

The background of the entire page is a light blue color. It features several petri dishes, some of which contain a dark purple or blue substance. A pipette tip is visible, positioned over one of the dishes. The overall aesthetic is scientific and clinical.

TriMark Publications

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# DIABETES, METABOLIC SYNDROME AND CARDIOVASCULAR DISEASE

*(SAMPLE COPY, NOT FOR RESALE)*

Reshaping Tomorrow's Diabetes Market

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## 1. Overview

### 1.1 Statement of Report

There has been a dramatic increase in the incidence of diabetes worldwide, which has been exacerbated by the growing obesity problem across the globe. Once thought of as primarily a childhood disease—sometimes referred to as juvenile diabetes, now mostly Type 1 diabetes—the obesity crisis linked to the adoption of high-fat, high-carbohydrate, high-calorie American diets has resulted in skyrocketing rates of diabetes among adults across the world. To compound the global diabetes epidemic, health professionals are witnessing an alarming increase in inflammatory diseases resulting from adult onset (*i.e.*, Type 2) diabetes. This phenomenon is referred to as “metabolic syndrome,” where a confluence of inflammatory conditions occur along with the diabetes. As a result, growing evidence appears to show that metabolic syndrome makes the diabetic patient susceptible to degenerative health conditions such as cardiovascular disease, stroke and, now believed, Alzheimer’s disease.

As the diabetes epidemic escalates, a new sense of urgency has taken hold. Proactive strategies for prevention of the disease are being put in place by international health organizations such as the World Health Organization, as well as by the health departments of industrialized and developing countries, and even at the local level where food ingredients regulations are being passed. This report charts the changing landscape of the global diabetic population and explores the added health concerns resulting from the metabolic syndrome phenomenon and one of its major risk factors: cardiovascular disease (CVD). Furthermore, this study evaluates widely-accepted therapeutic approaches to diabetes that are currently in use, while providing an in-depth analysis of emerging technologies that will be used to treat diabetes and other inflammatory diseases in the future.

### 1.2 About this Report

The main objectives of this report are to:

- Identify viable technology drivers through a comprehensive look at various platform technologies for diabetes, metabolic syndrome and CVD.
- Provide a complete understanding of the leading diabetes tests that are used for disease prediction, screening, and prognosis and monitoring, encompassing their basic principles and applications.
- Discover feasible market opportunities via an identification of high-growth applications in different therapeutic areas, with a focus on the largest and most rapidly expanding markets for diabetes, metabolic syndrome and CVD.
- Focus on global industry development through an in-depth analysis of the major world markets for diabetes therapeutics, including forecasts for growth.
- Summarize the blood glucose testing market, including definitions, processes and trends.

Market figures regarding the current value of the diabetes drug market are taken from the most recently available data of the global pharmaceutical industry. The following categories of diabetes drugs will be covered herein:

- Rapid-acting insulin.
- Short-activity insulin.
- Intermediate-acting insulin.
- Long-acting insulin.
- Ultra-long-acting insulin.
- Insulin mixtures.
- Sulfonylureas.
- Meglitinides.
- Biguanides.
- Thiazolidinediones.
- $\alpha$ -Glucosidase inhibitors.
- Incretin (GLP-1) mimetic.
- Amylin analog.
- Dipeptidyl peptidase IV inhibitors.

- Sodium-glucose co-transporter-2 (SGLT-2) inhibitors.
- 11 $\beta$ -Hydroxysteroid dehydrogenase Type 1 (11 $\beta$ -HSD1) inhibitors.
- AMP-activated protein kinase (AMPK) activators.
- Fatty acid synthase (FAS) inhibitors.
- Recombinant adiponectin derivatives.

This market analysis includes the use of charts and graphs to show product growth and marketplace trends. In addition, a discussion of the biology underlying diabetes provides the reader with a more comprehensive understanding of the possibilities for future treatment as well as avenues for possible R&D budgets.

In addition, this report will:

- Assess the diabetes, metabolic disease and CVD market drivers and bottlenecks, from the perspective of the medical and scientific research communities.
- Discuss the potential opportunities of the diabetes, obesity and metabolic disease market for various sectors of the medical and scientific community.
- Establish the current total market size and future growth of the diabetes, obesity and metabolic disease market and analyze the current size and growth of therapeutic segments.
- Provide current and forecasted market shares for each company.
- Discuss profit and business opportunities for each therapeutic segment.
- Provide strategic recommendations for near-term business opportunities.
- Assess current commercial applications used by the diabetes, obesity and metabolic disease market.
- Assess the blood glucose-testing business mode.

### 1.3 Scope of the Report

This report concentrates on the diabetes, metabolic syndrome and CVD therapies market segment in major worldwide markets. It will discuss the market size, growth rates and market components for instruments and reagents, controls and consumables used in blood glucose testing. Business trends, technology trends and developing areas of pharmaceutical therapies for diabetes, metabolic syndrome and CVD will also be addressed. The market for such therapies in clinical use is presented here in detail. In addition, the dollar volume of sales, both worldwide and in the U.S., are reported, and the factors that influence the size and growth of individual market segments are discussed. The market sizes and growth rates for the U.S. and world markets are described in detail.

Emphasis is on those companies that are actively developing and marketing therapies for diabetes, metabolic syndrome and CVD. Leading companies are discussed in depth with a section on the history of the company, the product line, business and marketing analysis, and a subjective commentary of the position of the company in its market. Certain topics are discussed only briefly when they are peripherally related to the major elements of this report. However, these topics may constitute an entirely different field or market. One such example is the category of instruments used in clinical chemistry testing. Although they form the foundation for molecular diagnostic testing of blood glucose levels, in the interest of brevity, these were not analyzed in depth in this report. The reader is encouraged to consult other TriMark Publications reports at <http://www.trimarkpublications.com> for a detailed discussion of important individual market segments related to diabetes, metabolic syndrome and CVD, such as clinical chemistry testing, high-growth diagnostic test markets, blood gas and electrolytes, over-the-counter (OTC) diagnostic testing markets, and point of care (POC) testing.

### 1.4 Methodology

The author of this report is a Ph.D. in biochemistry from the University of Minnesota, with many decades of experience in science writing and as a medical industry analyst. He has over 30 years of experience in laboratory testing and instrument and reagent development technology, as well as extensive experience in senior level positions in biotech and medical service companies. The senior editor is a Ph.D. in physiology from the University of Toronto and is a post doctoral research fellow in the Department of Cell and Systems Biology at the University of Toronto. The editor is a Ph.D. in life sciences from Jawaharlal Nehru University with an extensive background in molecular biology.

Company-specific information is obtained mainly from industry trade publications, academic journals, news and research articles, press releases and corporate websites, as well as annual reports for publicly-held firms. Additionally, sources of information include the non-governmental organizations (NGOs) such as the World Health Organization (WHO) and governmental entities like the U.S. Department of Health and Human Services (HHS) and U.S. federal agencies such as National Institutes of Health (NIH), Food and Drug Administration (FDA) and the Centers of Disease Control and Prevention (CDC). Where possible and practicable, the most recent data available have been used.

Some of the statistical information was taken from Biotechnology Associates' databases and from TriMark's private data stores. The information in this study was obtained from sources that we believe to be reliable, but we do not guarantee the accuracy, adequacy or completeness of any information or omission or for the results obtained by the use of such information. Key information from the business literature was used as a basis to conduct dialogue with and obtain expert opinion from market professionals regarding commercial potential and market sizes. Senior managers from major company players were interviewed for part of the information in this report.

### ***Primary Sources***

TriMark collects information from hundreds of Database Tables and many comprehensive multi-client research projects, as well as Sector Snapshots that it publishes annually. TriMark extracts relevant data and analytics from its research as part of this data collection.

### ***Secondary Sources***

TriMark uses research publications, journals, magazines, newspapers, newsletters, industry reports, investment research reports, trade and industry association reports, government-affiliated trade releases and other published information as part of its secondary research materials. The information is then analyzed and translated by the Industry Research Group into a TriMark study. The Editorial Group reviews the complete package with product and market forecasts, critical industry trends, threats and opportunities, competitive strategies and market share determinations.

### ***TriMark Publications Report, Research and Data Acquisition Structure***

The general sequence of research and analysis activity prior to the publication of every report in TriMark Publications includes the following items:

- Completing an extensive secondary research effort on an important market sector, including gathering all relevant information from corporate reporting, publicly-available data and proprietary databases.
- Formulating a study outline with the assigned writer, including important items, as follows:
  - Market and product segment grouping, and evaluating their relative significance.
  - Key competitors' evaluations, including their relative positions in the business and other relevant facts to prioritize diligence levels and assist in designing a primary research strategy.
  - End-user research to evaluate analytical significance in market estimation.
  - Supply chain research and analysis to identify any factors affecting the market.
  - New technology platforms and cutting-edge applications.
- Identifying the key technology and market trends that drive or affect these markets.
- Assessing the regional significance for each product and market segment for proper emphasis of further regional/national primary and secondary research.
- Completing a confirmatory primary research assessment of the report's findings with the assistance of expert panel partners from the industry being analyzed.

### 1.5 Executive Summary

Diabetes mellitus is a disease characterized by dysregulated levels of insulin, a pivotal hormone that regulates blood glucose levels. There are two main forms of diabetes: Type 1 and Type 2. Type 1 diabetes, once referred to as juvenile diabetes, is an autoimmune disease that is typically manifested in early childhood and results from the rapid and complete obliteration of the pancreatic beta cells that produce insulin. Delivery of insulin into the bloodstream is required, or else death will ensue. Type 2 diabetes, once referred to as adult onset diabetes, is heralded by a slow but progressive loss of pancreatic beta cell function and characterized by decreased responsiveness to insulin of many tissues responsible for central metabolism. Type 2 diabetes is commonly treated with oral anti-diabetes drugs that supplement endogenous uptake of glucose by peripheral tissues in order to clear the glucose from circulation as rapidly as possible. In addition, the Centers for Disease Control and Prevention (CDC) recently reported that nearly █% of people with Type 1 and Type 2 diabetes currently taking medication in the U.S. are treated with insulin; while █% of diagnosed diabetics (Type 1 or Type 2) are currently prescribed oral medication only.

The fasting plasma glucose (FPG) test is the preferred test to diagnose diabetes in children and non-pregnant adults. Criteria for the diagnosis of diabetes in non-pregnant adults are shown in the following table. Three ways to diagnose diabetes are available, and each must be confirmed on a subsequent day unless unequivocal symptoms of hyperglycemia are present. Although the 75g oral glucose tolerance test (OGTT) is more sensitive and modestly more specific than the FPG to diagnose diabetes, it is poorly reproducible and difficult to perform in practice. Because of ease of use, acceptability to patients, and lower cost, the FPG is the preferred diagnostic test. Although the OGTT is not recommended for routine clinical use, it may be useful for further evaluation of patients in whom diabetes is still strongly suspected but who have normal FPG or impaired fasting glucose (IFG). Due to lack of evidence on prognostic significance and diagnostic thresholds, the use of the A1C for the diagnosis of diabetes is not recommended at this time.

**Table 1.1: Criteria for the Diagnosis of Diabetes**

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<ul style="list-style-type: none"> <li>█</li> </ul>	or	<ul style="list-style-type: none"> <li>█</li> </ul>

Note: █  
Source: █

Compared to other disease markets, diabetes patients constitute an especially large market, comprised of █ patients in the U.S. and █ patients worldwide with Type 2 diabetes. Type 1 diabetes (f/k/a juvenile diabetes) is much less common than Type 2 diabetes (f/k/a adult-onset diabetes) and typically affects younger individuals. Type 1 diabetes usually begins before age █, although this is not without exception. In the U.S., the peak age at diagnosis is around █ years. Type 1 diabetes is associated with deficiency (or complete lack) of insulin. It is not known why, but the pancreatic islet cells fail to produce insulin in the quantities needed to maintain a normal blood glucose level. Without sufficient insulin, the blood glucose rises to levels that can cause symptoms associated with hyperglycemia, which also occur in Type 2 diabetes. It has been estimated that the yearly incidence of Type 1 diabetes is █ per █. Nearly █ Americans may suffer from this form of diabetes; each year more than █ children are diagnosed with diabetes in the U.S. That's █ children per day.

Far more prevalent is Type 2 diabetes, which plagues the other █% to █% of the diabetic population in the U.S. Because the prevalence of Type 2 diabetes has recently been described as epidemic, the impact of this disease in the near future will exceed current influence. In █, the global retail sales of diabetes drugs (oral and injectable) totaled \$█, which was █ the sales of \$█ only █ years ago.

Modern diabetes drugs can successfully treat the symptoms of diabetes but fail to suppress the progression of diabetes and diabetic complications. The primary area of pharmaceutical development for the treatment of Type 1 diabetes, an autoimmune disease, is insulin-delivery technologies. There are many consequences of this dramatic increase in the number of patients of diabetes. Foremost, diabetes is a disease for which long-term pharmacological maintenance is a necessity in virtually all cases. Moreover, this condition inexorably worsens over time and must be remedied by increased medication, including combination therapy. Secondly, diabetes is typically associated with a host of co-morbidities, including:

- Cardiovascular disease (CVD).
- Renal function.
- Deterioration of vision.
- Neuropathy.

These co-morbidities require vigilant surveillance and management, and in most cases, require pharmacological intervention that can incur high medical care costs. Key opinion leaders recognize these precipitating or interrelated conditions as a new disease state called “metabolic syndrome”. These efforts are intended to assist in early recognition and pharmacological intervention of patients at risk for diabetes. Of particular interest is the strong correlation between diabetes and CVD, a component of metabolic syndrome. As a result, diabetes experts are increasingly urging diabetes screening by cardiologists, and conversely, that endocrinologists prescribe CVD agents when diagnosing Type 2 diabetes. The net outcome of this trend will be an increased number of prescriptions written for both disease states.

Among the growing number of patients with diabetes are new patient subpopulations. Specifically, the indoctrination of an “American” lifestyle in many growing economies is resulting in increased prevalence of diabetes, even in developing nations. In addition, whereas diabetes was previously a health concern of the elderly, epidemiological data have shown that record numbers of middle-aged adults and children are now at risk or patients of this condition. Not only are the needs of these groups somewhat unique, their predominance also means that the average patient will require medical attention for decades longer than the typical diabetes patient in the past. This can have grave ramifications for the prevalence of co-morbidities such as:

- Dyslipidemia.
- Hypertension.
- Kidney failure.
- Psychological outcomes such as depression.

The societal burden for uncontrolled diabetes and/or debilitating diabetes-related complications extend beyond medical care: worker’s disability, unemployment and disturbance to family structure are just a few. As such, there has been mounting concern among policy-makers. In fact, the U.S. government has declared “war” on obesity, since it is a major health risk precipitating Type 2 diabetes. Quality of life and the monetary ramifications for government-supported healthcare are two key reasons for the government’s commitment to this issue. It is widely accepted that Type 2 diabetes is a largely preventable disorder, and research clearly confirms that the co-morbidities of diabetes can be forestalled or prevented with early and aggressive management of elevated glucose levels, the primary contributor to the co-morbid conditions of diabetes. The following list of facts about diabetes has been compiled from the [REDACTED], [REDACTED].

- Diabetes currently affects [REDACTED] people worldwide and is expected to affect [REDACTED] by [REDACTED].
- In [REDACTED], the five countries with the largest numbers of people with diabetes were: [REDACTED] ([REDACTED]), [REDACTED] ([REDACTED]), [REDACTED] ([REDACTED]), [REDACTED] ([REDACTED]) and [REDACTED] ([REDACTED]).
- In [REDACTED], the five countries with the highest diabetes prevalence in the adult population were: [REDACTED] ([REDACTED]%), [REDACTED] ([REDACTED]%), [REDACTED] ([REDACTED]%), [REDACTED] ([REDACTED]%) and [REDACTED] ([REDACTED]%).
- By [REDACTED], the largest increases in diabetes prevalence will take place in [REDACTED] countries.

- Each year a further [REDACTED] people develop diabetes.
- Each year [REDACTED] deaths are attributable to diabetes. An even greater number die from CVD, made worse by diabetes-related lipid disorders and hypertension.
- Every [REDACTED] seconds a person dies from diabetes-related causes.
- Every [REDACTED] seconds [REDACTED] people develop diabetes.
- Diabetes is the [REDACTED] leading cause of global death by disease.
- At least [REDACTED]% of all people with diabetes are unaware of their condition. In some countries, this figure may reach [REDACTED]%.
- Up to [REDACTED]% of Type 2 diabetes is preventable by adopting a healthy diet and increasing physical activity.
- Diabetes is the largest cause of kidney failure in developed countries and is responsible for huge dialysis costs.
- Type 2 diabetes has become the most frequent condition in people with kidney failure in countries of the Western world. The reported incidence varies between [REDACTED]% and [REDACTED]% in countries such as Germany and the U.S.
- [REDACTED] percent to [REDACTED]% of people with diabetes die of renal failure.
- It is estimated that more than [REDACTED] people worldwide are affected by diabetic retinopathy.
- Diabetic retinopathy is the leading cause of vision loss in adults of working age ([REDACTED] to [REDACTED] years) in industrialized countries.
- On an average, people with Type 2 diabetes will die [REDACTED] to [REDACTED] years before people without diabetes, mostly due to CVD.
- CVD is the major cause of death in diabetes, accounting for some [REDACTED]% of all diabetes fatalities, and much disability.
- People with Type 2 diabetes are over [REDACTED] as likely to have a heart attack or stroke as people who do not have diabetes. Indeed, people with Type 2 diabetes are as likely to suffer a heart attack as people without diabetes who have already had a heart attack.
- An estimated [REDACTED] U.S. residents have the metabolic syndrome.
- An estimated [REDACTED] in [REDACTED] [REDACTED] to [REDACTED]-year-old adolescents in the U.S., has the metabolic syndrome, or [REDACTED]% overall ([REDACTED]% for males; [REDACTED]% for females).

The [REDACTED] defines the metabolic syndrome as having three or more of the following abnormalities: Waist circumference greater than 102 cm (40 inches) in men and 88 cm (35 inches) in women.

- Triglyceride level of 150 mg/dL or higher.
- High-density lipoprotein (HDL) cholesterol level less than 40 mg/dL in men and 50 mg/dL in women.
- Blood pressure of 130/85 mm Hg or higher or drug treatment for hypertension.
- Fasting plasma glucose level of 100 mg/dL or higher.

Though widely accepted, and at times fiercely advocated, there has been an intense debate over the existence of the “metabolic syndrome” in academic circles. In the nearly two decades since the term joined the medical vernacular, the concept of the metabolic syndrome has, by now, been widely accepted by many clinicians as a useful and strong indicator of increased risk for diabetes and cardiovascular disease (CVD). But beyond definitions, opinions are widely divided about what metabolic syndrome means and the role that the diagnosis should serve in primary care. Some clinicians maintain that a diagnosis of metabolic syndrome is unnecessary, because better, more robust predictors of CVD, such as the Framingham Risk Assessment Score, exist, and a diagnosis of metabolic syndrome has no appreciable effect on either prognosis or treatment. While The American Diabetes Association (ADA) is fostering the concept of “cardio-metabolic risk,” the American Heart Association (AHA) continues to use the term metabolic syndrome.

In the words of Robert Eckel, MD, of the University of Colorado at Denver and Health Sciences Center, and former president of the AHA:

“Let’s not be so concerned about the term. If we change the term to cardio-metabolic risk, we’re still talking about the same elephant. We may be feeling the leg vs. the trunk, but the elephant is a clustering of risk factors that relate to cardiovascular disease and diabetes.”

The diabetes therapeutics market is divided into two primary pharmacological interventions: non-insulin, mostly oral anti-hyperglycemic agents; and insulin delivery technologies. Excessively high levels of circulating glucose is toxic to many organ systems, hence diabetes-related complications can arise when blood glucose levels go unchecked. To date, oral anti-diabetes agents address elevated glucose levels through a number of different mechanisms of action that are expanding rapidly as improved therapies enter the marketplace. In the category of insulin delivery, modifications are being developed to improve the rate of onset and duration of effect. Additionally, entirely novel types of delivery systems are also being developed. These non-injectable formulations are intended to provide alternatives to the pain, inconvenience and social stigma associated with the traditional method of needle-injections.

Currently, the key players in the diabetes market (and their principal products in this market) are Novo Nordisk (broad range of insulin products and a robust non-insulin anti-diabetic pipeline), Takeda (Actos<sup>®</sup>), GlaxoSmithKline (Avandia<sup>®</sup>), Eli Lilly (Humulin<sup>®</sup>, Humalog<sup>®</sup>, Byetta<sup>®</sup>) and Amylin pharmaceuticals (Byetta<sup>®</sup>, Symlin) and Merck & Co. (Januvia<sup>®</sup>), Bristol-Myers Squibb (BMS) and AstraZeneca, both of whom have strong presence in the CVD market, are also actively developing anti-diabetes drugs. A number of manufacturers also benefit from the wide use of anti-diabetes drugs that are already produced as generic medications (*e.g.*, metformin and most sulfonylureas).

Metformin, the sulfonylureas and the thiazolidinediones (TZDs) were the most prescribed classes of non-insulin anti-diabetic medications, accounting for █% of all prescriptions in the U.S. However, with metformin and the sulfonylureas without patent protection, and the newer drugs Byetta and Januvia only recently introduced in the market, the TZDs captured close to █% of the value of the non-insulin anti-diabetic market in the U.S. in █.

While currently available anti-diabetes agents are indispensable, such approaches are not free of clinical disadvantages. Hence, there is certainly room for new agents. For example, new options are emerging that are not associated with classical side effects of existing therapies, such as weight gain. Drugs that are able to address multiple co-morbidities associated with diabetes will also draw the attention of prescribers. Agents currently in the pipeline may enhance the ability to manage this condition at a premium acquisition cost, but are not likely to cure diabetes. Amelioration of diabetes-related complications will come more from early and aggressive intervention, a second factor that will expand the market.

Management of incretin levels represents a novel treatment among emerging oral agents. Increased levels of incretins have the potential to cause delayed gastric emptying and to stimulate insulin secretion, two processes that are favorable for diabetes management. Glucagon-like peptide 1 (GLP-1) has been found to be impaired in patients with Type 2 diabetes. GLP-1 and Dipeptidyl peptidase IV (DPP-IV) are two endogenous compounds that regulate incretins and are being explored for clinical use. DPP-IV is an enzyme that degrades endogenous GLP-1. Eli Lilly and Amylin’s Byetta (Exenatide), a GLP-1 agonist, the first in a class of anti-diabetic drugs based on incretin hormones, was approved by the U.S. Food and Drug Administration (FDA) in █.