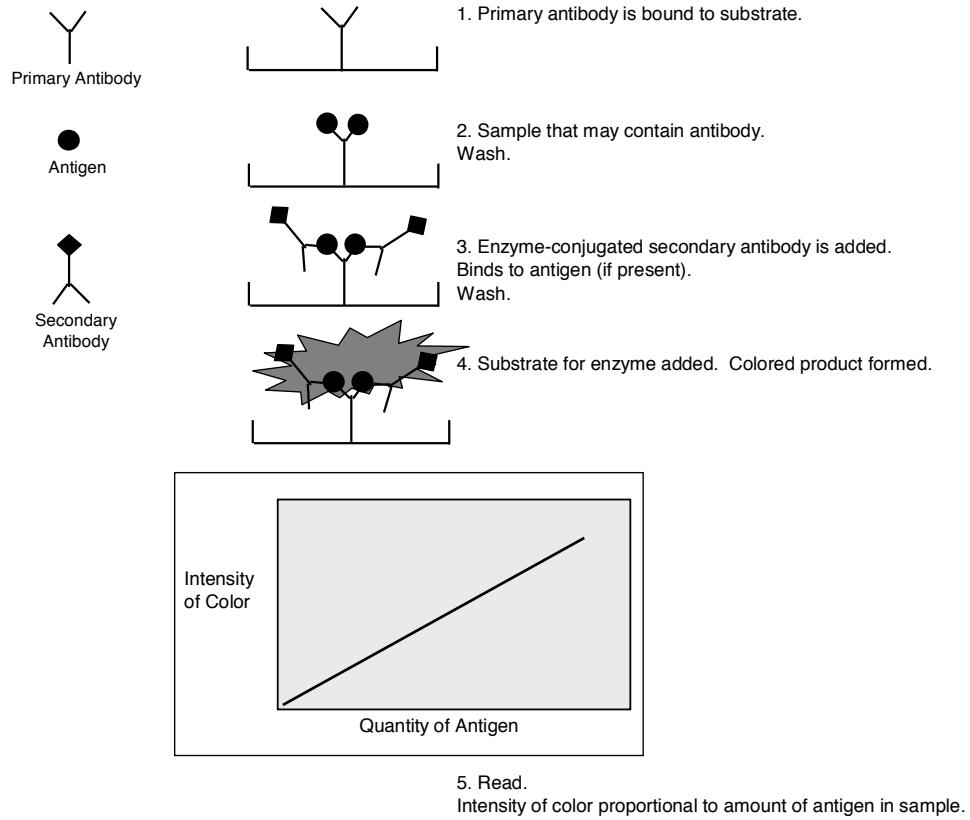
Appendix A: In Vitro Diagnostics

Basics of Immunodiagnostic Technology

Immunodiagnostics rely on the properties of antibodies and antigens to detect the presence of analytes in bodily fluid samples (e.g., urine, blood, and stool) with a high degree of specificity and sensitivity. Antibodies are proteins produced by the B-cells of the immune system in response to the presence of a foreign substance, an antigen. A cascade of processes leading to the elimination of the antigen from the body follows this recognition. Each antibody binds to a particular portion of an antigen, allowing for both a specific and sensitive recognition. The "lock-and-key" and "hand-in-glove" analogies are often drawn to illustrate this principle.

Immunoassays. Using monospecific antibodies produced by the methods described above, sensitive tests can be produced. A general type of immunoassay, the Enzyme Linked Immunosorbent Assay (ELISA), can be used to demonstrate the principles behind most immunoassays. As illustrated in figure 20, an antibody specific to the antigen (primary antibody) is bound to a solid support (for example, a plastic microtiter plate). A sample then is added that may contain the antigen, and a wash is performed to eliminate any nonspecific binding. A second antibody that recognizes another portion of the antigen is then added, and it also binds to the antigen, forming a sandwich. This antibody is added, or *conjugated*, to an enzyme. A molecule that the enzyme can work upon, or *substrate*, is added. The enzyme catalyzes a color-producing reaction that shows the presence of the analyte, or antigen, and then can be measured to quantify the amount of antigen present in a sample.

Figure 20
Biosite Diagnostics Incorporated
Immunoassay (ELISA)



Source: William Blair & Company, L.L.C. analysis

Antibody Production

Hybridoma technique. In an animal, millions of antibodies are produced in response to all manners of foreign substances found in the environment. Immunodiagnostics require antibodies of a single type to function accurately. Fortunately, methods have been devised that allow for the production of monospecific antibodies (monoclonal). The hybridoma technique facilitates this process. An animal is immunized with the antigen of interest, and a period of weeks elapses, allowing specific B-cells to proliferate and produce specific antibodies. The spleen of the animal—rich in B-cells—is removed, and the antibody-producing cells are isolated. B-cells are difficult to maintain in the lab and have a limited lifespan; thus, they are fused with tumor cells, or *myelomas*, resulting in hybrids that produce antibodies indefinitely. Assays are run to identify the population of cells producing the antibody of interest. These antibodies then can be collected and modified for use in diagnostics tests. This process can take up to 9 months and the cost of antibodies via this method is $2000-$3,000 per gram.

Phage display technique. Biosite uses an alternate method of antibody production that has been devised more recently that allows for rapid production of antibodies in a matter of weeks. This process—antibody phage display—uses bacteria and the viruses, or *phage*, that infect them as a mode of production. An animal is immunized with the antigen of interest, and B-cells are allowed to proliferate. The spleen is removed, and antibody producing B-cells are recovered. The genetic material that encodes the structure of the antibody is isolated and inserted into the phage's genetic material, creating a library. The phage then are allowed to infect the bacteria, which proliferate, and the phage proliferate as well. The phage produce antibodies on their surface, and these antibodies can be recovered after they escape from the bacteria. The phage producing the antibody of interest then can be recovered via an assay, as was done in the hybridoma technique. These phage then can be used to infect bacteria to produce the antibody in mass quantities. By going directly to the genetic material, antibodies can be modified and quickly easily without the costs and problems associated with growing animal cells and creating hybrids. This process can be completed in 3 weeks, and the cost of antibodies via this method is around $100 per gram.

Accuracy: Specificity and Sensitivity

Diagnostic tests are used in three ways—screening, direct diagnosis, and monitoring. For direct diagnosis, the test is used to help determine the nature of a disease in conjunction with observing signs and symptoms presented by an individual. Diagnostic screens are used to identify individuals in a healthy population who may have a particular disease, or are at risk of developing the disease in the future. Monitoring diagnostic tools measure the change in concentration of a particular substance over time (e.g., drugs or infectious organisms). For any of these uses, it is critical to have the most discriminatory tools available.

Measure of effectiveness. When determining the effectiveness of a diagnostic tool, the following two questions must be answered: How well can the test identify individuals who are disease positive, and likewise, how well can the test exclude those who are disease negative? Two measures are used to answer these questions—*sensitivity* and *specificity*. *Sensitivity* is the proportion of individuals in a sample who are disease positive who also test positive; s*pecificity* is the proportion of individuals in a sample who are disease negative who also test negative. Ideally, a diagnostic should be both highly sensitive (i.e., identifies as many individuals with the disease as possible) and specific (i.e., minimizes false positives).

Sensitivity = Number with disease that test positive / number of disease positive

Specificity = Number with disease that test negative / number of disease negative

Table 15
Biosite Diagnostics Incorporated
Hypothetical Diagnostic Results

	Disease		
Test	**Positive**	**Negative**	**Total**
Positive	7	4	11
Negative	3	86	89
Total	10	90	100

Source: William Blair & Company, L.L.C. estimates

For example, we refer to the following data in table 15. How would this test score for sensitivity and specificity?

The data tells us that this hypothetical test has a sensitivity of 70% and a specificity of 96%. Thus, while this particular test is very good at identifying those who do not have the disease, it misses 30% of those who do have it.

Sensitivity and specificity can be improved by altering both an assay's cutoffs and normal definition. By raising or lowering the cutoff points of an assay whose results vary over a range of values, these measures of effectiveness can be changed. Sensitivity and specificity can be thought of as a seesaw. For example, a higher cutoff will detect fewer cases lowering a test's sensitivity while improving its specificity and vice versa. Changing the definition of what is normal for a population, thus what is abnormal, is defined as the disease state. One can change the level of detection as well.

A diagnostic's sensitivity and specificity then can be used to calculate the predictive values of the test. By incorporating a ratio of the prevalence of the disease for a given population, one can determine the positive predictive value (i.e., probability that an individual who tests positive is indeed disease positive) and the negative predictive value (i.e., probability that an individual who tests negative is indeed disease negative) value of the test, which are further indices of effectiveness.

$$\textit{Positive Predictive Value} = \frac{(\textit{Prevalence} * \textit{Sensitivity})}{(\textit{Prevalence} * \textit{Sensitivity}) + (1 - \textit{Prevalence}) * (1 - \textit{Specificity})}$$

$$\textit{Negative Predictive Value} = \frac{([1 - \textit{Prevalence}] * \textit{Specificity})}{([1 - \textit{Prevalence}] * \textit{Specificity}) + (\textit{Prevalence} * [1 - \textit{Sensitivity}])}$$

For example, if the test above were a screening tool for a disease with a prevalence of 1%, it would have a positive predictive value of 37% and a negative predictive value of 99.6%. Thus, while only 37% of test positives would be true positives, almost 100% of those testing negative would be true negatives.

Coefficient of variation. A diagnostic tool's coefficient of variation is one last measure of effectiveness. Coefficient of variation is the variation witnessed within a single operator or control. It answers the question whether conducting the same test repeatedly would achieve the same result. Tests that possess a narrow band of variance offer a higher degree of effectiveness.

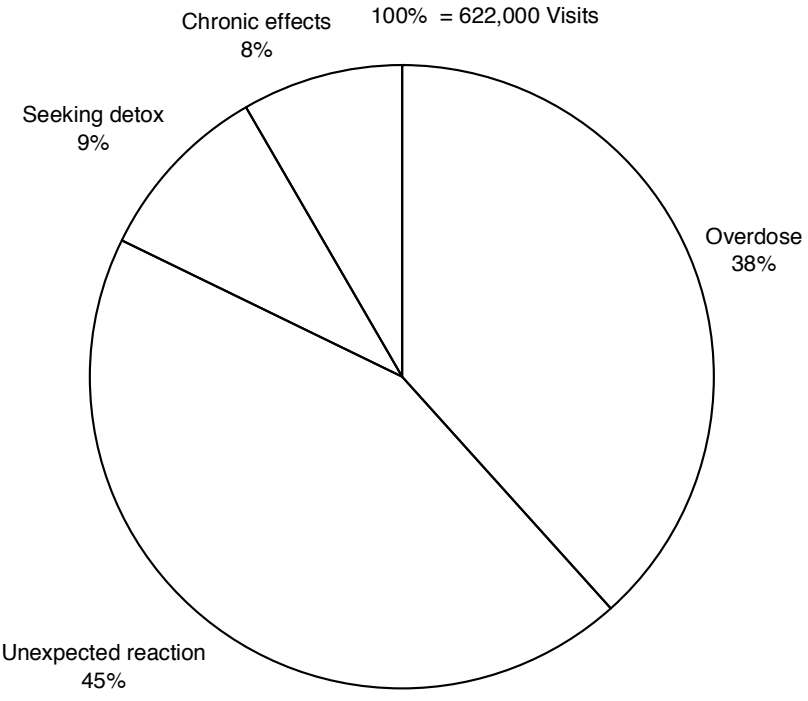
Appendix B: Relevant Medical Conditions

Abuse of Drugs

Drug abuse places an incredible strain on the United States, both economically and socially. The National Institute on Drug Abuse (NIDA) estimated that there were more than 13 million illicit drug users in the United States in 1996. In 1992, NIDA estimated the total burden of drug abuse was at $97.6 billion, while alcohol abuse added an additional cost of $148 billion. Commonly abused drugs include illicit substances such as amphetamines/methamphetamines ("speed," "crystal"), cocaine (crack), opiates (heroin), phencyclidine (angel dust), and tetrahydrocannabinol (marijuana), as well as prescription drugs like barbiturates (phenobarbital), benzodiazapines (Valium, Librium, halcion), tricyclic antidepressants (iElavilm, Tofranil), and methadone.

Drug abuse and the emergency department. Drug abuse was implicated in 487,600 visits to EDs, with unexpected reactions and overdoses accounting for 44% and 38%, respectively, as shown in figure 21. In certain situations, doctors often must discern between drug- and non-drug-induced symptoms to make the proper diagnosis. In other situations where the abuse is known but the substance is not, it is necessary to determine the specific drug before ordering a course of therapy. Studies show that admitted patients who have been abusing drugs have a average length of stay that is 2.2 days longer than those who do not abuse drugs. In these scenarios, information provided by diagnostic tests and the speed by which it is obtained is critical to the quality of care dispensed by the hospital.

Figure 21
Biosite Diagnostics Incorporated
Reported Reasons for Drug-related ED Visits



Source: Substance Abuse Mental Health Service Administration; William Blair & Company, L.L.C. analysis

A hospital has several platform options with which to conduct these tests. These include the use of chemical tests, immunodiagnostics, and gas chromatography/mass spectroscopy (GC/MS). GC/MS is the most specific method, but is also the most time-consuming, taking hours and involving complex equipment and sample preparation. Other testing methods might require batch testing of samples, leading to further delays. Neither offers the information on the STAT (short turnaround time) basis required for immediate decision making. Rapid diagnostic testing, such as Biosite's Triage® DOA panel, offers simple testing in the central lab or ED, yielding results for 8 possible substances in less than 15 minutes.

Other medical DOA testing. Each year, 7% of newborns are born to mothers who abuse drugs. Screening for illegal substances in the blood of both mother and child could lead to timely intervention—possibly curbing long-term effects attributed to drug abuse, as well as decreasing the $360 million annual cost of treating exposed infants.

Drug abuse and the workplace. Nonmedical testing consists of workplace screening, as well as tests conducted in drug rehabilitation centers and within the criminal justice system. In 1991, the American Management Association found that 63% of firms conducted some type of workplace drug testing. By 1997, the National Council on Alcoholism and Drug Dependence estimated that more than 75% of new hires were tested for illicit drug use. Furthermore, in 1997, 5% of these employees tested positive for drugs, although this was down from 18% in 1987. Workplace testing most often is conducted offsite at commercial labs, allowing employers to avoid the cost of maintaining onsite facilities and personnel.

When samples are collected onsite and are sent to an offsite testing facility, the sample must be accompanied by a Chain of Custody (COC) document that ensures the integrity of the specimen through the testing procedure. If this chain is broken, the test is ruled forensically inviable. When onsite testing is implemented at the workplace with the aid of rapid assay products like ExpressTest®, sample collection immediately is followed by testing. Thus, the need for a COC is limited to those tests that yield a positive result, requiring confirmation.

Acute Myocardial Infarction

Cardiovascular disease is responsible for 12 million, or 50%, of deaths globally each year and affects more than 60 million Americans. Cardiovascular disease is the leading cause of death in the United States. 14 million individuals are estimated to have some form of coronary artery disease, which causes both Unstable Angina (UA) and Acute Myocardial Infarction (AMI or heart attack). UA and AMI are the results of *ischemia*—an oxygen deficiency to some portion of the body. UA is a sporadic difference in oxygen supply relative to oxygen demand in the heart muscle tissue, resulting in chest pain. The oxygen shortage generally is due to obstruction of the coronary vessels that supply blood to the heart. These obstructions are caused by the progression or buildup of arthrosclerotic plaque along the walls of arteries. The fissuring of plaque, as seen in 80% of UA patients, can lead to platelet aggregation, cutting the oxygen supply to the heart and leading to the death of myocardial tissue. The death of heart muscle interferes with the heart's electrical function, leading to failure and death. Such an event is labeled a heart attack, or AMI. The American Heart Association estimates that 7.2 million people suffer from angina (both stable and unstable) in the United States, with 350,000 new cases occurring annually. There are more than 1 million cases of AMI each year.

Treatments. Treatments for UA and AMI consist of medical and surgical therapies. The purpose of UA treatments is to treat complications, control symptoms, and prevent the progression of UA to AMI. UA treatments consist of pain medication (nitroglycerin) as well as various medications that interfere with the formation of blood clots, such as aspirin, thrombin inhibitors, IIb/IIIa inhibitors ("super" aspirins) and beta-blockers. Studies have shown that the administration of such therapies can reduce the progression rate from UA to AMI by 31%.

AMI treatments include those listed for UA, as well as thrombolytic medication and surgical intervention. Thrombolytic treatments consist of clot-dissolving medications such as TPA and streptokinase, which seek to restore blood flow by removing obstructions. Various clinical trials have demonstrated the reduction of mortality by 50% in patients treated within 1-2 hours of onset. Some benefit has been shown for the use of thrombolytics for up to 12 hours after onset. If this window for medical intervention is closed due to delays in diagnosis, surgical intervention is used. Percutaneous Transluminal Coronary Angioplasty (PTCA) involves the threading of a catheter through a blood vessel to the obstruction. A balloon then is inflated to compress the plaque, clearing the way for blood flow. Scaffold-like devices known as stents often are used to hold arteries open after PTCA. PTCA has been shown to restore blood flow in 90% of cases, improving the 1-year survival rate to 96%. Bypasses such as the coronary artery bypass graft (CABG) also may be performed to restore blood flow. Bypasses involve rerouting blood using a grafted vein taken from another area of the body. These procedures also may be performed on those UA patients unresponsive to medication (refractive).

Risk. There is an extensive list of factors that places an individual at risk of developing some form of coronary artery disease. These include family history (heredity), sex (male), obesity, and elevated cholesterol levels. Other risk factors are hypertension, inactivity, cigarette use, stress, and chronic cocaine use (a link between chest pain and DOA). This long list might be a partial explanation for the disease's prevalence in the United States.

Emergency medicine and coronary artery disease. Each year, more than 6 million patients arrive in emergency departments (EDs) of hospitals with complaints of chest pain. Although UA and AMI are the two leading causes of these visits, there are many other potential causes, as listed in table 16, on the next page. In addition, 250,000 people die within 1 hour of the onset of pain—before making it to the hospital ED. The remaining 6 million are stratified, as shown in figure 5, with 1.1 million diagnosed with UA and 0.9 million found to have suffered AMI. To arrive at these diagnoses, patients must be triaged properly and quickly to administer therapies effectively.

As discussed earlier, the effectiveness of AMI treatments are time-sensitive; thus, any delay could result in an adverse outcome. The components of delays in treatment have been labeled the four Ds: Door, Data, Decision and Drug. Door consists of delays in arrival and triage; Data is the delay associated with the taking of EKG readings, as well as more recently, cardiac markers; Decision is the time spent deliberating the course of treatment; and Drug is the time necessary to initiate the treatment. Data, Decision and Drug are ED-related delays clinicians seek to minimize through improved practices and the institution of total quality-management protocols. The creation and proliferation of chest pain centers within the ED address these delays. Currently, there are more than 1,500 chest pain centers located in the United States. These facilities possess the staff and equipment necessary to diagnose and treat those patients presenting with chest pain effectively.

The World Health Organization defines AMI as exhibiting two of the following three criteria: ischemic pain for more than 20 minutes; elevated ST regions on EKG readings; and/or elevated serum cardiac markers. Since pain is a subjective indicator, doctors rely heavily on the latter two criteria.

Table 16
Biosite Diagnostics Incorporated
Causes of Chest Pain

		Cause	Organ System/Pathogenesis
Chest Pain (6 million-plus ED visits per year in the US)	**High Risk**	Myocardial Infarction	Cardiovascular (ischemic)
		Unstable Angina	Cardiovascular (ischemic)
		Aortic Dissection	Cardiovascular (nonischemic)
		Pericarditis	Cardiovascular (nonischemic)
		Pulmonary Embolus	Pulmonary
		Pneumothorax	Pulmonary
		Acute Chest Syndrome of Sickle Cell Disease	Hematological
		Esophageal Rupture (Boerhaave's Syndrome)	Gastrointestinal
	Moderate Risk	Pneumonia	Pulmonary
		Esophageal Disease	Gastrointestinal
		Peptic or Gastric Ulcer	Gastrointestinal
		Cholecystitis	Gastrointestinal
		Early Disseminated Lyme Disease	Infection
	Low Risk	Panic Disorders	Psychogenic
		Depression	Psychogenic
		Herpes	Infection
		Hyperventilation	Pulmonary
		Chest Wall Pain/Costochondritis	Neuromusculature
	Other Origin	Thoracic Endometrios	Neuromusculature
		Delayed Rupture of Splenic Hematoma	Hematological
		Gastric Anisakiasis	Gastrointestinal

Source: American College of Emergency Physicians; National Center for Health Statistics; Wilkerson Group; William Blair & Company, L.L.C. analysis

An EKG measures the electrical charge differential across the heart as it pumps. If damage to the tissue has occurred—AMI—the smooth movement of charge is interrupted, reflected by a change of voltage measured by the EKG.

Cardiac markers represent the most accurate technology currently available for the diagnosis of AMI. They are used in conjunction with an electrocardiogram (EKG), which alone only identifies about 40%-70% of AMIs. Cardiac markers are proteins released into the bloodstream as a result of heart-muscle damage. Mb and CK-MB are markers whose utility as a diagnostic indicator of AMI are well-studied and respected; troponins I and T are gaining acceptance in the medical community. Differentiating these markers are their specificity to heart damage and duration of elevated levels in the blood after onset of AMI, a comparison of which can be found in table 17 and a chart of the release characteristics can be seen in figure 22, on page 50. Mb is an oxygen-carrying protein found in high concentration in both skeletal and cardiac muscle. It is released into the circulatory system in large amounts approximately one hour after onset of AMI, making it a good early indicator of AMI with a high negative predictive value; it is cleared from the system within 24 hours. Mb's nonspecific nature relative to heart muscle limits its value, since renal failure, muscular disorders, and trauma also result in the release of Mb. CK-MB is a protein that is released into the bloodstream three to six hours after muscle damage and remains in the system for three days. It also is not entirely cardiac-muscle-specific and can be released due to trauma. These characteristics limit its value as a cardiac marker. Troponin I is particularly useful as a marker for several reasons. Troponin I is found in heart-muscle cells at concentrations that are much higher than that of CK-MB and Mb, and is absent from serum unless there has been some cardiac damage. This marker is released into the bloodstream 3-6 hours after onset of AMI and persists for 5-10 days. This persistence has allowed it to be used as a predictor of future cardiac events up to 30 days after onset of AMI. These cardiac-enzyme

properties enable the development of diagnostics that, as a panel, are particularly sensitive and specific for the detection of AMI. Other markers currently are being investigated to determine their utility in diagnosing both AMI and UA; these are listed in table 18.

The use of cardiac markers in conjunction with EKG readings has led to the development of triaging algorithms that offer superior rule in/rule out ability. An example of the algorithm developed by Dr. Alan Maisel of the University of California-San Diego is shown in figure 23. The algorithm progresses as follows. Upon presentation to the ED, patient history is taken, an EKG is started, and blood is drawn for the measurement of CK-Mb, Mb, and cTn-I. Results of this initial sampling serve as the baseline. Serial testing of the markers at three and nine hours post-presentation serves to stratify patients into risk groups of either having or not having suffered AMI. If it is determined that a patient has suffered AMI, appropriate treatment can be administered, whereas if AMI is ruled out, the patient can avoid costly admittance and be sent home safely. Studies have indicated that the use of this algorithm correctly ruled in 100% of patients with AMI, while adverse events in those sent home were minimal, and tremendous cost-savings were realized by the hospital. Table 19 contrasts the Maisel algorithm with others in use, showing that it appears to be the most clinically beneficial.

Table 17
Biosite Diagnostics Incorporated
Comparison of Cardiac Markers

	EKG	CK-MB*	Troponin I	Troponin T	Myoglobin
Sensitivity	40%-70%	90%-95%	83%-98%	83%-98%	70%-80%
Specificity	85%-98%	90%	93%-100%	93%-100%	82%-92%
Negative Predictive Value	90%-95%		99.7%	98.9%	
Positive Predictive Value	45%-75%		99.8%	98.9%	
Release Characteristics					
Appearance		3-8 hrs	4-6 hrs	3-4 hrs	1-3 hrs
Duration		36-48 hrs	5-10 days	14+ days	26 hrs

*Mass

Source: American Association of Clinical Chemists, American College of Emergency Physicians, NHAAP, Annals of Emergency Medicine, William Blair & Company, L.L.C. estimates

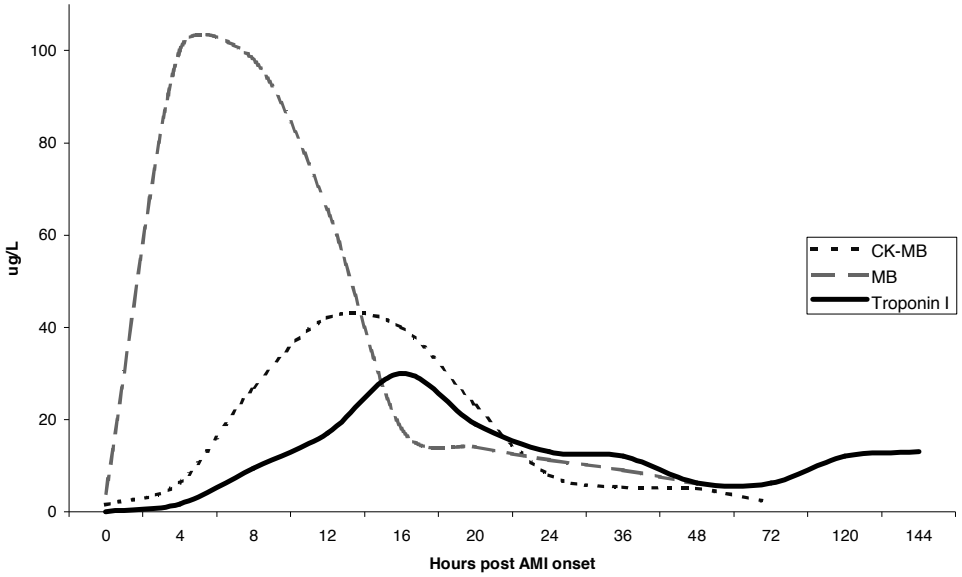
Table 18
Biosite Diagnostics Incorporated
Potential New Cardiac Markers

Potential Marker	Use*
Serum lactate	AMI
Myosin light chain	AMI
P-selectin	Ischemia/UA
Thrombus precurser protein	Ischemia/UA
Interleukcin-8	Ischemia/UA
C-reactive protein	Ischemia/UA
Troponin T	Ischemia/UA

* AMI: Acute Myocardial Infarction; UA: Unstable Angina

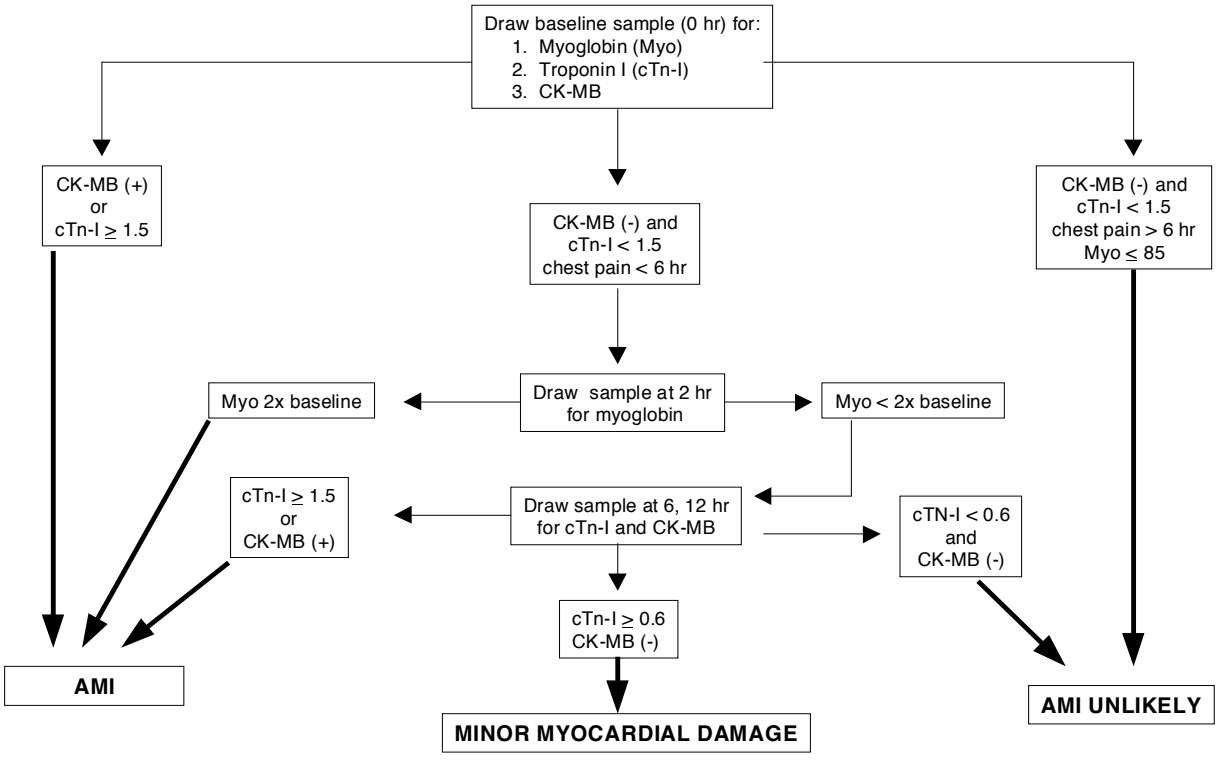
Source: American College of Emergency Physicians; Roche; Industry Interviews; William Blair & Company, L.L.C. analysis

Figure 22
Biosite Diagnostics Incorporated
Release Kinetics of Cardiac Markers



Source: Dade-Behring; Biosite; Wilkerson Group; William Blair & Company, L.L.C. estimates

Figure 23
Biosite Diagnostics Incorporated
Cardiac Marker Algorithm



Source: Topics in Emergency Medicine; William Blair & Company, L.L.C. estimates

Table 19
Biosite Diagnostics Incorporated
AMI Triage Protocols

Protocol	Measures	Location		Sensitivity	Specificity	Time to rule in/out
		Emergency Department	Central Lab			
Minimum	ECG	X		40-70%	85-98%	24 hrs
WHO Criteria	ECG	X		40-70%	85-98%	24 hrs
	CK-MB		X	90-95%	90%	
Qualatative Marker	ECG	X		40-70%	85-98%	12+ hrs
	Qualative Panel	X				
	Quantitative Panel		X			
Quantitative Maisel	ECG	X		40-70%	85-98%	12 hrs
	Quantitative Panel		Either			

Source: Biosite; Spectral; JAMA; NHLBI; William Blair & Company, L.L.C. estimates

Parasites and Enteric Bacteria

The morbidity statistics associated with intestinal infectious diseases are staggering. There are an estimated 99 million cases of pathogen-associated diarrhea each year. Approximately 8.2 million of these cases require hospitalization, resulting in a direct cost of $560 million. The CDC estimates that the total minimum cost of these illnesses is $23 billion per year. Infections may be caused by bacteria or protozoa and are responsible for diseases as diverse as “beaver fever” to colitis. These organisms can be acquired in several different ways. Some inhabit the gut as part of the natural flora, while others make their way into the digestive system by ingestion of contaminated food or drink.

Much has been made of the fact that many of the most severe infections are acquired in the hospital (nosocomial). According to the Centers for Disease Control, nosocomial infections are the 11th leading cause of death in the United States, accounting for more than 2 million infections annually. Particularly worrisome is the rate at which such infections are increasing—there was a 36% rise from 1975 to 1995. Of these infections, antibiotic-resistant microbes cause 70%. The rising rate has been attributed to misuse of antibiotics, poor enforcement of hygiene practices in hospitals, a higher prevalence of immunocompromised patients, and increased elderly populations.

Biosite is targeting three classes of gastrointestinal pathogens—*Clostridium difficile*, waterborne pathogens, and enteric bacteria. *Clostridium difficile* is the bacteria primarily responsible for hospital-acquired diarrhea. Waterborne pathogens *Giardia lamblia, Cryptosporidium parvum*, and *Entamoeba histolytica* are microbes that cause outbreaks of gastrointestinal disease, endangering the safety of community water supplies. Lastly, there are the enteric bacteria, which include E. coli and salmonella, which cause food poisoning (gastrointestinitis).

Clostridium difficile. *Clostridium difficile (C. difficile)* is an opportunistic, bacterial pathogen that is the leading cause of infectious nosocomial diarrhea (20%-45% of cases). It is estimated that some 3.5 million *C. difficile* tests are conducted in the United States annually. *C. difficile* is responsible for Clostridium-associated diarrhea (CAD), a disease whose

incidence is 3 cases per 1,000 hospital admissions, or 1-3 per 100,000 courses of aminopenicillin, cephalosporin, and clindamycin antibiotic therapy. *C. difficile* exists normally in the environment and is found to asymptomatically colonize 4% of adults and 15%-75% of neonates. CAD is associated with antibiotic therapy, since antibiotics alter the microbial population of the gut, allowing the proliferation of resistant, disease-causing microbes. Nosocomial cases of CAD are high for this very reason. Most patients admitted to a hospital undergo some form of antibiotic therapy, and some of these patients are immunocompromised as well (i.e., AIDS, elderly, and transplant patients), thus making them susceptible to infection.

Upon suspicion of CAD, a physician may order a test for the presence of *C. difficile*. There currently are several practiced methods—enzyme-linked immunosorbant assay (ELISA), latex agglutination, and the gold standard, the culture cytotoxin assay. Identification of the infectious agent and confirmation of toxicity are the goals of the test. Each of the aforementioned testing methods requires several hours before the delivery of results, and each requires several complex steps taking up to 48 hours (more if such tests are performed offsite) before yielding any clinically relevant information. None of these tests confirms both the presence of the bacteria and the toxic agent in a single procedure. Biosite's Triage® *C. difficile* panel tests directly for toxins A and the common antigen, confirming the presence of both the organism and the disease-causing toxin in a simple process, yielding results in 15 minutes, with a sensitivity of 98% and a specificity of 99.7%.

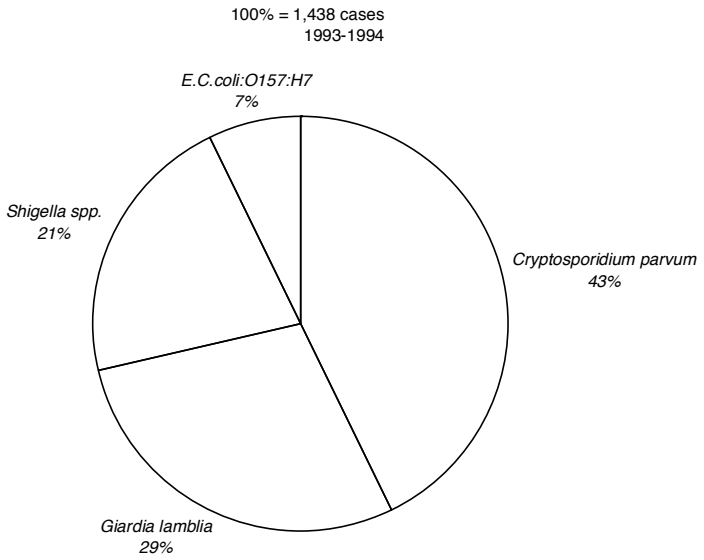
Upon diagnosis of CAD, patients are isolated and then undergo treatment with the antibiotic Vancomycin, and possibly surgical intervention in the most severe cases. Vancomycin is the last "silver bullet" in our fight against harmful microorganisms, and its misuse is leading to the development of super-microorganisms that are resistant to all forms of antibiotics currently available. The evolution of resistant bacteria has become a major concern for health care providers, and not enough steps are being taken to curb this problem. Thus, it is critical to have diagnostic tools to identify *C. difficile* quickly and accurately, both to minimize patient discomfort and to control the use of antibiotics in the hospital setting.

***The waterborne pathogens*—Giardia, Cryptosporidium, *and* Entamoeba.** *Giardia lamblia, Cryptosporidium parvum,* and *Entamoeba histolytica* are waterborne pathogens that are the scourge of travelers, campers, and the immunocompromised. These organisms are responsible for giardiasis, cryptosporidiosis, and amoebiasis, often in the form of widespread outbreaks endangering the safety of community water supplies. Figure 24, on the next page, illustrates the causes of cases in the United States in 1993 and 1994. The U.S. government recently revised the 1996 Safe Drinking Water Act, bringing much needed attention and funds ($870 million) to remedy this persistent danger.

Giardia lamblia is a heart-shaped protozoa that parasitizes the small intestine of humans and pigs. Affixing itself to the wall of the intestine, it interferes with normal fat absorption, causing diarrhea, dyspepsia, and malabsorption. In 1993, there were 5 outbreaks causing 385 cases of giardiasis, representing 29% of the outbreaks caused by a waterborne agent.

Cryptosporidium parvum is a cyst-forming protozoa that parasitizes the gastrointestinal tract of humans and other mammals, causing severe and sometimes fatal diarrhea. *Cryptosporidium* has been linked to 3 outbreaks and 403,237 cases of cryptosporidiosis, representing 43% of the outbreaks caused by a waterborne agent. An estimated 900 people die each year from severe cases of cryptosporidiosis. Of the cases in 1993, 403,000 were associated with a single outbreak in Milwaukee, where mismanagement of the municipal water supply led to endangerment of the public.

Figure 24
Biosite Diagnostics Incorporated
Waterborne Diseases By Agent



Source: Centers for Disease Control; William Blair & Company, L.L.C.

Entamoeba histolytica is a parasitic amoeba that colonizes the cecum and large colon of humans, causing amebic dysentery. If the organism enters the bloodstream, it can produce abscesses in organs such as the liver, kidney, and brain.

About 6 million diagnostic tests are conducted for these parasites annually. Currently, the presence of these disease-causing organisms is confirmed either by observing stool samples under the microscope to search for eggs and larvae or using "home-brewed" ELISAs or microtiter immunoassays. Again, the limitation with these tools is time and cost. The Triage® Parasite Panel from Biosite allows physicians to screen for the presence of all three pathogens easily, yielding clinically relevant information in 20 minutes.

Enteric bacteria. More than 250 diseases are linked to contaminated food or drink. These illnesses cause 6 million reported cases, 400-500 outbreaks, and 9,000 deaths annually. The common causative agents in most of these cases are infectious bacteria such as salmonella, E. coli, shigella, and campylobacter. These bacteria cause severe diarrhea and also can lead to other medical complications, such as kidney failure.

Three-and-a-half million stool cultures are conducted annually to diagnose and/or confirm the presence of these bacteria. The stool-culture method, though simple, is both time- and labor-intensive, yielding results in 48-72 hours. This delay effectively binds physician's hands. Biosite's development of a rapid assay, the Triage® Enteric, to accurately identify salmonella, E. coli, shigella, and campylobacter will reduce the testing time to 15 minutes and greatly reduce the labor associated with stool-culture testing, thereby cutting overall costs. Once diagnosed, a patient may be prescribed the antibiotic most effective against the specific infectious organism, or antibiotics may be withheld, depending on the bacteria identified and the state of the patient.

Appendix C: Regulatory Processes

Medical devices such as spinal implants and surgical systems are subject to government regulations in most countries. Therefore, Biosite's success in part hinges on its ability to achieve the necessary approvals and the time and expense of attaining those approvals.

Food and Drug Administration
The United States Food and Drug Administration (FDA) regulates medical devices, as well as medicines, cosmetics, food, the feed and drugs for farm animals and pets, and even radiation-emitting products like microwave ovens. To put this in perspective, the FDA regulates more than $1 trillion in products, or about a quarter of each dollar spent each year by consumers in the United States

Federal Food, Drug, and Cosmetics Act
The FDA first was granted limited authority over medical devices in 1938 through the Federal Food, Drug, and Cosmetics Act. The original intention of the Act was to grant the FDA the authority to seize misbranded or adulterated devices that were part of interstate trade. However, the FDA expanded its stated authority in certain circumstances by declaring a device a drug, thus requiring premarket approval. This self-expanded authority was upheld by the Supreme Court.

Medical Device Amendments
In 1976, Congress enacted the Medical Device Amendments, specifically subjecting medical devices to federal regulation. The amendments required good manufacturing practices (GMP) and created three levels of devices based on risk—Class I through III. In addition, two types of potential premarket authorization were defined—the premarket notification, or 510(k), and premarket approval (PMA).

Three Classes of Medical Devices
Products are classified based on risk, with riskier devices subject to greater controls. Of the approximately 1,700 classified medical devices, 45% are Class I, 47% are Class II, and 8% are Class III.

Class I devices pose minimal potential for harm and are subject to general controls.

- Register establishments with the FDA (strictly applies on U.S. establishments, but foreign establishments are also encouraged).
- List devices to be marketed with the FDA.
- Use good manufacturing processes (GMP) to make the devices (some Class I devices are exempt from parts of GMP).
- Label devices according to the proper labeling regulation.
- Submit 510(k) (premarket notification) prior to marketing a device (almost 75% of Class I devices are exempt from this).
- Examination gloves and elastic bandages are examples of Class I devices.

Class II devices are those for which special controls are needed in addition to the general controls described above. These controls might be postmarket surveillance or special labeling requirements. These devices are never exempt from premarket notification or GMP. Infusion pumps and powered wheelchairs are examples of Class II devices.

Class III devices are most strictly controlled, because they sustain life, present a potentially unreasonable risk of injury, or are crucial to prevent impairment of health. A PMA is required before the device can be marketed. This is a scientific review process requiring clinical trials to prove the safety and effectiveness of the product. Replacement heart valves and silicone gel-filled breast implants are examples of Class III devices that used the PMA process.

Some Class III devices may not require a PMA and might be able to obtain 510(k) clearance. These are devices that can show substantial equivalence to a device marketed before May 28, 1976, and for which there has been no published regulation specifically requiring a PMA for that device. Endosseous implants and pulse generators for pacemakers are examples of Class III devices that currently require only a 510(k).

Table 20
Biosite Diagnostics Incorporated
Classification of In Vitro Diagnostics

Product Type	Example	Process Required
Immunodiagnostic	DOA	510k
Immunodiagnostic	Toponin I	510k
Immunodiagnostic	Cyclosporin	PMA
Immunodiagnostic	Hepatitis	PLA

Source: FDA, William Blair & Company, L.L.C. estimates

510(k)
To use the 510(k) process, a new device must be shown to be substantially equivalent to a predicate device marketed prior to 1976—meaning, it has the same intended use and technological characteristics. Most devices—more than 90%—use the 510(k) process. The original act allowed a company to start marketing 90 days after submission if it had not received notification. However, this was amended through the Safe Medical Devices Act to require the company to wait to receive a notice of substantial equivalence from the FDA.

PMA
A PMA requires a thorough review of human clinical trials, as well as other tests of the device. To begin the clinical trials for the PMA, a company must receive an investigational device exemption (IDE) after describing the trial risks and protocols for the FDA. However, prior to any human trials, a company must obtain approval from the institutional review board (IRB) of the institution where it will conduct the trial. The IRB is an expert panel that assesses the risks involved in the trial. If the IRB determines that the device represents an insignificant risk, this approval alone is sufficient to begin the trial. The trial results then are reviewed by the FDA regarding both safety and efficacy. After a PMA is granted, supplements must be submitted if there are any design, labeling, or manufacturing changes that might affect the safety or efficacy of the device.

PLA
A PLA is another form of product approval. Issued by the FDA's Center for Biologics Evaluation and Research, PLAs follow a similar process as a PMA, yet pertain to devices that use biologicals such as antibodies and other blood derived products.

Clinical Laboratory Improvement Amendments (CLIA) of 1988
This amendment requires all labs conducting clinical testing to meet specified standards in personnel qualification, administration, and proficiency testing, patient test management, quality control and quality assurance. Three levels of regulatory control (waived, moderate and high complexity) have been instituted that dictate the certifications required of labs conducting these tests.

Safe Medical Devices Act (SMDA) of 1990
This act strengthened the enforcement authority of the FDA to monitor products that are marketed. For example, the SMDA gave the FDA authority to impose substantial civil monetary penalties for particular violations. In addition, it required summary of safety and effectiveness data for 510(k) filings, postmarket surveillance for certain devices, and reporting of death or injuries attributed to a device.

Medical Devices Amendments of 1992
These amendments helped clear up (and clean up) some of the regulations under the SMDA. For example, it created a single definition for which injuries must be reported. Also, it gave the FDA more leeway in issuing repair, replace, or refund orders for devices presenting unreasonable risks. Lastly, it gave the FDA more time to finalize device-tracking regulations.

Food and Drug Modernization Act of 1997
At the end of 1997, the U.S. Congress enacted legislation that was intended to make the FDA review process less arbitrary and more competitive with world standards without compromising the safety and efficacy of products marketed. The sections of the new law that apply to medical devices are highlighted below.

Investigational device exemptions (Section 201). When an applicant intends to perform a human clinical trial of any implantable or all Class III devices, the applicant has the opportunity to submit the plan in writing, and the FDA must meet with the applicant within 30 days. An official, binding record will be made of any agreement that is reached with the FDA.

Recognizing international device standards (Section 204). The FDA may officially recognize all or part of an international (or national) standard. Subsequently, an applicant may reference the standard in a Declaration of Conformity, which can be used to satisfy the requirement for a 510(k) or PMA. The FDA still may reject the Declaration if the information supplied does not prove compliance with the standard or the standard does not apply.

Data requirements for devices (Section 205). Changes to the law affect 510(k)s, PMAs, and manufacturing under PMAs.

- *Labeling claims for 510 (k)s.* If the Director of the Office of Device Evaluation (ODE) determines that there is a reasonable likelihood that a device will be used in an unintended way and that this use could cause harm, the ODE can require that a specific statement be placed in the labeling specifying the limitations for using the device. The device still would be found substantially equivalent.

- *Collaborative determination of PMA data requirements*. An applicant can request a meeting with the FDA to determine in advance what data will be necessary to support the safety and effectiveness of its device. The FDA must meet with the applicant and provide within 30 days of the meeting a binding, written document specifying what data is required to provide reasonable assurance. This chosen method also must be the least burdensome to satisfy the needs of the applicant.

- *Manufacturing under a PMA*. Changes to the manufacturing process that could affect the safety or efficacy of a product require only a written notice to the FDA, not a PMA supplement.

Exemptions from 510(k), including specific Class II devices (Section 206). If a Class I device is not intended for use that presents an unreasonable risk or injury or is not of substantial importance in preventing impairment of health, then it will not require a 510(k). In addition, the FDA will specify certain Class II devices that do not require 510(k)s. Examples of Class II devices that it has specified to date are clinical mercury thermometers, wheeled stretchers, blood-storage refrigerators, hematocrit measuring devices, and AC-powered adjustable hospital beds.

Risk-based classification of post-amendment Class III devices (Section 207). If an applicant receives a Not Substantially Equivalent (NSE) determination—placing the device into a Class III category—the applicant can request, within 30 days in writing, a reclassification of the product into Class I or II. The FDA has 60 days from the date of this request to classify the product in writing. If the device is classified Class I or II, then the applicant has received clearance and the device may be used by other applicants as predicate device for 510(k)s.

Review timeframes (Section 209). Changes were made to the law to further expedite the review processes for both 510(k)s and PMAs. Now, the law clearly states that the FDA must make 510(k) determinations no later than 90 days after receiving a submission. In addition, the FDA must meet with PMA applicants within 100 days of submission and prior to this meeting inform the applicant in writing of any deficiencies and what data would be needed to correct them.

Device tracking and postmarket surveillance (Sections 211 and 212). Manufacturers no longer automatically will be required to track devices or conduct postmarket surveillance. However, the FDA can specifically require that certain Class II or III devices be tracked or that postmarket surveillance be performed if the device satisfies one of the following conditions:

- Failure of the device would be reasonably likely to have serious adverse health consequences.
- The device is intended to be implanted for more than one year.
- The device is intended to sustain life outside a user facility.

The FDA may only order postmarket surveillance for up to three years without consent of the applicant.

Dispute resolution of scientific controversies (Section 404). The FDA is required to set up a process, which an applicant can invoke, to review scientific controversies when no other process is available. It will include an appropriate advisory committee or scientific panel.

Reengineering the Center for Devices and Radiological Health (CDRH)

Modular review process for PMAs. In the future, the FDA will review the needed scientific data for a PMA in modules as it becomes available. For example, all the data on animal testing would be reviewed, and if accepted, it would not be reexamined unless absolutely necessary. In addition to the other PMA modernization approaches discussed earlier, this

allows companies to ensure that the proper scientific and regulatory foundation is developed and accepted as the clinical trials proceed, rather than being told at the end that there were problems with early data.

New multitype 510(k) approach. For Class I and II products that still require 510(k)s, the CDRH will establish a system of three types of 510(k)—traditional, special, and abbreviated. The special 510(k) is for devices that have been modified, but the intended use has not changed, nor has the fundamental science of the technology. A company need only file a declaration of conformity to design controls and a short summary of the changes, and the FDA will process the application within 30 days. For a new device, if a manufacturer uses special controls or conforms to a standard, it may submit a summary of the special controls or a declaration of conformity to the standard to get an abbreviated 510(k).

Appendix D: Glossary

Acute myocardial infarction (AMI). Intense, sudden insufficiency of arterial or venous blood supply to the middle layer of the heart muscle (myocardium), which produces a macroscopic area of dead tissue.

American Heart Association (AHA). Public health association dedicated to providing education and information on fighting heart disease and stroke.

Analyte. Any substance or chemical mixture of blood, urine, or other body fluid that is analyzed.

Angina pectoris. Severe, constricting pain in the chest, often radiating from below the sternum to a shoulder (typically the left) and down the arm, due to inadequate flow of blood to the heart muscle (may be classified as stable of unstable angina).

Angiography. X-ray (radiography) of vessels after the injection of a contrast material impenetrable by radiation; usually requires needle insertion of a catheter, which is impenetrable by radiation, and positioning using the radiographic image. Often performed with a fluoroscope.

Antibody. Blood-protein molecule produced in immune response to the introduction of antigen (foreign body), which combines specifically with the antigen that induced its formation.

Antigen. Foreign molecule that induces the formation of antibody, which initiates an immune response.

Atherosclerosis. Distribution of fat-soluble (lipid) deposits in the interior of large and medium-sized arteries, which provokes hardening or calcification of these vessels.

Atrium. Upper chamber of the heart, which receives blood from the veins. There are two chambers, consisting of the right atrium, which receives deoxygenated blood, and left atrium, which receives oxygenated blood.

B-type natriuretic peptide (BNP). A potential in-vitro diagnostic marker for congestive heart failure (CHF).

CAD (coronary artery disease). Decrease in the amount of blood flow to the heart due to a narrowing of the blood vessels (coronary arteries) that deliver oxygen and nutrients to the heart. As a result, the heart cannot work efficiently. This decreases blood flow and oxygen to the entire body.

CCU (cardiac or critical care unit). Area of a hospital dedicated to the monitoring and treatment of admitted patients suffering from heart ailments.

CHD (congenital heart disease). Refers to a heart defect in which the heart or blood vessels near the heart do not develop normally before birth.

CHF (congestive heart failure). Condition in which the heart cannot pump enough blood to meet the needs to the body's other organs. As blood flow out of the heart slows, blood returning to the heart through the veins backs up, causing congestion (abnormal amount of fluid) in the tissues.

Cardiac marker. Molecules released as a result of a heart attack that can reflect this physiological change.

Chain of custody. The flow or list of people that come in contact with a laboratory sample.

Chest pain unit (CPU). A subsection of the ED or another special location where patients visiting the ED with chest pain are monitored to determine if they had a heart attack or are experiencing unstable angina.

Creatine kinase (CK). An enzyme catalyzing (initiating) a process important in muscle contraction.

CK-MB. A more specific form of creatine kinase (CK). It is an isozyme (a catalyst similar to an enzyme but different in its properties) that is elevated in plasma following myocardial infarction.

Clostridium difficile (C. difficile). A genus (group of similar species) of anaerobic (not requiring oxygen), sporeforming, motile (moving) bacteria found in the feces of newborn infants that is pathogenic (disease-causing) for human beings. Often the cause of colitis, diarrhea, and associated with a number of intestinal disease that require treatment with antibiotics.

CV (coefficient of variation). The ratio of the standard deviation (statistical index of the degree from the central tendency) to the mean (central tendency, or average of a set of numbers).

Creatine kinase. An enzyme initiating the reversible transfer of phosphate from phosphocreatine to ADP (adenosine 5'-diphosphate—primary energy currency of a cell) forming creatine and ATP (adenosine 5'-triphosphate—a muscle enzyme), important in muscle contraction. This isozymes (catalysts similar to an enzyme but different in their properties) is used as a cardiac marker, as defined above, due to its elevated levels in the blood following a heart attack.

Cryptosporidium. Type of parasite (e.g., organism that lives in a host and depends on the host for its own survival) that is an important disease-causing pathogen of calves and other domestic animals and common opportunistic parasites of humans that flourish under conditions of compromised immune function.

Cyclosporine. Immunosuppressant (e.g., lowers the body's immune or disease-fighting response) used to inhibit organ transplant rejection.

Cytotoxin. A substance, which may be an antibody, that inhibits or prevents the functions of cells and/or causes destruction of cells.

Diagnosis related group (DRG). A classification of patients by diagnosis or surgical procedure into major diagnostic categories (containing specific diseases and/or procedures) for the purpose of determining payment of hospitalization charges; based on the premise that treatment for similar medical diagnoses generate similar costs.

ECG. One of two abbreviations for electrocardiogram (defined below).

ELISA (enzyme-linked immunosorbent assay). An antibody-based diagnostic test.

ED (emergency department). Area of a hospital that treats patients with sudden illness and injuries; sometimes referred to as the ER or emergency room.

EKG. One of two abbreviations for *electrocardiogram* (defined below).

Electrocardiogram. Graphic record of the electrical currents that pass through the heart muscle and initiate its contraction, producing a heartbeat; also referred to as ECG or EKG.

Endotoxin. A bacterial poison.

Entamoeba. A genus of amoeba (single-cell organism) parasite in the cecum (first part of the large intestine) and large bowel; most species are relatively harmless to the host.

Enteric. Relating to the intestine.

Fibrin. A filamentous protein associated with blood clotting.

Giardia. A genus of parasite flagellates (organisms with whiplike locomotion) that live in the small intestine.

GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries). A series of clinical trials for the assessment of the treatment of cardiovascular disease.

Immunoassay. Detection and testing of substances using antibodies.

Immunosuppressive. Substance that prevents or interferes with the response of the body's immune system.

In vitro diagnostic. Diagnosing a condition or ailment outside the body, such as a test tube or culture media.

Ischemia. Local anemia (e.g., less-than-normal number of red blood cells or hemoglobin) and subsequently lower oxygen supply due to a mechanical obstruction of the blood supply, often caused by arterial narrowing.

Ischemic heart disease. Inadequate blood supply (circulation) to the heart due to blockage of the blood vessels to the heart.

LBP (lipopoly saccharide binding protein). A combination or complex of lipid and carbohydrate that acts like an endotoxin and is released from the cell walls of pathogenic organisms, which produces a physical disturbance or septic (toxic) shock.

Myocardial infarction. See "acute myocardial infarction."

Myocardium. Middle layer of the heart, consisting of cardiac muscle.

Myoglobin (Mb). Oxygen-transporting and storage protein of muscle that resembles blood hemoglobin in function but contains only one subunit and has a smaller atomic weight.

Myosin. A blood protein present in muscle that forms the thick filaments in muscle.

Necrosis. Disease-caused death of one or more cells, or of a portion of tissue or organ resulting from irreversible damage.

Negative predictive value. An expression of the likelihood that a given test result correlates with the absence of disease. The ratio of patients without the disease who test negative to the entire population of individuals with a negative test (see section on accuracy).

Nosocomial. Hospital-acquired infection.

Occlusion. A closure or closed area.

Parasite. An organism that lives on or in another and draws its nourishment therefrom.

Perfusion. Flow of blood or other fluid.

Plaque. Buildup of lipids along the walls of the arteries.

Point of care (POC). Location where treatment is rendered or administrated to a patient.

Point-of-care testing (POCT). Testing done at the point of care, as opposed to a central location such as a central hospital laboratory or commercial laboratory.

Positive predictive value. An expression of the likelihood that a given test result correlates with the presence of disease; ratio of patients with the disease who test positive to the entire population of individuals with a positive test result (see section on accuracy).

Reagent rental. Program in which a medical device manufacturer provides equipment to a medical facility for testing, which in return agrees to purchase reagents exclusively from the same device manufacturer at prices higher than the reagents would have been had the instrument been purchased outright.

Sensitivity. The proportion of individuals with a positive test result for the disease that the test intended to reveal (see section on accuracy).

Serial testing. Repeated testing over time as part of diagnostic protocol.

Specificity. The proportion of individuals with negative test results for the disease that the test intended to reveal (see section on accuracy).

ST elevation. Part of the EKG reading that indicates the portion of the heart that has experienced cell death.

STAT. Immediate or short turnaround time.

Thrombosis. Formation or presence of a clot in the cardiovascular system formed during from components of blood; clotting within a blood vessel that may cause an infarction (sudden insufficiency of arterial or venous blood supply that produces a macroscopic area of dead tissue) of tissues supplied by the vessel.

Triage. The initial examining and sorting of patients by likely medical condition and the particular medical condition's likely risks and severity.

Troponins. A three-subunit (C, T, and I) complex of regulatory proteins found in striated heart muscle. In healthy individuals, the serum levels of these proteins are very low, since there is little turnover (death) of cardiac cells. Damage to cardiac tissue as a result of AMI leads to the release of these proteins in or free forms, thus lending themselves to a very specific assay for AMI.

Cardiac Troponin C (cTn C). Calcium-binding 18 kDa subunit of the troponin complex.

Cardiac Troponin T (cTn T). Tropomyosin-binding 37 kDa subunit of the troponin complex.

Cardiac Troponin I (cTn I). Inhibitor of the calcium-dependent actomyosin ATPase.

Unstable angina. Severe constricting pain in the chest of coronary origin occurring in response to progressively *less* exercise or fewer other stimuli than ordinarily required to produce result; often leads to acute myocardial infarction.

Ventricle. Lower chambers of the heart that receive blood from the atrium and pump it out to the body through the arteries. There are two chambers consisting of the right ventricle, which receives deoxygenated blood from the right atrium and drives it out to the lung through the pulmonary artery, and left ventricle, which receives oxygenated blood from the left atrium and drives it out of the body through the aorta.