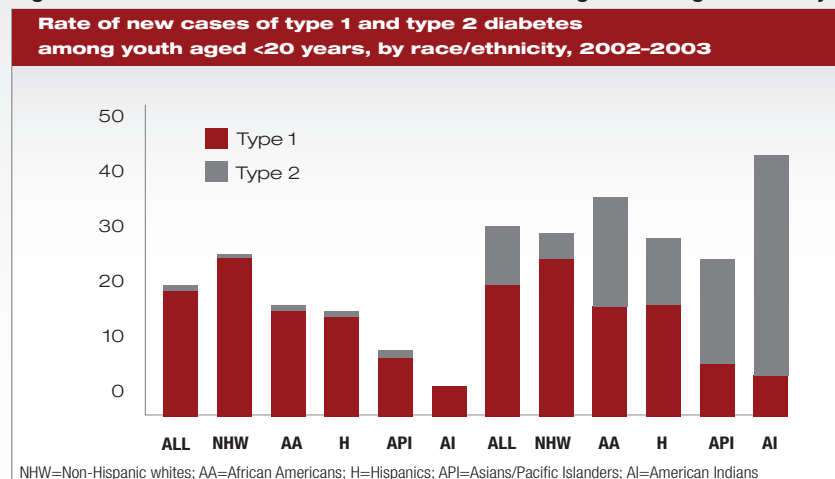


Fig. 5. Rate of New Cases of T1 and T2D Among Youth Aged &lt;20 by Race/Ethnicity 2002-2003



Source: CDC, SEARCH for Diabetes in Youth Study, Best Industry Research

Table 1. Diabetes Statistics at a Glance

<b>Diabetes Prevalence in the United States, 2007</b>	
Undiagnosed diabetes	5.7 million people
Diagnosed Diabetes	17.9 million
Pre-diabetes	57 million
<b>Economic Implications of diabetes in the United States, 2007</b>	
Annual economic cost of diabetes	\$174 billion
Costs due to medical expenditures	\$117 billion
Diabetes care	\$27 billion
Diabetes related complications	\$58 billion
Excess medical costs	\$31 billion
Indirect costs	\$58 billion
Diabetes related hospitalizations	24.3 million days
Average cost of hospital inpatient day due to diabetes	\$1,853
Average cost of hospital inpatient day due to complications related to diabetes	\$2,281
<b>Diabetes Mortality, 2007</b>	
Number of deaths due to diabetes	72,507
Number of deaths due contributed due to diabetes	233,619

### Meglitinides

Like sulfonylureas, meglitinides also stimulate the pancreatic beta cells to release insulin by closing the potassium channels of the cells and opening the sodium channels instead. Meglitinides enhance insulin release from the pancreas over a short period of time and only when the glucose level is high. Thus producing less risk of hypoglycemia than sulfonylureas.

There are two drugs belonging to this class which are used for type 2 diabetes treatment:

**Table 5. Key Meglitinides Available in the United States, 2009**

Generic name	Brand name	Brand manufacturer
Repaglinide	Prandin	Novo Nordisks
Nateglinide	Starlix	Bristol Myers Squibb

Meglitinides are short acting and are much more expensive than sulfonylureas.

### Biguanides

Biguanides decrease blood glucose by decreasing glucose produced by the liver. Biguanides offer a lower risk of hypoglycemia, minimal impact on weight and are very economical to use. Biguanides are used with extreme caution in patients with liver or kidney problems due to lactic acid build up. Use of biguanides also increases gastrointestinal side effects such as, nausea and diarrhea.

Metformin, a biguanide, is now considered synonymous with type 2 diabetes treatment. Glucophage is the branded version of metformin marketed by Bristol Myers Squibb. Since losing its patent in 2002, Glucophage it is now available as generic metformin. Some of the common generic metformin available on the market are Fortamet, Glumetza and Riomet. Glucophage is also available in extended release versions Glucophage ER and Glucophage XL. A liquid form of metformin, Riomet, is manufactured by Ranbaxy Pharmaceuticals Inc.

### Thiazolidinediones

Thiazolidinediones, also known as the glitazone group or (TZDs) of medicines, work by reducing the glucose produced by the liver and help to increase uptake of insulin in muscle and fat areas. Currently, rosiglitazone (brand name Avandia) and pioglitazone (ACTOS) are the only two TZDs available on the market. Troglitazone (Rezulin), the first TZD available in the market, was withdrawn from the market by its manufacturer, Parke-Davis, in March 2001 due to increased instances of drug induced hepatitis.

**Table 6. Key Thiazolidinediones Available in the United States, 2009**

Generic name	Brand name	Brand manufacturer
Rosiglitazone	Avandia	GSK
Rosiglitazone and glimipiride	Avandaryl	GSK
Rosiglitazone and metformin	Avandamet	GSK
Pioglitazone	ACTOS	Takeda Pharmaceuticals
Pioglitazone and metformin	ACTOplus met	Takeda Pharmaceuticals
Pioglitazone and metformin (extended release)	ACTOplus met XR	Takeda Pharmaceuticals

There have been concerns expressed by the medical community that both Avandia and ACTOS may increase cardiovascular risks. Other disadvantages of this class of drugs are an increased risk of edema, fracture, anemia, LDL cholesterol, and a high cost for treatment. Since the earlier drug, troglitazone, was taken off market due to liver complications, hepatic side effects of this class are being monitored.

Type 2 diabetics are usually administered insulin in addition to the oral anti-diabetics. Close to 19 million Americans are currently diagnosed with type 2 diabetes and hence, require medications which will lower their blood glucose. Of these, approximately 25 to 30 percent of type 2 diabetics are required to take insulin on a regular basis. An increasing aging population, sedentary lifestyle, obesity and high intake of junk food are the main factors leading to higher incidences of type 2 diabetes. This increase in number of type 2 diabetes incidence, coupled with improved diabetes management programs is leading to high growth of the insulin market.

### Insulin Products in Development

Table 14. Insulin Products in Development, 2009

Product Name	Class	Company	Status
APIDRA SoloSTAR	Insulin	Sanofi Aventis	Approved in February 2009
NovoMix 50 and 70	Insulin Mix	Novo Nordisk	Filed
AFRESA	Inhaled Insulin	MannKind Corporation	Pending FDA approval
VIAject	Very rapid acting injectable insulin	Biodel, Inc.	Phase 3
N5401	Insulin	Novo Nordisk	Phase 2
ORMD-0801	Oral insulin capsule	Oramed	Phase 2B
NA	Rapid acting insulin nasal spray	MDRNA	Phase 2 completed
HDV1	Injectable short acting insulin	Diasome Pharmaceuticals	Phase 2
HDV-B	Injectable basal long acting insulin	Diasome Pharmaceuticals	Phase 2
Oral HDV-I	Oral insulin	Diasome Pharmaceuticals	Phase 2
Oral-lyn	Insulin spray	Generix Biotechnology	Phase in 2 in United States
Nasulin	Intranasal insulin	CPEX Pharmaceuticals	Phase 2
VIAtab	Oral insulin formulation	Biodel Inc	Phase 1
ODose	Inhaled insulin	MicroDose Technologies	Phase 1
NA	Basal Insulin analog	Eli Lilly	Phase 1
UStrip	Transdermal insulin patch	Dermisonics	Phase 1
Intesulin	Oral insulin	Coremed	Phase 1
Alveair	Inhaled insulin	Coremed	Phase 1
AT1391	Transdermal insulin patch	Altea Therapeutics	Phase 1

There are only two products currently in the late phase of development, AFRESA by MannKind Corporation and VIAject by Biodel Inc. AFRESA, an inhaled insulin system, has already been accepted by the FDA for the approval process and if the FDA is convinced about its efficacy and safety, it should be on the market by 2010. VIAject is extremely rapid acting injectable insulin compared to other rapid acting insulin. Biodel intends to file for NDA during the latter half of 2009. Once approved, Biodel will be the fourth company in the United States which markets insulin.

### Overview of the Oral and Non-Insulin Injectable Anti-diabetic Market in the United States

For types 2 diabetes, oral anti-diabetics are the first line of action adopted by physicians. Most of these medications aim to increase insulin production or enhance insulin absorption by the blood. Approximately 25 percent of patients suffering from type 2 diabetes require external insulin in addition to oral drugs. The oral anti-diabetic market in the United States is mainly comprised of 6 major segments as mentioned below (For convenience, this section also includes the anti-diabetic injectables such as Byetta and Symlin):

### **Metformin for Treatment of PCOS**

Prescription of metformin for treatment of PCOS (polycystic ovary syndrome) is very common. Metformin alleviates the symptoms of PCOS and is widely prescribed by gynecologists. Metformin has been found to reduce androgen levels in women, thereby increasing the chances of ovulation. Also, PCOS women are found to be insulin resistant. Metformin increases the cell's response to insulin which also leads to weight loss.

### **Metformin in Breast Cancer**

Metformin is slowly finding its use in the treatment of breast cancer. Many studies have shown that the use of metformin may boost response to chemotherapy for breast cancer treatment. It was also found that metformin inhibited cellular proliferation, reduced colony formation and caused partial cell cycle arrest at the G(1) checkpoint. Use of metformin led to activation of the AMP kinase pathway (which is a cellular energy sensor of the cells) and an important pathway for the prevention of cancer. Therefore metformin is being considered as a potential breast cancer treatment weapon.

### **Prevention of Diabetes**

A study called Diabetes Prevention Program revealed that use of metformin in pre-diabetic people can reduce their chances to get diabetes by 30 percent. In high risk pre-diabetic patients, metformin is considered to be used to prevent the onset of full-fledged diabetes.

### **Key Customer Group for Anti-diabetics**

Though it is the patient who finally uses anti-diabetic, for pharmaceutical companies, the physician is the key customer as he/she prescribes the drug. Approximately 20 percent of diabetic patients seen by PCP have diabetes. It is believed that more than 90 percent of diabetes is managed by PCPs while less than 10 percent are referred to specialists such as endocrinologists.

There is a shortage of endocrinologists in the United States. This has impaired the access to care for high risk diabetic patients. In many cases, the wait time to see an endocrinologist is as much as 3 to 9 months and many of these clinics are closed for new patients. Currently, there may be 7000 to 10,000 positions available in the United States for endocrinologists.

PCPs are currently the key prescribers of anti-diabetics. Some higher end and expensive drugs are however, more prescribed by endocrinologists. While most of the messages for PCPs and endocrinologists are similar, companies tend to focus heavily on educating the PCP about their products. Many companies feel the awareness of diabetes is not up to the mark with PCPs. Companies need to provide additional information to them regarding the side effects and contraindications.

### **Sales Force Analysis**

There are no new products expected to enter the anti-diabetics market for at least a year. Still, the market has seen changes in the sales team. The sales team by pharmaceutical companies target PCPs, specialists, as well as hospitals. However, many companies are now looking towards trimming their sales team due to economic factors. One such example is Amylin Pharmaceuticals. Amylin cut down its sales team by 35 percent when its Byetta sales dropped due to the pancreatitis risk scare. This helped Amylin to save \$45 million by 2010. Cutting down the sales team size may help companies to streamline their effort and focus more seriously on products.

GSK also downsized its sales force by 12 percent, which included sales representatives for Avandia, as Avandia sales nosedived due to the FDA black box warning. As newer products get ready to enter the market, sales teams may be expanded to overcome the additional responsibility of efficient marketing. In December 2008, Sanofi also reportedly reduced its sales team by 10 percent as a measure to realign its team to better meet customer needs.