Changes in the Characteristics of New Drug Applications for the Treatment and Prevention of Diabetes Mellitus

by

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Submitted to the Department of Civil and Environmental Engineering and the Engineering Systems Division
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Abstract

Efforts in managing diabetes, including the medical advances in novel therapies and public health policies of disease control and prevention, have not reduced the disease prevalence since 1990s. I analyze this phenomenon from the technology and policy viewpoints underlying diabetes treatment and prevention, in order to control and manage the disease in a cost-benefit balanced manner.

The innovative performance of the antidiabetic drug therapy is investigated by analyzing the fifteen New Drug Applications (NDAs) of the antidiabetics approved by the US Food and Drug Administration since the early 1990s. I examine the characteristics of the clinical trials supporting NDAs and observe how the complexity of clinical trials has changed over time. Nine out of the twenty-five selected indicators are found to exhibit an increasing trend of complexity. The trend is more pronounced in the oral antiglycemics group (seven indicators) than the subcutaneous group (two indicators). Interestingly, this trend in increasing complexity in clinical trials is generally consistent with that of the increasing R&D costs in the pharmaceutical industry, possibly account for the declining innovative performance of the industry over the time period under investigation.

A system dynamics approach is applied to assess current public health policies in diabetes control and prevention. The benefit of system thinking is to avoid potential policy resistance by identifying the problematic characteristics of the system, such as time-delays, feedback, and structure of stocks and flows. For diabetes management, the public health system can be considered a "dynamic-complex" system in terms of current policy made by the National Diabetes Control and Prevention Program. Despite providing earlier and expanded screening as well as improved availability and accessibility of treatment for diabetes, the policy results in the increase of prevalence. More undiagnosed people are diagnosed, thus increasing the incidence, whereas people already diagnosed prolong their lifespan due to the better and more accessible medical care. A future successful chronic disease management program should systematically integrate the efforts from both the treatment and prevention perspectives.

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[1] Antoine de Saint-Exupery, *Wind, Sand and Stars,* Orlando, FL: Harcourt Brace &Company, 1992

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Glossary

Acarbose: generic name of Precose™, an antidiabetic drug in the chemical class of AGI

Actos™: brand name of pioglitazone, an antidiabetic drug in the chemical class of TZD

Alpha-glucosidase Inhibitor (AGI): a chemical class of oral antidiabetic agents acting by delaying gastrointestinal absorption of carbohydrates

Amaryl™: brand name of glimepiride, an antidiabetic drug in the chemical class of SU

American Diabetes Association (ADA): an American health organization providing research, information and advocacy in diabetes.

Apidra™: brand name of Glulisine, a short-acting insulin drug by injection

Aspart: generic name of Novolog™, a short-acting insulin drug by injection

Avandia™: brand name of rosiglitazone, an antidiabetic drug in the chemical class of TZD

Beta-cell: a type of cell in the pancreas, producing and releasing insulin

Biguanide: a chemical class of oral antidiabetic agents acting by decreasing hepatic glucose production

Blood glucose: blood sugar

Detemir: generic name of Levemir™, a long-acting insulin drug by injection

Diabetes Mellitus: a disorder that blood sugar levels are abnormally high because the body does not produce sufficient insulin or is resistant to the insulin that is produced

Diabetes: refers to diabetes mellitus specifically in this thesis

Dipeptidyl Peptidase-4 Inhibitor (DPP4i): a chemical class of oral antidiabetic agents acting by enhancing a natural body system that lowers blood sugar, called the incretin system

Exubera™: brand name of insulin inhaled, a recombinant insulin drug

Fasting Plasma Glucose (FPG): a measurement of blood sugar levels

Glargine: generic name of Lantus™, a long-acting insulin drug by injection

Glimepiride: generic name of Amaryl™, an antidiabetic drug in the chemical class of SU

Glucagon: a 29-amino acid polypeptide acting as an important hormone in carbohydrate metabolism

Glucophage™: brand name of metformin, an antidiabetic drug in the chemical class of biguanide

Sulfonylurea (SU): a chemical class of oral antidiabetic agents acting by stimulating insulin secretion

Glulisine: generic name of Apidra™, a short-acting insulin drug by injection

Glycemia: the concentration of glucose in the blood

Glyset™: brand name of meglitol, an antidiabetic drug in the chemical class of AGI

High Density Lipoprotein (HDL): used to indicate the level of "good cholesterol" in blood

Humalog™: brand name of lispro, a short-acting insulin drug by injection

Insulin Inhaled: generic name of Exubera™, a recombinant insulin drug

Insulin Secretagogues: agents that can promote insulin secretion

Insulin: a hormone released from the pancreas, controlling the amount of sugar in the blood

Januvia™: brand name of sitagliptin, an antidiabetic drug in the chemical class of DPP4i

Lantus™: brand name of glargine, a long-acting insulin drug by injection

Levemir™: brand name of detemir, a long-acting insulin drug by injection

Low Density Lipoprotein (LDL): used to indicate the level of "good cholesterol" in blood

Meglitinide: a chemical class of oral antidiabetic agents acting by stimulating insulin secretion from the pancreas

Meglitol: generic name of Glyset™, an antidiabetic drug in the chemical class of AGI

Metformin: generic name of Glucophage™, an antidiabetic drug in the chemical class of biguanide

Nateglinide: generic name of Starlix™, an antidiabetic drug in the chemical class of Meglitinide

National Diabetes Data Group (NDDG): a research group in NIH, focusing on collection, analysis, and dissemination of data on diabetes and complications

National Institute of Diabetes Digestive and Kidney Diseases (NIDDK): part of the NIH, conducting and supporting research on diabetes, digestive and kidney diseases

National Institute of Health (NIH): an agency of the US Department of Health and Human Services; the primary agency of the US government responsible for biomedical research

Nephropathy: a disease or medical disorder of the kidney

New Drug Application (NDA): an application submitted by the manufacturer of a "new drug" to the FDA

Novolog™: brand name of aspart, a short-acting insulin drug by injection

Oral Glucose Tolerance Test (OGTT): a diagnostic test for diabetes

Pancreas: an organ that can secret insulin

Phase I trials: studies in the first research phase during the clinical stage, focusing on the clinical pharmacology and toxicity

Phase II trials: studies in the second research phase during the clinical stage, focusing on an initial clinical investigation for treatment effect

Phase III trials: studies in the third research phase during the clinical stage, focusing on a full-scale evaluation of treatment

Phase IV trials: studies in the fourth research phase during the clinical stage, focusing on the post-marketing surveillance

Pioglitazone: generic name of Actos™, an antidiabetic drug in the chemical class of TZD

Pramlinitide: generic name of Symlin™, a glucagon-lowering drug by injection

Prandin™: brand name of repaglinide, an antidiabetic drug in the chemical class of meglitinide

Precose™: brand name of Acarbose, an antidiabetic drug in the chemical class of AGI

Prescription Drug User Fees Act (PDUFA): a program authorizing FDA to collect user fees from prescription drugs for the purpose of expanding staffs and resources in drug evaluation

Repaglinide: generic name of Prandin™, an antidiabetic drug in the chemical class of meglitinide

Retinopathy: a disease of the retina, especially one that is noninflammatory and associated with damage to the blood vessels of the retina

Rosiglitazone: generic name of Avandia™, an antidiabetic drug in the chemical class of TZD

Sitagliptin: generic name of Januvia™, an antidiabetic drug in the chemical class of DPP4i

Starlix™: brand name of nateglinide, an antidiabetic drug in the chemical class of meglitinide

Sulfonylurea (SU): a chemical class of oral antidiabetic agents acting by stimulating insulin secretion

Symlin™: brand name of pramlinitide, a glucagon-lowering drug by injection

Thiazolidinedione: a chemical class of oral antidiabetic agents that can reduce insulin resistance by increasing insulin sensitivity in the peripheral tissue

Triglyceride: an important lipid (fat) in the blood, constrained in fat cells, and can be broken down and used to provide energy for the body's metabolic processes

Type 1 Diabetes: juvenile-onset; insulin-dependent-diabetes mellitus (IDDM)

Type 2 Diabetes: adult-onset; non-insulin-dependent-diabetes mellitus (NIDDM)

World Health Organization (WHO): a specialized agency of the United Nations that acts as a coordinating authority on international public health, headquartered in Geneva, Switzerland

ABSTRACT

Diabetes mellitus (diabetes) creates a heavy burden on the current healthcare system due to the high morbidity and mortality rate from. Efforts in managing diabetes, including the medical advances in novel therapies and public health policies of disease control and prevention, have not reduced the disease prevalence since 1990s, and indeed prevalence has increased. I analyze this phenomenon from the technology and policy viewpoints underlying diabetes treatment and prevention, in order to control and manage the disease in a cost-benefit balanced manner

The innovative performance of antidiabetic drug therapy is investigated by analyzing the fifteen New Drug Applications (NDAs) of the antidiabetics approved by the US Food and Drug Administration (FDA) since the early 1990s. I examine the characteristics of the clinical trials supporting NDAs and observe how the complexity of clinical trials has changed over time. Nine out of the twenty-five selected indicators are found to exhibit an increasing trend of complexity. The trend is more pronounced in the oral antiglycemics group (seven indicators) than the subcutaneous group (two indicators). Interestingly, this trend of increasing complexity in clinical trials is generally consistent with that of increasing R&D costs in the pharmaceutical industry, suggesting a partial plausible explanation for the declining innovative performance of the industry observed over the time period under investigation.

A system dynamics approach is applied to assess the current public health policies in diabetes control and prevention. This approach emphasizes the importance of system thinking, critical for designing a public health policy and particularly important in chronic diseases management. The benefit of system thinking is to avoid potential policy

resistance by identifying the problematic characteristics of the system, such as time-delays, feedback, and structure of stocks and flows. In the case of diabetes management, the public health system can be considered a "dynamic-complex" system in terms of current policies made by the National Diabetes Control and Prevention Program. Despite providing earlier and expanded screening as well as improved availability and accessibility of treatment for diabetes, the policy results in an increase of prevalence. More undiagnosed people are diagnosed, this increases the incidence, and people already diagnosed prolong their lifespan due to the better and more accessible medical care. As a consequence, the policy fails to reach the goal of reducing prevalence. A future successful chronic disease management should integrate the efforts from both the treatment and prevention perspectives in a systematic way. Understanding the drivers for developing treatment and prevention is critical to achieving a robust healthcare system.

1 BACKGROUND

A recent report by the Congressional Budget Office studied the phenomena of rising costs and declining performance in R&D of the pharmaceutical industry. It identified 17 therapeutic classes where the industry's recent R&D spending has been directed[1]. The products in each of these 17 therapeutic classes: (1) include at least three brand-name drugs ranked in the top 200 for prescriptions in 2003; and (2) are mostly newer drugs since sales of brand-name drugs typically drop sharply once generic versions become available. The 17 therapeutic classes are summarized in the following table:

Table 1.1 Leading Therapeutic Classes in 2003

Ranking	Therapeutic Class (Major subclasses)	Number of Drugs in the Top 200	Total Sales (Billions of dollars)	Prescriptions (Millions of units sold)
1	Antidepressants (SSRIs, SNRIs)	8	11.6	114.5
2	Antihyperlipidemics (Statins)	6	11.1	108.4
3	Antiulcerants (Proton-pump inhibitors)	5	10.4	70.0
4	Antihypertensives (ARBs, ACE inhibitors)	11	5.8	88.1
5	Antibiotics (Broad- and medium-spectrum)	9	5.5	89.2
6	Antidiabetics (Oral, injectable)	6	4.9	63.5
7	Antiarthritics (COX-2 inhibitors)	4	4.8	48.4
8	Antipsychotics	3	4.2	20.2
9	Antihistamines (Oral)	3	4.1	63.2
10	Neurological Drugs (For seizures or pain)	5	4.0	36.2
11	Other Vascular Drugs (Calcium- or beta-blockers)	7	3.7	68.7
12	Antiasthmatics	5	3.6	28.1
13	Analgesics (Nonnarcotic)	3	2.8	20.1
14	Bone Density Regulators	4	2.3	32.0
15	Oral Contraceptives	3	2.1	44.4
16	Antiallergy Drugs (Nasal steroids)	4	2.0	29.9
17	Analeptics (ADHD treatments)	3	1.3	16.9

(Source: Adapted from the Congressional Budget Office, *A CBO Study-Research and Development in the Pharmaceutical Industry*, Oct. 2006)

This thesis represents an attempt to shed some light on why R&D costs have risen and performance in the pharmaceutical industry has suffered. It is based on "Changes in the Characteristics of Pivotal Clinical Trials in Support of New Drug Applications for

Antidiabetics," a report produced by a collaborative project between the US Food and Drug Administration (FDA) and the Center for Biomedical Innovation at MIT. The report was designed to study changes in the characteristics of pivotal clinical trials in support of approved New Drug Applications (NDAs) since 1990s. To examine these changes, the research team initially selected nine therapeutic classes, including antibiotics, antihypertensives, antidiabetics, anti-cholesterol agents, anti-coagulants, anti-HIV agents, anti-fungals, oncology drugs, and CNS drugs. Understanding how complexity in clinical trials for NDAs has evolved over time will hopefully give us insights as to whether these changes correlate with the trend of increasing costs and declining performance in R&D of the pharmaceutical industry. The goal of this project is to improve efficiency in approval of NDAs without compromising safety and also to achieve more cost-effective decision-making in R&D investment. Ideally, novel therapies are delivered to the public in a timely fashion with a reasonable price without tradeoffs in safety.

Since the early 1990s, clinical trials referenced in NDAs approved by the FDA for antidiabetic treatments have become more complex over time. If true, this hypothesis may help in part to explain the rising costs of R&D in the pharmaceutical industry, but I leave analysis of the relationship between increasing complexity and costs as a future research topic. Section 1 includes the background information for this thesis. Section 2 introduces the definition, classification, and diagnostic criteria of diabetes mellitus. Section 3 discusses the etiology, complications, and treatment for the disease. Section 4 focuses on changes in the characteristics of the clinical trials that support the NDAs for antidiabetic drugs, and investigates plausible causes for these changes. Section 5 elaborates on certain policy issues associated with the treatment and prevention of

diabetes. Section 6 summarizes the conclusions of my thesis and discusses the future perspectives.

2 INTRODUCTION TO DIABETES MELLITUS

Diabetes mellitus (diabetes) is a growing health problem worldwide. In the United States, the number of people with diabetes has grown since 1990 at a rate much greater than that of the general population[2]. Diabetes is a disease with high mortality and consumes a substantial portion of the health care resources with its complications. It was the sixth leading cause of death in the US in 2002. In the same year, this disease accounted for a total cost of $132 billion--$92 billion in direct costs and $40 billion in indirect costs--for the healthcare system in the US. According to the latest report from the National Institutes of Health (NIH) in 2005, 1.5 million new cases of diabetes were diagnosed in the population aged 20 years old or older. Currently in the United States, 20.8 million people, seven percent of the total population in the country, have diabetes--with 14.6 million diagnosed and 6.2 million undiagnosed. Worldwide, more than 230 million people have diabetes. This number is projected to exceed 350 million by 2025[3].

2.1 Definition

Diabetes mellitus is a disorder in which blood sugar (glucose) levels are abnormally high because the body does not produce insulin or is resistant to the insulin that is produced.

Insulin, a hormone released from the pancreas, controls the amount of sugar in the blood. When a person eats or drinks, food is broken down into materials that include sugar, a source of energy that the body needs to function. Sugar is absorbed into the

bloodstream and stimulates the pancreas to produce insulin. Insulin allows sugar to move from the blood into the cells. Once inside the cells, sugar is converted to energy, which is either used immediately or stored until it is needed.

The levels of sugar in the blood vary normally throughout the day. They rise after a meal and return to normal within about two hours after eating. Once the levels of sugar in the blood return to normal, insulin production decreases. If the body does not produce enough insulin to move the sugar into the cells, the resulting high levels of sugar in the blood and the inadequate amount of sugar in the cells together produce the symptoms and complications of diabetes.

Doctors often use the full name diabetes mellitus, DM, rather than diabetes alone, to distinguish this disorder from diabetes insipidus, a relatively rare disease that does not affect blood sugar levels. In the scope of this thesis I focus only on diabetes mellitus, thus I will use the term "diabetes" to refer to diabetes mellitus.

2.2 Classification

In contrast to an earlier classification based on age of onset or type of therapy, diabetes is currently classified on the basis of the pathogenic (disease-causing) process leading to hyperglycemia (high blood sugar levels)[4]. Since diabetes comprises a heterogeneous group of disorders characterized by high blood glucose levels, the major types of diabetes have been identified and classified by the World Health Organization (WHO) and the National Diabetes Data Group (NDDG) of NIH in the US. These classifications are: type 1, type 2, gestational diabetes, and other types of diabetes secondary to or associated with other conditions. The scope of discussion in this thesis is limited to the first two types of diabetes, i.e. type 1 and type 2.

2.2.1 Type 1 Diabetes-IDDM

In type 1 diabetes (formally called insulin-dependent diabetes mellitus, IDDM, or juvenile-onset diabetes), more than 90 percent of the insulin-producing cells of the pancreas are permanently destroyed. The pancreas, therefore, produces little or no insulin. Only 10 percent of all people with diabetes are type 1. Most people with type 1 diabetes develop the disease before age 30.

Scientists believe that an environmental factor--possibly a viral infection, or a nutritional factor in childhood or early adulthood--causes the immune system to destroy the insulin-producing cells of the pancreas. A genetic predisposition may make some people more susceptible to the environmental factor[5].

2.2.2 Type 2 Diabetes-NIDDM

In type 2 diabetes (formally called non-insulin-dependent diabetes, NIDDM, or adult-onset diabetes), the pancreas continues to produce insulin, sometimes even at higher than normal levels. However, the body develops resistance to the effects of insulin, so there is not enough insulin to meet the body's needs.

Type 2 may occur in children and adolescents, but it usually begins in people older than 30 and becomes progressively more common with age. Certain racial and cultural groups are at increased risk of developing type 2 diabetes, including African-Americans and Hispanic-Americans, who have a twofold to threefold increased risk. Type 2 diabetes also tends to run in families.

Obesity is the major risk factor for developing type 2 diabetes, and 80 percent to 90 percent of people with this disease are obese[6]. Obesity causes insulin resistance; obese people need very large amounts of insulin to maintain normal blood sugar levels.

In addition, certain diseases and drugs can affect the way the body uses insulin and can also lead to type 2 diabetes.

Type 2 diabetes has also become an epidemic worldwide in the past several decades due to the advancing age of the global population, substantially increased prevalence of obesity, and decreased physical activity, all of which have been attributed to increased adoption of a Western lifestyle. In the US, almost eight percent of the adult population and 19 percent of the population older than the age of 65 years has diabetes[7]. There are 800,000 new cases of diabetes per year, almost all of which are type 2.

2.3 Diagnosis for Diabetes in a Clinical Setting

Generally, medical tests are performed to screen for disease, diagnose disease, classify and measure the severity of disease, and monitor the course of a disease, especially its response to treatment. A screening test (for the purpose of detecting a disease when there is no evidence that a person has the disease) must be accurate, relatively inexpensive, carry little risk of injury, and cause little or no discomfort. On the other hand, a diagnostic test (for the purpose of confirming or ruling out a disease when there is suspicion that a person has the disease) does not have the same requirements because of potential consequence for the patient.

Diagnosis of diabetes defines a group at high risk for micro- and macrovascular disease. The diagnosis has profound implications for an individual from both a medical and financial standpoint. Thus it is important to set up diagnostic criteria that act as valid predictive metrics for identifying the development of diabetes at an early stage. Furthermore, early and accurate diagnosis is needed to achieve effective disease management, i.e. to prevent development of severe complications in later stages.

Treating complications has been the major cost and a heavy burden to the medical system. An American Diabetes Association (ADA) report[8] estimated that treating diabetes in the US cost $132 billion in 2002. Healthcare spending for a patient with diabetes is more than double what spending would be for a patient without diabetes.

Diagnostic criteria are also slightly different between a clinical setting and an epidemiologic setting. For the purpose of studying the characteristics of clinical trials for antidiabetics in this research, I only consider diagnostic criteria in a clinical setting.

The classic symptoms of diabetes include polyuria (urinating large amounts frequently), polydipsia (abnormal thirst due to excessive urination), recurrent infections, unexplained weight loss, high levels of glycosuria (presence of sugar in urine), and in severe cases, drowsiness and coma. According to the recommendations from NDDG and WHO, in the absence of unequivocal hyperglycemia and acute metabolic decompensation, an asymptomatic person with blood glucose values just above the diagnostic cut-off value needs an additional plasma/blood glucose test result with a value in the diabetic range for further diagnostic confirmation. A medical practitioner may obtain the glucose concentration via one of the following measurements:

(1) a casual, or random blood glucose, defined as without regard to time since the last meal, along with the presence of classic diabetic symptoms;

(2) a fasting plasma glucose (FPG), measured after at least eight hours of fast or no caloric intake;

(3) a two-hour plasma glucose (2-h PG), measured in an oral-glucose-tolerance-test (OGTT, see **Appendix A**)

Among the above three measurements, OGTT is generally regarded as the gold standard and final reference for the diagnosis of diabetes; however, accessibility and availability may be constrained due to logistic or economic reasons.

2.4 Evolution of Diagnostic Criteria from 1980s

In 1985, WHO issued the diagnostic criteria for diabetes (WHO-1985 criteria). This is summarized in the following table:

Table 2.1 WHO-1985 Diagnostic Criteria for Diabetes

Blood Sugar Levels (units: mg/dL)	Whole blood		Plasma	
	Venous	Capillary	Venous	Capillary
Random (with symptoms)	180	200	200	220
Fasting	120	120	140	140
2-hour post glucose load	180	200	200	220

(Source: *1999 WHO report in Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications*)

2.4.1 The ADA-1997 Criteria

In 1997, the ADA Expert Committee proposed a revision to the widely used WHO-1985 diagnostic criteria for diabetes in lowering the cutoff value for FPG from 140mg/dL to 126mg/dL, intending to reduce the discrepancy between this measurement and the 2-h PG cutoff value. Meanwhile, ADA also gave primacy to the use of FPG. A Japanese study also confirmed the fasting value to be more predictive of mortality than the 2-hour value[9].

2.4.2 The WHO-1999 Criteria

In recognition of a more predictive value, WHO revised its 1985 criteria in 1999, lowering the diagnostic value of FPG from 140mg/dL to 126mg/dL and also the value for whole blood from 120mg/dL to 110mg/dL. **Table 2.2** summarizes the changes (marked in yellow). Despite the fact that the ADA-1997 criteria and WHO-1999 criteria share the

same threshold value of FPG, ADA's advocacy for adopting FPG and phasing out 2-h PG remains controversial in the medical community. I will discuss the debates regarding adoption of either the ADA-1997 or WHO-1999 criteria in **Section 5.1.**

Table 2.2 WHO-99 Diagnostic Criteria for Diabetes

Blood Glucose Levels	Whole blood		Plasma	
(units: mg/dL)	Venous	Capillary	Venous	Capillary
Random (with symptoms)	180	200	200	220
Fasting	110	110	126	126
2-hour post glucose load	180	200	200	220

(Source: ibid.)

2.4.3 Glycosylated Hemoglobin

Besides measuring raw blood glucose concentrations, doctors can measure the level of a protein in the blood, hemoglobin A1c (also called glycolated or glycosylated hemoglobin; HbA1c) for diagnostic purposes. This is most useful in confirming the diagnosis in adults in whom the levels of sugar in the blood are only mildly elevated. Doctors can also use HbA1c to monitor antidiabetic treatment. When the blood sugar levels are high, changes occur in the hemoglobin, the protein that carries oxygen in the blood. HbA1c, reflecting average glycemia over a period of weeks, can give equal or almost equal sensitivity (the likelihood that it will produce abnormal results for people with the disease being tested for) and specificity (the likelihood that it will produce normal results for people without that disease) to glucose measurement. However, since HbA1c measurement is not available in many parts of the world and also not well standardized, it is not recommended as an alternative means for diagnosing diabetes by WHO. In the clinical trials under investigation in this thesis, HbA1c is fairly commonly used in the inclusion/exclusion criteria when screening patients, and is also used as an endpoint to assess the efficacy of a drug.

3 TREATMENT FOR DIABETES

3.1 Etiologies of Diabetes

3.1.1 Type 1 Diabetes

The etiologies, or causes of disease, are different for type 1A and type 1B diabetes. Type 1A, which comprises the majority of type 1 diabetes, results from autoimmune beta cell destruction, and leads to absolute insulin deficiency. In contrast, type 1B diabetes is idiopathic (without apparent cause). Individuals with type 1B diabetes lack evidence of an autoimmune destructive process of the beta cells; they develop insulin deficiency by still unknown mechanisms and are prone to ketosis (overproduction of ketones). Relatively few type 1 patients are in the type 1B category; this form of diabetes is more common among individuals of African and Asian origin[10].

3.1.2 Type 2 Diabetes

Type 2 diabetes is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production. Distinct genetic and metabolic defects in insulin action and/or secretion give rise to the common phenotype of hyperglycemia in type 2 diabetes. Type 2 diabetes is preceded by a period of abnormal glucose homeostasis (state of equilibrium) classified as impaired fasting glucose or impaired glucose intolerance. Individuals with type 2 diabetes do not need insulin to survive. Because of the distinct pathogenic processes in this type of diabetes, treating this disease requires pharmacologic agents that target specific metabolic derangements. I will discuss these drug therapies in **Section 3.3**.

This form of diabetes is frequently undiagnosed for many years since the hyperglycemia is often not severe enough to provoke obvious symptoms of diabetes. Nevertheless, such patients are at risk of developing macrovascular and microvascular complications.

Noticeably, according to many studies obesity is strongly associated with several major health risks, including diabetes. The majority of patients with type 2 diabetes are obese, and obesity itself causes or aggravates insulin resistance[11]. Among the patients with type 2 diabetes, many of those who are not obese by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region. A related concern raised by this observation relates to the increasing population of overweight or obese people in the US, which has most likely contributed substantially to the burden of chronic health conditions[12]. Additionally, type 2 diabetes also correlates with ethnicity. Medical research has shown several racial and ethnic groups in the US are at particularly high risk for type 2 diabetes, including African Americans, Hispanics, Asian and Pacific Islanders, and Native Americans[13].

3.2 Complications

3.2.1 Acute

The acute metabolic complications of diabetes include diabetic ketoacidosis (DKA) and hyperosmolar nonketotic state (HNS). DKA was formerly considered as a hallmark of type 1 diabetes, but it can also occur in type 2 diabetics treated with oral glucose-lowering agents (these patients are often of Hispanic or African-American descent)[14]. HNS is primarily seen in individuals with type 2 diabetes.

DKA is a condition in which a person's breath smells like nail polish remover due to ketones escaping in the breath. Without treatment, DKA can progress to coma and death, sometimes within hours. Due to lack of insulin, most cells cannot use the sugar that is in the blood. Cells still need energy to survive, and they switch to a back-up mechanism to obtain energy from fat cells, which break down to produce compounds called ketones. Ketones provide some energy to cells but also make the blood too acidic (ketoacidosis). The initial symptoms of DKA include excessive thirst (polydipsia) and urination (polyuria), weight loss, nausea, vomiting, fatigue, and abdominal pain--particularly in children. Breathing tends to become deep and rapid (the Kussmaul breathing) as the body attempts to correct the blood's acidicity.

HNS is caused by insulin deficiency and inadequate fluid intake. The prototypical patients with HNS are elderly individuals with type 2 diabetes, with a several week history of polyuria, weight loss, and diminished oral intake of fluid that results in mental confusion, lethargy (tiredness), or coma. Unlike DKA, HNS does not involve the production of ketones, and therefore does not cause symptoms of nausea, vomiting, or abdominal pain and the Kussmaul respirations.

3.2.2 Chronic

The chronic complications of diabetes affect many organ systems and are responsible for the majority of morbidity and mortality associated with this disease. 70 percent of type 2 diabetic patients die of cardiovascular disease[15]. In the US, the estimated cost of providing care for diabetes and its complications is $100 billion per year, with half the cost attributable to direct care[16]. Chronic complications are summarized in the following table:

Table 3.1 Long-term Complications of Diabetes

Tissue or Organ Affected	Complications
Blood vessels	• Poor circulation causes wounds to heal poorly and can lead to heart disease, stroke, gangrene (death of tissue) of the feet and hands, erectile dysfunction, and infections.
Eyes	• Decreased vision and, ultimately, blindness • Cataracts (clouding in the lens of the eye, which impairs vision) • Glaucoma (elevation of the pressure in one of the chambers of the eye that can decrease vision and lead to blindness)
Kidney	• Poor kidney function • Kidney failure
Nerves	• Sudden or gradual weakness of a leg • Reduced sensations, tingling, and pain in the hands and feet • Chronic damage to nerves
Autonomic nerves system	• Swings in blood pressure • Swallowing difficulties and altered digestive function, with bouts of diarrhea
Skin	• Sores, deep infections (diabetic ulcers) • Poor healing
Blood	• Increased susceptibility to infection, especially of the urinary tract and skin
Connective Tissue	• Carpal tunnel syndrome (a painful compression of the median nerve as it passes through the wrist) • Dupuytren's contracture (a progressive shrinking of the bands of fibrous tissue (called fascia) inside the palms, producing a curling in of the fingers that eventually can result in a clawlike hand)

(Source: *The Merck Manual of Medical Information*, 2nd Edition)

3.3 Therapies for Diabetes

3.3.1 An Overview

The overall goals of therapies for type 1 and type 2 diabetes are to: (1) eliminate symptoms related to hyperglycemia; (2) reduce or eliminate the long-term microvascular and macrovascular complications of diabetes; and (3) allow the patients to achieve as normal a lifestyle as possible[17].

Change of lifestyle (including diet, exercise, and weight control), insulin intervention, and oral antihyperglycemic (glucose-lowering) agents are three major

therapies against diabetes. The main goal of these therapies is to maintain the level of blood sugar within the normal range. The importance of blood sugar control lies in preventing microvascular complications[18,19,20]. Although maintaining blood sugar completely within the normal level is difficult, keeping the level as close to the normal level as possible can still effectively prevent the development of complications. The main problem in treating diabetes by controlling blood sugar levels is an increased risk of overshooting, resulting in low blood sugar levels (hypoglycemia)[21].

(1) Treating Type 1 Diabetes

The ADA recommendations for treating type 1 diabetes focus on achieving goals for fasting, bedtime glycemic control, and HbA1c targets, as summarized in **Table 3.2** (the targets of glycemic control is also discussed later in **Section 3.3.2.**).

According to a study by the Diabetes Control and Complications Trial Research Group, intensive therapy has proved to be most effective in delaying the onset and also slowing the progression of diabetic long-term complications for type 1 diabetic patients[22]. According to this study, intensive treatment--defined by the goal of maintaining blood glucose concentrations close to the normal range--can decrease the frequency and severity of long-term microvascular and neurologic complications, which cause major morbidity and mortality in patients with type 1 diabetes. Another study shows the that intensive therapy reduces the risk of cardiovascular disease in type 1 diabetic patients[23].

Intensive treatment consists of three or more daily injections of insulin or treatment with an external insulin pump, with dose adjustments based on at least four self-monitored glucose measurements per day. Daily glucose goals are 70 to 120 mg per deciliter before meals and peak levels of less than 180 mg per deciliter after meals. The

goal for HbA1c is less than 6.05 percent. In contrast, conventional therapy has no glucose goals beyond those needed to prevent symptoms of hyperglycemia and hypoglycemia and consists of only one or two daily injections of insulin.

(2) Treating Type 2 Diabetes

A traditional approach to treating type 2 diabetes involves a stepwise introduction of nonmedication (lifestyle) approaches followed by oral glucose-lowering agents. Insulin, despite being the most potent and durable therapy, is generally saved for last, presumably because of the need to administer it by injection. The stepwise strategy is usually applied at a slow pace with long delays between steps. By the time patients with type 2 diabetes are treated with insulin, they usually have had diabetes for more than 10 to 15 years and have established complications[24]. This treatment approach is illustrated in **Figure 3.1**.

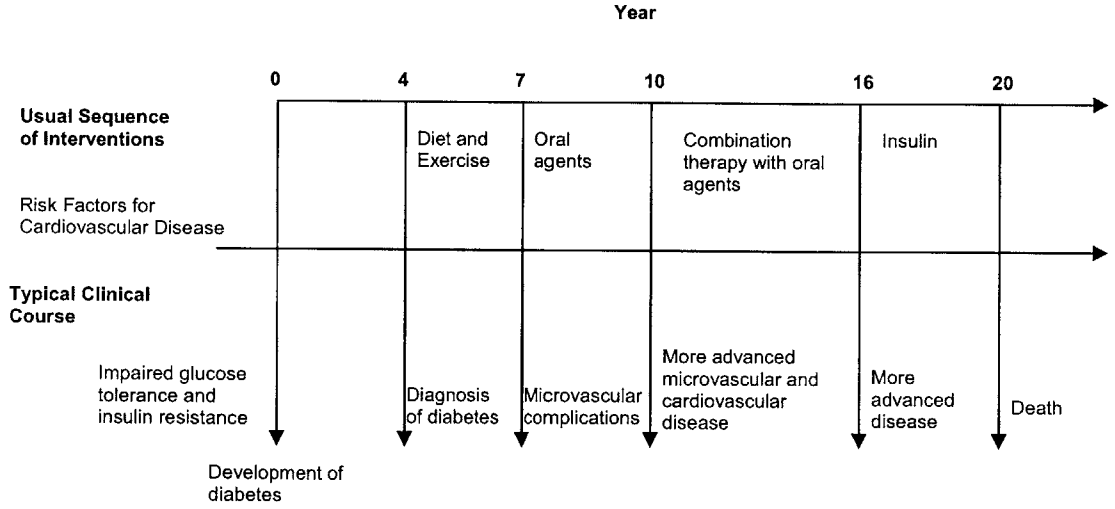


Figure 3.1 The Typical Clinical Course of Type 2 Diabetes, Including the Progression of Glycemia and the Development of Complications, and the Usual Sequence of Interventions (Source: *Initial Management of Glycemia in Type 2 Diabetes Mellitus*, NEJM 2002)

Glycemia appears to increase progressively along with the presence of diabetes, as a result of decreasing beta-cell function[25]. However, at least some beta-cell dysfunction is reversible, and insulin secretion can be restored by lowering glycemia, either with diet and exercise or with hypoglycemic medications[26].

Type 2 diabetes has been labeled as coronary heart disease risk equivalent. Guidelines from the National Cholesterol Education Program[27] and ADA[28] both acknowledge that the presence of diabetes is a risk factor equivalent to having preexisting coronary artery disease[29] and have therefore adjusted treatment goals accordingly. Thus, another critical element as part of the comprehensive diabetes care in treating type 2 diabetes is to aggressively detect lipid abnormalities in order to lower the risk of developing long-term complications, particularly cardiovascular disease, which account for the 70 percent mortality of type 2 diabetes.

Care of patients with type 2 diabetes has been revolutionized throughout the past several years--first, through the realization of the importance of tight glycemic control in forestalling complications, and second, by the availability of several unique classes of oral antidiabetic agents.

When monotherapy (using one single oral antihyperglycemia agent) fails to achieve the targets of glycemic control--metabolic control worsens within five years after the initiation of an oral hypoglycemic agent--clinicians will use combination therapy to achieve better and more effective glycemic control to treat type 2 diabetes. The UK Prospective Diabetes Study clearly demonstrated that type 2 diabetes is a progressive disease. After three years, for example, only 50 percent of type 2 patients were

adequately controlled with a single drug, and after nine years, this percentage had decreased to 25 percent[30].

The principle behind combination therapy is to use drugs with different mechanisms of action. The first commonly used combination regime--insulin at bedtime and sulfonylurea (SU) during the day--combines two drugs to increase insulin levels[31]. Other popular combinations are SU and metformin, metformin and thiazolidinedione (TZD), and SU and TZD. Another common combination therapy is oral agent/insulin therapy. When using bedtime basal insulin (NPH or glargine), continuing one or two daytime doses of oral mediation is reasonable. Combining SUs with insulin lowers insulin doses (25%-50%) with less weight gain, but increases cost. Metformin with insulin results in similar metabolic control, less weight gain, lower insulin doses, and fewer hypoglycemic episodes than insulin alone or insulin/SU therapy. Thus, metformin and insulin may be the best combination for the majority of patients with type 2 diabetes who do not have contraindications. Although TZDs are effective insulin sensitizers, TZDs are more expensive compared to SUs and metformin (see price comparison of the oral agents in **Table 3.4.**).

The increasing number of available medications has given clinicians more choices for first-line therapy and for changing or combining medications when the metabolic disorder worsens over time. Several recommendation guidelines for the treatment of type 2 diabetes have been published[32], which emphasize the long-term maintenance of glycemic control, as estimated by levels of glycosylated hemoglobin (HbA1c), in an effort to keep these levels as close to the non-diabetic range as is safely possible. They also emphasize the initiation of treatment with metformin in patients who have newly

diagnosed disease (concurrent with lifestyle interventions) and the changing of medications no less frequently than every three months if glycosylated hemoglobin levels are seven percent or more (See **Figure 3.2**). The algorithm provided in the guidelines includes early, aggressive use of insulin, the most powerful antidiabetic drug, when metabolic goals are not achieved. SUs, TZDs, and insulin are included as possible second-step medications to be combined with metformin and lifestyle interventions if metabolic goals are not achieved or maintained[33].

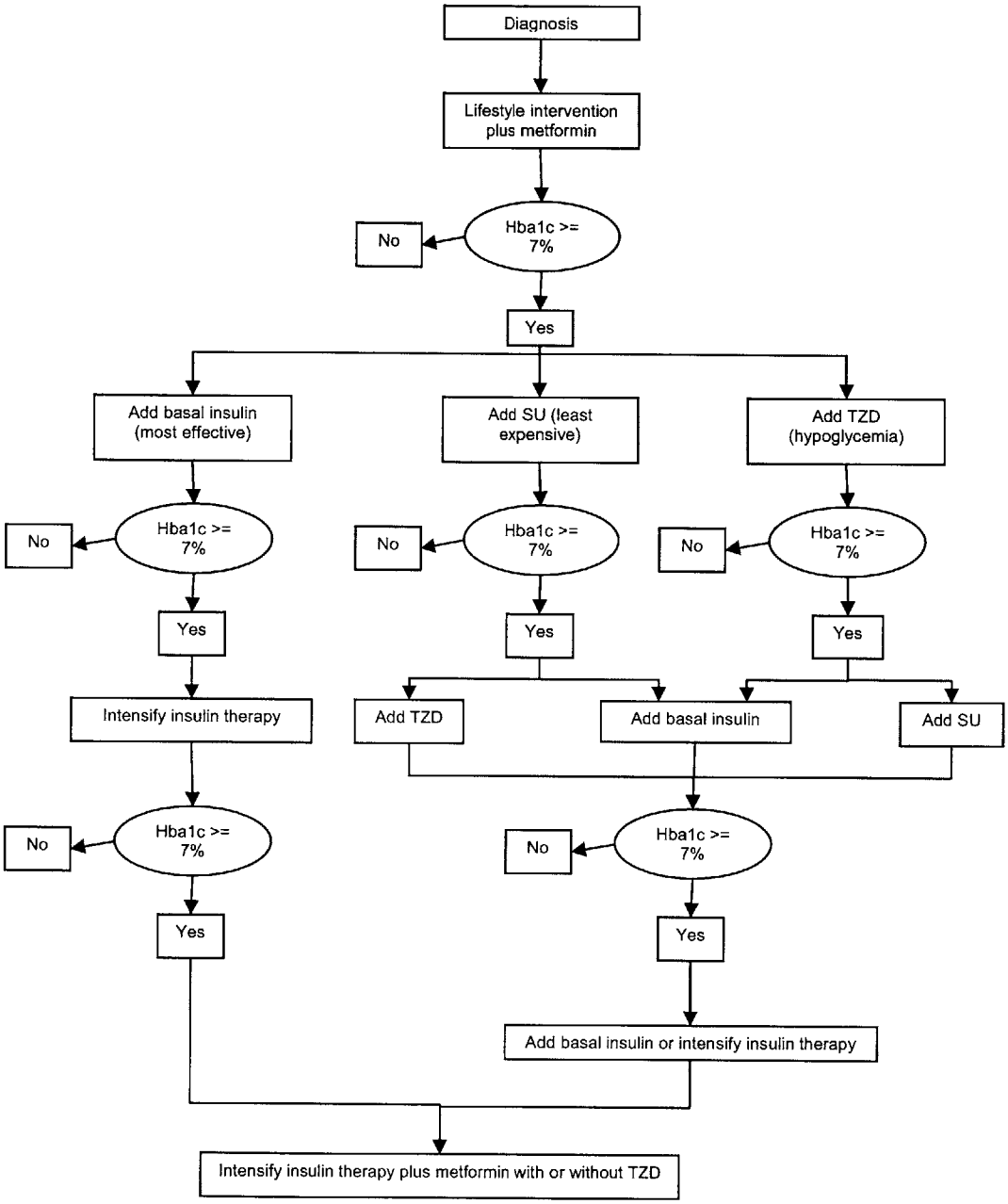


Figure 3.2 Metabolic Management of Type 2 Diabetes (Source: *Thiazolidinediones for Initial Treatment of Type 2 Diabetes?* NEJM Dec. 2006)

3.3.2 Goals of Therapy

Establishing a target level of glycemic control is essential in order to reduce or eliminate the complications of diabetes. The target for glycemic control (as reflected by HbA1c) must be individualized, and the goals of therapy should be developed in consultation with the patient after considering a number of medical, social, and life-style issues.

The ADA's recommended goals of treatment, including target levels of blood sugar, blood pressure, and blood lipids, are summarized in **Table 3.2.** Studies have shown that aggressive treatment of hypertension also reduces the risk of retinopathy, nephropathy, and certain cardiovascular outcomes[34]. Reducing low-density lipoprotein cholesterol levels[35,36] and reducing triglyceride levels while raising high-density lipoprotein cholesterol levels[37] can decrease the risk of cardiovascular disease.

Table 3.2 ADA's Recommended Goals of Treatment for Diabetes in Nonpregnant Adults

Variable	Value	
Glucose		
Glycosylated hemoglobin (HbA1C)	<7	%
Fasting plasma glucose (FPG)	90-130	mg/dL
Peak postprandial glucose	<180	mg/dL
Blood Pressure		
Systolic	<130	mm Hg
Diastolic	<80	mm Hg
Lipids		
Low-density lipoprotein cholesterol (LDL)	<100	mg/dL
High-density lipoprotein cholesterol (HDL)	>45	mg/dL
Triglyceride	<200	mg/dL

(Source: *Initial Management of Glycemia in Type 2 Diabetes Mellitus*, NEJM 2002)

3.3.3 Drug Therapy

1) Insulin Therapy

Insulin is a pancreatic hormone that regulates carbohydrate metabolism. It plays a critical role in regulating blood sugar. Insulin is used medically in patients with type 1 diabetes and may be needed by patients with type 2 diabetes for intermittent or continuous glycemic control. Over time, some people develop resistance to insulin. Because the injected insulin is not exactly like the insulin the body manufactures, the body can produce antibodies to the insulin. These antibodies interfere with the insulin's activity, and as a result, a person with insulin resistance must take very large doses.

The goals of insulin therapy in both type 1 and type 2 diabetes are to reach the target HbA1c level with a low rate of hypoglycemic episodes and the least amount of weight gain. Goals must be individualized since older patients with type 2 diabetes and with no complications may not benefit from intensive therapy. Certain types of insulin may be mixed together in an injection to achieve the best control of blood sugar while other types cannot be mixed together and may require two separate injections. Some insulin can be purchased already mixed together, such as regular and NPH insulin, to allow for injection of both types of insulin at the same time. Hypoglycemia is the most common adverse effect of insulin therapy. Newer insulin therapies, including physiologic basal-prandial insulin and insulin analogues (molecules with similar chemical or structural properties) may convey similar function or activity, may be faster-acting, or have better bioavailability, when compared to insulin. Through genetic engineering of the underlying DNA, the primary amino acid sequence of insulin can be changed to alter its ADME characteristics, which include absorption, distribution,

metabolism, and excretion, These developments are changing clinical care for the diabetic[38].

According to the definitions from NIDDK, insulin products are available in four forms--rapid-acting, short-acting, intermediate-acting, and long-acting--depending on the speed of onset (how quickly the insulin starts to work after it is injected), peak time (the period of time when the insulin is most effective in lowering blood sugar levels), and duration of action (how long the insulin remains working in the body). These four different forms may be injected separately or mixed in the same syringe. Rapid-acting insulin, which is known by brand names such as Humalog, Novolog, and Apidra, is the fastest and shortest acting. It is often used by people who take several daily injections and is injected after eating (post-prandially). It reaches its maximum activity in 45 to 90 minutes and works for 3 to 4 hours. Short-acting insulin starts to work in 30 minutes, reaches its maximum effect in 2 to 5 hours, and works for 5 to 8 hours. Intermediate-acting insulin, such as Neutral Protamine Hagedorn (NPH; isophane insulin), starts to work in 1 to 3 hours, reaches is maximum activity in 6 to 12 hours, and works for 16 to 24 hours. This type of insulin may be used in the morning to provide coverage for the first part of the day or in the evening to provide coverage during the night. Traditionally, NPH was the primary basal insulin and the most regularly-prescribed primary prandial insulin. Long-acting insulin, including Lantus and Levemir, starts to work in 4 to 6 hours, reaches its maximum effect in 8 to 20 hours, and works for 24 to 28 hours. A comparison of insulin products is summarized in the following table:

Table 3.3 Currently Available Insulin Products

Insulin	Onset	Peak	Effective Duration
Rapid-acting			
Lispro (Humalog) Aspart (Novolog) Glulisine (Apidra)	5-15 min	45-90 min	3-4 h
Short-acting			
Regular insulin	30 min	2-5 h	5-8 h
Intermediate-acting			
Isophane insulin (NPH)	1-3 h	6-12 h	16-24 h
Long-acting			
Detemir (Levemir) Glargine (Lantus)	4-6 h	8-20 h	24-28 h

(Source: Adapted from a report of NIDDK)

Insulin has to enter the body's bloodstream to be effective. Unlike many medicines, insulin cannot be taken orally (swallowed as a pill or tablet) since it loses its activity when going through the gastrointestinal tract. Insulin is therefore delivered into the body by injection under the skin (subcutaneously) into the fat layer, usually in the arm, thigh, or abdominal wall. Recently in January 2006, FDA approved an insulin agent with an alternative delivery system (i.e. needle-free), called Exubera, a rapid-acting insulin agent in dry-powder form inhaled into the lungs (intrapulmonary) through a patient's mouth using a specially designed inhaler.

The choice of insulin is complex. While some people, especially older people, take the same amount of insulin every day, others adjust the insulin dose daily depending on their diet, exercise, and blood sugar patterns. In addition, insulin needs may change if a person experiences weight changes, emotional stress, or illness--particularly infection[39]. Several factors are considered before making choice of insulin[40]:

- Willingness to monitor blood sugar levels: How willing and able the person is to monitor the blood sugar levels and adjust the insulin dosage;
- Daily activity levels: How varied the person's daily activity is;
- Understanding of the disease: How adept the person is at learning about and understanding the disease;
- Stability of blood sugar levels: How stable the person's blood sugar levels are during the day and from day to day.

2) Oral Glucose-lowering therapy

Until 1995, only one category of oral antihyperglycemic medicines was available in the U.S--the sulfonylureas (SUs). Since sulfonylurea drugs were first introduced to the US market in 1954, the number of oral antihyperglycemic agent classes, each with its unique mechanism of action, has increased five-fold in the past ten years, to include classes such as biguanides first introduced to the US in 1995, alpha-glucosidase inhibitors (AGIs) in 1996, thiazolidinediones (TZD) in 1997, and non-sulfonylurea (non-SU) insulin secretagogues in 1997[41]. Recently in October 2006, a new oral agent, a Dipeptidyl Peptidase-4 Inhibitor (DPP-4i), was introduced to the market. The following table gives an overview of the oral glucose-lowering agents.

Table 3.4 Oral Antihyperglycemic Agents: Drug Class, Mechanism, and Potency

Antidiabetic Drug Class	Mechanism	Generic Name	Trade Name	Approval Date	Reduction in HbA1c (%)
Sulfonylureas (SU)	Increase insulin secretion, i.e. insulin secretagogues	glimepiride	Amaryl	1994	1-2
Biguanides	Reduce hepatic glucose production, i.e. insulin sensitizers	metformin	Glucophage	1993	1-2
Alpha-glucosidase Inhibitors (AGIs)	Delay gastrointestinal absorption of carbohydrate, i.e. starch blockers	acarbose	Precose	1994	0.5-1
		meglitol	Glyset	1995	
Thiazolidinediones (TZD)	Increase insulin sensitivity, i.e. insulin sensitizers	rosiglitazone	Avandia	1998	1-2
		pioglitazone	Actos	1999	
Meglitinides (Non-SU Secretagogues)	Increase insulin secretion, i.e. insulin secretagogues	repaglinide	Prandin	1997	1-2
		nateglinide	Starlix	1999	0.5-1
Dipeptidyl Peptidase-4 Inhibitors (DPP-4i)	Increase active levels of incretins to help regulate blood sugar	Sitagliptin	Januvia	2006	N/A

(Source: Cook D.A. et al., *Concise Review for Clinicians: Type 2 Diabetes Mellitus*)

a) Sulfonylurea

Sulfonylureas (SUs), which are considered insulin secretagogues, act by stimulating insulin secretion and are a reasonable first choice for oral therapy, although metformin (from the biguanide class) is preferred in obese patients. SUs reduce both fasting and postprandial glucose. SUs are inexpensive compared to other oral antihyperglycemic agents, but they can cause hypoglycemia which at times can be a serious problem. Since its first discovery, two generations of SUs have been developed. At maximum doses, first-generation agents are similar in potency to second-generation agents but have a longer half-life, a greater incidence of hypoglycemia, and more frequent drug interactions. Thus, the second-generation SUs are generally preferred. For these new agents, an advantage to a more rapid onset of action is better coverage of the postprandial glucose rise, but the short half-life of such agents requires more than once-a-day dosing.

Nowadays, new SU drugs with fewer side effects have been used as "monotherapy" or as part of combination therapy with other types of antidiabetics to treat diabetic patients.

b) Biguanide

Currently metformin is the only drug in the biguanide class available in the US market; both phenformin and buformin were withdrawn from the market due to the risk of lactic acidosis (toxic effects) in 1978[42]. Although available internationally (in Europe) for decades, metformin was not released to the US market until 1993[43]. Metformin is the oral agent of the first choice in obese patients. In contrast to the SU, metformin does not stimulate insulin secretion. The drug acts by decreasing hepatic glucose production; it is therefore considered as an insulin sensitizer, and is the only oral agent shown to decrease total mortality. Metformin should not cause hypoglycemia when used alone, does not contribute to weight gain as much as other diabetes medications, and has beneficial albeit limited effect on lipid profile (lowering triglycerides and LDL, raising HDL)[44].

c) Alpha-glucosidase Inhibitor

Alpha-glucosidase Inhibitors (AGIs) act by delaying gastrointestinal absorption of carbohydrates (controlling the blood sugar by slowing down the digestion and absorption of carbohydrates in the small intestine after meals by blocking the enzyme that digests carbohydrates), i.e. starch blockers. As such, they must be taken at the beginning of a meal, and can mitigate postprandial glucose elevation[45,46]. The efficacy of AGIs is considerably less than either SUs or metformin (summarized in **Table 3.4**). Their greatest effect is on postprandial glucose levels, whereas the effect on FPG levels is small.

d) Thiazolidinedione

In 1997, troglitazone, a thiazolidinedione (TZD), was introduced in the US, but was later removed from the market due to the risk of hepatotoxicity (liver damage). Currently, TZDs are represented by rosiglitazone (Avandia) and pioglitazone (Actos). TZDs are designed to reduce insulin resistance by increasing insulin sensitivity in peripheral tissue. They do not cause hypoglycemia when used alone, and may reduce insulin resistance. In both placebo-controlled and comparison trials, TZDs generally lower HbA1c as much as SUs and metformin, and more than the AGIs (summarized in **Table 3.4**). One study[47] has shown that in addition to the role as an insulin sensitizer, the TZDs also have certain benefits in improving lipid profile and reducing cardiac events. TZDs can increase the concentration of HDL cholesterol (good cholesterol) and reduce the concentration of triglycerides. TZDs also slightly reduce blood pressure.

e) Meglitinides

Meglitinides, considered as non-SU insulin secretagogues, have a similar mechanism as SUs--stimulating insulin secretion from the pancreas--but the duration of effect is much shorter than with SUs. Meglitinides can cause hypoglycemia if taken without food. The drug class of meglitinides is represented by two drugs--repaglinide (Prandin) and nateglinide (Starlix). Nateglinide requires dose adjustment in patients with hepatic impairment. The efficacy of repaglinide is similar to SUs whereas nateglinide appears to be somewhat less potent a secretagogue[48] (summarized in **Table 3.4**).

f) Dipeptidyl Peptidase-4 Inhibitor

Distinct from the mechanism of other oral agents, Dipeptidyl Peptidase-4 Inhibitors (DPP-4is) act by enhancing a natural body system that lowers blood sugar, called the

incretin system. When blood sugar increases, incretins work in two ways to help the body regulate high blood sugar levels: they trigger the pancreas to increase insulin and signal the liver to reduce glucose production. DPP-4is enhance the body's own ability to control blood sugar levels by increasing the active levels of these incretin hormones in the body, helping to decrease blood sugar levels in patients with type 2 diabetes[49]. Sitagliptin is currently the only approved and available DPP-4i in the US (approved by FDA on October 16, 2006).

Table 3.5 summarizes the comparison in costs among the oral antihyperglycemic drugs.

Table 3.5 Summary of Available Oral Agents and Costs

Antidiabetic Class	Administration			Monthly Retail Cost, $	Comparative Cost, $/day
	strength (mg)	dosage administration	total # of tablets per month		
Sulfonylureas					
Amaryl (glimepiride)	4	2 tablets/dose, qd	60	60	2-3
Biguanides					
Glucophage (metformin)	500	2 tablets/dose, bid	120	102	3-4
Alpha-glucosidase inhibitors					
Precose (acarbose)	100	1 tablet/dose, tid	90	78	2-3
Glyset (meglitol)	50	1 tablet/dose, tid	90	73	2-3
Thiazolidinediones					
Avandia (rosiglitazone)	4	1 tablet/dose, bid	60	175	>4
Actos (pioglitazone)	45	1 tablet/dose, qd	30	169	>4
Meglitinides					
Prandin (repaglinide)	2	2 tablets/dose, tid	180	165	>4
Starlix (nateglinide)	120	1 tablet/dose, tid	90	103	3-4

* qd indicates one time daily; bid, two times daily; tid, three times daily.
** Cost is based on the mean of retail costs in 2001 at 3 New Haven County, Connecticut, national chain pharmacies and is adapted from Inzucchi's Yale Diabetes Center Facts and Guidelines 2001. (Source: *Oral Antihyperglycemic Therapy for Type 2 Diabetes*[50])

3.3.4 A Look at the Pipeline

According to a report from the Pharmaceutical Researchers and Manufacturers of America (PhRMA), currently there are 24 new diabetes medicines in development. These experimental pharmaceutical treatments include[51]:

- A protein to promote increased insulin secretion when blood glucose levels are high but not when they are normal;
- Dual-acting sensitizers that increase muscle cell uptake of blood sugar and inhibit the liver's production of blood sugars, as well as reduce blood lipid levels; and
- Drugs that are designed to lessen diabetic nerve disease and complications involving small blood vessels, such as those in the eye or kidney.

4 CHANGES IN CLINICAL TRIALS OF NDAs FOR ANTIDIABETICS

A New Drug Application (NDA) is an application submitted by the manufacturer of a "new drug" to the FDA, after clinical trials have been completed, for a license to market the drug for a specified indication. According to the definition by the Center for Drug Evaluation and Research of FDA, a "new drug" can include a new molecule entity (NME) or can also be an active substance previously sold in a different form[52]. In this section, I study the clinical trials submitted in support of NDAs for fifteen antidiabetic drugs since the early 1990s (shown in **Table 4.1**), including eight oral agents, six subcutaneous insulin agents, and one inhaled insulin agent. The purpose is to investigate changes in the design of clinical trials in support of NDAs.

Table 4.1 List of Antidiabetic Drugs

Submission Date	Drug Class	Generic Name	Trade Name	Group by Route of Administration	First in Class: Yes (+) / No (-)	Priority (+) / Standard (-)
09-1993	Biguanide	metformin	Glucophage	Oral	+	+
08-1994	SU	glimepiride	Amaryl	Oral	-	-
09-1994	AGI	acarbose	Precose	Oral	-	-
12-1995	AGI	meglitol	Glyset	Oral	-	-
07-1997	Meglitinide	repaglinide	Prandin	Oral	+	+
11-1998	TZD	rosiglitazone	Avandia	Oral	+	+
12-1999	Meglitinide	nateglinide	Starlix	Oral	-	-
12-2005	DPP-4i	Sitagliptin	Januvia	Oral	+	-
03-1995	short-acting insulin	insulin lispro	Humalog	Subcutaneous	-	-
09-1998	short-acting insulin	insulin aspart	Novolog	Subcutaneous	-	-
04-1999	long-acting insulin	insulin glargine	Lantus	Subcutaneous	-	-
12-2000	glucagon lowering	pramlinitide	Symlin	Subcutaneous	-	-
12-2002	long-acting insulin	insulin detemir	Levemir	Subcutaneous	-	-
06-2003	short-acting insulin	insulin glulisine	Apidra	Subcutaneous	-	-
12-2004	insulin	insulin inhaled	Exubera	Inhaled	-	-

Under 21CFR314.50 regarding an application of a drug for human use, the legislative definition and requirements of the content and format include:

1. Application form.
2. Index.
3. Summary.
4. Technical sections.
5. Samples and labeling.
6. Case reports forms and tabulations.
7. Other.

Among all, the technical section--comprised of the following--includes the most important and useful information for my research, particularly the clinical data and statistical section:

a. Chemistry, manufacturing, and control section.
b. Nonclinical pharmacology and toxicology section.
c. Human pharmacokinetics and bioavailability section.
d. Microbiology section.
e. Clinical data section.
f. Statistical section.
g. Pediatric use section.

4.1 Clinical Trials

The definition of a clinical trial is a research study in human volunteers to answer specific health questions about vaccines or new therapies or new ways of using known treatments. Clinical trials are used to determine whether new drugs or treatments are both safe and efficacious (effective). The essential characteristic of a clinical trial is that one uses the results based on a limited sample size of patients in the study to make inferences about how a future treatment could be applied to the general patient population. According to 21CFR314.126, "an adequate and well-controlled study" has the following characteristics:

1. The objectives and the content of the investigation are clearly stated, summarizing the proposed or actual analysis methods, protocol for the study, and the report of the underlying results.

2. The study uses a design, which permits an adequate comparison with respect to a control, to provide a quantitative assessment of the drug effect. As such, placebo concurrent, dose-comparison concurrent, no treatment concurrent, active treatment concurrent, and historical controls are commonly used examples.
3. The method of selecting subjects provides the adequate assurance, under the basis that patients have the disease or condition being studied, or evidence of susceptibility and exposure to the condition against which prophylaxis (i.e. treatment to prevent disease) is directed.
4. The method of assigning patients to treatment and control groups minimizes bias and is intended to assure comparability of the groups with respect to pertinent variables such as age, sex, severity of disease, duration of disease, and use of drugs or therapy other than the test drug.
5. Adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data. The protocol and report of the study should describe the procedure used to accomplish this, such as blinding (a clinical trial is "blind" if participants are unaware of whether they are in the experimental or control arm of the study; also called masked).
6. The methods of assessment of subjects' response are well-defined and reliable.
7. There is an analysis of the results of the study, critical to adequately assessing the drug effects.

Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people. In the legislative language (21CFR314.126), the purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from

other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation.

Trials are in four phases: Phase I tests a new drug or treatment in a small group; Phase II expands the study to a larger group of people; Phase III expands the study to an even larger group of people; and Phase IV takes place after the drug or treatment has been licensed and marketed.

4.1.1 Phase I Trials: Clinical Pharmacology and Toxicity

Clinical pharmacology is intended to include the initial introduction of a drug into man. The first experiments in man are primarily concerned with drug safety, not efficacy, and hence are usually performed on human volunteers. However, with some new drugs, for ethical or scientific considerations, the initial introduction into man is more properly done in selected patients. The first objective is to determine an acceptable drug dosage, i.e. how much can be given without causing serious side-effects. Such information is often obtained from dose-escalation experiments, in which a volunteer is subjected to increasing doses of the drug according to a predetermined schedule. Phase I also involves studies of drug metabolism and bioavailability, i.e. drug dynamic and metabolic studies, such as absorption studies. Later, studies of multiple doses will also be undertaken to determine appropriate dose schedules for use in Phase II. After studies in normal volunteers, the initial trials in patients will also be of the Phase I type. Typically, Phase I studies might require a total of around 20-80 subjects and patients[53].

4.1.2 Phase II Trials: Initial Clinical Investigation for Treatment Effect

Phase II trials are fairly small-scale investigations into the effectiveness and safety of a drug, and require close monitoring of each patient. These trials can sometimes be set up as a screening process of selecting out those relatively few drugs of genuine potential from the larger number of inactive or overly toxic compounds, so that the chosen drugs may proceed to Phase III trials. The size of the Phase II trials seldom goes beyond 100-200 patients per drug.

4.1.3 Phase III Trials: Full-scale Evaluation of Treatment

After a drug is shown to be reasonably effective, it is essential to compare it either with placebo or with the current standard treatment(s) for the same condition in a large trial involving a substantial number of patients. Generally, a full-scale Phase III trial is the most rigorous and extensive type of scientific clinical investigation of a new treatment.

4.1.4 Phase IV Trials: Post-marketing Surveillance

Phase IV trials include research programs after a drug is approved for marketing. FDA may specify actions as post-marketing commitments in the approval letter of an NDA.

In light of the FDA's published Guidance of General Considerations for the Clinical Evaluation for Drugs, there are several types of post-marketing clinical trials including[54]:

1) Additional studies to elucidate the incidence of adverse reactions to explore a specific pharmacologic effect, or to obtain more information of a circumscribed nature.

2) Large scale, long-term studies to determine the effect of a drug on morbidity and mortality.
3) Additional clinical trials similar to those in Phase III to supplement premarketing data where it has been deemed in the public interest to release a drug for more widespread use prior to acquisition of all data which would ordinarily be obtained before marketing.
4) Clinical trials in a patient population not adequately studied in the premarketing phase, e.g. children.
5) Clinical trials for an indication from which it is presumed that the drug, once available, will be used.

4.2 Drug Evaluation in FDA

The Center for Drug Evaluation and Research (CDER) is one division of FDA with about 2,200 employees, the largest of the five centers in the FDA, with a charter to regulate human drugs for safety and effectiveness--reviewing drugs before marketing, watching for drug problems, monitoring drug information and advertising, and protecting drug quality[55]. Hence, regarding NDA submission, CDER is in charge of reviewing and evaluating the results of clinical trials submitted by pharmaceutical sponsors to approve a drug as safe and efficacious to be licensed and marketed in the US.

4.2.1 Review of NDA

CDER has different project teams to perform drug reviews, which allow team members to apply their individual special technical expertise to review applications. The project teams include[56]:

1. **Biologists, biochemists and immunologists**: to evaluate the manufacturing processes for biological products to ensure the continued purity, potency and safety of these products; also to provide insights into the mechanism of action as well as potential and observed adverse events associated with specific products.
2. **Chemists**: focusing on how a drug is manufactured to make sure that the manufacturing control, quality control testing, and packaging are adequate to preserve the drug product's identity, strength, potency, purity and stability.
3. **Clinical pharmacologist and biopharmaceutists**: to evaluate factors that influence the relationship between the body's response and the drug dose as well as evaluate the rate and extent to which a drug's active ingredient is available to the body and the way it is distributed, metabolized and eliminated; also to assess the clinical significance to changes the body's response to drugs through the use of exposure-response relationships and check for interactions between drugs.
4. **Microbiologists**: to evaluate the effects of anti-infective drugs on germs. These medicines--antibiotics, antivirals and antifungals—are intended to affect the germs instead of patients. Another group of microbiologists evaluates the manufacturing processes and tests for sterile products, such as those used intravenously (administered into blood vessels).
5. **Pharmacologists and toxicologists**: to evaluate the effects of the drug on laboratory animals in short-term and long-term studies, including the potential based on animal studies for drugs to induce birth defects for cancer in humans.

6. **Physicians**: to evaluate the results of the clinical trials, including the drug's adverse and therapeutic effects, and determine whether the benefits of the product outweigh the known risks at the proposed working doses.
7. **Project managers**: to orchestrate and coordinate the drug review team's interactions, efforts and reviews; also to serve as the regulatory expert for the review team and as the primary contact for the drug industry.
8. **Safety reviewers**: to propose and evaluate risk management plans as well as review proposed brand names, packaging and labeling to minimize errors when a drug is prescribed, dispensed or administered.

In the scope of this thesis in analyzing changes of characteristics of clinical trials, I focus on pivotal trials--essential to approval of an NDA in terms of safety and effectiveness--from the FDA's view (to approve an NDA), and from the sponsor's view (to acquire the approval of an NDA). However, whether a clinical trial is considered as a pivotal trial may vary from the FDA's viewpoint or from the sponsor's.

4.2.2 FDA's Guidelines on Submission of Clinical Trials

Under the 21CFR10.115 clause of "Good Guidance Practice," guidance consists of documents prepared for FDA staff, applicants/sponsors, and the public that describe the agency's interpretation of policy on a regulatory issue. In light of the definition, these documents include, but are not limited to documents that relate to: the design, production, labeling, promotion, manufacturing, and testing of regulated products; the processing, content, and evaluation or approval/submissions; and inspection and enforcement policies. On this legislative ground, FDA has issued guidelines for drug development programs in the US since 1977. The guidelines include recommendations on how Phase I, II, and III

trials should be structured for drugs, including the procedure, subject and setting of clinical trials. These guidelines include Guidance for General Considerations for the Clinical Evaluation of Drugs, and also guidances in several other specific disease areas, for instance drugs for anxiety, depression, treatment of osteoarthritis, inflammation, diarrhea, lipid-altering, weight-control etc[57].

4.3 Data Sources

The data for the analysis work in this research come from three sources: the Drugs@FDA public website, the CDER's Division File System (DFS) database and the CDER's Action Package archival system. The Drugs@FDA is a public website providing information on a drug's characteristics: general information (drug name, active ingredient(s), NDA number, company, chemical type, review classification, strength, dosage form and route of administration), approval history, letter, review and related documents, and label information. However, due to proprietary reasons, a fair amount of relevant material is often redacted. Thus, the DFS and the Action Package have become two major sources in my research. Both the DFS and the Action Package hold complete electronic information for an NDA's approval, including the following elements:

- Action letter(s)
- Discipline reviews (chemistry, medical, labeling, chemistry/manufacturing/ controls, and consults)
- Correspondence from the FDA to Sponsor (letters and faxes)
- Internal FDA correspondence (emails and inspection results)
- Meeting notes

Because the FDA has began the electronic archival process only in the 1980s, the DFS database holds more complete review reports of newer NDAs while the Action Package is more useful to access data for older NDAs.

Among the files available for approval of an NDA--either from the DFS or the Action Package--the Medical Officer's Review is the most insightful in that it is a comprehensive evaluation and assessment of a drug's safety and efficacy, with emphasis on pivotal trials from the FDA's view in order to approve the NDA. In addition, the Statistical Review and the Clinical Pharmacology Review may also be useful for collecting data for analysis.

4.4 Methodology of Analysis

The following procedure, categorized by two stages and four steps, is applied to perform data analysis and hypothesis validation:

Stage 1 (completed at FDA)

Step 1: Generate the hypothesis and define the metrics.

Step 2: Create the data collection instrument from the CDER DFS database and Action Packages.

Stage 2 (completed at MIT)

Step 3: Display distribution of data points by different complexity indicators, respectively, in response to a fixed X variable (the Submission Date, SDATE). Then, run the multiple regression analyses by different groups of route of administration (i.e. the oral vs. the subcutaneous vs. the inhaled)

Step 4: Validate the hypothesis with the insights acquired by comparing results from the regression analyses and discuss observations on trends in complexity. When comparing

the outcomes of the regression analyses, I assess the statistical significance of each regression equation based on the P-value of the coefficient. The assessment is denoted by accenting the coefficient in the regression equation with a positive mark ("+") when statistically significant, as defined in the following table:

Table 4.2 Statistical Significance of Regression Equations

P-value	Statistical Significance of Coefficient Estimate in Regression Equation
If P-value < 0.01	+++ / ---
If 0.01< P-value < 0.05	++ / --
If 0.05< P-value < 0.1	+ / -
If P-value > 0.1	0

*Note that "0" is a zero, meaning not significantly different from zero.

An overview of the analysis process is summarized in the following figure:

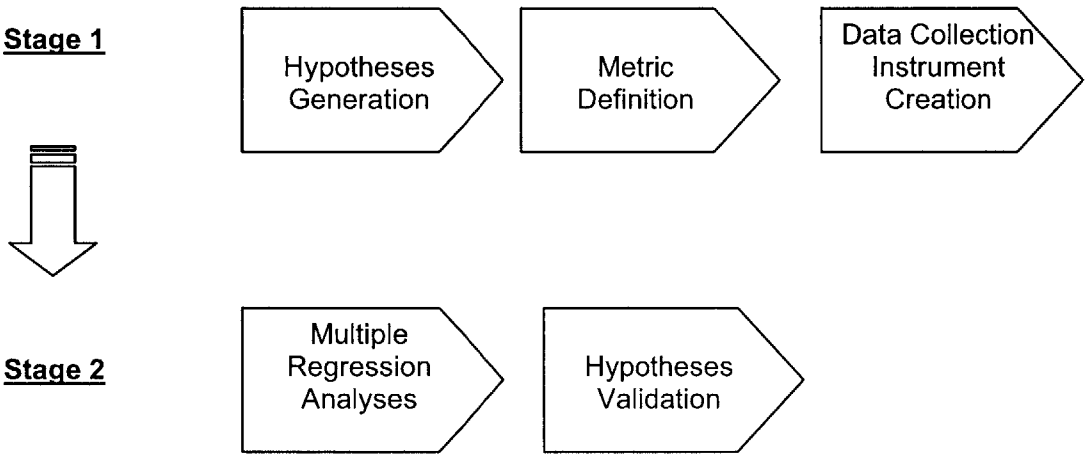


Figure 4.1 Overview of Analysis Process

4.5 Data Collection Instrument

For each of the approved antidiabetics for which complete data were available, selected relevant information was extracted from the reviews, captured on a data collection sheet (the data collection instrument), and entered into a database for further

analysis. The following table summarizes the data collection instrument designed for use in this research:

Table 4.3 Data Collection Instrument

NDA SUMMARY	PIVOTAL TRIAL SUMMARY
Drug Identification 1. NDA # 2. Generic Name 3. Brand Name 4. Sponsor Name 5. Therapeutic Class	**Study Design** 1. Study Name 2. Study Features
General Reviewing Information 1. FDA Reviewing Division 2. # of Review Cycles 3. Priority/Standard 4. Fast Track/Accelerated Subpart H 5. First in Class (Y/N) 6. Submission Date 7. Approval Date	**Study Structure** 1. Comparator 2. Dosages 3. Dose Frequency 4. Dose Duration 5. # of Patients Enrolled 6. # of Drop-Outs 7. Attrition (%)
Dosage 1. Route of Administration 2. Dosage Form 3. Dosage Strengths 4. Inpatient/Outpatient	**Endpoints** 1. Primary 2. Secondary
Safety 1. Black Box Warning at Approval 2. Black Box Warning Ever 3. # of Patients in Safety Database	**Study Size** # of Total Patients in Pivotal Trials
Study Summary 1. Indications a. Applied b. Approved 2. Special Studies a. Elderly (>65 yrs) b. Pediatric c. Cardiac d. Liver Insufficiency e. Renal Insufficiency 3. # of Pivotal Trials a. According to sponsor b. According to FDA 4. Total Studies in NDA 5. # of Drug/Drug Interaction Studies	

Post-Marketing Commitments 1. Safety 2. Clinical 3. Pediatric 4. Special Population Studies	

(Source: Adapted from Dere M.E. et al, *Changes in Characteristics of Pivotal Clinical Trials in Support of Approved New Drug Applications for Antibiotics*, 2006)

4.6 Metrics to Observe Changes in Clinical Trial Designs Supporting NDAs

I define the following twenty-five quantitative variables as the indicators of complexity to observe in NDAs of the antidiabetics approved by the FDA since the early 1990s. Among the twenty-five indicators, seventeen are related to evaluating efficacy of a drug, six to evaluating safety, and two are related to more general information (e.g. Review Time, Total Number of Studies for NDA).

1. Review Time (**REVTIME**, Month) = Approval Date – Submission Date (SDATE, Month)
2. Total Number of Studies for NDA (include all studies to establish the safety and efficacy parameters and as well as the tolerability, pharmacokinetic and pharmacodynamic parameters of the drug) (**NSTUDIES**)
3. Total Number of Patients in Safety Database (**NSAFETY**)
4. Total Number of Special Studies in NDA (**NSPECSTD**)
5. Number of Special Studies in Elderly Population (**NSPELD**)
6. Number of Special Studies in Liver Impaired Population (**NSPECLIV**)
7. Number of Special Studies in Renal Impaired Population (**NSPECREN**)
8. Total Number of Drug-Drug Interaction Studies in NDA (**NINTERST**)
9. Number of Indications Proposed by Sponsor (**NINDSP**)

10. Number of Indications Approved by FDA (**NINDFDA**)
11. Number of Pivotal Trials Submitted by Sponsor (**NPIVSP**)
12. Number of Pivotal Trials for FDA to Approve NDA (**NPIVFDA**)
13. Number of Patients in Pivotal Trials Submitted by Sponsor (**NPATSP**)
14. Number of Patients in Pivotal Trials for FDA to Approve NDA (**NPATFDA**)
15. Patients per Pivotal Trial Submitted by Sponsor = Number of Patients in Pivotal Trials Submitted by Sponsor / Number of Pivotal Trials Submitted by Sponsor (**AVNPATSP**)
16. Patients per Pivotal Trial for FDA to Approve NDA = Number of Patients in Pivotal Trials for FDA to Approve NDA / Number of Pivotal Trials for FDA to Approve NDA (**AVNPATFDA**)
17. Average Number of Patients to Support Each Indication Proposed by Sponsor = Number of Patients in Pivotal Trials Submitted by Sponsor / Number of Indications Proposed by Sponsor (**AVNPINDSP**)
18. Average Number of Patients to Support Each Indication Approved by FDA = Number of Patients in Pivotal Trials for FDA to Approve NDA / Number of Indications Approved by FDA (**AVNPINDFDA**)
19. Average Number of Pivotal Trials to Support Each Indication Proposed by Sponsor = Number of Pivotal Trials Submitted by Sponsor / Number of Indications Proposed by Sponsor (**AVNTINDSP**)
20. Average Number of Pivotal Trials to Support Each Indication Approved by FDA = Number of Pivotal Trials for FDA to Approve NDA / Number of Indications Approved by FDA (**AVNTINDFDA**)

21. Number of Comparators in Pivotal Trials (**NARM**)

22. Length of Follow-up Period in Pivotal Trials (**FOLTM**, Days)

23. Number of Primary Endpoints in Pivotal Trials (**NPEND**)

24. Number of Secondary Endpoints in Pivotal Trials (**NSEND**)

25. Dose Duration (**DOSDUR**)

4.7 Results from the Multiple Regression Analyses

The details of the multiple regression analyses by twenty-five indicators are provided in **Appendix B** and **Appendix C**. I summarize results in the following section.

4.8 Observations of Trends

The scope of this thesis focuses on fifteen antidiabetic drugs with submission dates from 1990, including oral, subcutaneous, and inhaled agents. The observations of trends in changes of the characteristics of clinical trials referenced in NDAs based on regression analyses are also summarized in the following table (Note: One drug in my sample is Exubera, an inhalant that is neither subcutaneous nor oral, and contains insulin. To preserve confidentiality in the figures that follow, this observation will not be plotted, even though it is included in the pooled regression):

Table 4.4 Summary of Trends in Changes of Clinical Trials in Antidiabetic NDAs by Statistical Significance

	Indicator		Results		
			Oral	Subcutaneous	Pooled
	General				
1	Review Time	**REVTIME**	0	0	0
2	Total Number of Studies for NDA	**NSTUDIES**	0	0	0
	Safety-Specific				
3	Total Number of Patients in Safety Database	**NSAFETY**	0	0	0
4	Total Number of Special Studies in NDA	**NSPECSTD**	++	0	0
5	Number of Special Studies in Elderly Population	**NSPELD**	+	0	0
6	Number of Special Studies in Liver Impaired Population	**NSPECLIV**	0	0	0
7	Number of Special Studies in Renal Impaired Population	**SPECREN**	0	0	--
8	Total Number of Drug-drug Interaction Studies in NDA	**NINTERST**	0	0	0
	Efficacy-Specific				
9	Number of Indications Proposed by Sponsor	**NINDSP**	0	++	0
10	Number of Indications Approved by FDA	**NINDFDA**	0	++	0
11	Number of Pivotal Trials Submitted by Sponsor	**NPIVSP**	0	0	0
12	Number of Pivotal Trials for FDA to Approve NDA	**NPIVFDA**	+	0	0
13	Number of Patients in Pivotal Trials Submitted by Sponsor	**NPATSP**	0	0	0
14	Number of Patients in Pivotal Trials for FDA to Approve NDA	**NPATFDA**	+++	0	0
15	Patients per Pivotal Trial Submitted by Sponsor	**AVNPATSP**	0	0	0
16	Patients per Pivotal Trial for FDA to Approve NDA	**AVNPATFDA**	0	0	0
17	Average Number of Patients to Support Each Indication Proposed by Sponsor	**AVNPINDSP**	0	0	0
18	Average Number of Patients to Support Each Indication Approved by FDA	**AVNPINDFDA**	+++	---	0
19	Average Number of Pivotal Trials to Support Each Indication Proposed by Sponsor	**AVNTINDSP**	0	0	0
20	Average Number of Pivotal Trials to Support Each Indication Approved by FDA	**AVNTINDFDA**	+	---	0
21	Number of Arms in Pivotal Trials	**NARM**	0	0	0
22	Length of Follow-up Period in Pivotal Trials	**FOLTM**	+	0	0
23	Number of Primary Endpoints in Pivotal Trials	**NPEND**	0	-	-
24	Number of Secondary Endpoints in Pivotal Trials	**NSEND**	0	0	0
25	Dose Duration	**DOSDUR**	0	0	0

* "+++" meaning a positive trend with statistical significance (with p-value < 0.01); "---" meaning a negative trend with statistical significance (with p-value < 0.01)

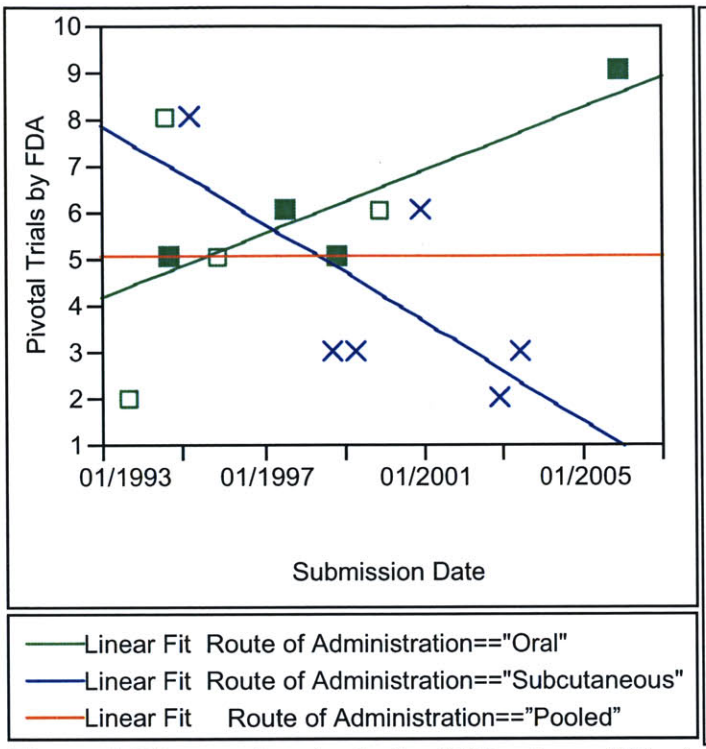
* "++" meaning a positive pattern trending to statistical significance (with 0.01 < p-value < 0.05) ; "--" meaning a negative pattern trending to statistical significance (with 0.01 < p-value < 0.05)

* "+" meaning a positive pattern with slight trending to statistical significance (with 0.05 < p-value < 0.1); "- " meaning a negative pattern with slight trending to statistical significance (with 0.05 < p-value < 0.1)

* "0" meaning not significantly different from zero

4.8.1 Oral vs. Subcutaneous

Among the twenty-five sets of analyses by different indicators, the oral group showed an increasing trend in fourteen indicators while the subcutaneous group only showed an increasing trend in eight. In the analyses, I often observed quite different--even opposite--trends in the two groups when grouping the antidiabetics by route of administration, for instance, in the following six indicators: Number of Pivotal Trials for FDA to Approve NDA (NPIVFDA), Number of Patients in Pivotal Trials for FDA to Approve NDA (NPATFDA), Average Number of Patients to Support Each Indication Proposed by Sponsor (AVNPINDSP), Average Number of Patients to Support Each Indication Approved by FDA (AVNPINDFDA), Average Number of Pivotal Trials to Support Each Indication Proposed by Sponsor (AVNTINDSP), and Average Number of Pivotal Trials to Support Each Indication Approved by FDA (AVNTINDFDA). Due to the opposite phenomena I observed in each group, they often cancelled out the patterns and resulted in no obvious composite trend when I pooled all agents for analysis. These results are presented in the following figures:



The regression equations:

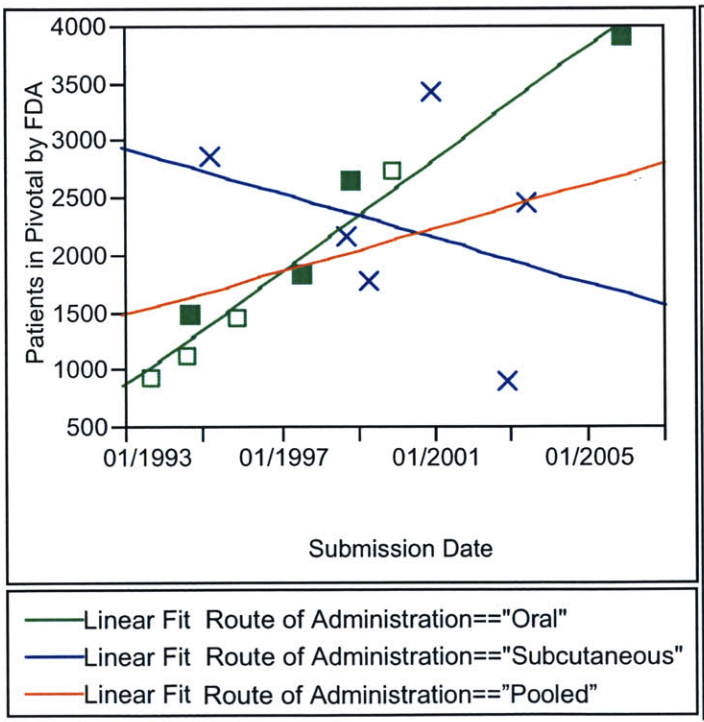
For the oral agents:
$NPIVFDA^{+} = 4.377^{+} + 0.028\ SDATE^{+}$
($R^2 = 0.415$; P-value = 0.276)

For the subcutaneous agents:
$NPIVFDA = 7.593 - 0.044\ SDATE$
($R^2 = 0.488$; P-value = 0.123)

For all agents (Pooled):
$NPIVFDA = 5.067 + 0.000002\ SDATE$
($R^2 < 0.001$; P-value = 0.999)

(For details, see **Appendix C**)

Figure 4.2 Regression Analysis of "Number of Pivotal Trials for FDA to Approve NDA" By "Submission Date"



The regression equations:

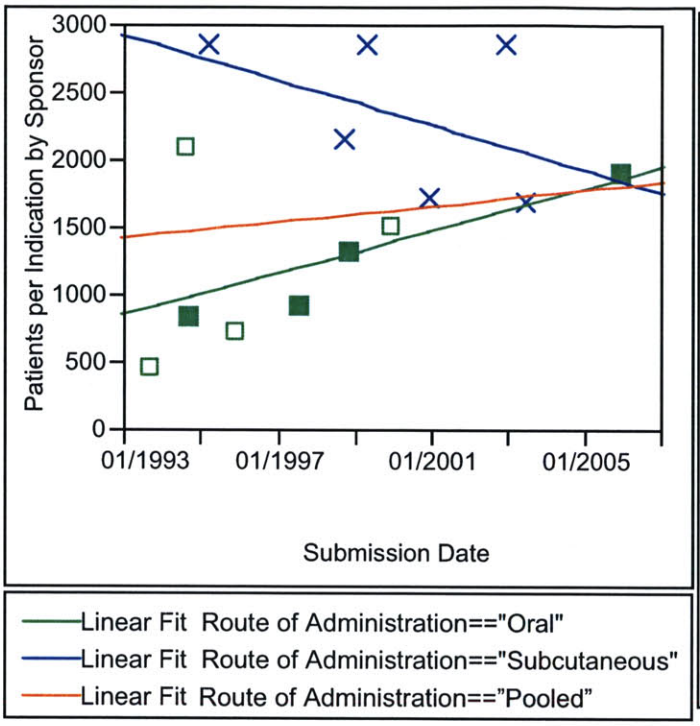
For the oral agents:
$NPATFDA^{+++} = 1011.196^{+++} + 20.425\ SDATE^{+++}$
($R^2 = 0.963$; P-value <0.0001)

For the subcutaneous agents:
$NPATFDA = 2878.582 - 8.173\ SDATE$
($R^2 = 0.117$; P-value = 0.507)

For all agents (Pooled):
$NPATFDA = 1531.686 + 7.877\ SDATE$
($R^2 = 0.166$; P-value = 0.132)

(For details, see **Appendix C**)

Figure 4.3 Regression Analysis of "Number of Patients in Pivotal Trials for FDA to Approve NDA" By "Submission Date"



The regression equations:

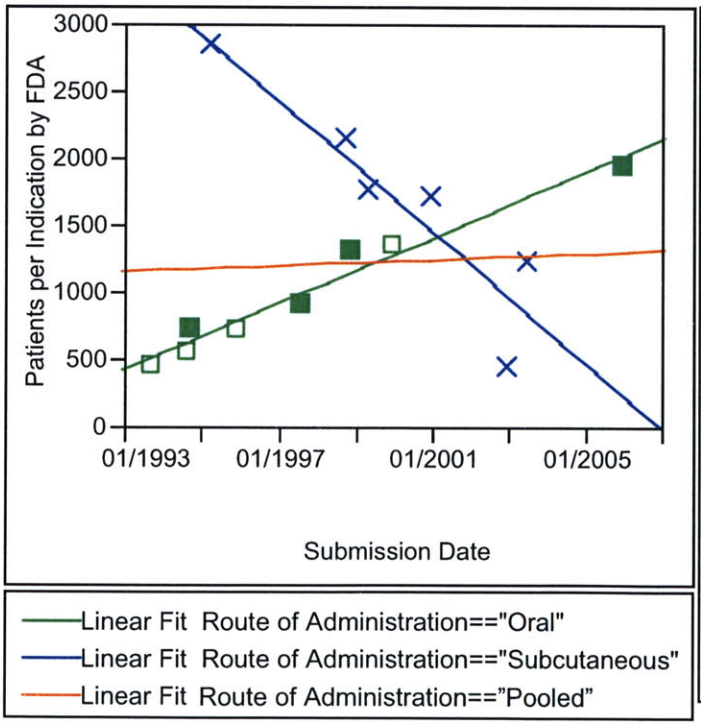
For the oral agents:
AVNPINDSP =
898.451 + 6.545 SDATE
(R^2 = 0.293; P-value = 0.166)

For the subcutaneous agents:
AVNPINDSP =
2879.571 - 6.954 SDATE
(R^2 = 0.199; P-value = 0.375)

For all agents (Pooled):
AVNPINDSP =
1443.915 + 2.453 SDATE
(R^2 = 0.019; P-value = 0.628)

(For details, see **Appendix C**)

Figure 4.4 Regression Analysis of "Average Number of Patients to Support Each Indication Applied by Sponsor" By "Submission Date"



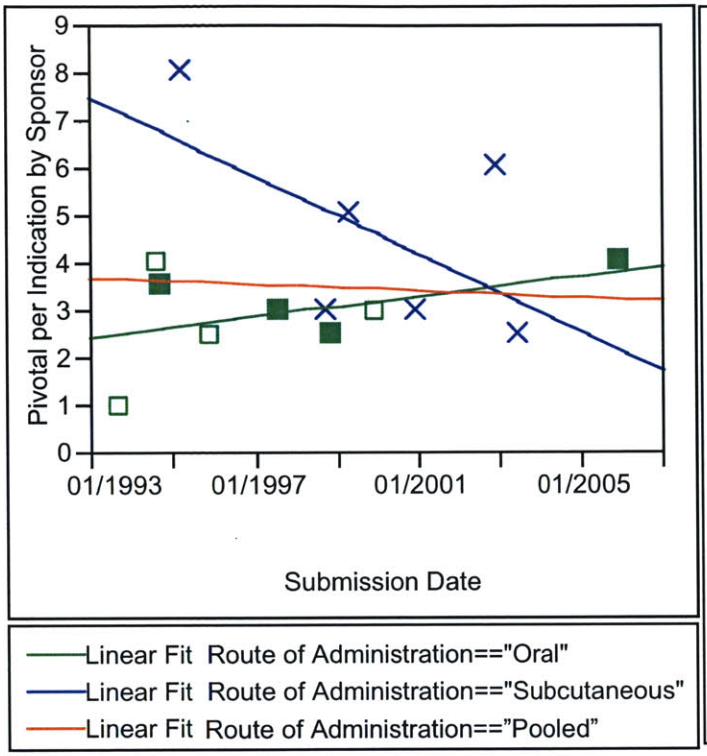
The regression equations:

For the oral agents:
$AVNPINDFDA^{+++}$ =
505.598^{+++}
+ 10.212 $SDATE^{+++}$
(R^2 = 0.963; P-value <0.0001)

For the subcutaneous agents:
$AVNPINDFDA^{---}$ =
3264.087^{---}
- 20.360 $SDATE^{---}$
(R^2 = 0.847; P-value = 0.009)

For all agents (Pooled):
AVNPINDFDA =
1164.924 + 0.958 SDATE
(R^2 = 0.004; P-value = 0.827)
(For details, see **Appendix C**)

Figure 4.5 Regression Analysis of "Average Number of Patients to Support Each Indication Approved by FDA" By "Submission Date"



The regression equations:

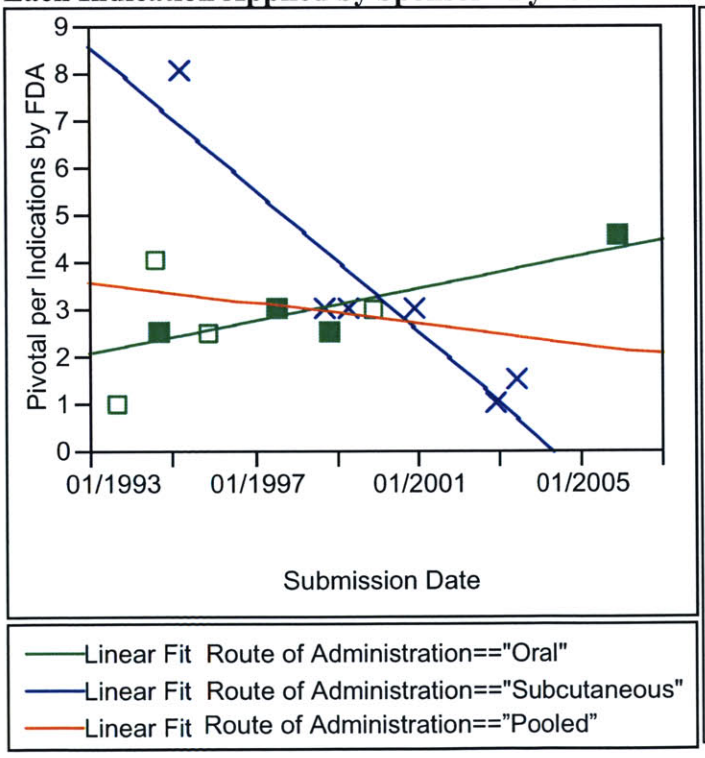
For the oral agents:
AVNTINDSP =
2.505 + 0.009 SDATE
(R^2 = 0.193; P-value = 0.276)

For the subcutaneous agents:
AVNTINDSP =
7.238 - 0.034 SDATE
(R^2 = 0.338; P-value = 0.226)

For all agents (Pooled):
AVNTINDSP =
3.667 - 0.003 SDATE
(R^2 = 0.005; P-value = 0.794)

(For details, see **Appendix C**)

Figure 4.6 Regression Analysis of "Average Number of Pivotal Trials to Support Each Indication Applied by Sponsor" By "Submission Date"



The regression equations:

For the oral agents:
$AVNTINDFDA^{+}$ =
2.189^{+} + 0.014 $SDATE^{+}$
(R^2 = 0.415; P-value = 0.085)

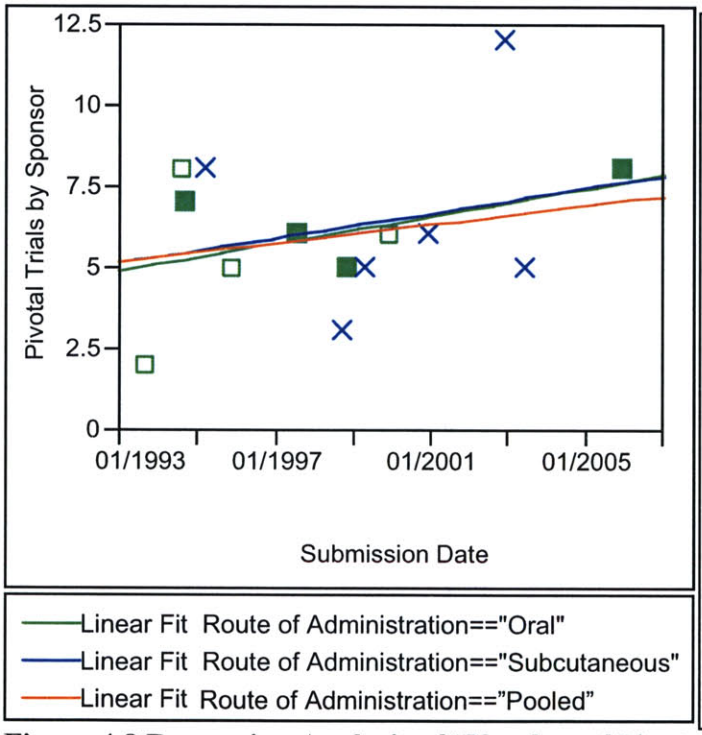
For the subcutaneous agents:
$AVNTINDFDA^{---}$ = 8.129^{---}
- 0.063 $SDATE^{---}$
(R^2 = 0.860; P-value = 0.008)

For all agents (Pooled):
AVNTINDFDA =
3.508 - 0.009 SDATE
(R^2 = 0.059; P-value = 0.381)

(For details, see **Appendix C**)

Figure 4.7 Regression Analysis of "Average Number of Pivotal Trials to Support Each Indication Approved by FDA" By "Submission Date"

In the subset of the seventeen efficacy-specific indicators among the total twenty-five indicators, first, I observed an increasing trend in the following five indicators for both groups: Number of Pivotal Trials Submitted by Sponsor (NPIVSP), Number of Patients in Pivotal Trials Submitted by Sponsor (NPATSP), Patients per Pivotal Trial Submitted by Sponsor (AVNPATSP), Patients per Pivotal Trial for FDA to Approve NDA (AVNPATFDA), and Length of Follow-up Period in Pivotal Trials (FOLTM). These results are presented in the following figures:



The regression equations:

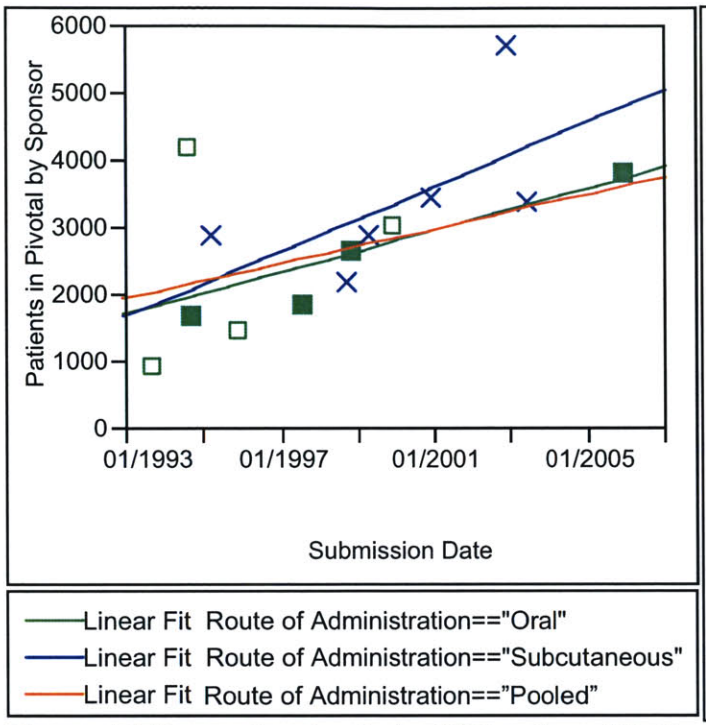
For the oral agents:
NPIVSP =
5.010 + 0.018 SDATE
(R^2 = 0.193; P-value = 0.276)

For the subcutaneous agents:
NPIVSP =
5.253 + 0.016 SDATE
(R^2 = 0.035; P-value = 0.723)

For all agents (Pooled):
NPIVSP =
5.260 + 0.012 SDATE
(R^2 = 0.059; P-value = 0.383)

(For details, see **Appendix C**)

Figure 4.8 Regression Analysis of "Number of Pivotal Trials Submitted by Sponsor" By "Submission Date"



The regression equations:

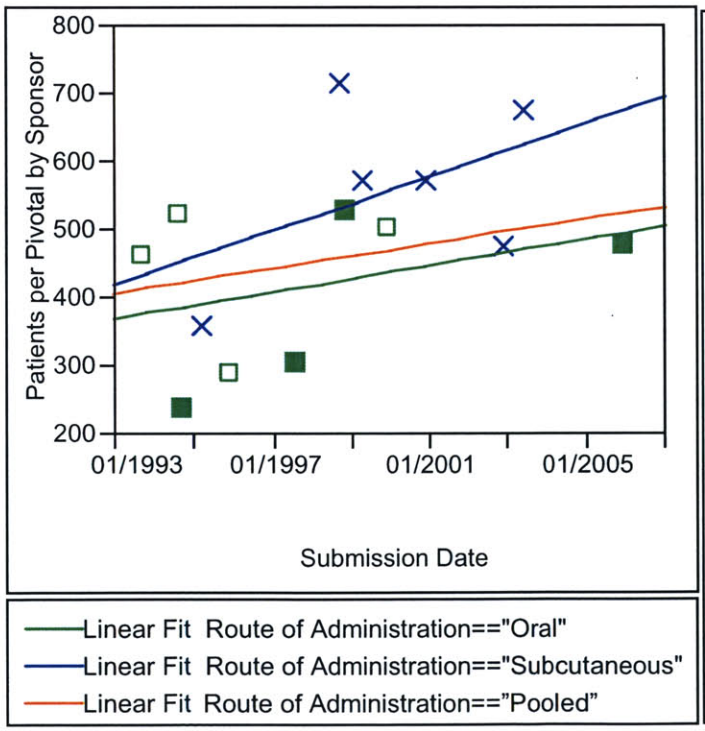
For the oral agents:
NPATSP =
1796.902 + 13.090 SDATE
(R^2 = 0.293; P-value = 0.166)

For the subcutaneous agents:
NPATSP =
1806.760 + 20.203 SDATE
(R^2 = 0.373; P-value = 0.198)

For all agents (Pooled):
NPATSP =
2021.892 + 10.795 SDATE
(R^2 = 0.164; P-value = 0.134)

(For details, see **Appendix C**)

Figure 4.9 Regression Analysis of "Number of Patients in Pivotal Trials Submitted by Sponsor" By "Submission Date"



The regression equations:

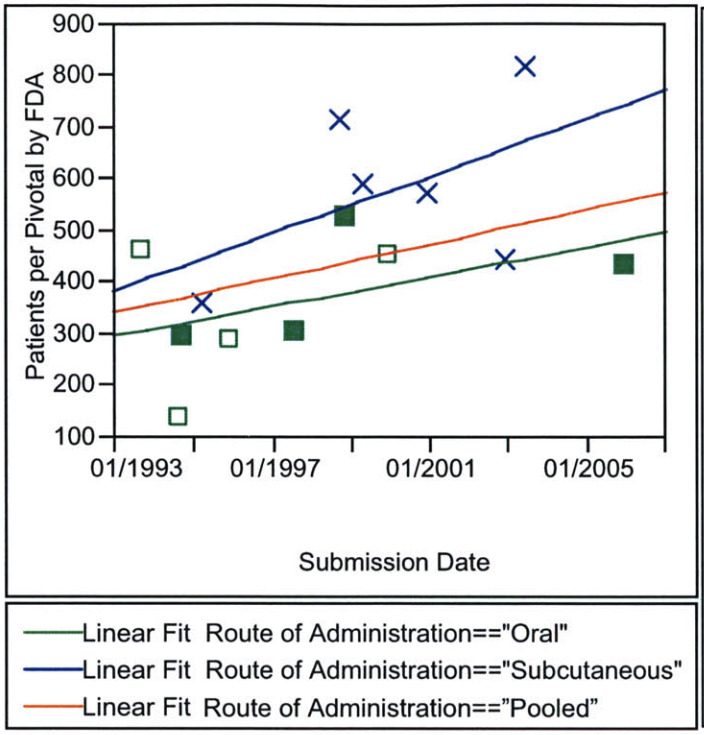
For the oral agents:
AVNPATSP =
375.714 + 0.791 SDATE
(R^2 = 0.105; P-value = 0.434)

For the subcutaneous agents:
AVNPATSP =
430.830 + 1.638 SDATE
(R^2 = 0.211; P-value = 0.360)

For all agents (Pooled):
AVNPATSP =
412.079 + 0.749 SDATE
(R^2 = 0.059; P-value = 0.383)

(For details, see **Appendix C**)

Figure 4.10 Regression Analysis of "Patients per Pivotal Trials Submitted by Sponsor" By "Submission Date"



The regression equations:

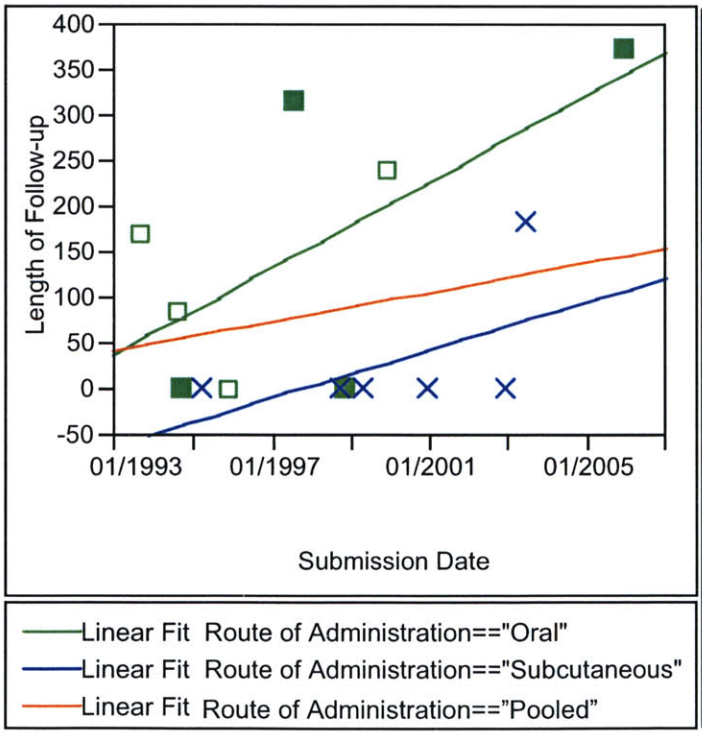
For the oral agents:
AVNPATFDA =
304.756 + 1.181 SDATE
(R^2= 0.201; P-value = 0.265)

For the subcutaneous agents:
AVNPATFDA =
400.352 + 2.305 SDATE
(R^2 = 0.252; P-value = 0.310)

For all agents (Pooled):
AVNPATFDA =
351.284 + 1.379 SDATE
(R^2 = 0.131; P-value = 0.184)

(For details, see **Appendix C**)

Figure 4.11 Regression Analysis of "Patients per Pivotal Trials for FDA to Approve NDA" By "Submission Date"



The regression equations:

For the oral agents:
$FOLTM^+$ =
$51.753^+ + 1.966\ SDATE^+$
(R^2 = 0.403; P-value = 0.091)

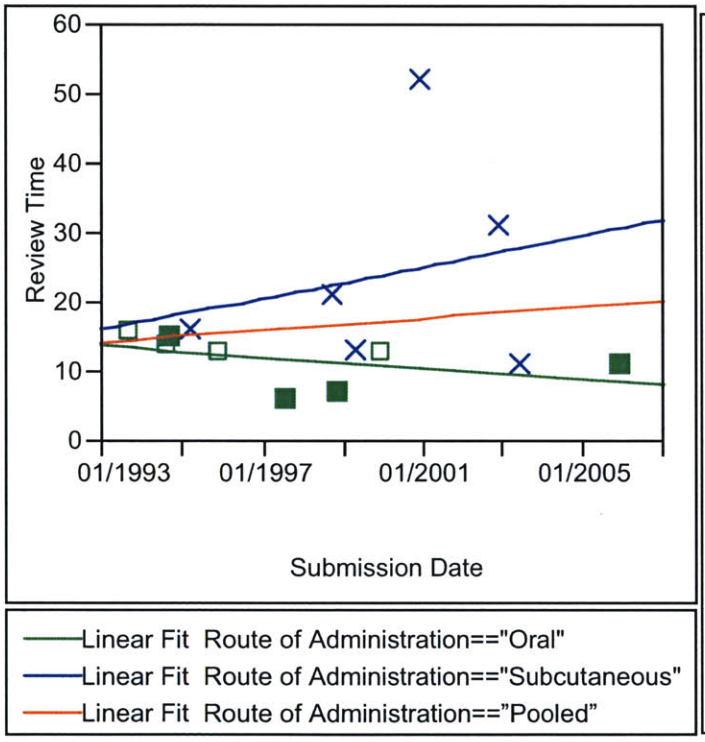
For the subcutaneous agents:
FOLTM =
-54.439 + 1.091 SDATE
(R^2 = 0.290; P-value = 0.270)

For all agents (Pooled):
FOLTM =
46.527 + 0.666 SDATE
(R^2 = 0.058; P-value = 0.387)

(For details, see **Appendix C**)

Figure 4.12 Regression Analysis of "Length of Follow-up Period in Pivotal Trials" By "Submission Date"

In the following three indicators: Review Time (REVTIME), Number of Indications Proposed by Sponsor (NINDSP), and Number of Indications Approved by FDA (NINDFDA), only the subcutaneous group showed an increasing trend while the oral group showed no trend or even a decreasing trend. These results are presented in the following figures:



The regression equations:

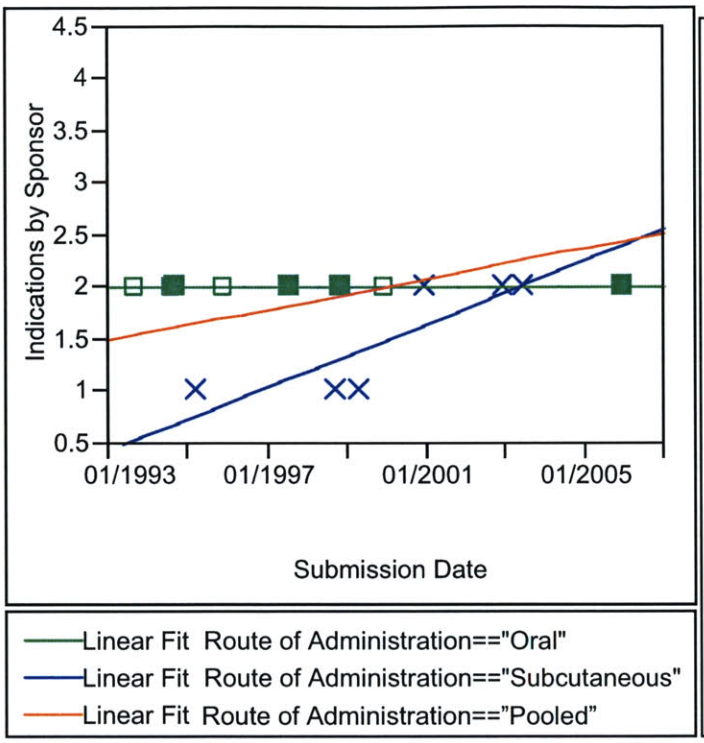
For the oral agents:
REVTIME =
13.453 - 0.033 SDATE
(R^2 = 0.186; P-value = 0.286)

For the subcutaneous agents:
REVTIME =
16.713 + 0.094 SDATE
(R^2 = 0.050; P-value = 0.672)

For all agents (Pooled):
REVTIME =
14.531 + 0.035 SDATE
(R^2 = 0.022; P-value = 0.600)

(For details, see **Appendix C**)

Figure 4.13 Regression Analysis of "Review Time" By "Submission Date"



The regression equations:

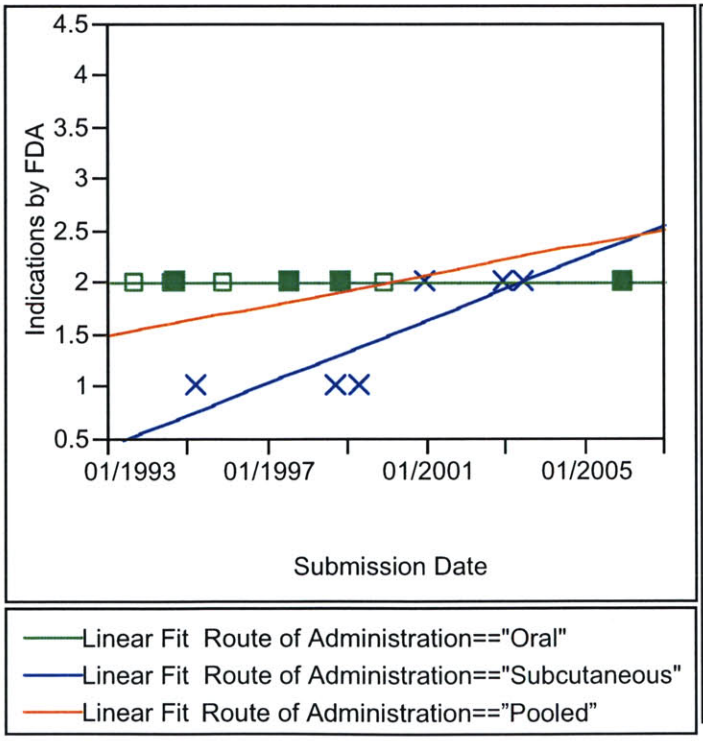
For the oral agents:
NINDSP = 2

For the subcutaneous agents:
$NINDSP^{++} = 0.518^{++} + 0.013\ SDATE^{++}$ ($R^2 = 0.716$; P-value = 0.034)

For all agents (Pooled):
NINDSP = 1.531 + 0.006 SDATE
($R^2 = 0.167$; P-value = 0.131)

(For details, see **Appendix C**)

Figure 4.14 Regression Analysis of "Number of Indications Applied by Sponsor" By "Submission Date"



The regression equations:

For the oral agents:
NINDFDA = 2

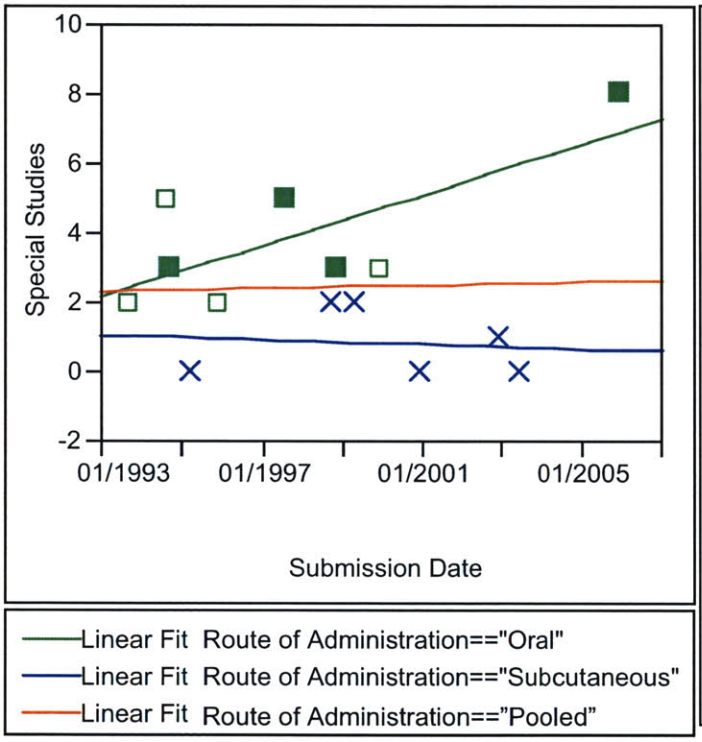
For the subcutaneous agents:
$NINDFDA^{++} = 0.518^{++} + 0.013\ SDATE^{++}$
($R^2 = 0.716$; P-value = 0.034)

For all agents (Pooled):
NINDFDA = 1.531 + 0.006 SDATE
($R^2 = 0.167$; P-value = 0.131)

(For details, see **Appendix C**)

Figure 4.15 Regression Analysis of "Number of Indications Approved by FDA" By "Submission Date"

In the subset of safety-specific indicators, I observed an increasing trend in the oral group with the following three indicators: Total Number of Special Studies in NDA (NSPECSTD), Number of Special Studies in Elderly Population (NSPELD), and Number of Special Studies in Liver Impaired Population (NSPELIV). No obvious trend was observed in the subcutaneous group. These results are presented in the following figures:



The regression equations:

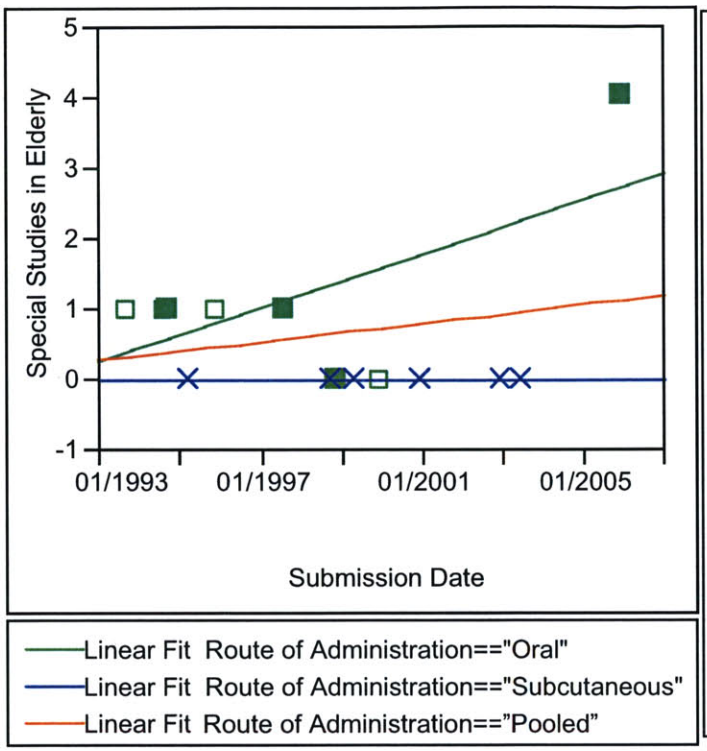
For the oral agents:
$NSPECSTD^{++} = 2.411^{++} + 0.030\ SDATE^{++}$
($R^2 = 0.515$; P-value = 0.045)

For the subcutaneous agents:
$NSPECSTD = 1.045 - 0.003\ SDATE$
($R^2 = 0.010$; P-value = 0.848)

For all agents (Pooled):
$NSPECSTD = 2.345 + 0.002\ SDATE$
($R^2 = 0.001$; P-value = 0.889)

(For details, see **Appendix C**)

Figure 4.16 Regression Analysis of "Total Number of Special Studies" By "Submission Date"



The regression equations:

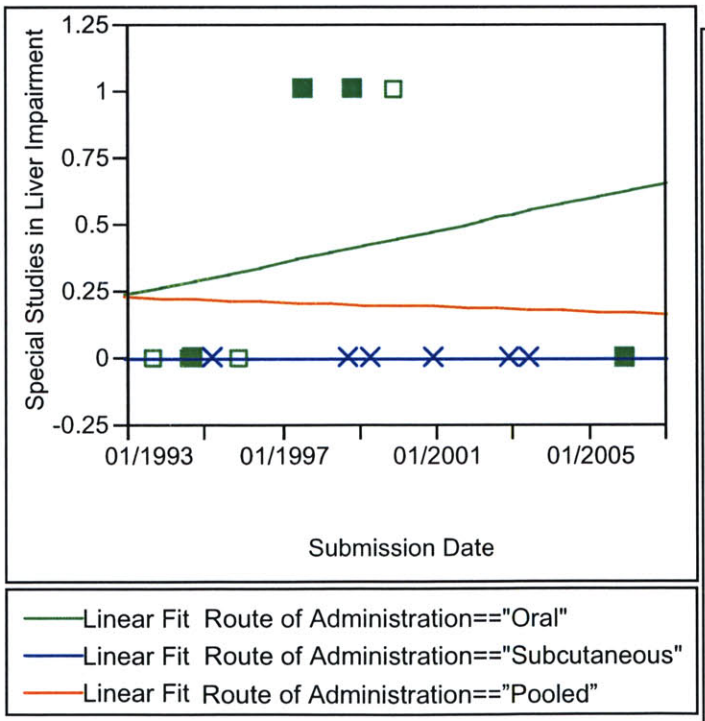
For the oral agents:
$NSPELD^{+} = 0.360^{+} + 0.016\ SDATE^{+}$
(R^2= 0.373; P-value = 0.108)

For the subcutaneous agents:
NSPELD = 0

For all agents (Pooled):
NSPELD = 0.310 + 0.005 SDATE
(R^2= 0.060; P-value = 0.381)

(For details, see **Appendix C**)

Figure 4.17 Regression Analysis of "Number of Special Studies in Elderly Population" By "Submission Date"



The regression equations:

For the oral agents:
NSPECLIV = 0.253 + 0.003 SDATE
(R^2 = 0.055; P-value = 0.577)

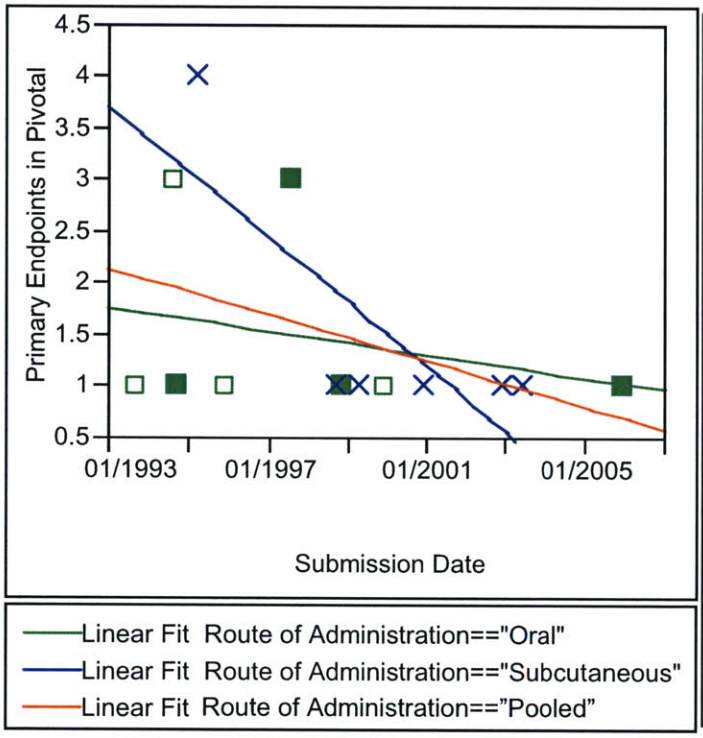
For the subcutaneous agents:
NSPECLIV = 0

For all agents (Pooled):
NSPECLIV = 0.225 - 0.0003 SDATE
(R^2 = 0.002; P-value = 0.879)

(For details, see **Appendix C**)

Figure 4.18 Regression Analysis of "Number of Special Studies in Liver Impaired Population" By "Submission Date"

In only two efficacy-specific indicators: Number of Primary Endpoints in Pivotal Trials (NPEND) and Number of Secondary Endpoints in Pivotal Trials (NSEND), both related to selection of endpoints to evaluate the patient response, I observed a decreasing trend in both groups. These results are shown in the following figures:



The regression equations:

For the oral agents:
NPEND =
1.725 - 0.005 SDATE
(R^2 = 0.059; P-value = 0.564)

For the subcutaneous agents:
NPEND^{-} =
3.533^{-} - 0.026 SDATE^{-}
(R^2 = 0.614; P-value = 0.065)

For all agents (Pooled):
NPEND^{-} =
2.073^{-} - 0.009 SDATE^{-}
(R^2 = 0.192; P-value = 0.103)

(For details, see **Appendix C**)

Figure 4.19 Regression Analysis of "Number of Primary Endpoints in Pivotal Trials" By "Submission Date"

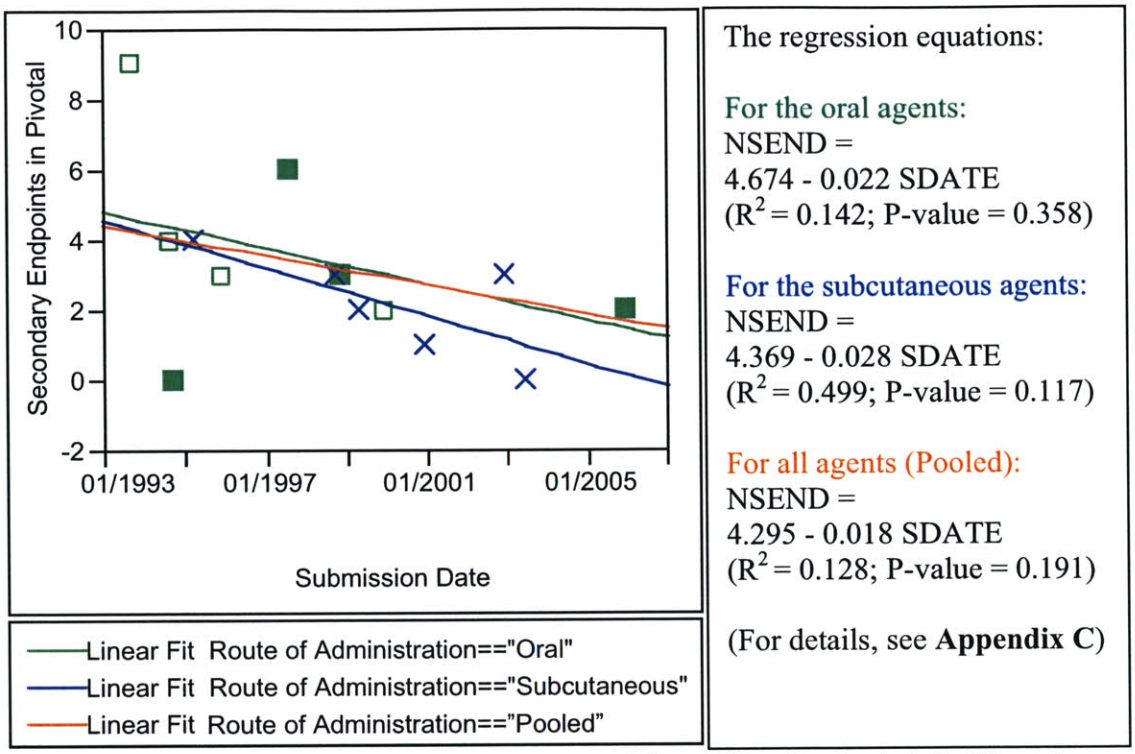


Figure 4.20 Regression Analysis of "Number of Secondary Endpoints in Pivotal Trials" By "Submission Date"

4.8.2 FDA vs. Sponsor

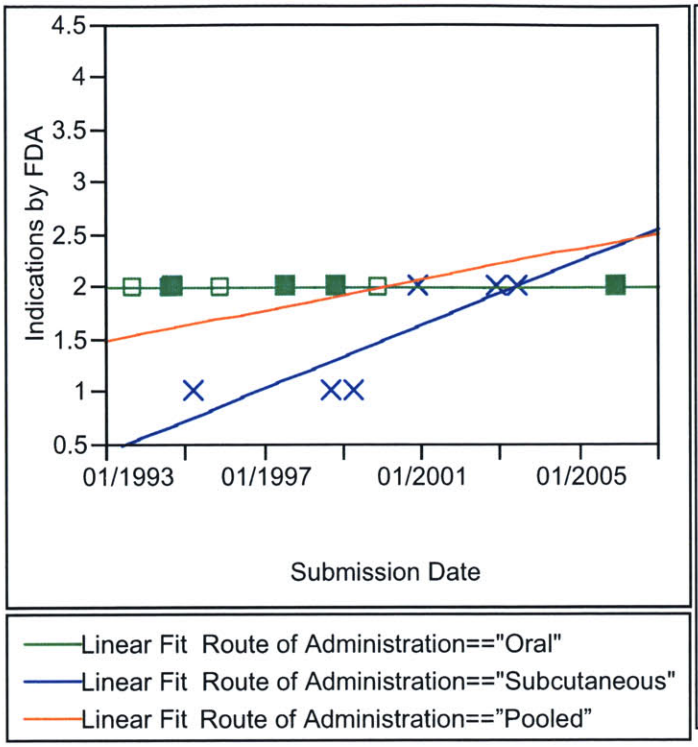
Another interesting finding in my research is that the indicators related to FDA's evaluation of the data in the NDAs showed more statistical significance when compared to those related to the sponsor's NDA submission. Here, I summarize these results in **Table 4.5**.

Table 4.5 Statistical Significance of Indicators between the FDA and the Sponsor

Indicators		Results		
		Oral	Subcutaneous	Pooled
FDA's Evaluation Related				
Number of Indications	**NINDFDA**	0	+	0
Number of Pivotal Trials	**NPIVFDA**	+	0	0
Number of Patients in Pivotal Trials	**NPATFDA**	+++	0	0
Patients per Pivotal Trial	**AVNPATFDA**	0	0	0
Average Number of Patients to Support Each Indication	**AVNPINDFDA**	+++	---	0
Average Number of Pivotal Trials to Support Each Indication	**AVNTINDFDA**	+	---	0
Sponsor's Submission Related				
Number of Indications	**NINDSP**	0	++	0
Number of Pivotal Trials	**NPIVSP**	0	0	0
Number of Patients in Pivotal Trials	**NPATSP**	0	0	0
Patients per Pivotal Trial	**AVNPATSP**	0	0	0
Average Number of Patients to Support Each Indication	**AVNPINDSP**	0	0	0
Average Number of Pivotal Trials to Support Each Indication	**AVNTINDSP**	0	0	0

* "+++" meaning a positive trend with statistical significance (with p-value < 0.01); "---" meaning a negative trend with statistical significance (with p-value < 0.01)
* "++" meaning a positive pattern trending to statistical significance (with 0.01 < p-value < 0.05) ; "--" meaning a negative pattern trending to statistical significance (with 0.01 < p-value < 0.05)
* "+" meaning a positive pattern with slight trending to statistical significance (with 0.05 < p-value < 0.1); "-" meaning a negative pattern with slight trending to statistical significance (with 0.05 < p-value < 0.1)
* "0" meaning not significantly different from zero

I also present the results related to the FDA's evaluation, which show more statistical significance in the trend, in the figures below:



The regression equations:

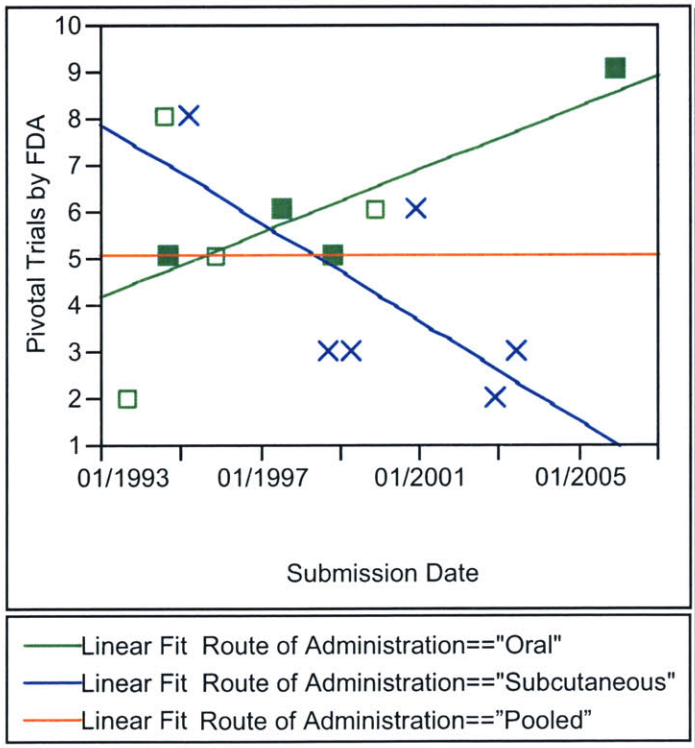
For the oral agents:
NINDFDA = 2

For the subcutaneous agents:
$NINDFDA^{++} = 0.518^{++} + 0.013\ SDATE^{++}$
($R^2 = 0.716$; P-value = 0.034)

For all agents (Pooled):
NINDFDA =
1.531 + 0.006 SDATE
($R^2 = 0.167$; P-value = 0.131)

(For details, see **Appendix C**)

Figure 4.21 Regression Analysis of "Number of Indications Approved by FDA" By "Submission Date"



The regression equations:

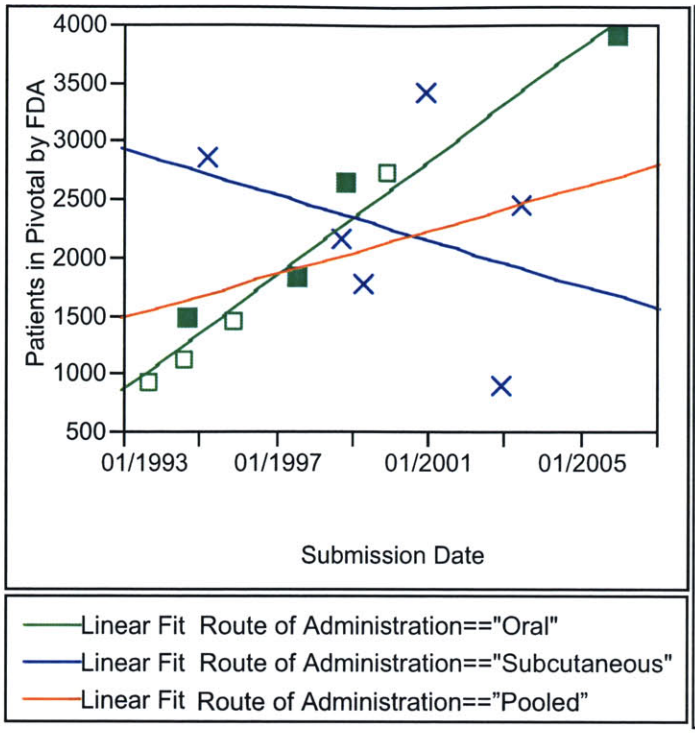
For the oral agents:
$NPIVFDA^{+} = 4.377^{+} + 0.028\ SDATE^{+}$
($R^2 = 0.415$; P-value = 0.276)

For the subcutaneous agents:
NPIVFDA =
7.593 - 0.044 SDATE
($R^2 = 0.488$; P-value = 0.123)

For all agents (Pooled):
NPIVFDA =
5.067 + 0.000002 SDATE
($R^2 < 0.001$; P-value = 0.999)

(For details, see **Appendix C**)

Figure 4.22 Regression Analysis of "Number of Pivotal Trials for FDA to Approve NDA" By "Submission Date"



The regression equations:

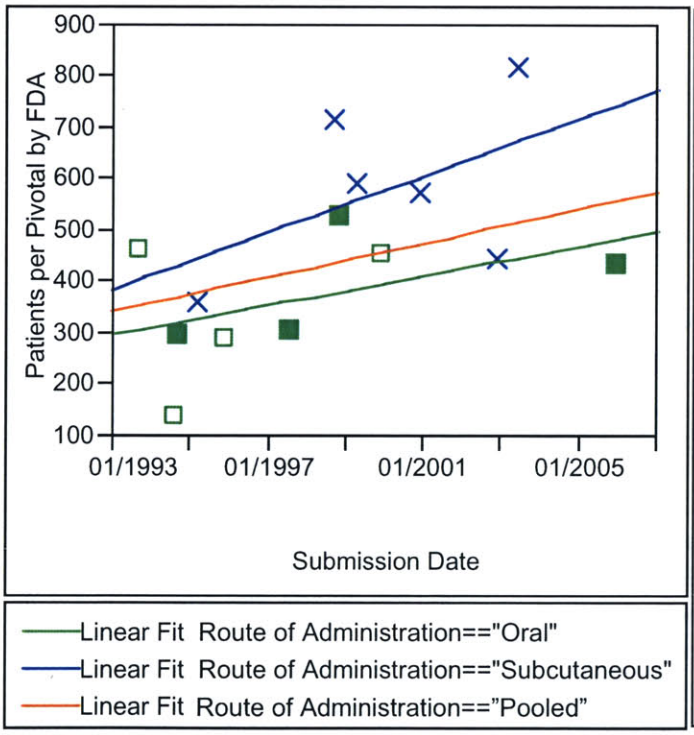
For the oral agents:
$NPATFDA^{+++} = 1011.196^{+++} + 20.425\ SDATE^{+++}$
($R^2 = 0.963$; P-value <0.0001)

For the subcutaneous agents:
NPATFDA =
2878.582 - 8.173 SDATE
($R^2 = 0.117$; P-value = 0.507)

For all agents (Pooled):
NPATFDA =
1531.686 + 7.877 SDATE
($R^2 = 0.166$; P-value = 0.132)

(For details, see **Appendix C**)

Figure 4.23 Regression Analysis of "Number of Patients in Pivotal Trials for FDA to Approve NDA" By "Submission Date"



The regression equations:

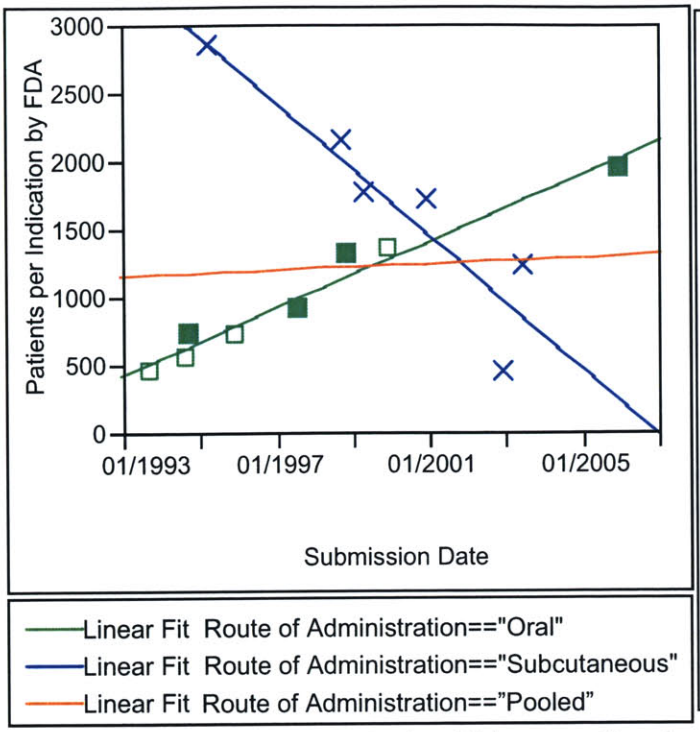
For the oral agents:
AVNPATFDA =
304.756 + 1.181 SDATE
($R^2 = 0.201$; P-value = 0.265)

For the subcutaneous agents:
AVNPATFDA =
400.352 + 2.305 SDATE
($R^2 = 0.252$; P-value = 0.310)

For all agents (Pooled):
AVNPATFDA =
351.284 + 1.379 SDATE
($R^2 = 0.131$; P-value = 0.184)

(For details, see **Appendix C**)

Figure 4.24 Regression Analysis of "Patients per Pivotal Trials for FDA to Approve NDA" By "Submission Date"



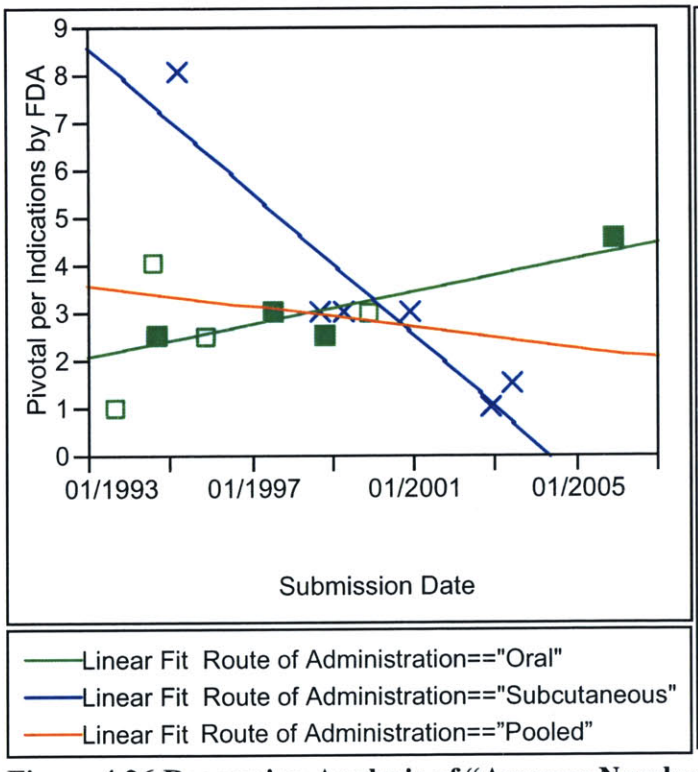
The regression equations:

For the oral agents:
$AVNPINDFDA^{+++} = 505.598^{+++} + 10.212\ SDATE^{+++}$
($R^2 = 0.963$; P-value <0.0001)

For the subcutaneous agents:
$AVNPINDFDA^{---} = 3264.087^{---} - 20.360\ SDATE^{---}$
($R^2 = 0.847$; P-value = 0.009)

For all agents (Pooled):
AVNPINDFDA = 1164.924 + 0.958 SDATE
($R^2 = 0.004$; P-value = 0.827)
(For details, see **Appendix C**)

Figure 4.25 Regression Analysis of "Average Number of Patients to Support Each Indication Approved by FDA" By "Submission Date"



The regression equations:

For the oral agents:
$AVNTINDFDA^{+} = 2.189^{+} + 0.014\ SDATE^{+}$
($R^2 = 0.415$; P-value = 0.085)

For the subcutaneous agents:
$AVNTINDFDA^{---} = 8.129^{---} - 0.063\ SDATE^{---}$
($R^2 = 0.860$; P-value = 0.008)

For all agents (Pooled):
AVNTINDFDA = 3.508 - 0.009 SDATE
($R^2 = 0.059$; P-value = 0.381)

(For details, see **Appendix C**)

Figure 4.26 Regression Analysis of "Average Number of Pivotal Trials to Support Each Indication Approved by FDA" By "Submission Date"

4.9 Post-marketing Commitments

In this section, I provide more qualitative analyses regarding post-marketing commitments in the antidiabetic NDAs I study.

When comparing the post-marketing commitments (PMCs) of the oral antihyperglycemic agents, there appears to be an increasing trend in the PMC of safety and pediatric studies, as summarized in the following table and figure:

Table 4.6 Summary of Post-marketing Commitments for Oral Antihyperglycemic Agents

	Oral Antihyperglycemic Agents							
	Glucophage	Amaryl	Precose	Glyset	Prandin	Avandia	Starlix	Januvia
Safety	0	0	0	0	1	1	0	1
Clinical	1	0	0	0	0	0	0	1
Pediatric	0	0	0	0	0	0	1	1
Special Population Studies	0	0	0	0	1	0	0	0
Others (Chemistry, Manufacturing and Controls)	0	0	0	0	0	0	0	0
Total PMCs	1	0	0	0	2	1	1	3

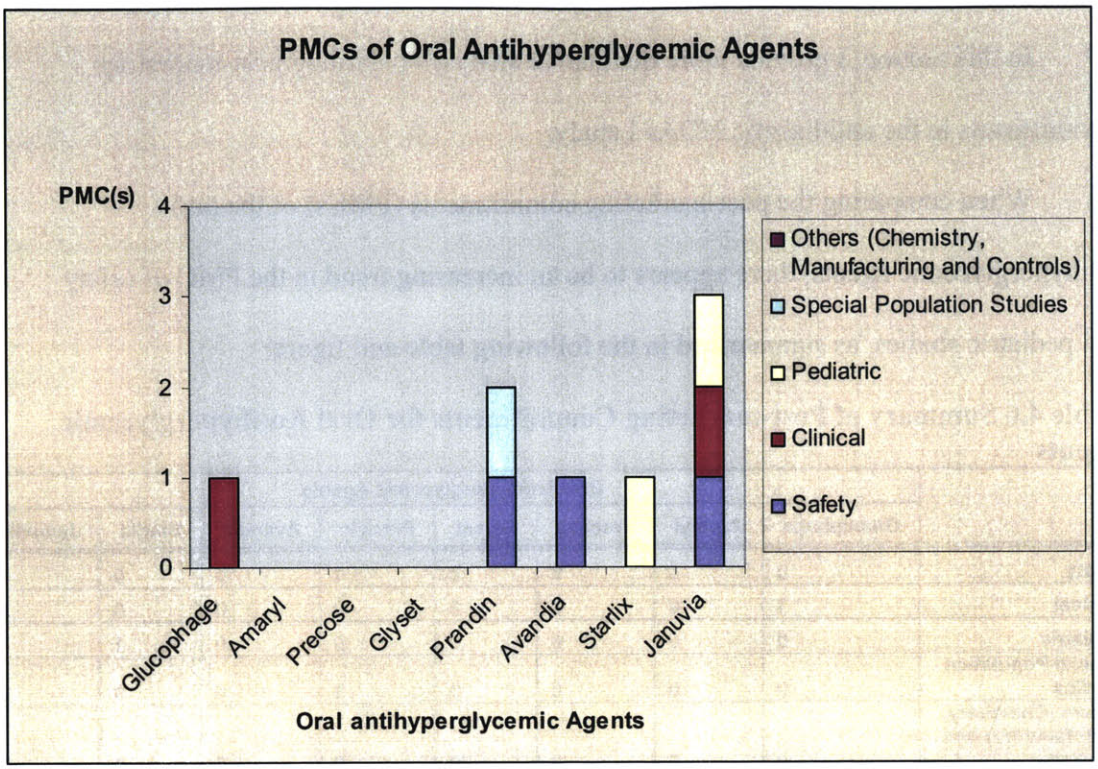


Figure 4.27 Post-marketing Commitments of Oral Antihyperglycemic Agents

Overall in the subcutaneous group, there appears to be a decreasing trend in the total number of PMCs, despite the fact that the pediatric study is often requested by FDA as a PMC. This is because insulin is considered as standard care in treating type 1 diabetes, which has its onset in children and adolescents. However, only the inhaled insulin has more PMCs due to safety concerns. These results are summarized in the following table and figure:

Table 4.7 Summary of Post-marketing Commitments for Insulin Agents

	Insulin Agents						
	Subcutaneous						Inhaled
	Humalog	Novolog	Lantus	Symlin	Levemir	Apidra	Exubera
Safety	0	0	0	1	0	0	1
Clinical	1	0	1	1	0	0	1
Pediatric	1	1	0	1	1	1	1
Special Population Studies	1	1	0	0	0	0	0
Others (Chemistry, Manufacturing and Controls)	1	0	1	0	0	0	1
Total PMCs	4	2	2	3	1	1	4

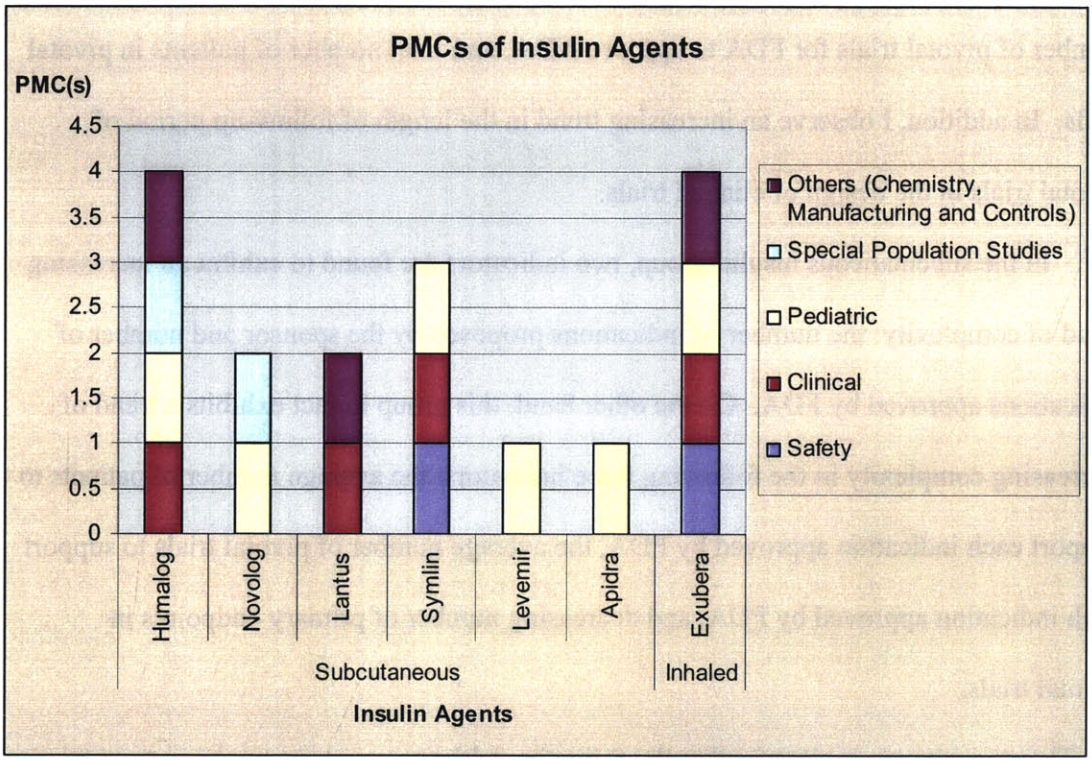


Figure 4.28 Post-marketing Commitments of Insulin Agents

4.10 Summary of Observations

Comparing the characteristics of the clinical trials in the 15 antidiabetic NDAs approved by the FDA in the early 1990s, I observe different trends in these two groups--the oral glucose-lowering and subcutaneous insulin. Among the selected 25 indicators, seven of them exhibit increasing complexity in the oral group; two others suggest

increasing complexity in the subcutaneous group. More surprisingly, three indicators suggest an otherwise decreasing trend of complexity.

Regarding to the safety evaluation of the oral agent group, I observe an increasing trend in the total number of special studies for NDA, particularly in the elderly population. With respect to the evaluation of a drug's efficacy, four indicators suggest an increasing complexity: the average number of patients for FDA to approve each indication, the average number of pivotal trials for FDA to approve each indication, total number of pivotal trials for FDA to approve NDA, and total number of patients in pivotal trials. In addition, I observe an increasing trend in the length of follow-up period of pivotal trials in the design of clinical trials.

In the subcutaneous insulin group, two indicators are found to exhibit an increasing trend of complexity: the number of indications proposed by the sponsor and number of indications approved by FDA. On the other hand, this group in fact exhibits a trend of decreasing complexity in the following three indicators: the average number of patients to support each indication approved by FDA, the average number of pivotal trials to support each indication approved by FDA, and decreasing number of primary endpoints in pivotal trials.

These results are summarized in the following table:

Table 4.8 Summary of Complexity Changes in Antidiabetics

Agents / Complexity	Oral Antiglycemics	Subcutaneous Insulin
Increasing Complexity	• Total Number of Special Studies in NDA • Number of Special Studies in Elderly Population • Average Number of Patients for FDA to Approve Each Indication • Average Number of Pivotal Trials for FDA to Approve Each Indication • Number of Pivotal Trials for FDA to Approve NDA • Number of Patients in pivotal trials • Length of Follow-up Period in Pivotal Trials	• Number of Indications Proposed by Sponsor • Number of Indications Approved by FDA
Decreasing Complexity	0	• Average Number of Patients for FDA to Approve Each Indication • Average Number of Pivotal Trials for FDA to Approve Each Indication • Number of Primary Endpoints in Pivotal Trials

Based on the observations mentioned above, nine out of the twenty-five selected indicators are found to exhibit an increasing trend of complexity. The trend is more pronounced in the oral antiglycemics group (seven indicators) than the subcutaneous group (two indicators). While there is no obvious overall tendency in the Total Number of Studies for NDA over time, the aforementioned observations suggest a complexity increase in the clinical trials referenced in the NDAs of antidiabetics since the early 1990s, which may have correlated to the rising R&D costs in the pharmaceutical industry.

5 DISCUSSION OF POLICY ISSUES

5.1 Debate of ADA-1997 and WHO-1999 Diagnostic Criteria

Changes in the threshold levels for blood glucose have begun to identify more people with diabetes and changes in the definition of pre-diabetes have identified more people who are likely to develop type 2 diabetes. The advocacy by WHO in using FPG in the ADA-1997 criteria remains controversial. Particularly, it remains uncertain whether these criteria will increase or decrease the measured prevalence of diabetes. While some studies[58,59] demonstrated the benefits of using the ADA-1997 criteria, including the simplicity of obtaining a FPG value and decreased undiagnosed cases among subjects with low FPG, these same studies or other studies[60] also addressed concerns. One concern was that cases diagnosed by the ADA-1997 criteria are more likely to have hyperglycemia with higher HbA1c values and a greater proportion of values above the normal range. Also, these cases are more likely to have increased undiagnosed cases due to omission of the 2-h PG and underestimate glucose abnormalities more with increasing age. In another study[61], research showed that the WHO-1999 criteria are more likely to diagnose diabetes in lean individuals while the ADA-1997 criteria are more likely to identify middle aged obese individuals. This result, however, raised the question: should the criteria adopted in designing clinical trials depend on the phenotypes of subjects?

I summarized the diagnostic criteria used as the patient inclusion/exclusion criteria for the clinical trials referenced in the antidiabetic NDAs in my thesis (see **Section 4**). Interestingly , I observed a trend of adopting the WHO-1999 criteria (which

accommodates the ADA-1997 Criteria) in the oral group and a trend of more adoption of HbA1c as part of the inclusion/exclusion criteria in the insulin group since 1999 (see the comparison in **Table 5.1**).

Table 5.1 Summary of the Diagnostic Criteria Used in the Patient Inclusion/Exclusion Criteria in Clinical Trials for Antidiabetic NDAs

Submission Date	Drug Class	Generic Name	Trade Name	Group by Route of Administration	Sponsor	Sponsor's Origin of Country	Diagnostic Criteria
1993	Biguanide	metformin	Glucophage	Oral	Lipha	France (EU)	WHO-85
1994	SU	glimepiride	Amaryl	Oral	HMR	Germany (EU)	WHO-85
1994	AGI	acarbose	Precose	Oral	Bayer Pharms	Germany (EU)	Diagnosed > 6 months
1995	AGI	meglitol	Glyset	Oral	Bayer	Germany (EU)	Diagnosed >6 months; HbA1c
1997	Meglitinide	repaglinide	Prandin	Oral	Novo Nordisk Inc	Denmark (EU)	Diagnosed >3 months; HbA1c
1998	TZD	rosiglitazone	Avandia	Oral	SB Pharmaco	US	WHO-85
1999	Meglitinide	nateglinide	Starlix	Oral	Novartis	Switzerland (EU)	WHO-85; HbA1c
2005	DPP-4i	Sitagliptin	Januvia	Oral	Merck Co Inc	US	WHO-99; HbA1c
1995	Insulin	lispro	Humalog	Subcutaneous	Lilly	US	Diagnosed
1998	Insulin	aspartate	Novolog	Subcutaneous	Novo Nordisk Inc	Denmark (EU)	Diagnosed >24months
1999	Insulin	glargine	Lantus	Subcutaneous	Aventis Pharms	France (EU)	Diagnosed Type 1; HbA1c
2000	Glucagon Lowering	pramlinitide	Symlin	Subcutaneous	Amylin	US	Diagnosed Type 1; HbA1c
2002	Insulin	detemir	Levemir	Subcutaneous	Novo Nordisk Inc	Denmark (EU)	Diagnosed Type 1; HbA1c
2003	Insulin	glulisine	Apidra	Subcutaneous	Aventis Pharms	France (EU)	Diagnosed; HbA1c
2004	Insulin	insulin recombinant human	Exubera	Inhalation	Pfizer	US	Diagnosed; HbA1c

I consider this phenomenon--more prevalent adoption of WHO-1999 (which was revised from WHO-1985 by incorporating ADA-1997)--as an effort of regulatory harmonization (seeking regulatory convergence). Since 1980s, the international community started harmonizing regulatory requirements for the pharmaceutical industry. In 1990, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), which brings together the regulatory authorities and pharmaceutical firms of Europe, Japan, and US to discuss scientific and technical aspects of pharmaceutical product registration, was established.

A recent study, which concluded an increasing trend in the globalization of clinical trials[62], also shed some light on the importance of regulatory harmonization in today's drug development. In the pharmaceutical industry, firms' investments are with multinational asset specificity (meaning that assets are specific to international transactions). This creates incentives for firms to push for common regulations across borders since regulatory diversity may inhibit effective use of assets and increase transaction costs. These investments include human, dedicated, physical, site, and brand specificity[63].

5.2 R&D of the Pharmaceutical Industry

The pharmaceutical industry--considered an R&D-intensive industry--spends more money on research and development, relative to its sales revenue, than any other industry in the US. In addition, the industry's real (inflation-adjusted) spending on R&D has grown between threefold and sixfold over the past 25 years. This increase has been closely matched by growth in drug sales, according to an estimate by the Congressional Budget Office in a report released in October 2006[64]. However, there has been little change in the number of innovative new drugs approved for use each year, even though the federal government has streamlined its drug-approval process (PDUFA, see **Appendix D**). This has generated concern over whether the innovative performance in this industry has declined and what drivers are contributing to this trend.

5.2.1 R&D Intensity

The pharmaceutical industry is one of the most research-intensive industries in the US. Pharmaceutical firms invest as much as five times more in R&D, relative to their sales, than the average US manufacturing firm[65]. Over the past 25 years, the R&D intensity of the industry (defined as the ratio of R&D spending to total sales revenue) has grown by about 50 percent (see **Figure 5.1**).

Interestingly, the pattern of the growth in the industry's R&D intensity does not quite match the pattern of the growth in the industry's R&D spending (see **Figure 5.2**). According to the data from PhRMA[66], while the industry's R&D spending has soared since 1980s, the industry's R&D intensity reached the high of more than 20 percent in 1990s and has hovered around 18 percent since then.

5.2.2 Assessment of R&D Performance

According to the estimate in the report[67] by the Congressional Budget Office, total spending on health-related R&D by the drug industry and the federal government has tripled since 1990 in real terms. However, the number of innovative new drugs approved by FDA each year has not shown a comparable upward trend. Thus, by defining the number of drugs approved per dollar of R&D as a measurement of R&D performance, the report concludes that the innovative performance of the industry appears to have declined[68].

5.2.3 Costs of R&D

The average success rate for new molecular entities (NMEs) illustrates how relatively few drugs survive the clinical-trial process (see **Figure 5.3** and **5.4**).

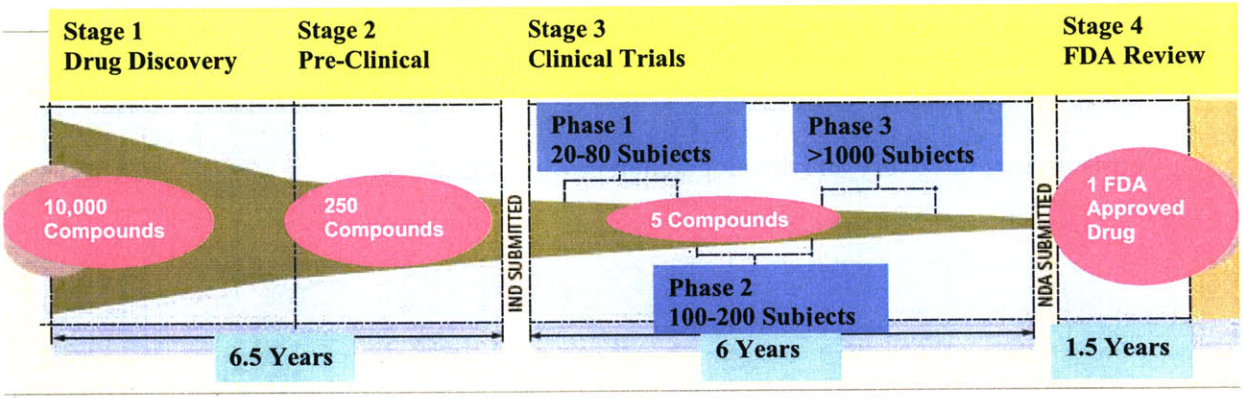


Figure 5.3 An Overview of a Drug Pipeline (Source: Adapted from www.innovation.org)

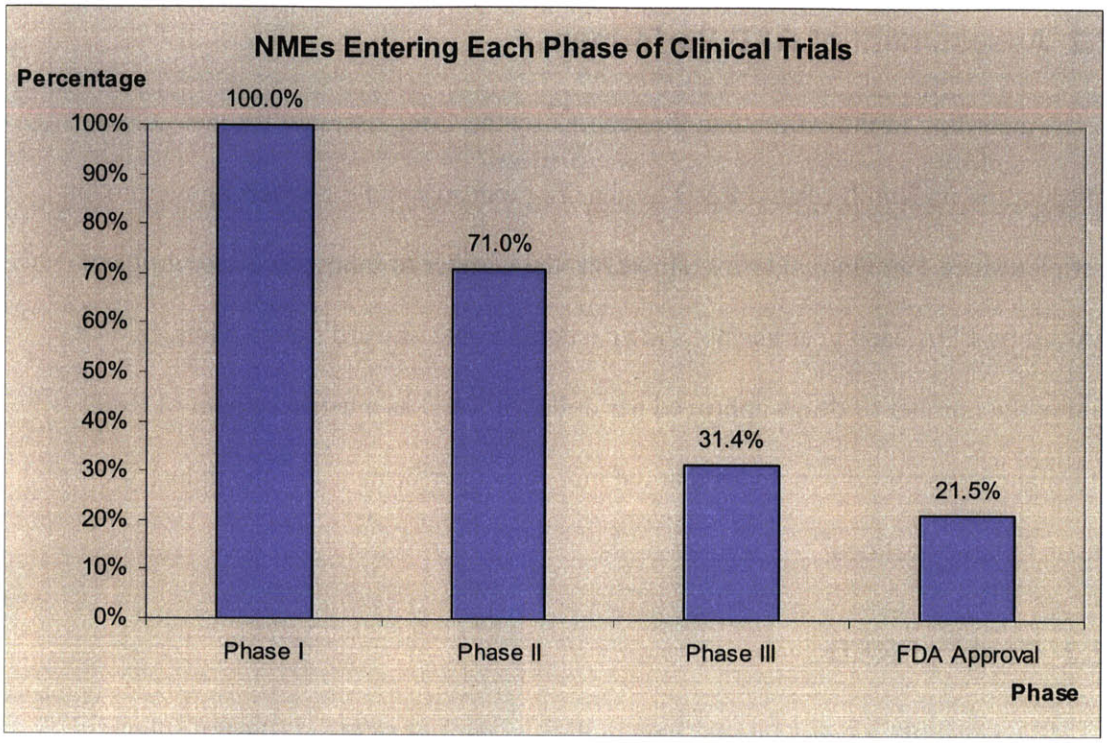


Figure 5.4 Percentage of New Molecular Entities Entering Each Phase of Clinical Trials (Source: Generated from the DHG Study, *The Price of Innovation: New Estimates of Drug Development Costs*)

According to the report by PhRMA[69], its members' R&D costs in the preclinical phase and Phase III after entering the clinical stage account for more than half of R&D costs in drug discovery and development (shown in **Figure 5.5**).

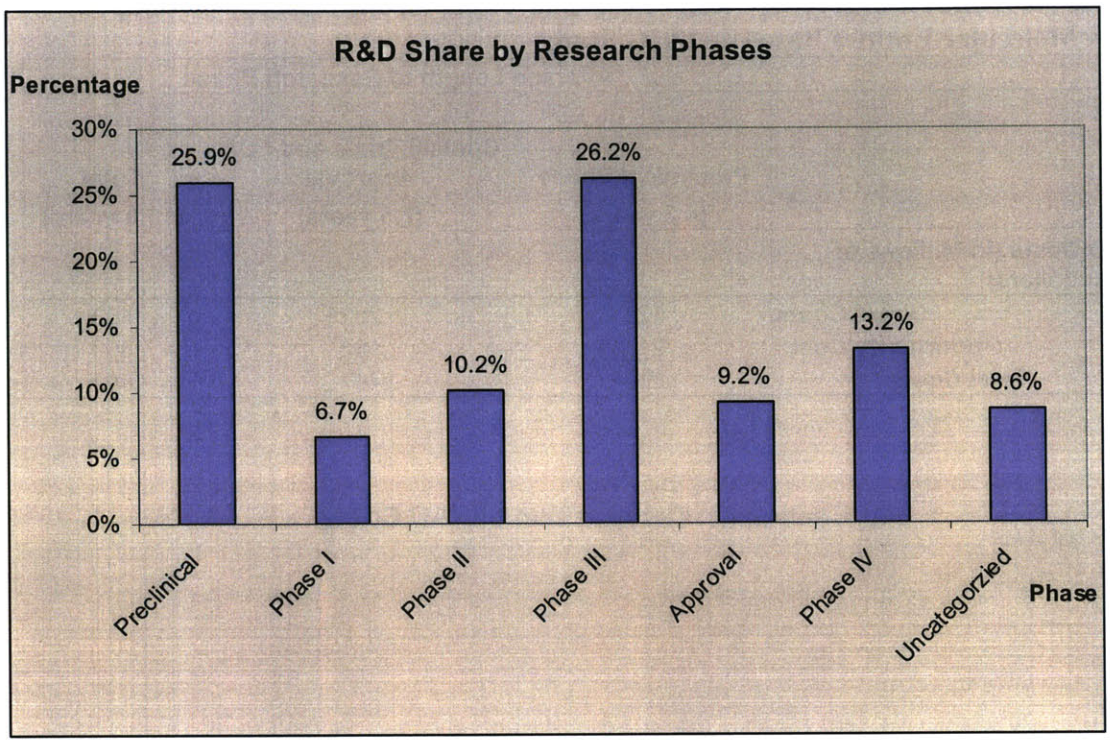


Figure 5.5 Share of R&D Costs of PhRMA Members by Research Phases
(Source: Generated from PhRMA, *Pharmaceutical Industry Profile 2006*)

A frequently cited study by Joseph DiMasi, Ronald Hansen, and Henry Grawski (DHG study)[70] estimated that the average cost of successfully developing an NME, including R&D spending on filed drug projects, was $802 million in 2000. This estimate included the direct costs and opportunity costs (the costs associated with keeping capital tied up in a specific drug development project for a given period; in other words, the foregone interest or earnings that a company might have gained from investing its capital in other ways). A breakdown of this estimated figure is shown in **Table 5.2** and **Figure 5.6**.

Table 5.2 Estimate of Average R&D Costs and Times for Successfully Developed New Molecular Entities Based on DHG Study

	Average Length of Research Phase		
	Preclinical Phase (4.3 years)	Clinical Trials and FDA Approval (7.5 years)	Total (11.8 years)
R&D Costs (in Millions of 2000 dollars)			
Direct Costs	121	282	403
Opportunity Costs	214	185	399
Total Costs	**335**	**467**	**802**

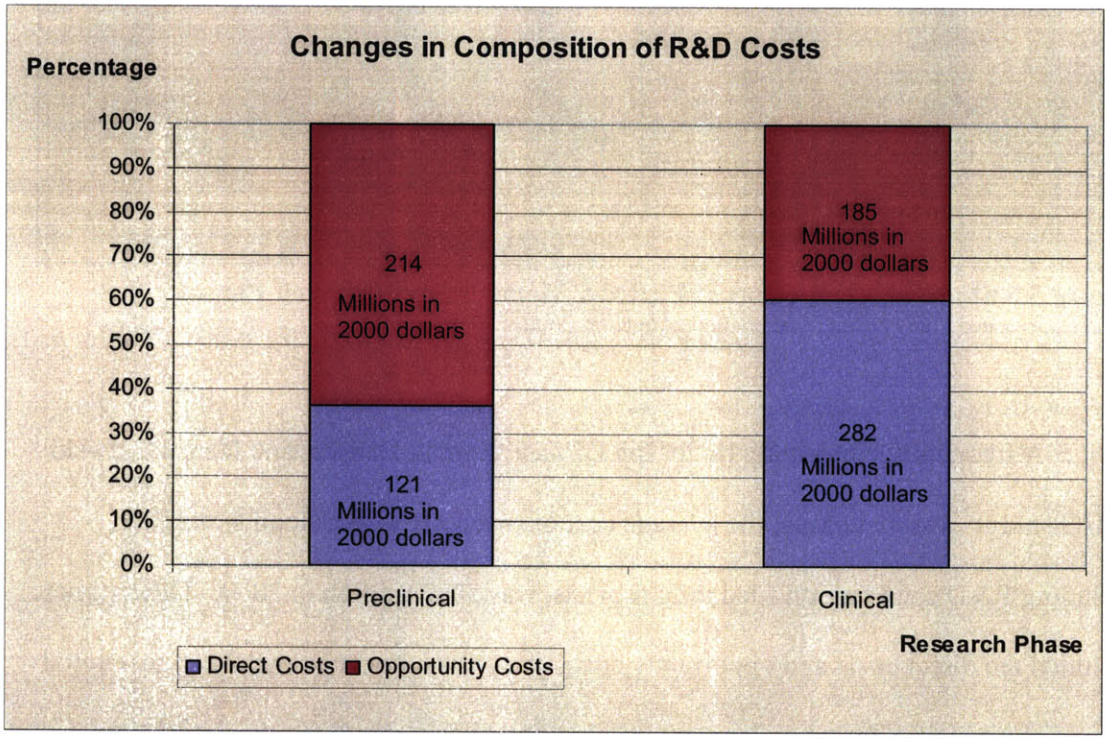


Figure 5.6 Changes in Composition of R&D Costs by Different Research Phases

5.2.4 Drivers for Rising R&D Costs

Various surveys conducted between 1976 and 2000 suggest that the average amount that surveyed firms reported spending on R&D of NMEs, during that period, increased nearly sixfold in real term (inflation-adjusted)[71]. This trend is summarized in the figure below.

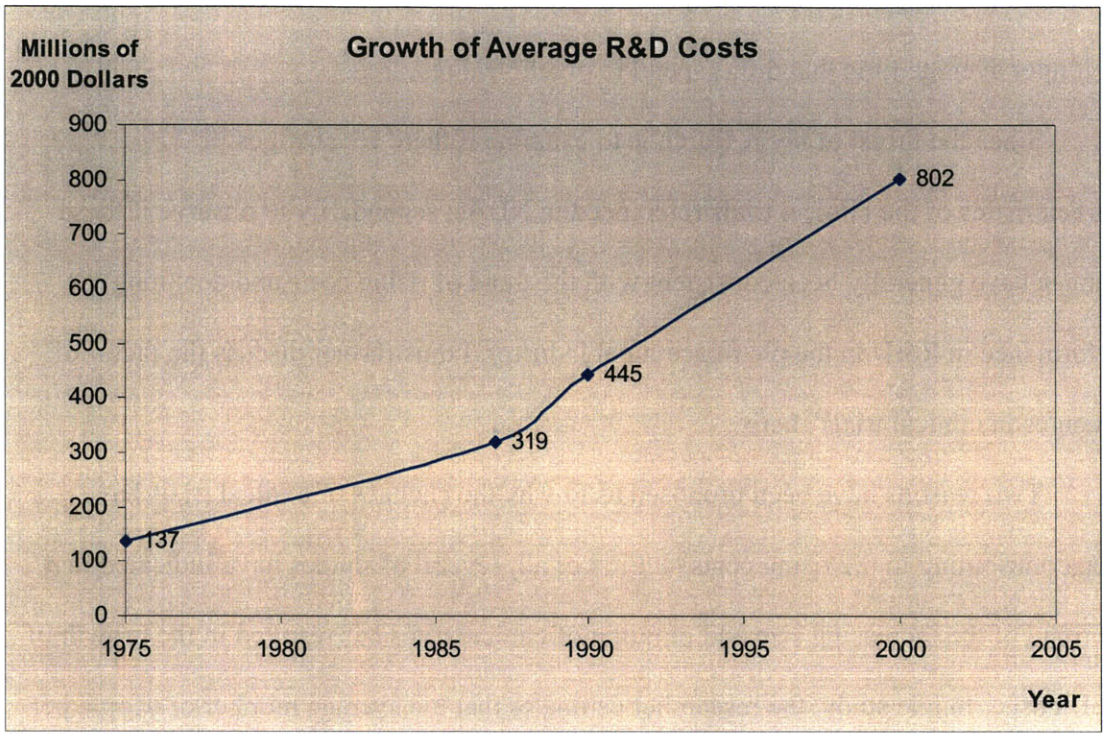


Figure 5.7 Estimates of Growth in Average R&D Costs in the Drug Industry
(Source: Generated based on CBO, "*A CBO Study-Research and Development in the Pharmaceutical Industry*")

Several factors have been mentioned in the DHG study as drivers for the trend of rising R&D costs in the pharmaceutical industry, including:

- **Higher Failure Rate**: An increase in the percentage of drug projects that fail in clinical trials;
- **Changes in Clinical Trials**: A trend toward bigger and lengthier clinical trials as well as possible rise in the number of trials that firms are conducting (including trials for marketing purposes, such as to differentiate a product from its competitors);
- **Changes in the Types of Drugs Being Developed**: A shift in the types of drugs that companies work on toward those intended to treat chronic and degenerative disease;
- **Scientific Advances**: Advances in the research technology and in the scientific opportunities facing the pharmaceutical industry, including the increased commercialization of basic research, as firms more often pay for access to basic

research findings that in earlier years might have been freely available, as well as longer average time that drugs spend in preclinical research.

Since the thrust of my research is to examine if there are changes in characteristics of the clinical trials referenced in NDAs; secondarily to observe if these changes have generally been consistent with the trend of rising costs and declining performance in R&D in the pharmaceutical industry, I thus further discuss the factor of "changes in clinical trials" here.

Two reasons have been proposed as to why the changes of clinical trials have been contributing to the rising costs[72]. First of all, several of studies have indicated that the trend of the increasing size and duration of clinical trials has resulted in the growth of R&D costs. In one study, the researcher estimates that the average number of people per trial grew by 7.5 percent annually, from 2,300 in 1980s to more than 5,600 by the early 2000s[73]. The other study shows that the average length of the clinical trial phase increased by 27 percent over the 1980s and then declined by four percent over the 1990s[74].

The second reason is the intention of marketing and product differentiation. Companies may be undertaking more clinical trials now than in the past, performing head-to-head trials (trials designed to compare a drug with other drugs rather than a placebo) to prove a drug's non-inferiority[75], or, in some cases, even its superiority. In some cases, a firm may sponsor clinical trials whose primary purpose is to familiarize participating doctors with the company's new drugs; such trials may not even be intended to be scientifically rigorous[76]. A recent study concludes that doctors, who conduct clinical trials sponsored by a pharmaceutical company, subsequently increase their

subscription frequency of the drug from the sponsoring firm[77]. In other cases, firms may face pressure from health insurers to demonstrate their drugs' superiority with scientific rigor as a condition of being included in insurers' formularies of the preferred drugs. Such tests, establishing a drug's superiority to available substitutes, also allow firms to set higher prices[78]. However, the quality of differences between approved drugs are likely to be smaller than differences between a drug and a placebo, so showing that the differences with clinical and statistical significance may require larger and more costly clinical trials.

5.3 Applying System thinking in Diabetes Management

A chronic disease, diabetes, similar to other dynamically complex problems, is characterized by long delays between causes and effects. The public effort to address such complexity is characterized by multiple concurrent goals that may conflict with one another. For example, although the original goal of policy planners is to reduce the diabetes prevalence and the consequent deaths due to its complications, the fact is that fewer deaths would lead to an otherwise increased patient population, and thus the prevalence. Given such interconnections, a satisfactory solution will be found not in focusing on one single aspect of the overall health system--such as detection, or risk factor reduction--but rather in addressing all major components together as a system[79].

5.3.1 System Dynamics Approach

(1) Dynamic Complexity

A general definition of complexity is in terms of the number of components or possible states in a system. The "dynamic complexity" refers to the often counterintuitive behavior of complex systems that arises from the interactions of the agents over time[80].

(2) Characteristics of Complex Systems

The following are the characteristics of the complex systems:

- Constantly changing;
- Tightly coupled;
- Governed by feedback;
- Nonlinear;
- History-dependent;
- Self-organizing;
- Adaptive and evolving;
- Characterized by trade-offs;
- Counterintuitive; and
- Policy Resistant.

(3) Challenges in Decision-Making in a Complex World

Even though the world is dynamic, evolving, and interconnected, we tend to make decisions using mental models that are static, narrow, and reductionist. Among all the elements of the dynamic complexity, people find the most problematic are feedback, time delays, and stocks and flows[81].

Social systems contain the intricate networks of the feedback processes, both self-reinforcing (positive) and self-correcting (negative) loops. However, studies show that people recognize few feedbacks; rather, people usually think in short and causal chains, tend to assume each effect has a single cause, and often cease their search for explanations when the first sufficient cause is found[82,83].

The time delays in the feedback are common and particularly troublesome. The delays slow down the accumulation of evidence. More problematically, the short- and long-run impacts of our policies are often different. For example, smoking gives immediate pleasure while increasing the potential risk of developing the lung cancer over decades.

The stocks and flows, which alter the stocks, are fundamental. The concept of the prevalence (stock) and incidence (flow) in epidemiology is such an example. However, our intuitive understanding of the stocks and flows is poor in two ways. First, people possess their own limited scope, based on their narrow mental models, in thoroughly identifying the feedback between stocks and flows in the entire network. Second, people have poor intuitive sense of the process of accumulation in the stocks. Most people can perceive the system inputs and outputs and assume that they are intuitively correlated (e.g. the more the incidence of HIV, the greater the number of people with HIV will be)[84]. However, stocks integrate (accumulate) their net inflows, from both inputs and outputs. A stock rises even though the net inflow falls, as long as the net inflow is positive. For instance, the number of people with HIV continues to rise even as incidence falls--prevalence falls only when infection falls below mortality. A poor understanding of accumulation may pose a profound consequence in public health during policy making.

The National Diabetes Prevention and Control Program (NDPCP) will be used as an example to illustrate this point. It is discussed in **Section 5.3.2**.

The following figure demonstrates how policy resistance may occur when the policy fails to reach, and even alter, its original goal because of the unawareness of the hidden side effects (**Figure 5.8**).

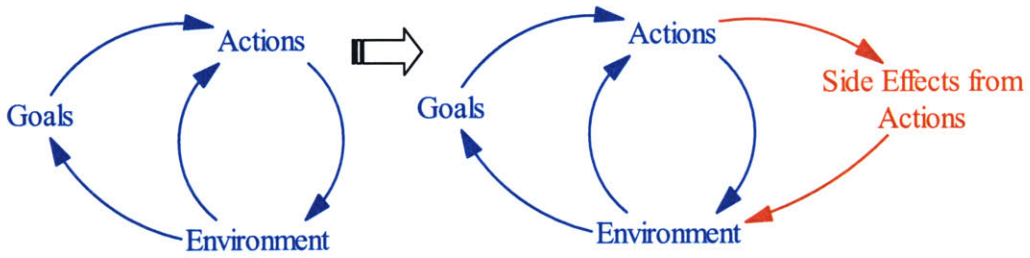


Figure 5.8 Policy Resistance Due to Side Effects of the Policy

5.3.2 Challenges in Diabetes Management

A study, using System Dynamics as a methodology of simulation modeling and experimentation to assess a policy from the Center for Disease Control and Prevention (CDC)--the National Diabetes Prevention and Control Program (NDPCP), concludes the following characteristic dynamics, as challenges encountered in the complex system of diabetes management[85]:

(1) The role of obesity in driving the growth of prediabetes and diabetes prevalence;

(2) The side effect of the action--a "backing up" phenomenon: when actions (such as NDPCP's policies of early and expanded detection, improved treatment with better quality, availability and accessibility) reduce outflow for the stock (population of the diabetes patients) causes a buildup in that stock (more prevalence of diabetes). As

such, it may undercut the benefits of management and control efforts (the more patients with diabetes, the more health care resources needed).

(3) The inability of management and control efforts, which seek to reduce diabetes prevalence in the long term (CDC lacks the ability of upstream management for prevention of diabetes, such as changing people's lifestyle by improving diet, reducing obesity, and increasing physical activity); and

(4) The significant time delays between the primary prevention efforts and downstream improvements (e.g. screening and treatment) in diabetes outcomes.

The basic structure of this model is summarized as follows (more details are listed in **Appendix E**).

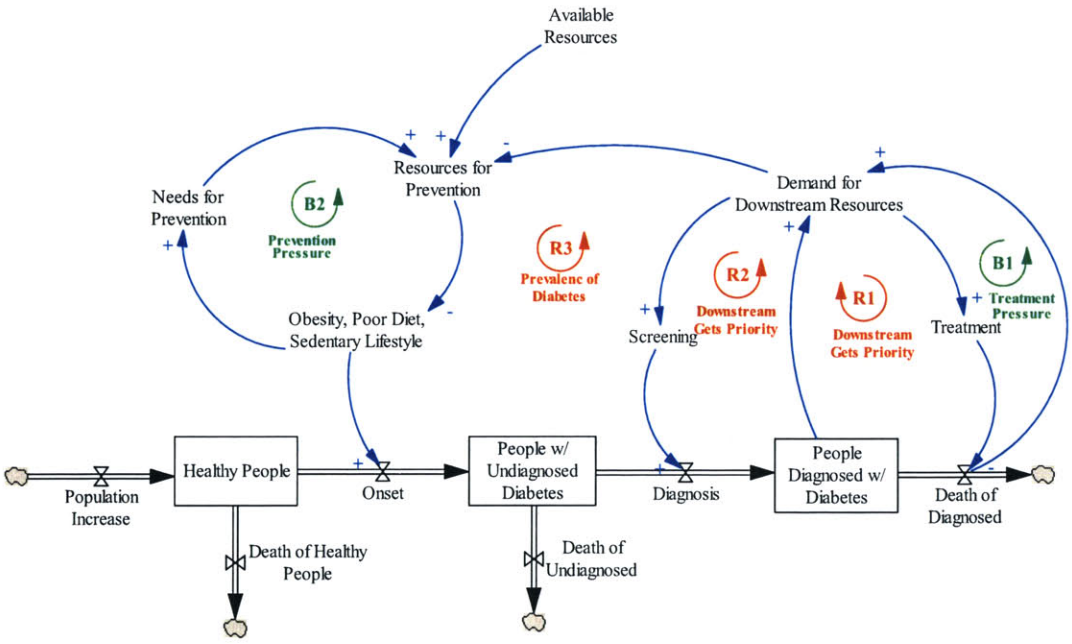


Figure 5.9 System Dynamics Model for Diabetes Management (Source: Based on Sterman J., *Dynamics of the Diabetes Epidemic*; Jones A.P. et al., *Understanding Diabetes Population Dynamics through Simulation Modeling and Experimentation*; Homer J.B. et al., *System Dynamics Modeling for Public Health: Background and Opportunities*)

6 CONCLUSION

6.1 Summary

In this thesis, I study the chronic disease, diabetes mellitus (diabetes), including its definition, classification, etiologies and complications. Due to morbidity and mortality of its complications, this disease has been causing a huge burden on the health care system. Medical advances in novel therapies and public health policies of disease control and prevention have been undertaken to manage the disease. Despite all these efforts, the prevalence of diabetes still increases over time. I thus investigate this phenomenon by analyzing technology and policy in the treatment and prevention of diabetes in order to achieve the goal of managing the disease in a manner of balancing costs and benefits.

With respect to treatment, I inspect the innovative performance in the antidiabetic drug therapy. I analyze fifteen New Drug Applications (NDAs) of the antidiabetics from the 1990s. I examine the characteristics of clinical trials supporting NDAs and seek to uncover trends in how the complexity of clinical trials has changed over time. In the statistical analyses of the twenty-five indicators of complexity I select to measure the changes in clinical trials, I find nine out of the twenty-five selected indicators to exhibit an increasing trend of complexity. The trend is more pronounced in the oral antiglycemics group (seven indicators) than the subcutaneous group (two indicators). Noticeably, this trend of increasing complexity in clinical trials is generally consistent with the trend of increasing R&D costs in the pharmaceutical industry, and may have partially explained

the declining performance and innovation of the industry over the time period under investigation.

I also assess the current public health policies in diabetes control and prevention by a system dynamics approach. This approach emphasizes the importance of system thinking, which is extremely essential for the public health policy, particularly in the arena chronic diseases management. Considering the public health system as a "dynamic-complex" system, during policy-design phase, recognition of characteristics of time-delays, stocks and flows, and feedbacks in the system can make the policy more efficacious. In the case of diabetes management, the policy of the National Diabetes Control and Prevention Program provides earlier and expanded screening and also improves availability and accessibility of treatment for diabetes. Despite these management and control efforts, this policy, rather than reducing the prevalence of diabetes, in fact increases the prevalence. The counterintuitive result addresses the consequence of failure in system thinking.

A successful chronic disease management has an enormous role in the public health system. It requires collective efforts from the perspective of treatment and prevention. Understanding the drivers for developing treatment and prevention is critical to achieve a robust healthcare system.

6.2 Limits and the Future Perspectives

Since I only examined the antidiabetics from the 1990s, the limited sample size may have imposed some constraints. In spite of time frame and the limited data points (eight oral antihyperglycemic agents, six subcutaneous insulin agents, and one inhaled insulin agent), several sets of analyses still showed statistical significance, as I have

discussed in previous sections. Additionally, except for the chemical class of SUs--the oldest antidiabetic agent--most of the development of antidiabetics occurred in 1990s, which contributes to the legitimacy of this research timeframe.

As for the future perspectives, a promising avenue is to examine other therapeutic classes of drugs and compare the trends observed in antidiabetics with that from other classes of drugs. As such, one may also be able to trace back the development of other earlier antidiabetics in order to acquire a more complete picture of the trend in changes of characteristics of clinical trials for NDAs.

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Appendix A Oral Glucose Tolerance Test

The Oral Glucose Tolerance Test (OGTT) is principally used for diagnosis when blood glucose levels are equivocal in epidemiological studies. The test is not recommended for clinical use.

The OGTT should be performed in the morning after at least three days of unrestricted diet (greater than 150g of carbohydrate daily) and usual physical activity. The test should be preceded by an overnight fast of 8-14 hours, during which water may be drunk. Smoking is not permitted during the test. The presence of factors that influence interpretation of the test must be recorded (e.g. medications, inactivity, infection, etc.)

After collection of the fasting blood sample, the subject should drink 75g of anhydrous glucose or 82.5g of glucose monohydrate (or partial hydrolysates of starch of the equivalent carbohydrate content) in 250-300ml of water over the course of 5 minutes. For children, the test load should be 1.75g of glucose per kg body weight up to a total of 75g of glucose. Timing of the test is from the beginning of the drink. Blood samples must be collected two hours after the test load.

Appendix A Oral Glucose Tolerance Test

The Oral Glucose Tolerance Test (OGTT) is principally used for diagnosis when blood glucose levels are equivocal in epidemiological studies. The test is not recommended for clinical use.

The OGTT should be performed in the morning after at least three days of unrestricted diet (greater than 150g of carbohydrate daily) and usual physical activity. The test should be preceded by an overnight fast of 8-14 hours, during which water may be drunk. Smoking is not permitted during the test. The presence of factors that influence interpretation of the test must be recorded (e.g. medications, inactivity, infection, etc.)

After collection of the fasting blood sample, the subject should drink 75g of anhydrous glucose or 82.5g of glucose monohydrate (or partial hydrolysates of starch of the equivalent carbohydrate content) in 250-300ml of water over the course of 5 minutes. For children, the test load should be 1.75g of glucose per kg body weight up to a total of 75g of glucose. Timing of the test is from the beginning of the drink. Blood samples must be collected two hours after the test load.

Appendix B Observations on Complexity from 25 Indicators

Analysis 1: "Review Time" as an Indicator of Complexity over Time

<Definition of Indicator> "Review Time (REVTIME, Months)" equals to an NDA's "Approval Date" subtract by its "Submission Date (SDATE)."

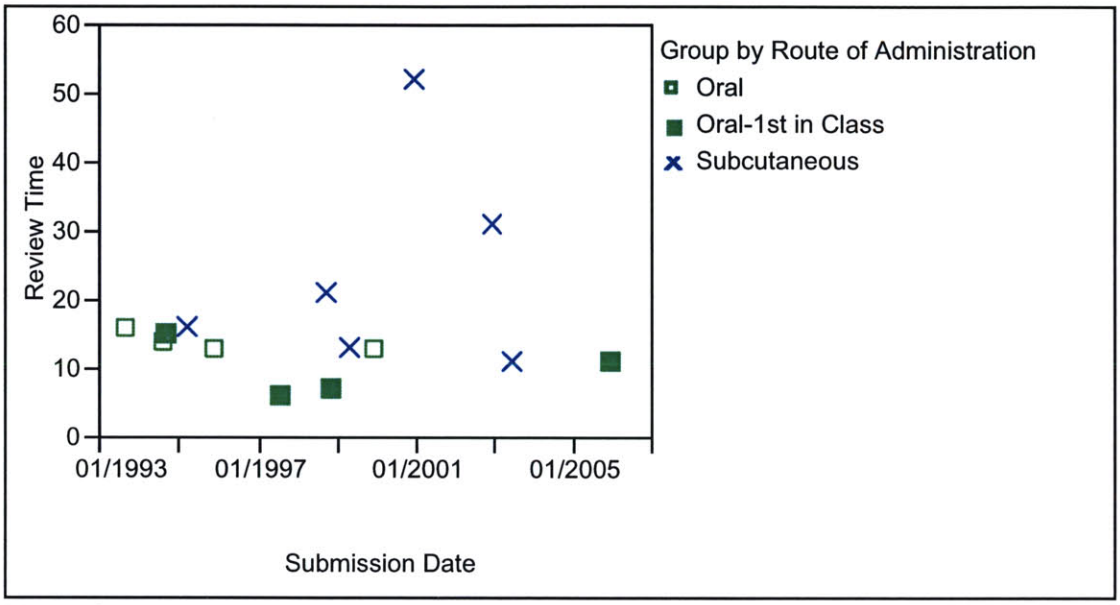


Figure 1 Distribution of "Review Time" By "Submission Date"

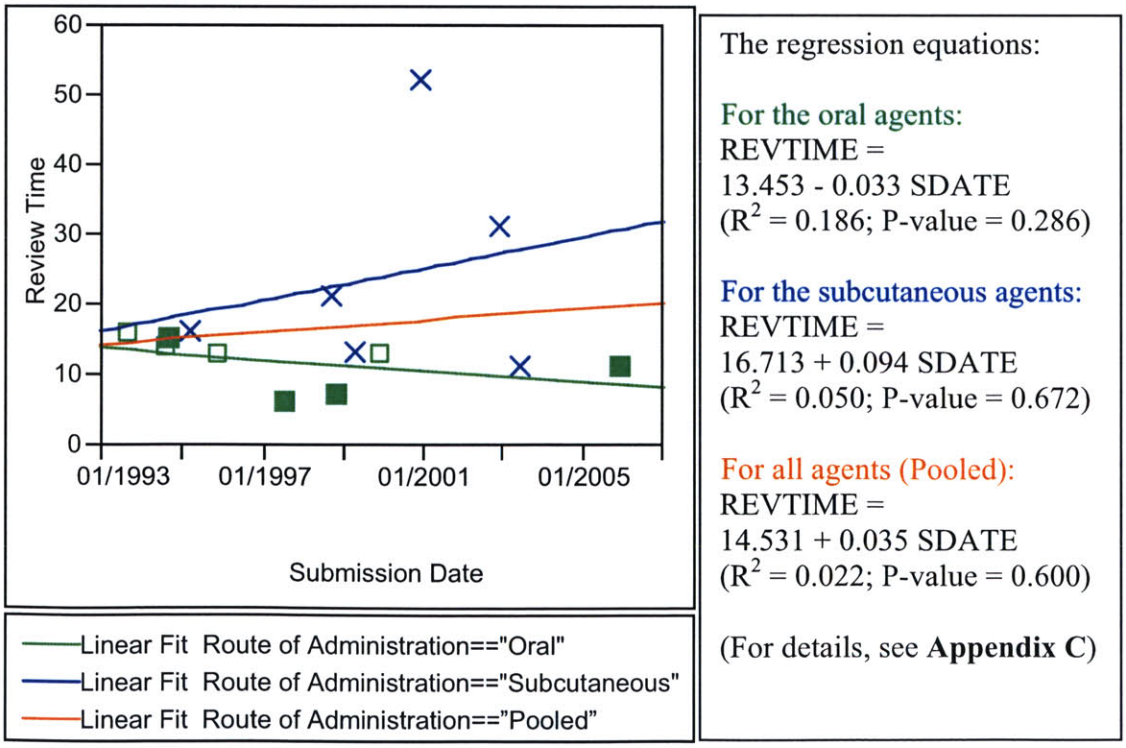


Figure 2 Regression Analysis of "Review Time" By "Submission Date"

Analysis 2: "Total Number of Studies for NDA" as an Indicator of Complexity over Time

<Definition of Indicator> "Total Number of Studies for NDA (NSTUDIES)" include all studies to establish the safety and efficacy parameters and as well as the tolerability, pharmacokinetic and pharmacodynamic parameters of the drug.

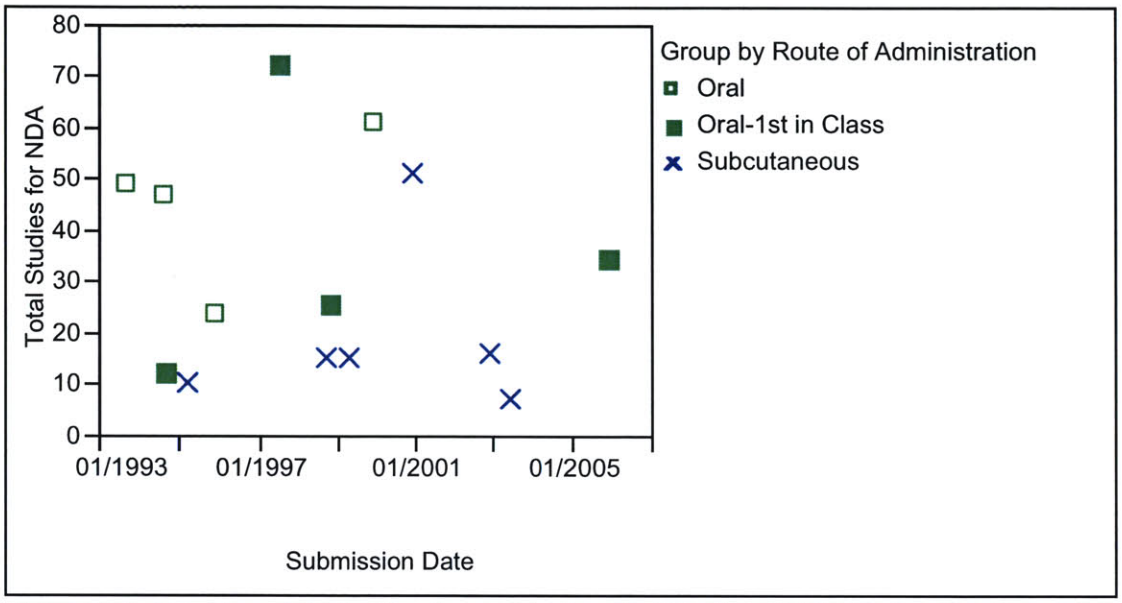
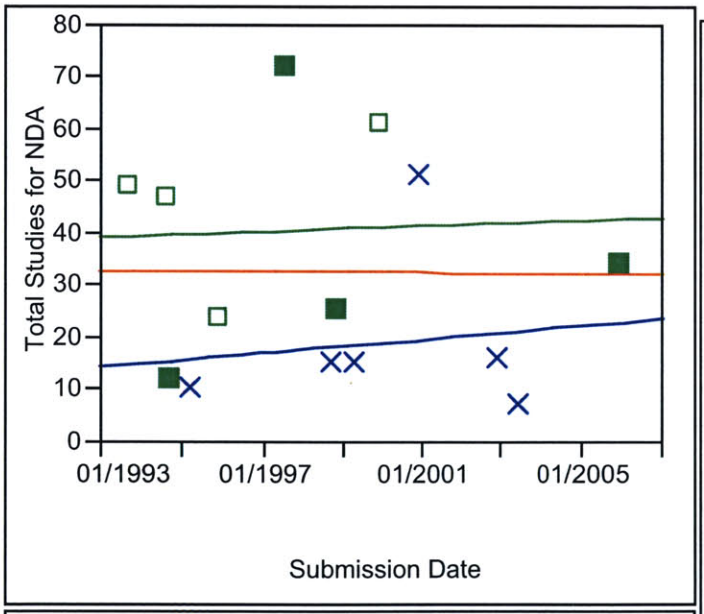


Figure 3 Distribution of "Total Number of Studies for NDA" By "Submission Date"



The regression equations:

For the oral agents:
NSTUDIES =
39.470 + 0.021 SDATE
(R^2 = 0.003; P-value = 0.906)

For the subcutaneous agents:
NSTUDIES =
14.646 + 0.056 SDATE
(R^2 = 0.016; P-value = 0.809)

For all agents (Pooled):
NSTUDIES =
32.799 - 0.004 SDATE
(R^2 < 0.001; P-value = 0.974)

(For details, see **Appendix C**)

Figure 4 Regression Analysis of "Total Number of Studies for NDA" By "Submission Date"

Analysis 3: "Total Number of Patients in Safety Database" as an Indicator of Complexity over Time

<Definition of Indicator> Total Number of Patients in Safety Database (NSAFETY)

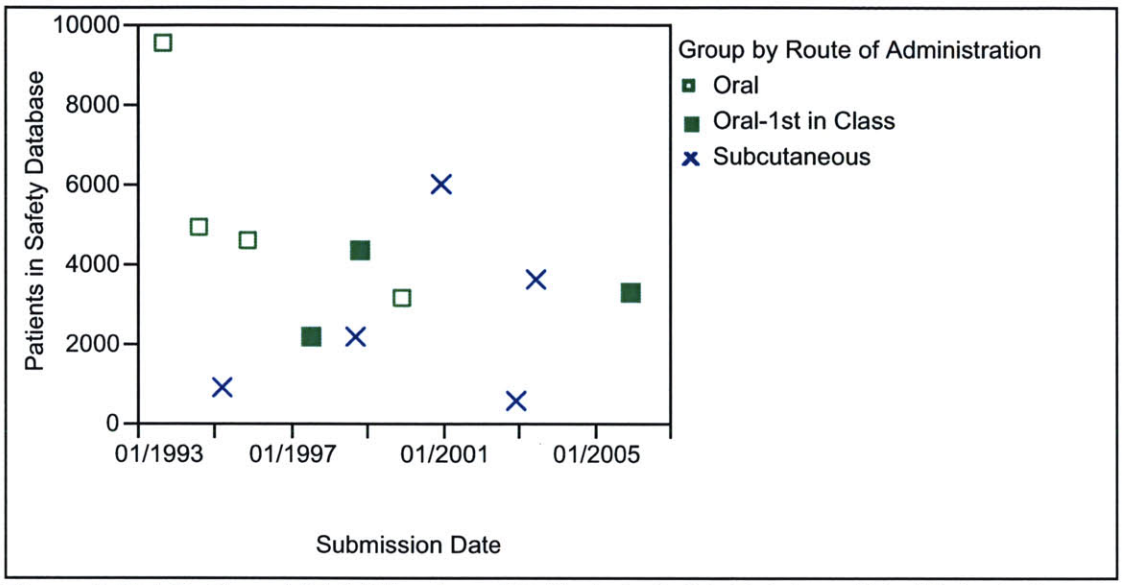
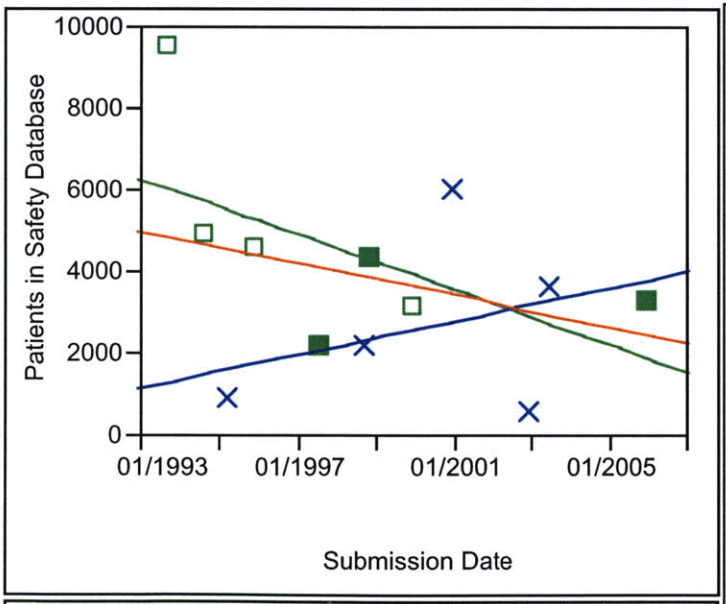


Figure 5 Distribution of "Total Number of Patients in Safety Database" By "Submission Date"



The regression equations:

For the oral agents:
NSAFETY =
6069.688 - 28.331 SDATE
(R^2 = 0.346; P-value = 0.165)

For the subcutaneous agents:
NSAFETY =
1269 +17 SDATE
(R^2 = 0.096; P-value = 0.613)

For all agents (Pooled):
NSAFETY =
4890.805 - 16.492 SDATE
(R^2= 0.117; P-value = 0.252)

(For details, see **Appendix C**)

Analysis 4: "Total Number of Special Studies" as an Indicator of Complexity over Time

<Definition of Indicator> Total Number of Special Studies in NDA (NSPECSTD)

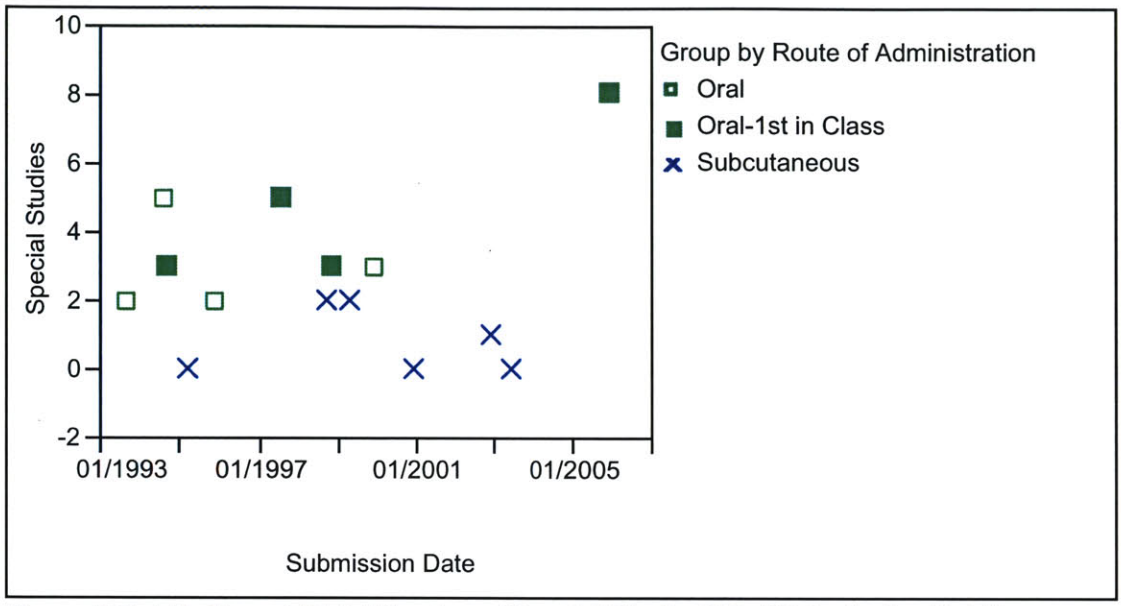
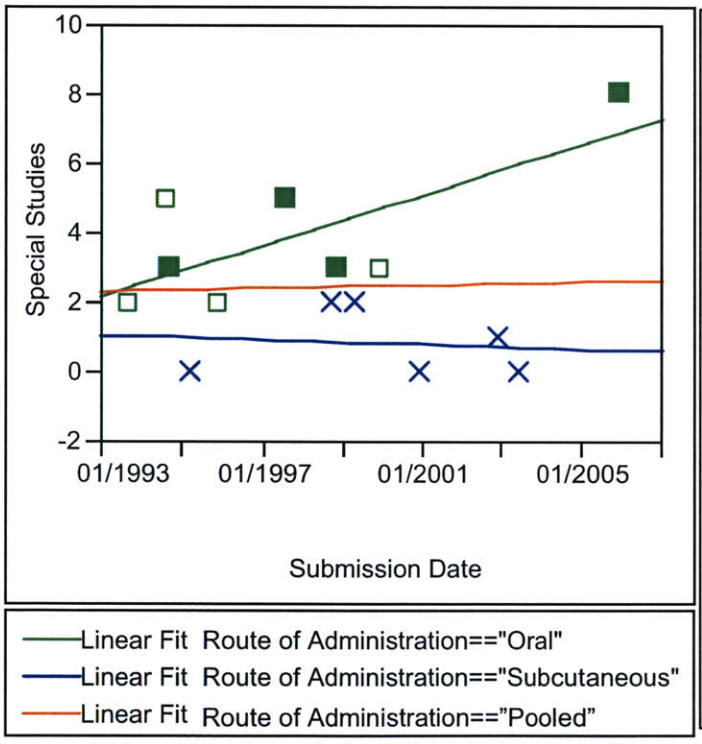


Figure 7 Distribution of "Total Number of Special Studies" By "Submission Date"



The regression equations:

For the oral agents:
$NSPECSTD^{++} = 2.411^{++} + 0.030\ SDATE^{++}$
($R^2 = 0.515$; P-value = 0.045)

For the subcutaneous agents:
$NSPECSTD = 1.045 - 0.003\ SDATE$
($R^2 = 0.010$; P-value = 0.848)

For all agents (Pooled):
$NSPECSTD = 2.345 + 0.002\ SDATE$
($R^2 = 0.001$; P-value = 0.889)

(For details, see **Appendix C**)

Figure 8 Regression Analysis of "Total Number of Special Studies" By "Submission Date"

Analysis 5: "Number of Special Studies in Elderly Population" as an Indicator of Complexity over Time

<Definition of Indicator> Number of Special Studies in Elderly Population (NSPELD)

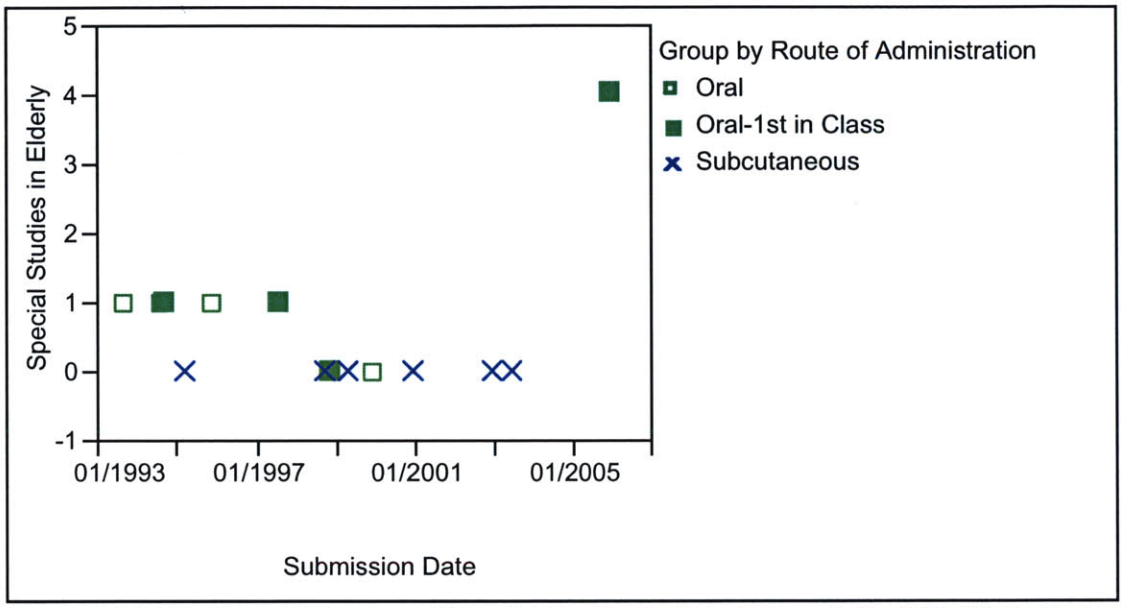


Figure 9 Distribution of "Number of Special Studies in Elderly Population" By "Submission Date"

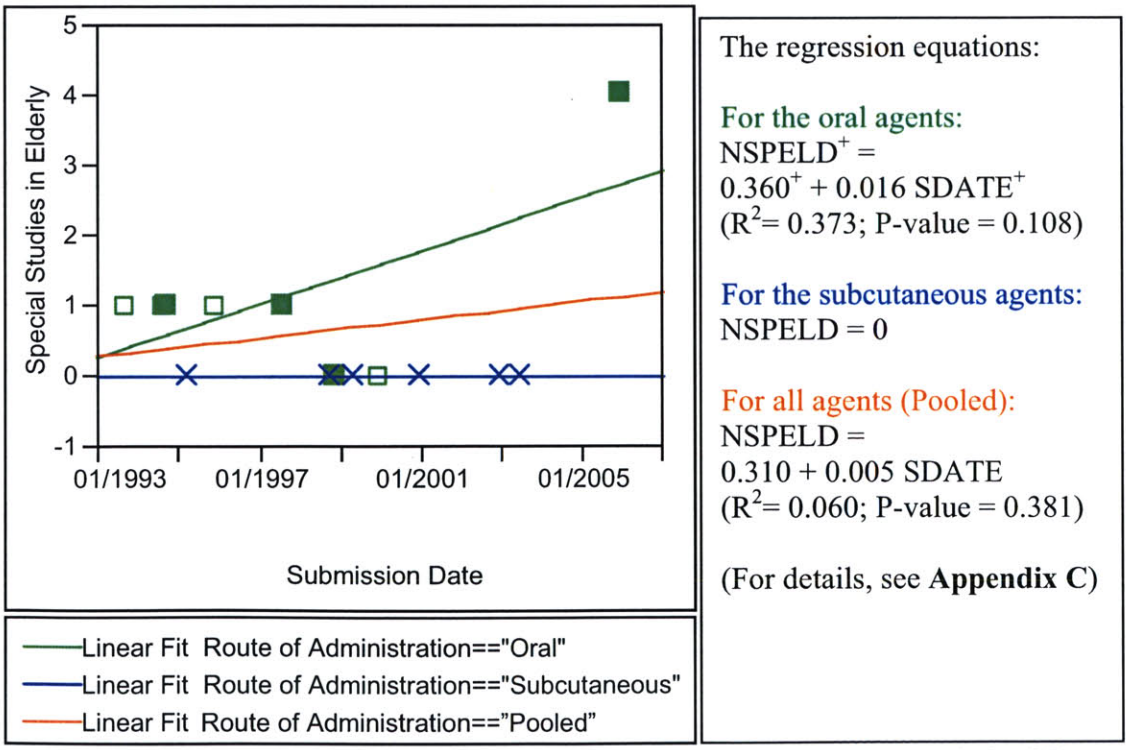


Figure 10 Regression Analysis of "Number of Special Studies in Elderly Population" By "Submission Date"

Analysis 6: "Number of Special Studies in Liver Impaired Population" as an Indicator of Complexity over Time

<Definition of Indicator> Number of Special Studies in Liver Impaired Population (NSPECLIV)

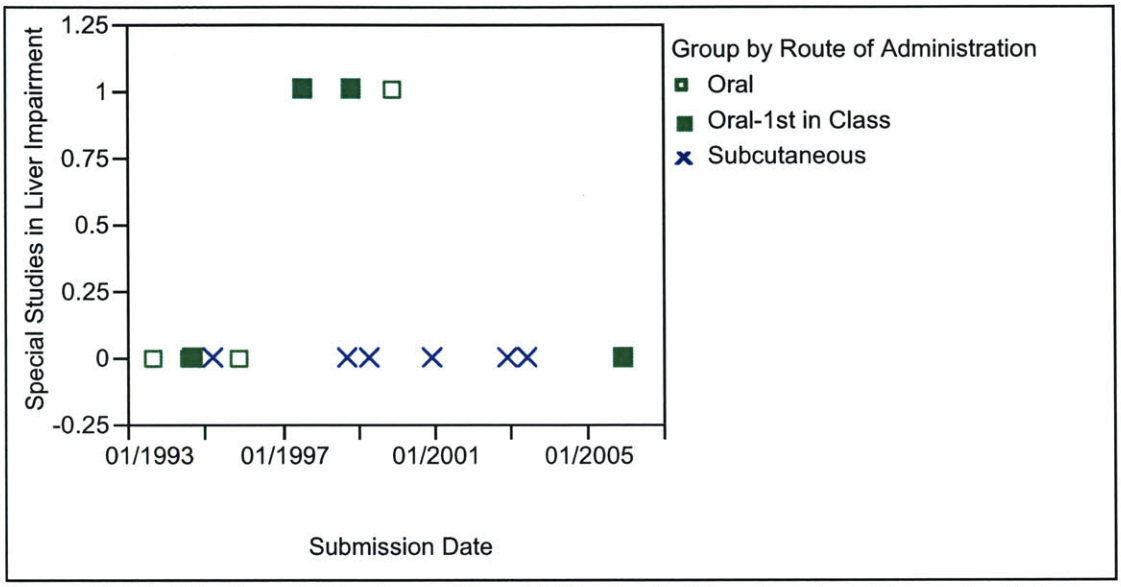
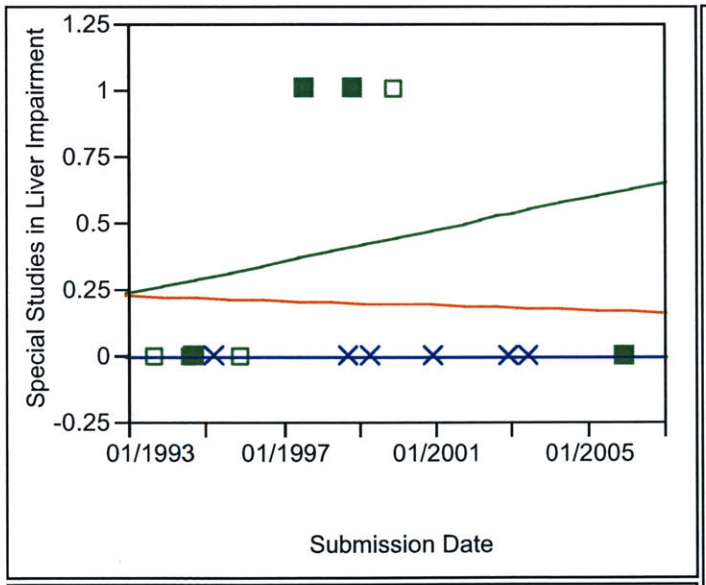


Figure 11 Distribution of "Number of Special Studies in Liver Impaired Population" By "Submission Date"



The regression equations:

For the oral agents:
NSPECLIV =
0.253 + 0.003 SDATE
(R^2 = 0.055; P-value = 0.577)

For the subcutaneous agents:
NSPECLIV = 0

For all agents (Pooled):
NSPECLIV =
0.225 - 0.0003 SDATE
(R^2 = 0.002; P-value = 0.879)

(For details, see **Appendix C**)

Figure 12 Regression Analysis of "Number of Special Studies in Liver Impaired Population" By "Submission Date"

Analysis 7: "Number of Special Studies in Renal Impaired Population" as an Indicator of Complexity over Time

<Definition of Indicator> Number of Special Studies in Renal Impaired Population (NSPECREN)

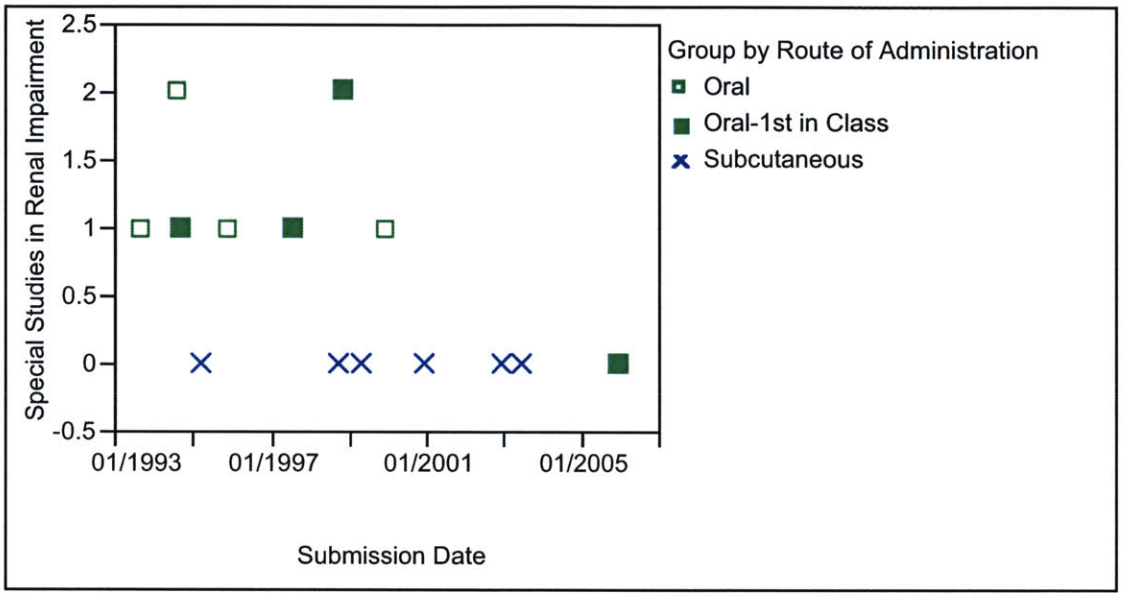


Figure 13 Distribution of "Number of Special Studies in Renal Impaired Population" By "Submission Date"

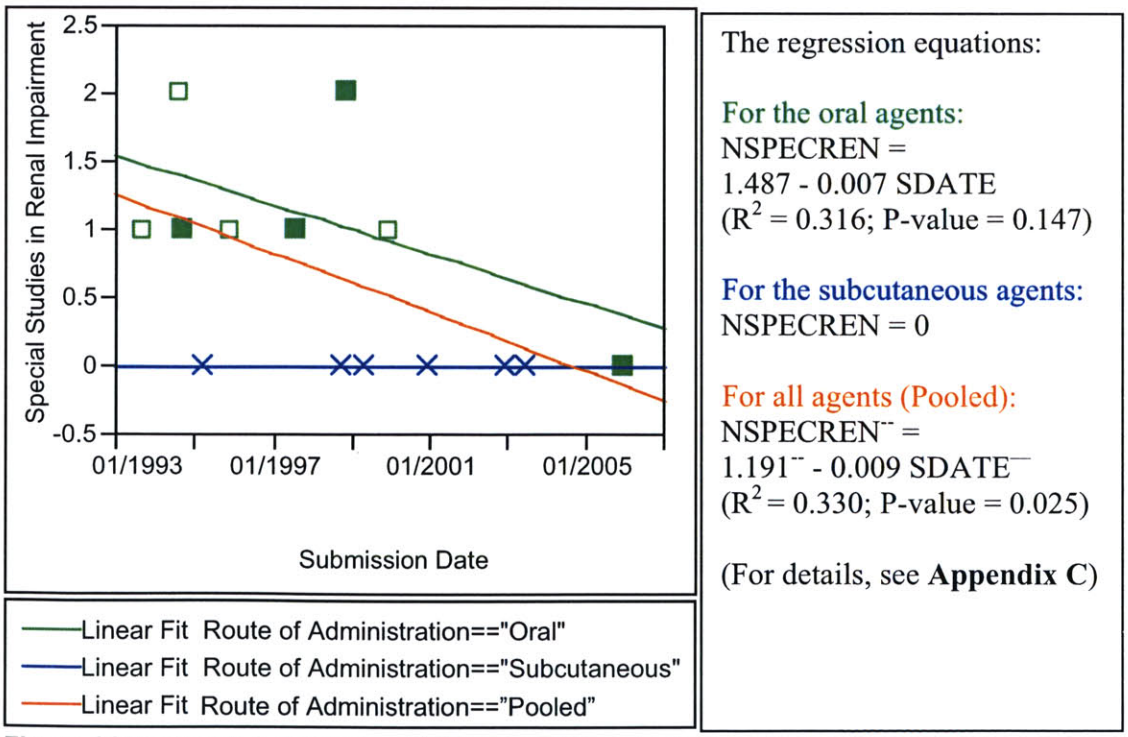


Figure 14 Regression Analysis of "Number of Special Studies in Renal Impaired Population" By "Submission Date"

Analysis 8: "Total Number of Drug-drug Interaction Studies" as an Indicator of Complexity over Time

<Definition of Indicator> Total Number of Drug-Drug Interaction Studies in NDA (NINTERST)

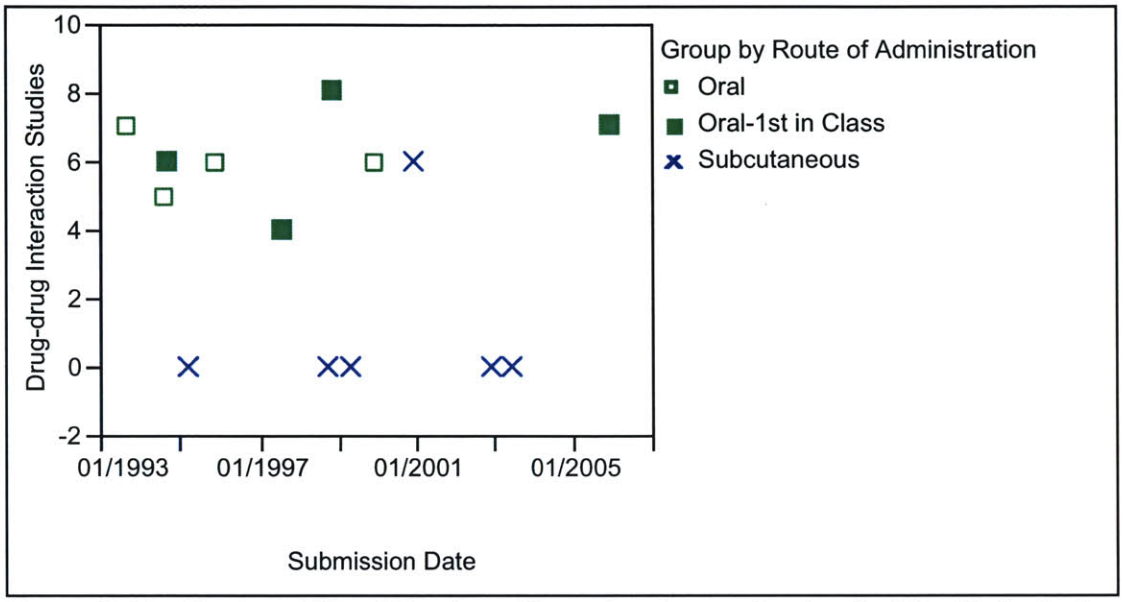
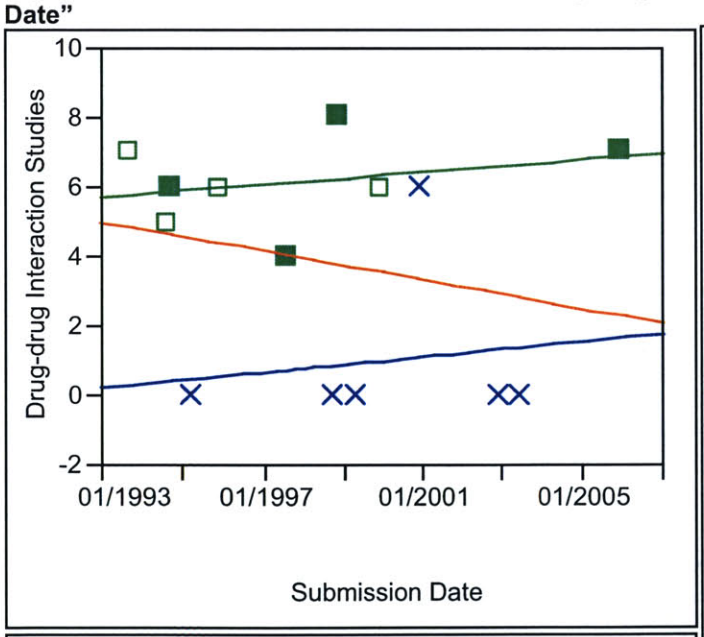
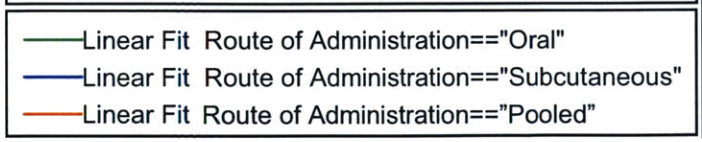


Figure 15 Distribution of "Total Number of Drug-drug Interaction Studies" By "Submission Date"





The regression equations:

For the oral agents:
NINTERST =
5.769 + 0.007 SDATE
(R^2 = 0.081; P-value = 0.494)

For the subcutaneous agents:
NINTERST =
0.284 + 0.009 SDATE
(R^2 = 0.019; P-value = 0.794)

For all agents (Pooled):
NINTERST =
4.872 - 0.017 SDATE
(R^2 = 0.067; P-value = 0.352)

(For details, see **Appendix C**)

Figure 16 Regression Analysis of "Total Number of Drug-drug Interaction Studies" By "Submission Date"

Analysis 9: "Number of Indications Proposed by Sponsor" as an Indicator of Complexity over Time

<Definition of Indicator> Number of Indications Proposed by Sponsor (NINDSP)

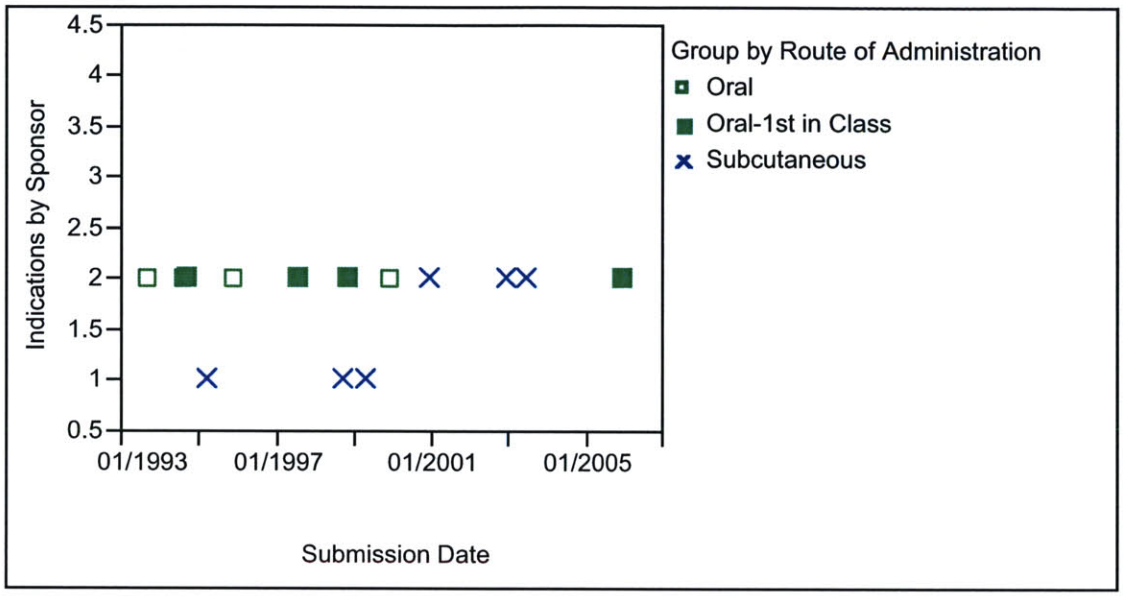


Figure 17 Distribution of "Number of Indications Proposed by Sponsor" By "Submission Date"

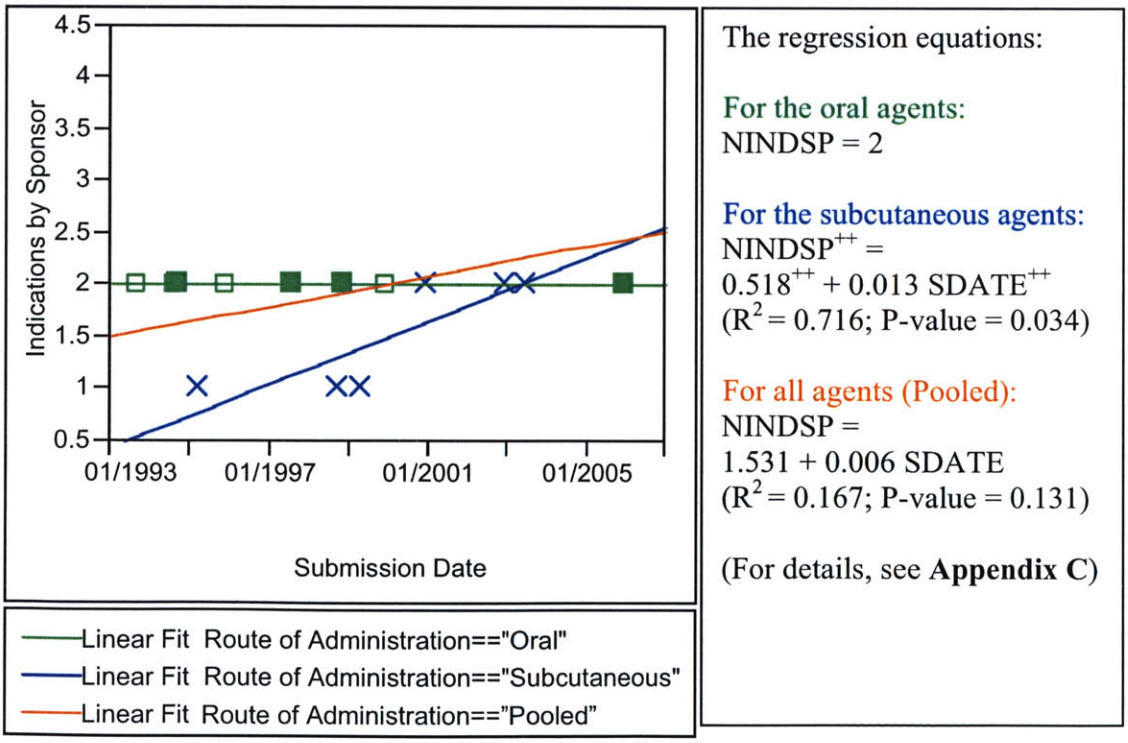


Figure 18 Regression Analysis of "Number of Indications Proposed by Sponsor" By "Submission Date"

Analysis 10: "Number of Indications Approved by FDA" as an Indicator of Complexity over Time

<Definition of Indicator> Number of Indications Approved by FDA (NINDFDA)

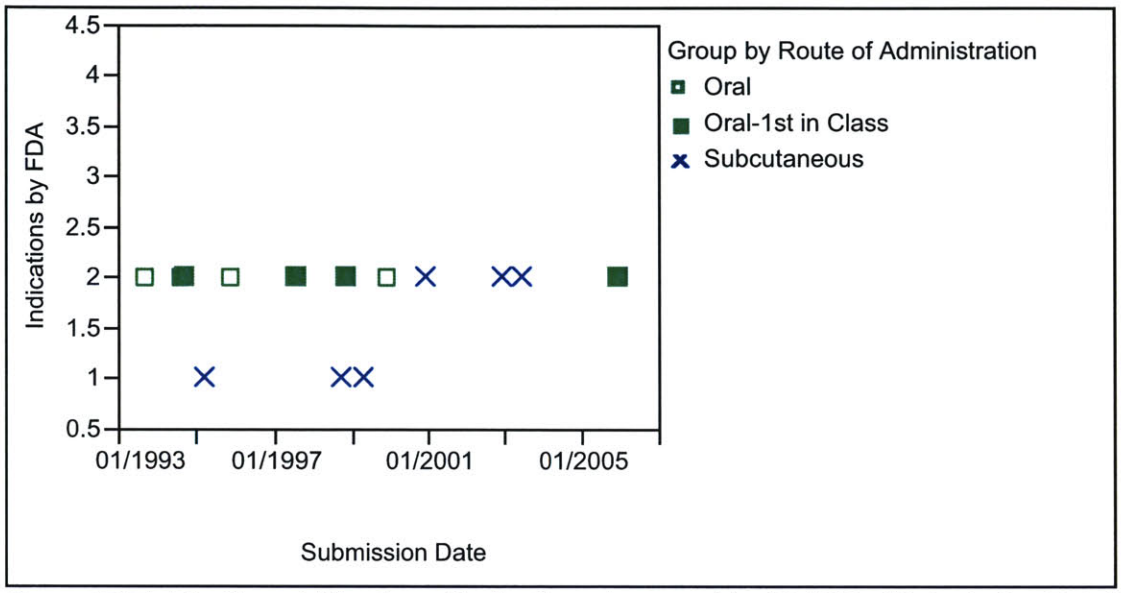
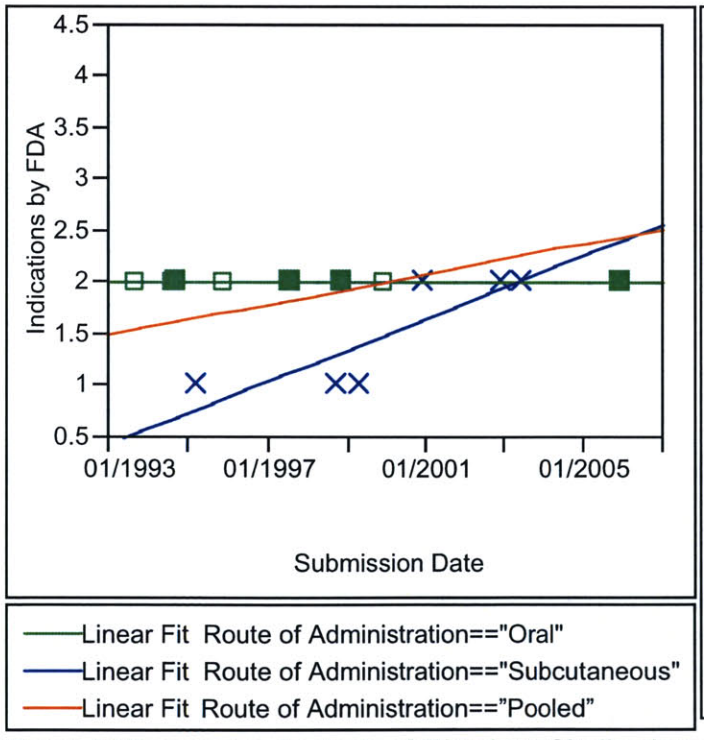


Figure 19 Distribution of "Number of Indications Approved by FDA" By "Submission Date"



The regression equations:

For the oral agents:
NINDFDA = 2

For the subcutaneous agents:
$NINDFDA^{++} = 0.518^{++} + 0.013\ SDATE^{++}$
($R^2 = 0.716$; P-value = 0.034)

For all agents (Pooled):
NINDFDA =
1.531 + 0.006 SDATE
($R^2 = 0.167$; P-value = 0.131)

(For details, see **Appendix C**)

Figure 20 Regression Analysis of "Number of Indications Approved by FDA" By "Submission Date"

Analysis 11: "Number of Pivotal Trials Submitted by Sponsor" as an Indicator of Complexity over Time

<Definition of Indicator> Number of Pivotal Trials Submitted by Sponsor (NPIVSP)

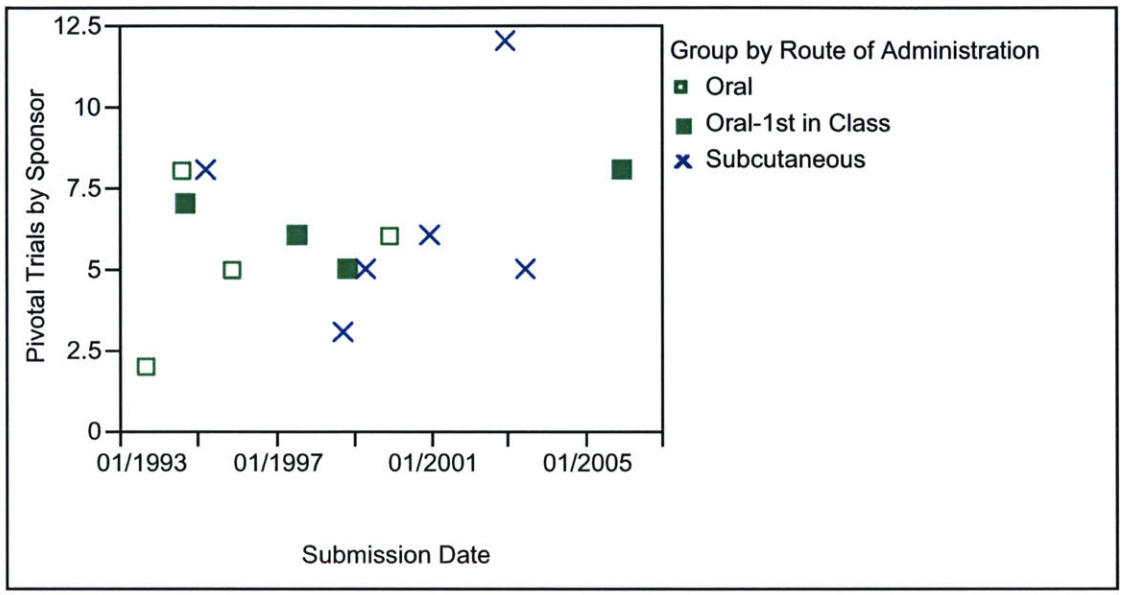
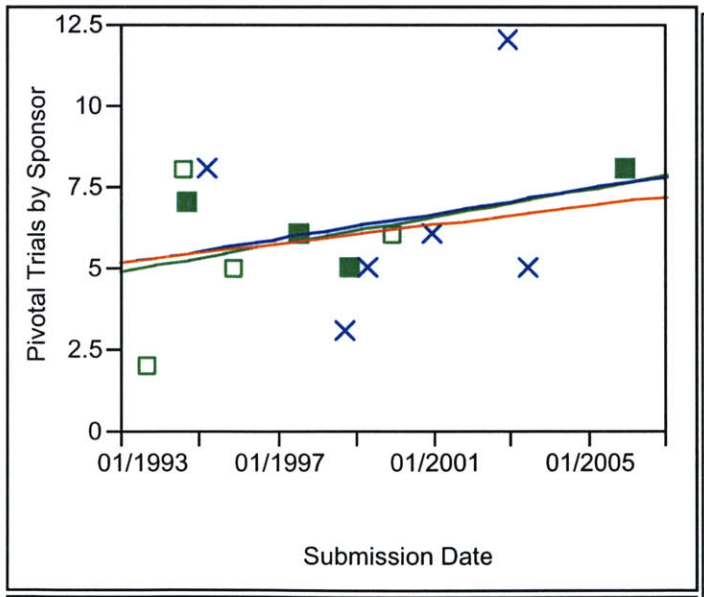


Figure 21 Distribution of "Number of Pivotal Trials Submitted by Sponsor" By "Submission Date"



The regression equations:

For the oral agents:
NPIVSP =
5.010 + 0.018 SDATE
(R^2 = 0.193; P-value = 0.276)

For the subcutaneous agents:
NPIVSP =
5.253 + 0.016 SDATE
(R^2 = 0.035; P-value = 0.723)

For all agents (Pooled):
NPIVSP =
5.260 + 0.012 SDATE
(R^2 = 0.059; P-value = 0.383)

(For details, see **Appendix C**)

Figure 22 Regression Analysis of "Number of Pivotal Trials Submitted by Sponsor" By "Submission Date"

Analysis 12: "Number of Pivotal Trials for FDA to Approve NDA" as an Indicator of Complexity over Time

<Definition of Indicator> Number of Pivotal Trials for FDA to Approve NDA (NPIVFDA)

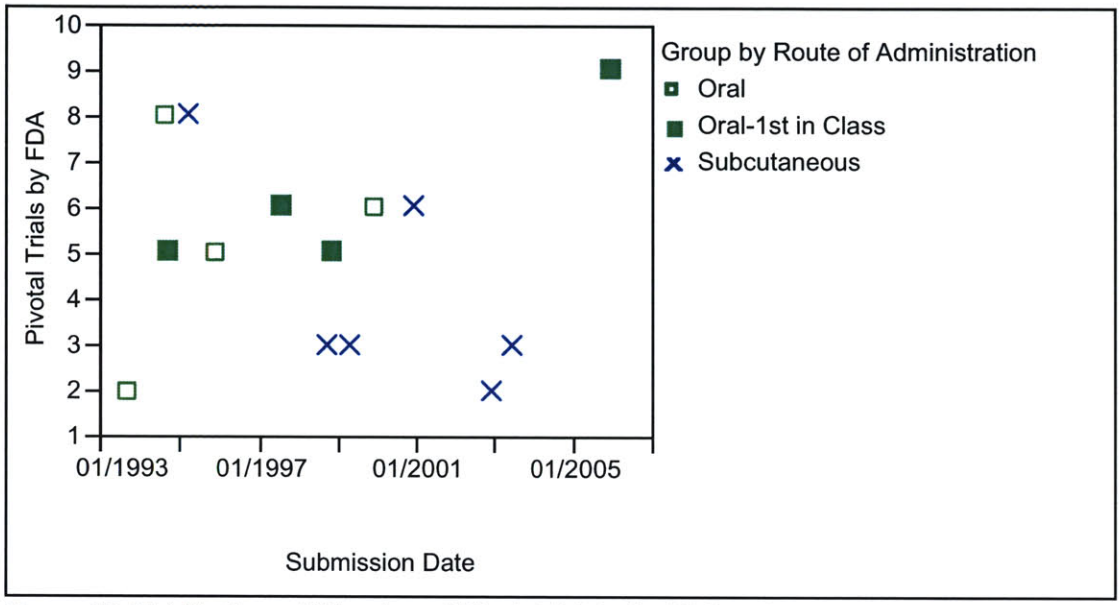


Figure 23 Distribution of "Number of Pivotal Trials for FDA to Approve NDA" By "Submission Date"

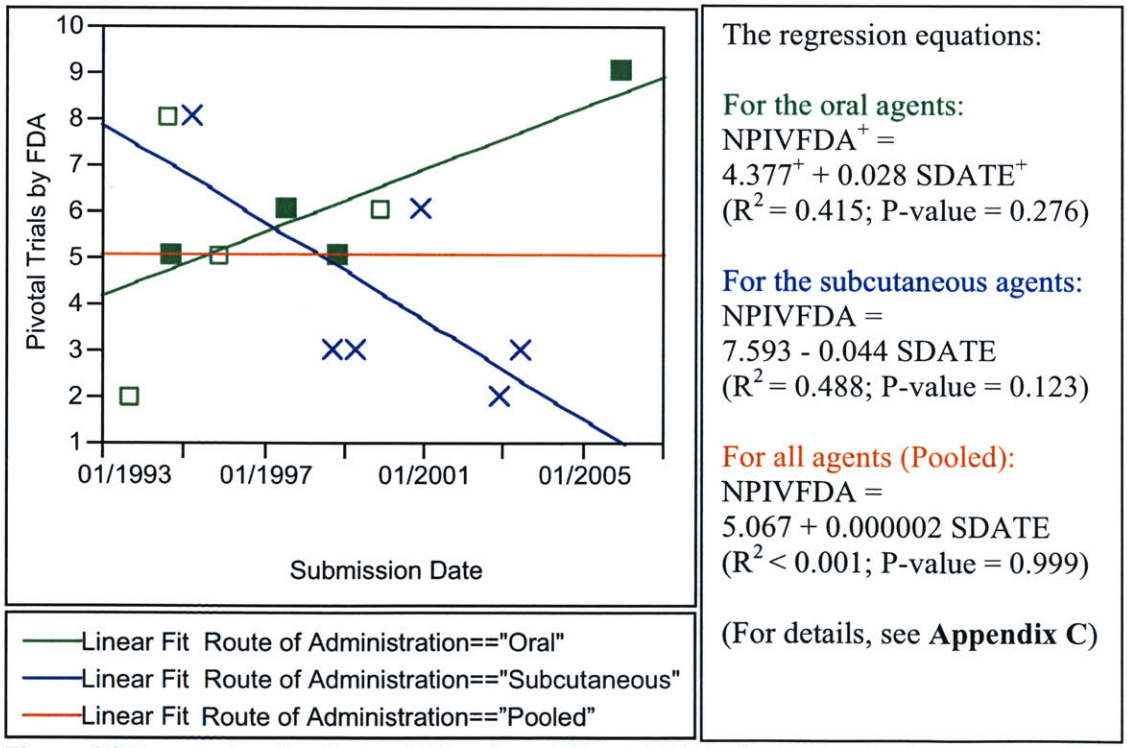


Figure 24 Regression Analysis of "Number of Pivotal Trials for FDA to Approve NDA" By "Submission Date"

Analysis 13: "Number of Patients in Pivotal Trials Submitted by Sponsor" as an Indicator of Complexity over Time

<Definition of Indicator> Number of Patients in Pivotal Trials Submitted by Sponsor (NPATSP)

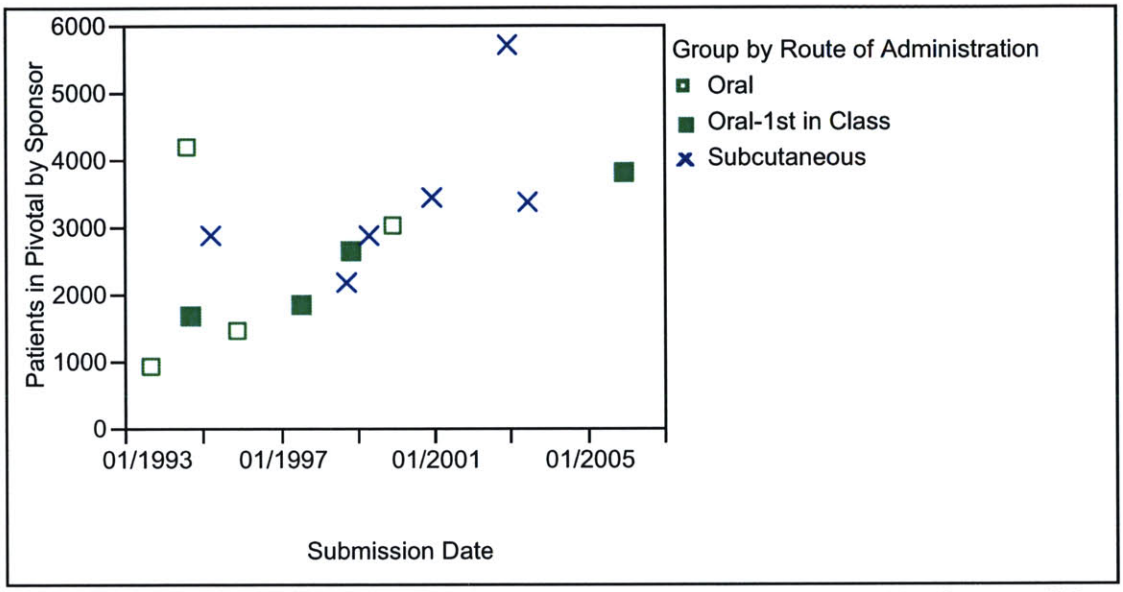


Figure 25 Distribution of "Number of Patients in Pivotal Trials Submitted by Sponsor" By "Submission Date"

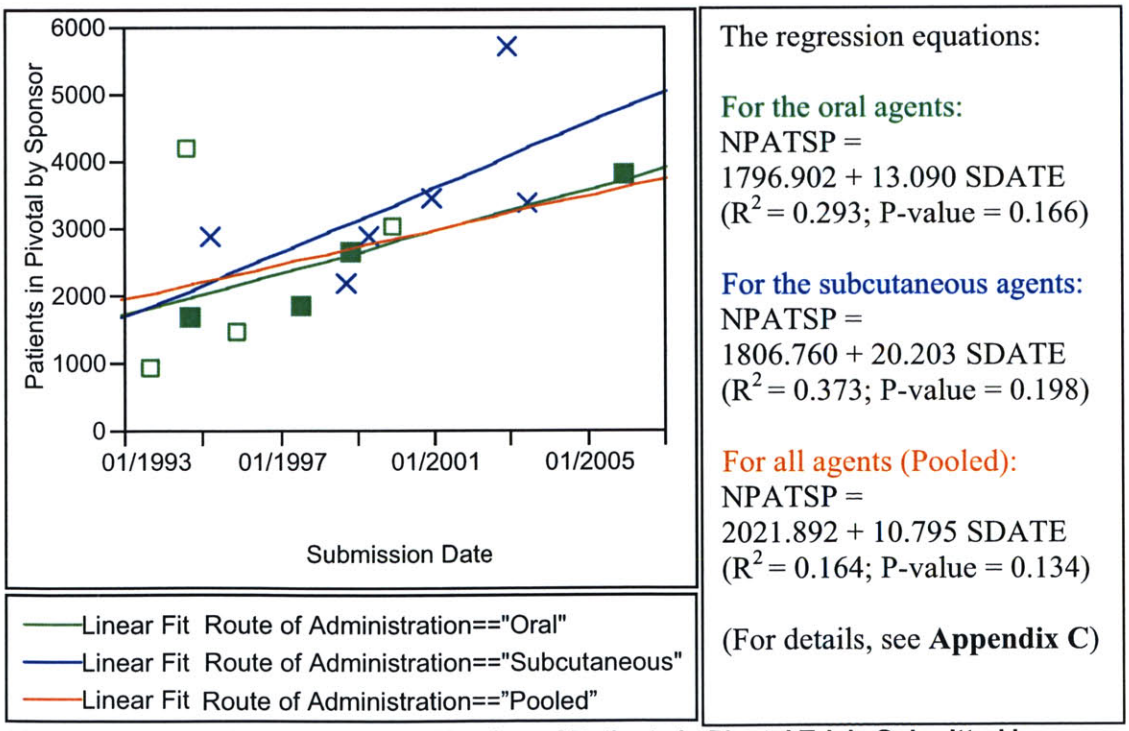


Figure 26 Regression Analysis of "Number of Patients in Pivotal Trials Submitted by Sponsor" By "Submission Date"

Analysis 14: "Number of Patients in Pivotal Trials for FDA to Approve NDA" as an Indicator of Complexity over Time

<Definition of Indicator> Number of Patients in Pivotal Trials for FDA to Approve NDA (NPATFDA)

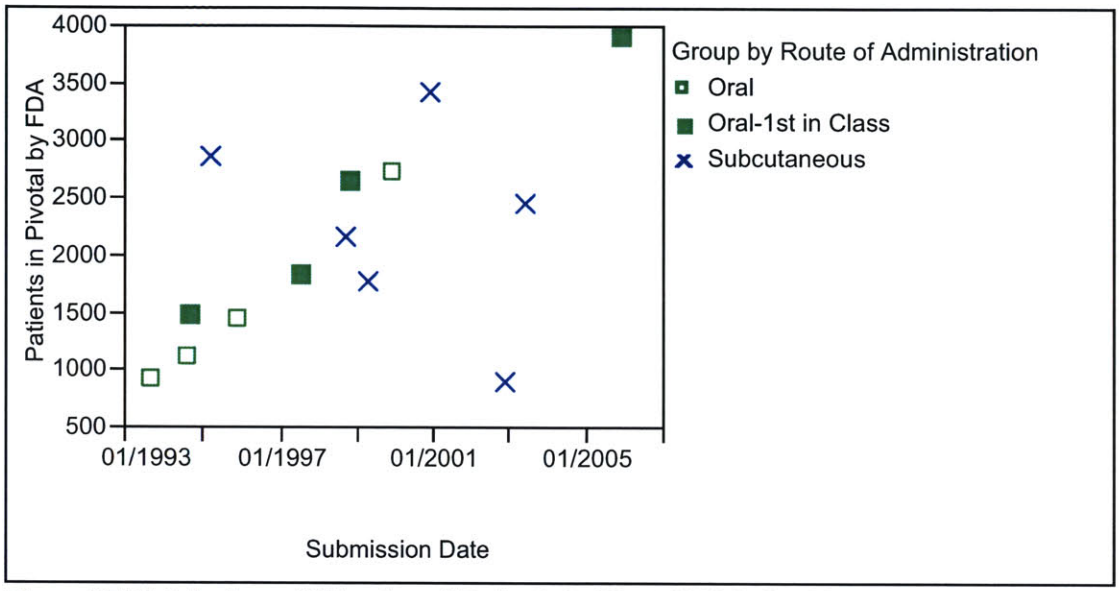


Figure 27 Distribution of "Number of Patients in Pivotal Trials for FDA to Approve NDA" By "Submission Date"

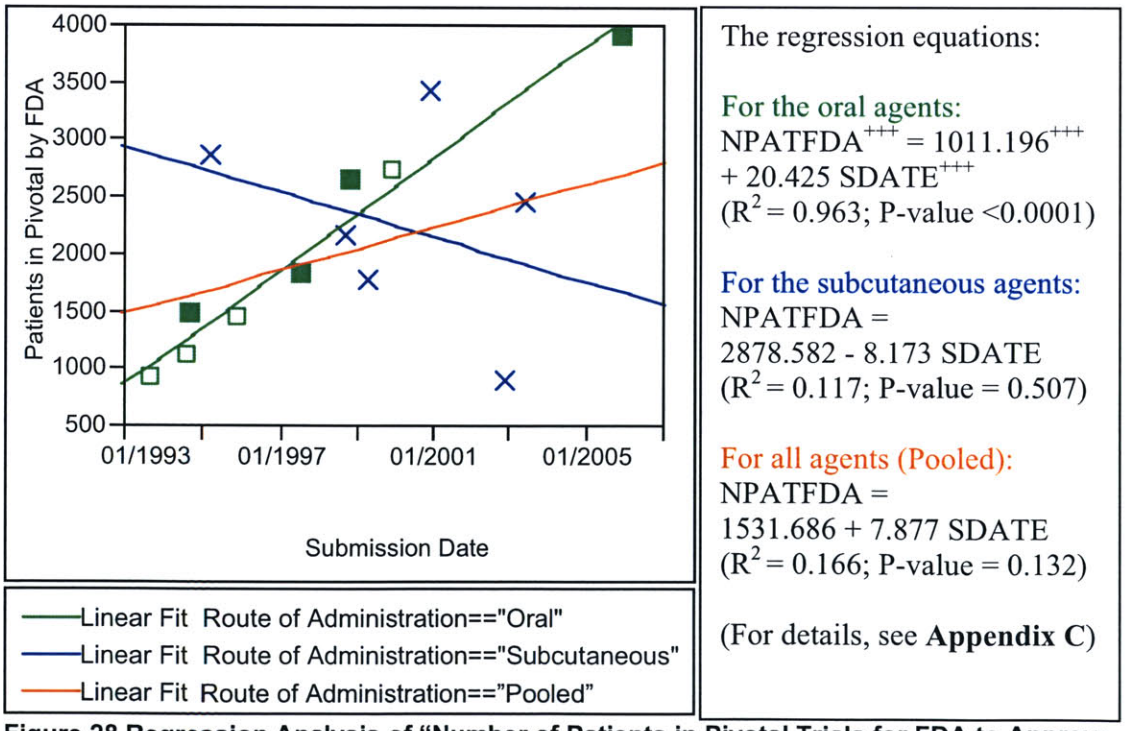


Figure 28 Regression Analysis of "Number of Patients in Pivotal Trials for FDA to Approve NDA" By "Submission Date"

Analysis 15: "Patients per Pivotal Trials Submitted by Sponsor" as an Indicator of Complexity over Time

<Definition of Indicator> "Patients per Pivotal Trials Submitted by Sponsor (AVNPATSP)" equals to "Number of Patients in Pivotal Trials Submitted by Sponsor" divided by "Number of Pivotal Trials Submitted by Sponsor."

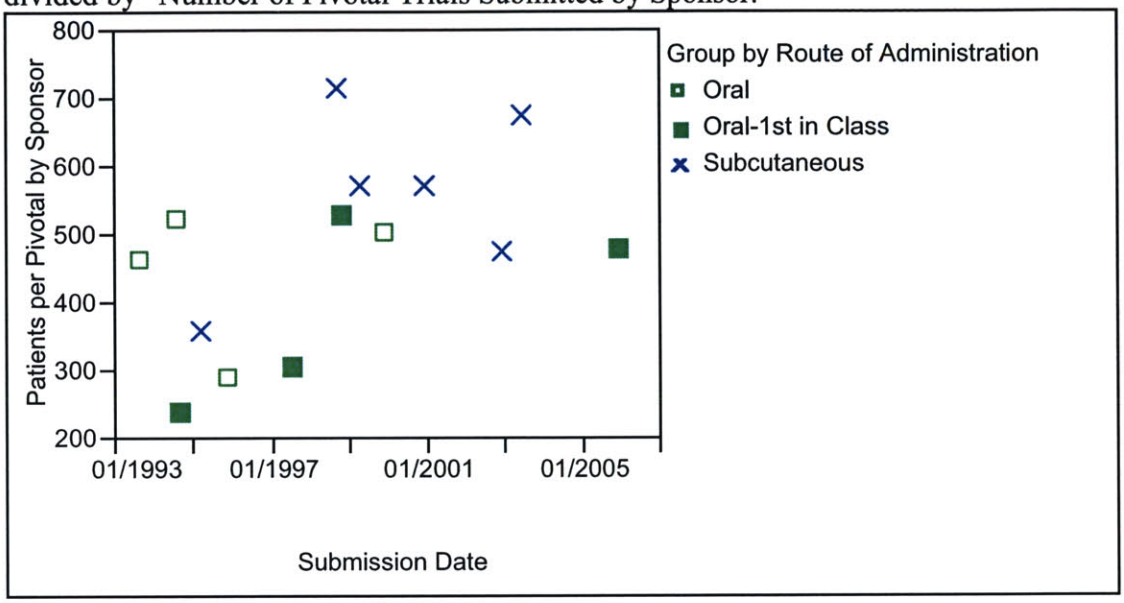
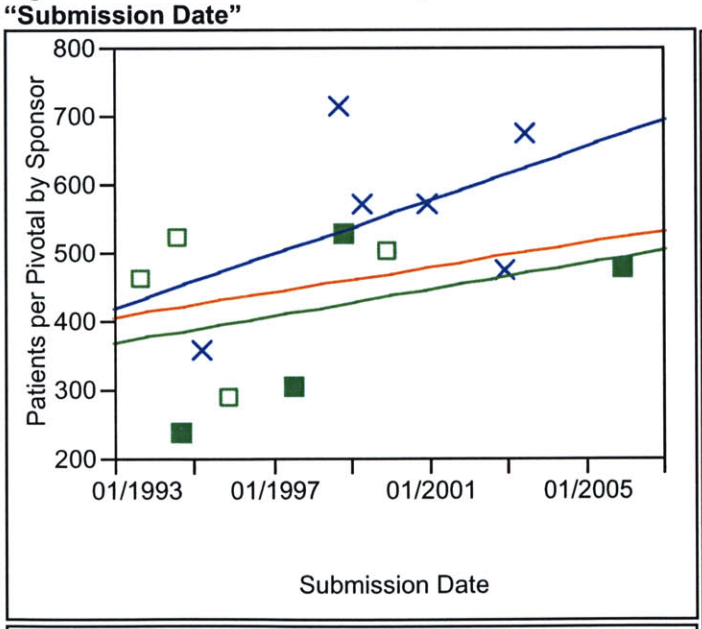
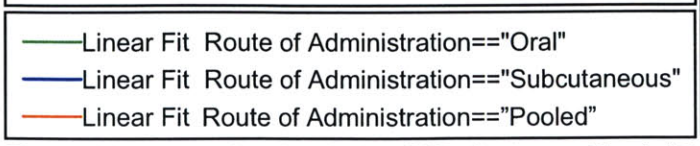


Figure 29 Distribution of Patients per Pivotal Trials Submitted by Sponsor "" By "Submission Date"





The regression equations:

For the oral agents:
AVNPATSP =
375.714 + 0.791 SDATE
(R^2 = 0.105; P-value = 0.434)

For the subcutaneous agents:
AVNPATSP =
430.830 + 1.638 SDATE
(R^2 = 0.211; P-value = 0.360)

For all agents (Pooled):
AVNPATSP =
412.079 + 0.749 SDATE
(R^2 = 0.059; P-value = 0.383)

(For details, see **Appendix C**)

Figure 30 Regression Analysis of "Patients per Pivotal Trials Submitted by Sponsor" By "Submission Date"

Analysis 16: "Patients per Pivotal Trials for FDA to Approve NDA" as an Indicator of Complexity over Time

<Definition of Indicator> "Patients per Pivotal Trials for FDA to Approve NDA (AVNPATFDA)" equals to "Number of Patients in Pivotal Trials for FDA to Approve NDA" divided by "Number of Pivotal Trials for FDA to Approve NDA"

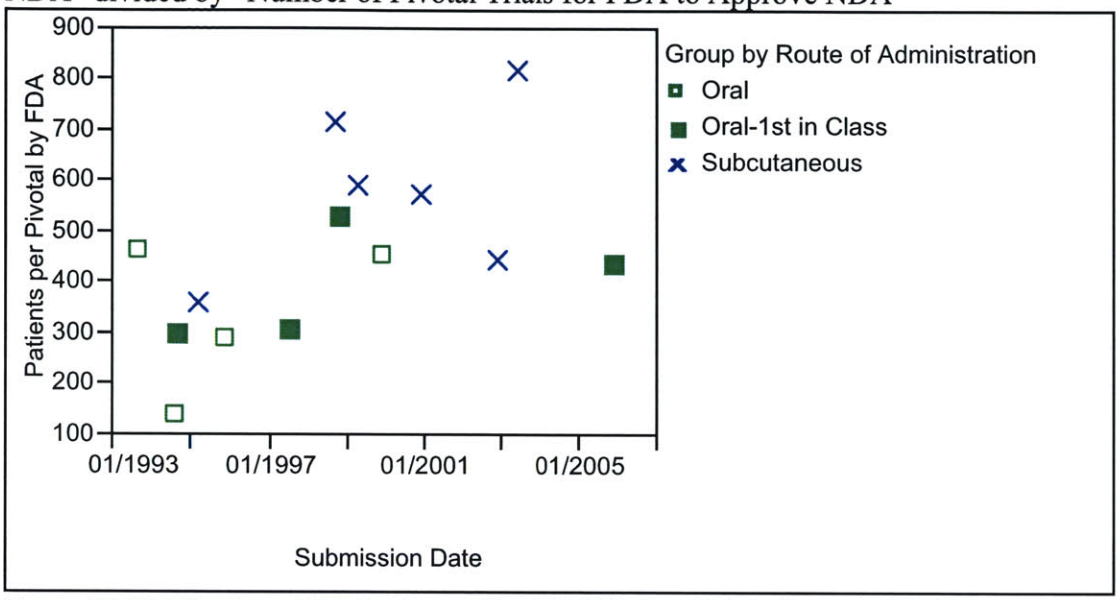
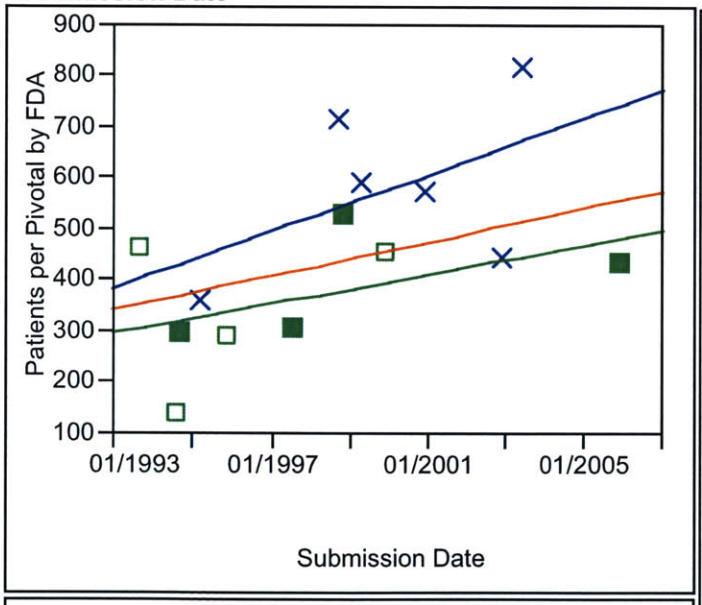


Figure 31 Distribution of "Patients per Pivotal Trials for FDA to Approve NDA" By "Submission Date"



The regression equations:

For the oral agents:
AVNPATFDA =
304.756 + 1.181 SDATE
(R^2= 0.201; P-value = 0.265)

For the subcutaneous agents:
AVNPATFDA =
400.352 + 2.305 SDATE
(R^2 = 0.252; P-value = 0.310)

For all agents (Pooled):
AVNPATFDA =
351.284 + 1.379 SDATE
(R^2 = 0.131; P-value = 0.184)

(For details, see **Appendix C**)

Figure 32 Regression Analysis of "Patients per Pivotal Trials for FDA to Approve NDA" By "Submission Date"

Analysis 17: "Average Number of Patients to Support Each Indication Proposed by Sponsor" as an Indicator of Complexity over Time

<Definition of Indicator> "Average Number of Patients to Support Each Indication Proposed by Sponsor (AVNPINDSP)" equals to "Number of Patients in Pivotal Trials Submitted by Sponsor" divided by "Number of Indications Proposed by Sponsor."

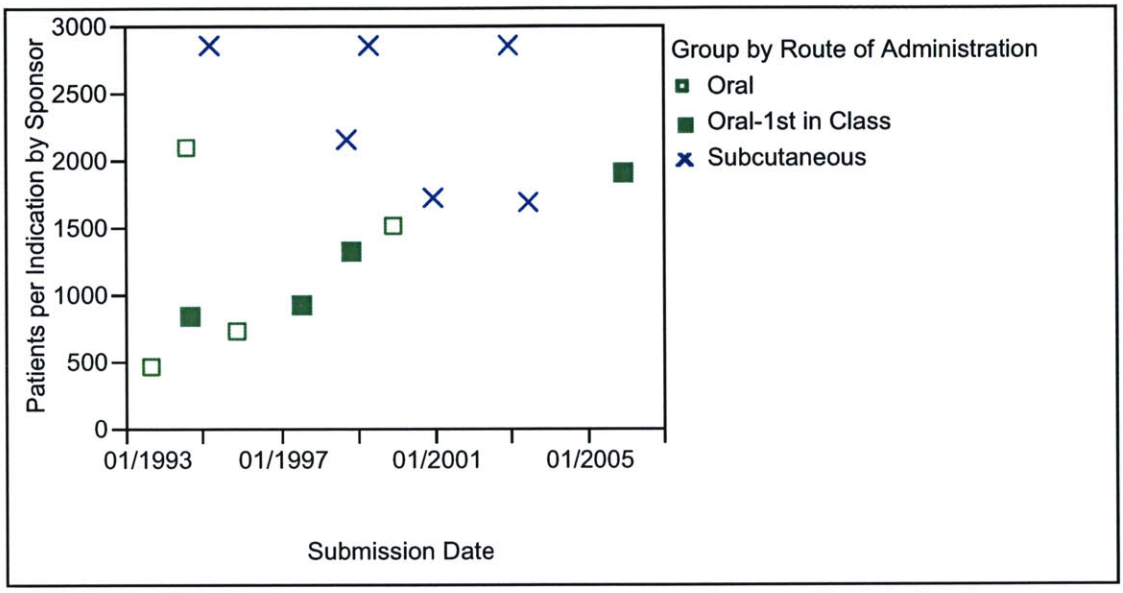
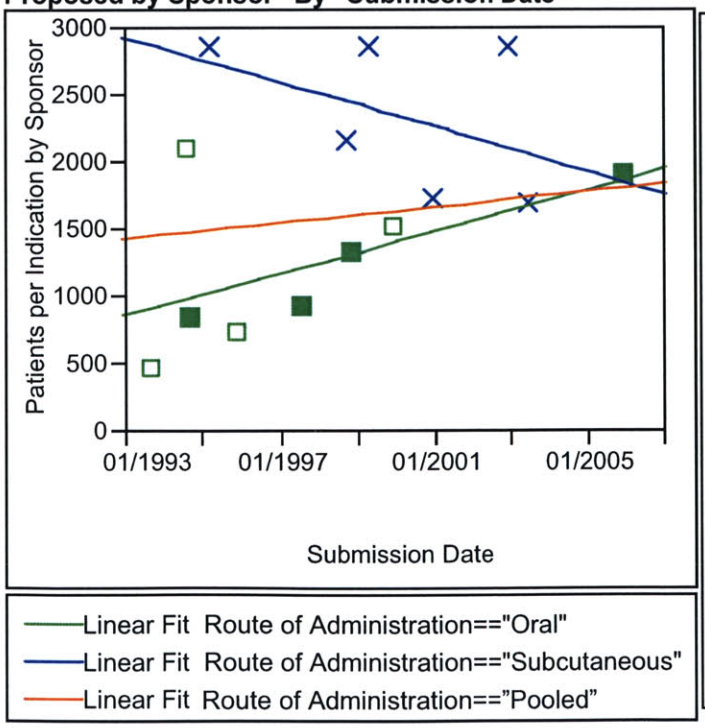


Figure 33 Distribution of "Average Number of Patients to Support Each Indication Proposed by Sponsor" By "Submission Date"



The regression equations:

For the oral agents:
AVNPINDSP =
898.451 + 6.545 SDATE
(R^2 = 0.293; P-value = 0.166)

For the subcutaneous agents:
AVNPINDSP =
2879.571 - 6.954 SDATE
(R^2 = 0.199; P-value = 0.375)

For all agents (Pooled):
AVNPINDSP =
1443.915 + 2.453 SDATE
(R^2 = 0.019; P-value = 0.628)

(For details, see **Appendix C**)

Figure 34 Regression Analysis of "Average Number of Patients to Support Each Indication Proposed by Sponsor" By "Submission Date"

Analysis 18: "Average Number of Patients to Support Each Indication Approved by FDA" as an Indicator of Complexity over Time

<Definition of Indicator> "Average Number of Patients to Support Each Indication Approved by FDA (AVNPINDFDA)" equals to "Number of Patients in Pivotal Trials for FDA to Approve NDA" divided by "Number of Indications Approved by FDA."

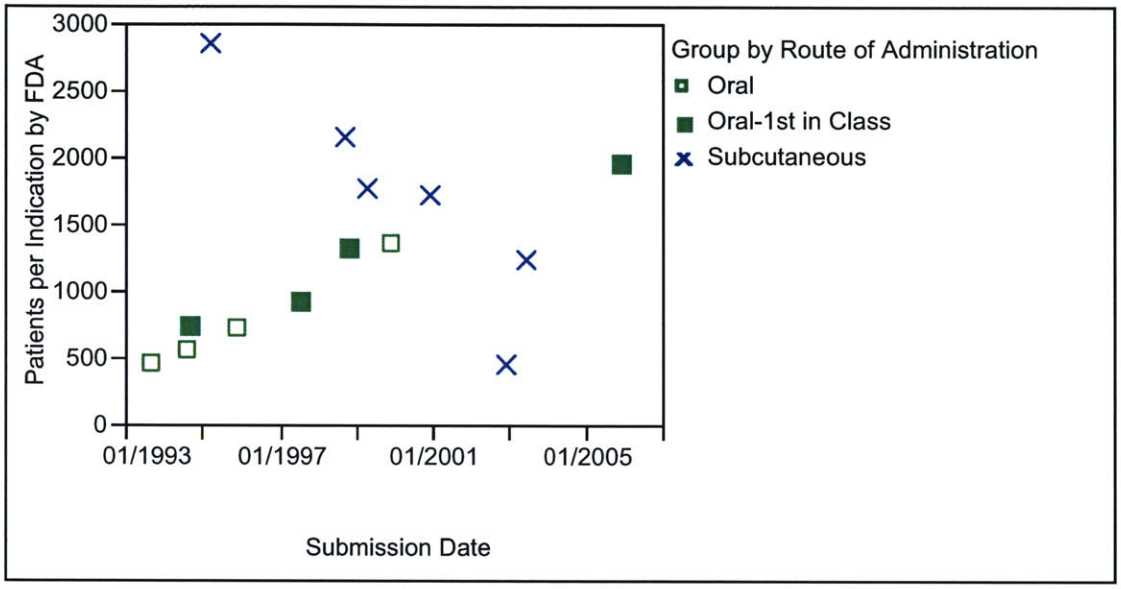
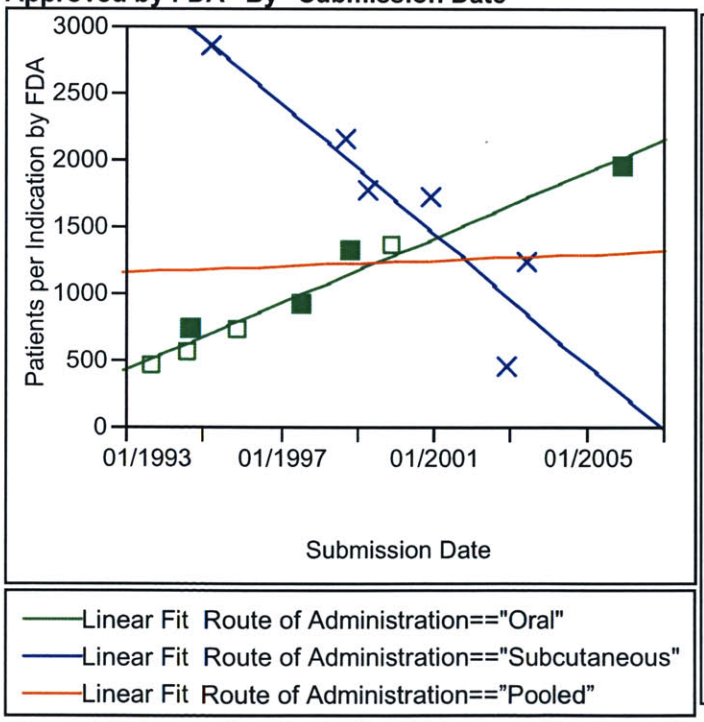


Figure 35 Distribution of "Average Number of Patients to Support Each Indication Approved by FDA" By "Submission Date"



The regression equations:

For the oral agents:
$AVNPINDFDA^{+++} = 505.598^{+++} + 10.212\ SDATE^{+++}$
($R^2 = 0.963$; P-value <0.0001)

For the subcutaneous agents:
$AVNPINDFDA^{---} = 3264.087^{---} - 20.360\ SDATE^{---}$
($R^2 = 0.847$; P-value = 0.009)

For all agents (Pooled):
$AVNPINDFDA = 1164.924 + 0.958\ SDATE$
($R^2 = 0.004$; P-value = 0.827)
(For details, see **Appendix C**)

Figure 36 Regression Analysis of "Average Number of Patients to Support Each Indication Approved by FDA" By "Submission Date"

Analysis 19: "Average Number of Pivotal Trials to Support Each Indication Proposed by Sponsor" as an Indicator of Complexity over Time

<Definition of Indicator> "Average Number of Pivotal Trials to Support Each Indication Proposed by Sponsor (AVNTINDSP)" equals to "Number of Pivotal Trials Submitted by Sponsor" divided by "Number of Indications Proposed by Sponsor."

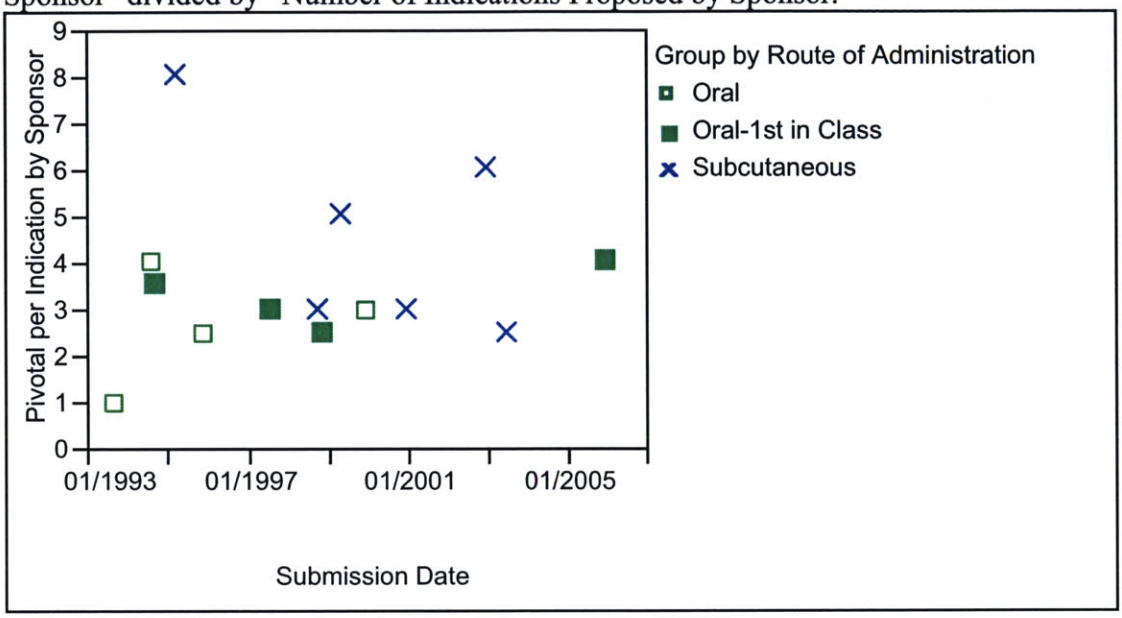


Figure 37 Distribution of "Average Number of Pivotal Trials to Support Each Indication Proposed by Sponsor" By "Submission Date"

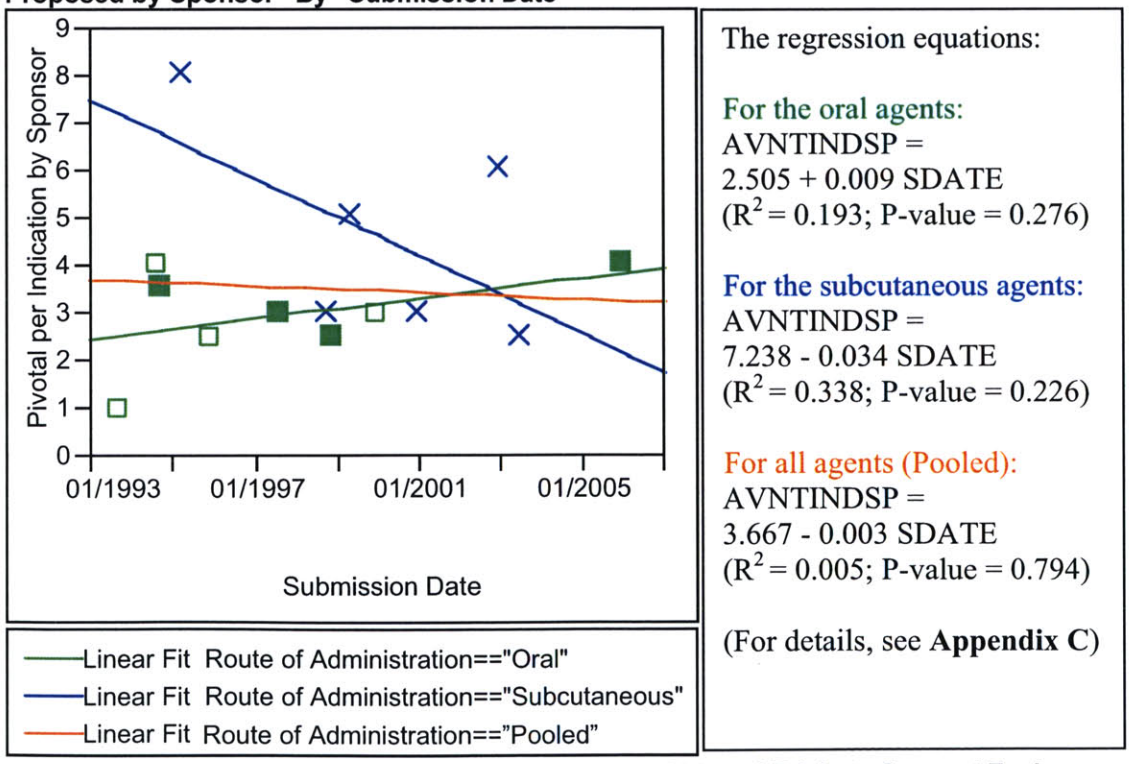


Figure 38 Regression Analysis of "Average Number of Pivotal Trials to Support Each Indication Proposed by Sponsor" By "Submission Date"

Analysis 20: "Average Number of Pivotal Trials to Support Each Indication Approved by FDA" as an Indicator of Complexity over Time

<Definition of Indicator> "Average Number of Pivotal Trials to Support Each Indication Approved by FDA (AVNTINDFDA)" equals to "Number of Pivotal Trials for FDA to Approve NDA" divided by "Number of Indications Approved by FDA."

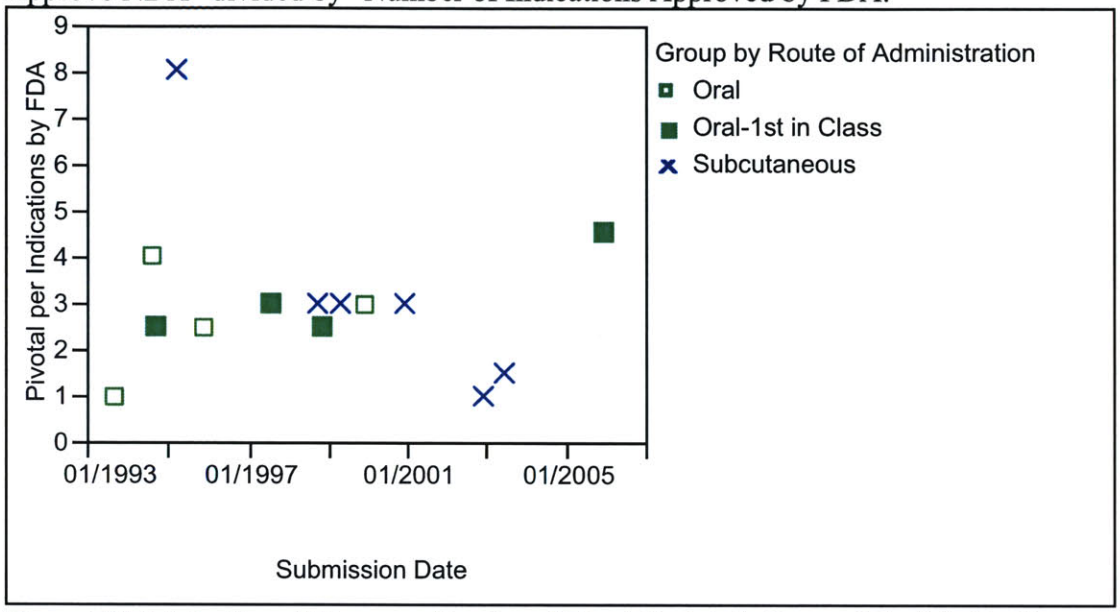
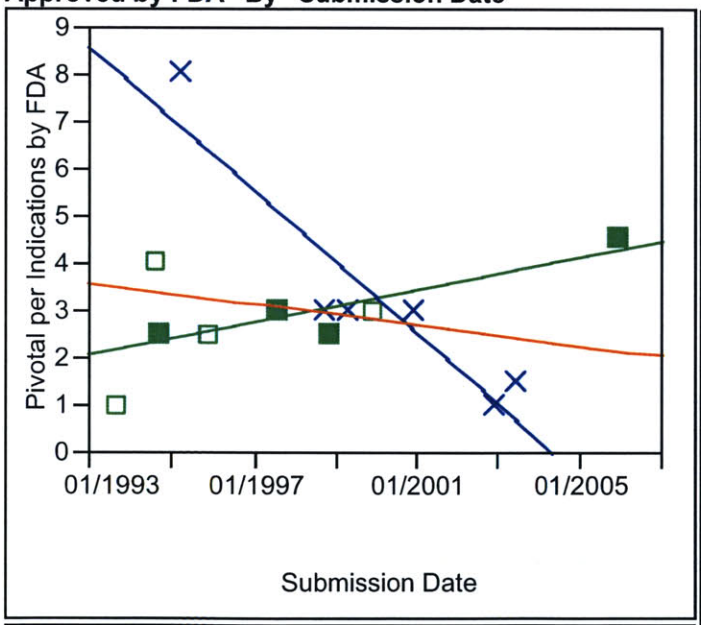


Figure 39 Distribution of "Average Number of Pivotal Trials to Support Each Indication Approved by FDA" By "Submission Date"



The regression equations:

For the oral agents:
$AVNTINDFDA^{+} = 2.189^{+} + 0.014\ SDATE^{+}$
($R^2 = 0.415$; P-value = 0.085)

For the subcutaneous agents:
$AVNTINDFDA^{---} = 8.129^{---} - 0.063\ SDATE^{---}$
($R^2 = 0.860$; P-value = 0.008)

For all agents (Pooled):
$AVNTINDFDA = 3.508 - 0.009\ SDATE$
($R^2 = 0.059$; P-value = 0.381)

(For details, see **Appendix C**)

Figure 40 Regression Analysis of "Average Number of Pivotal Trials to Support Each Indication Approved by FDA" By "Submission Date"

Analysis 21: "Number of Arms in Pivotal Trials" as an Indicator of Complexity over Time

<Definition of Indicator> Number of Arms in Pivotal Trials (NARM)

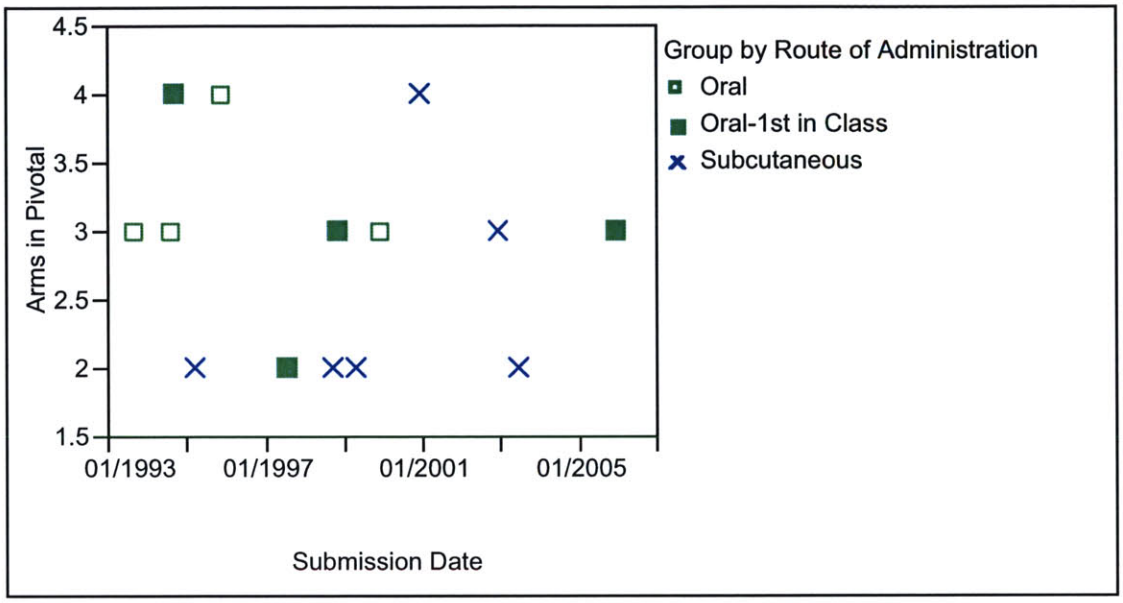


Figure 41 Distribution of "Number of Arms in Pivotal Trials" By "Submission Date"

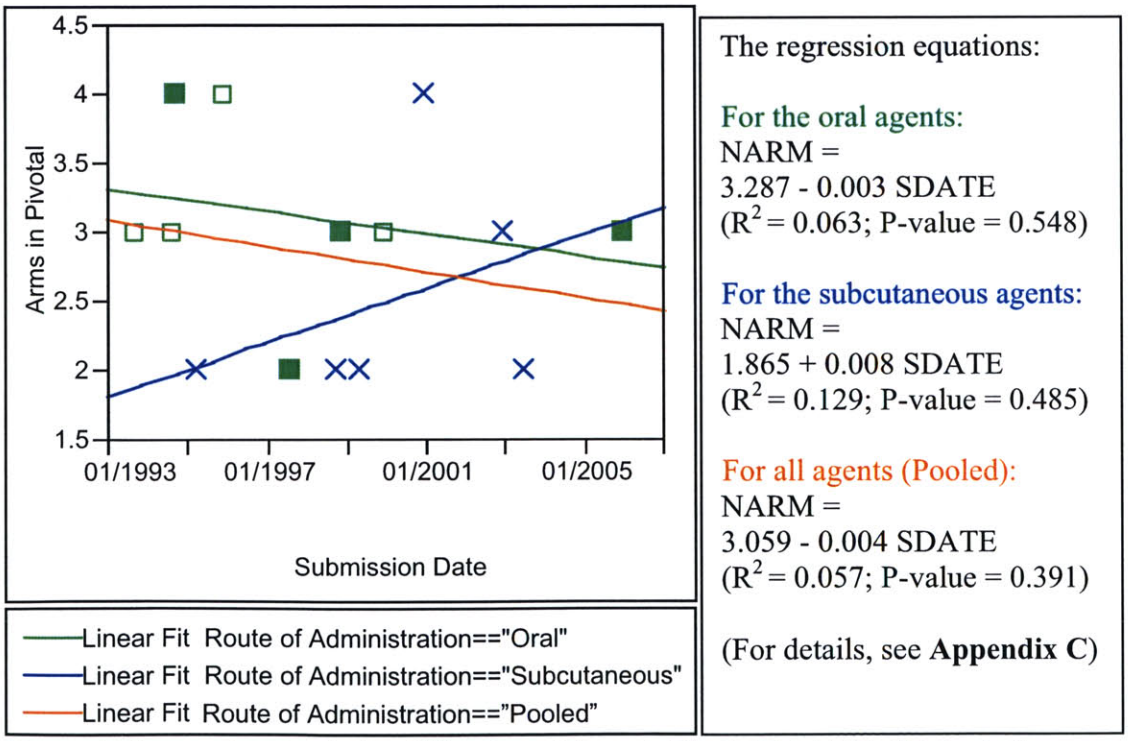


Figure 42 Regression Analysis of "Number of Arms in Pivotal Trials" By "Submission Date"

Analysis 22: "Length of Follow-up Period in Pivotal Trials" as an Indicator of Complexity over Time

<Definition of Indicator> Length of Follow-up Period in Pivotal Trials (FOLTM, Days)

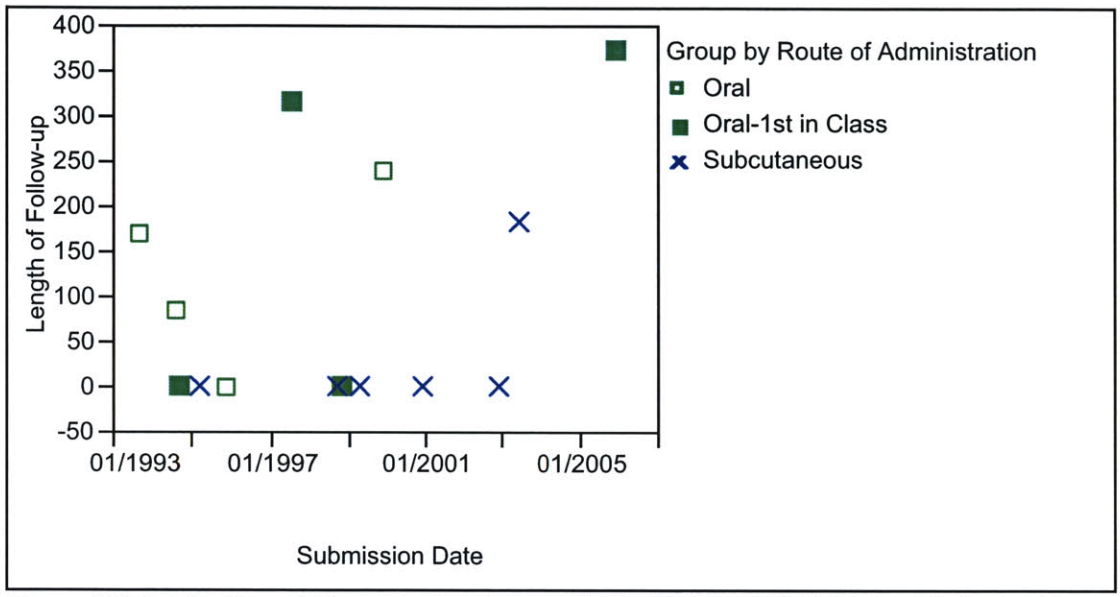
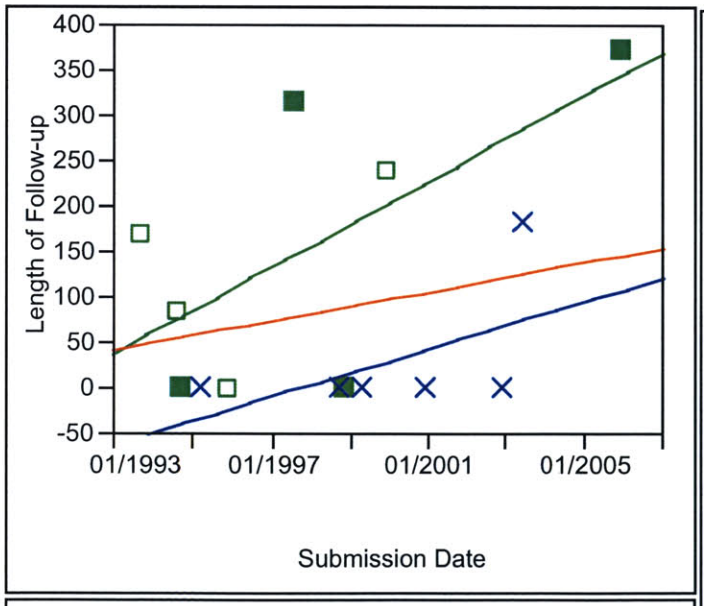


Figure 43 Distribution of "Length of Follow-up Period in Pivotal Trials" By "Submission Date"



The regression equations:

For the oral agents:
$FOLTM^{+} = 51.753^{+} + 1.966\ SDATE^{+}$
($R^2 = 0.403$; P-value = 0.091)

For the subcutaneous agents:
$FOLTM = -54.439 + 1.091\ SDATE$
($R^2 = 0.290$; P-value = 0.270)

For all agents (Pooled):
$FOLTM = 46.527 + 0.666\ SDATE$
($R^2 = 0.058$; P-value = 0.387)

(For details, see **Appendix C**)

Figure 44 Regression Analysis of "Length of Follow-up Period in Pivotal Trials" By "Submission Date"

Analysis 23: "Number of Primary Endpoints in Pivotal Trials" as an Indicator of Complexity over Time

<Definition of Indicator> Number of Primary Endpoints in Pivotal Trials (NPEND)

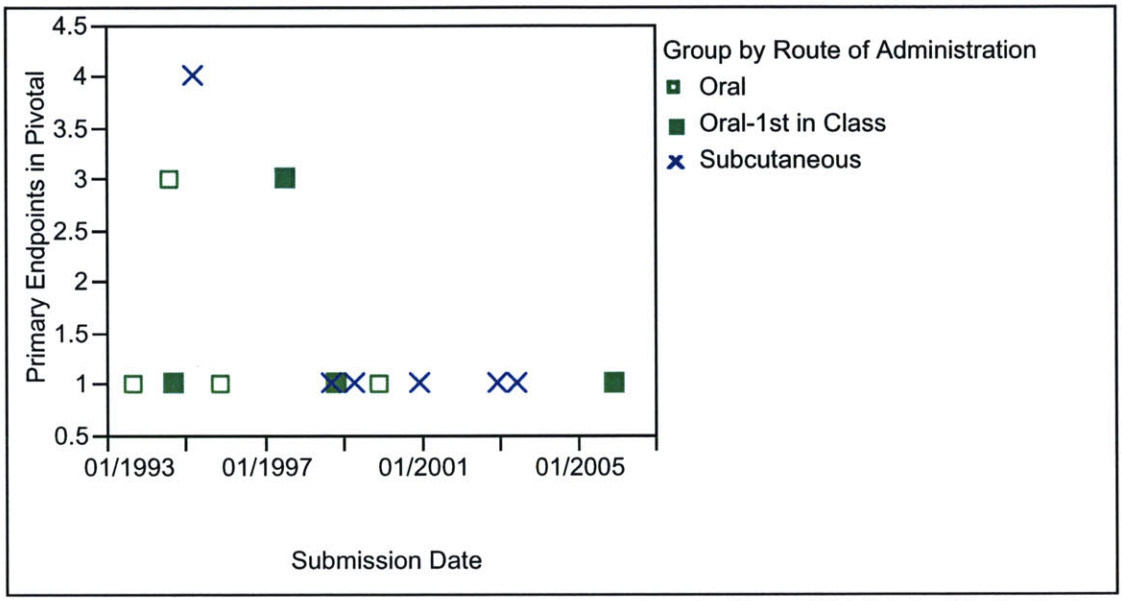
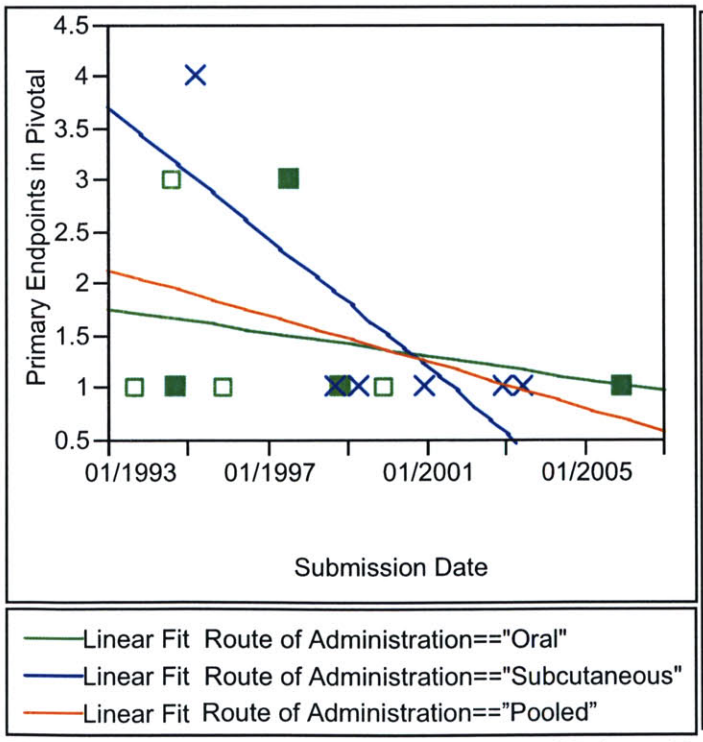


Figure 45 Distribution of "Number of Primary Endpoints in Pivotal Trials" By "Submission Date"



The regression equations:

For the oral agents:
NPEND =
1.725 - 0.005 SDATE
(R^2 = 0.059; P-value = 0.564)

For the subcutaneous agents:
NPEND^{-} =
3.533^{-} - 0.026 SDATE^{-}
(R^2 = 0.614; P-value = 0.065)

For all agents (Pooled):
NPEND^{-} =
2.073^{-} - 0.009 SDATE^{-}
(R^2 = 0.192; P-value = 0.103)

(For details, see **Appendix C**)

Figure 46 Regression Analysis of "Number of Primary Endpoints in Pivotal Trials" By "Submission Date"

Analysis 24: "Number of Secondary Endpoints in Pivotal Trials" as an Indicator of Complexity over Time

<Definition of Indicator> Number of Secondary Endpoints in Pivotal Trials (NSEND)

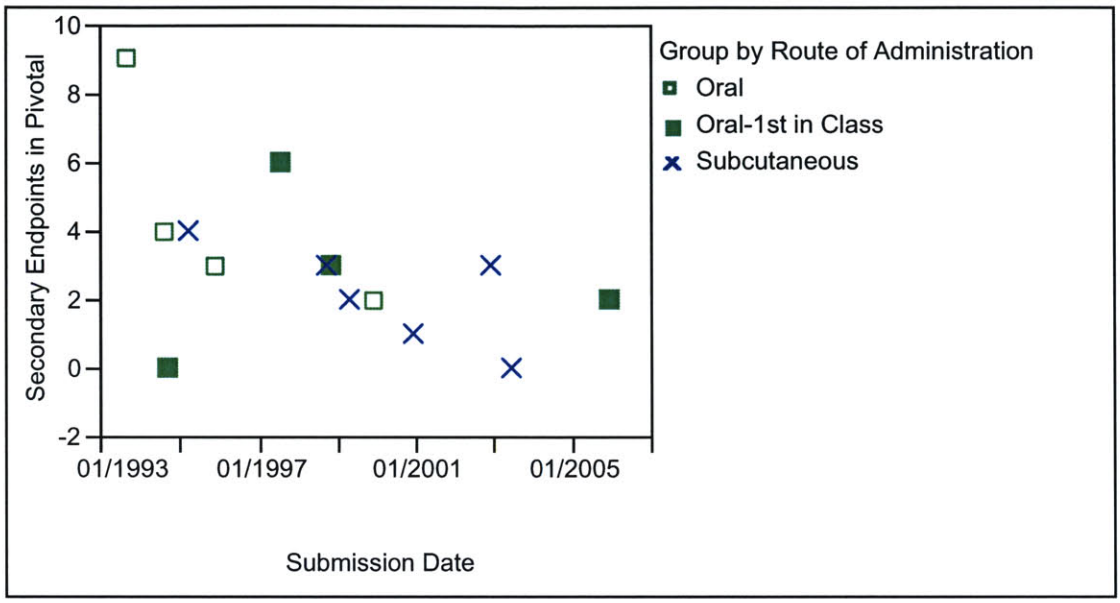


Figure 47 Distribution of "Number of Secondary Endpoints in Pivotal Trials" By "Submission Date"

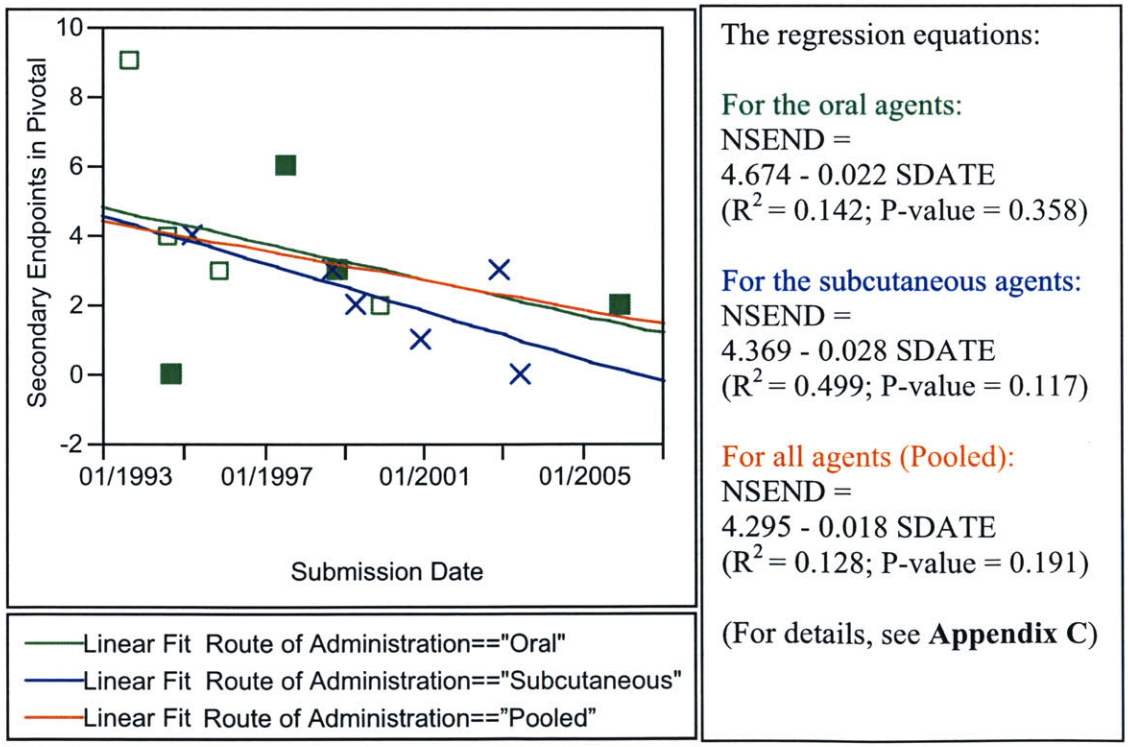


Figure 48 Regression Analysis of "Number of Secondary Endpoints in Pivotal Trials" By "Submission Date"

Analysis 25: "Dose Duration" as an Indicator of Complexity over Time

<Definition of Indicator> Dose Duration in Pivotal Trials (DOSDUR)

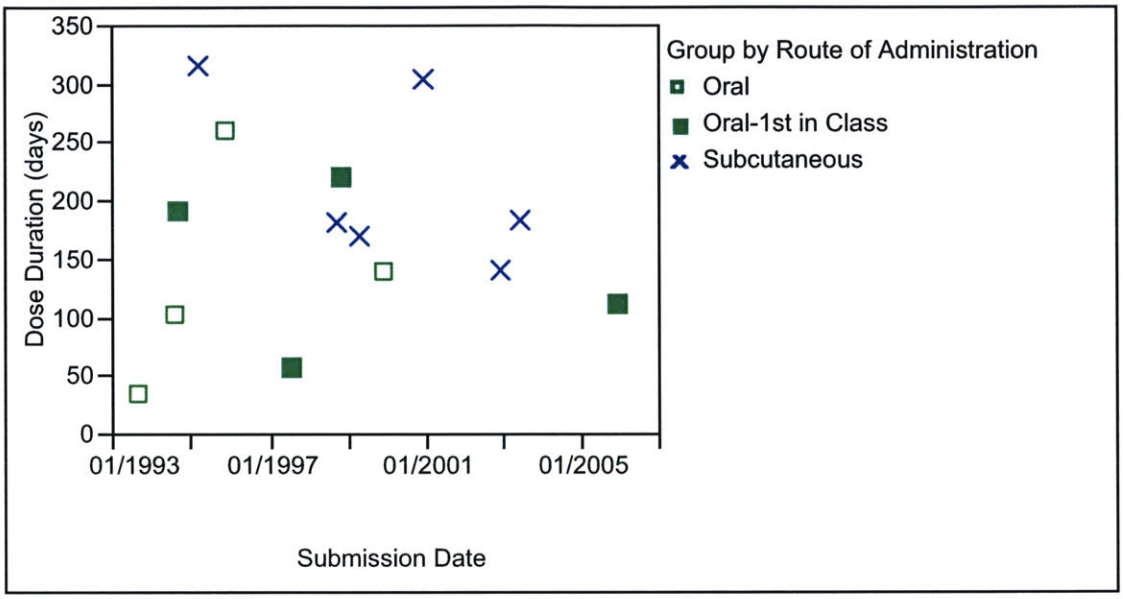


Figure 49 Distribution of "Dose Duration in Pivotal Trials" By "Submission Date"

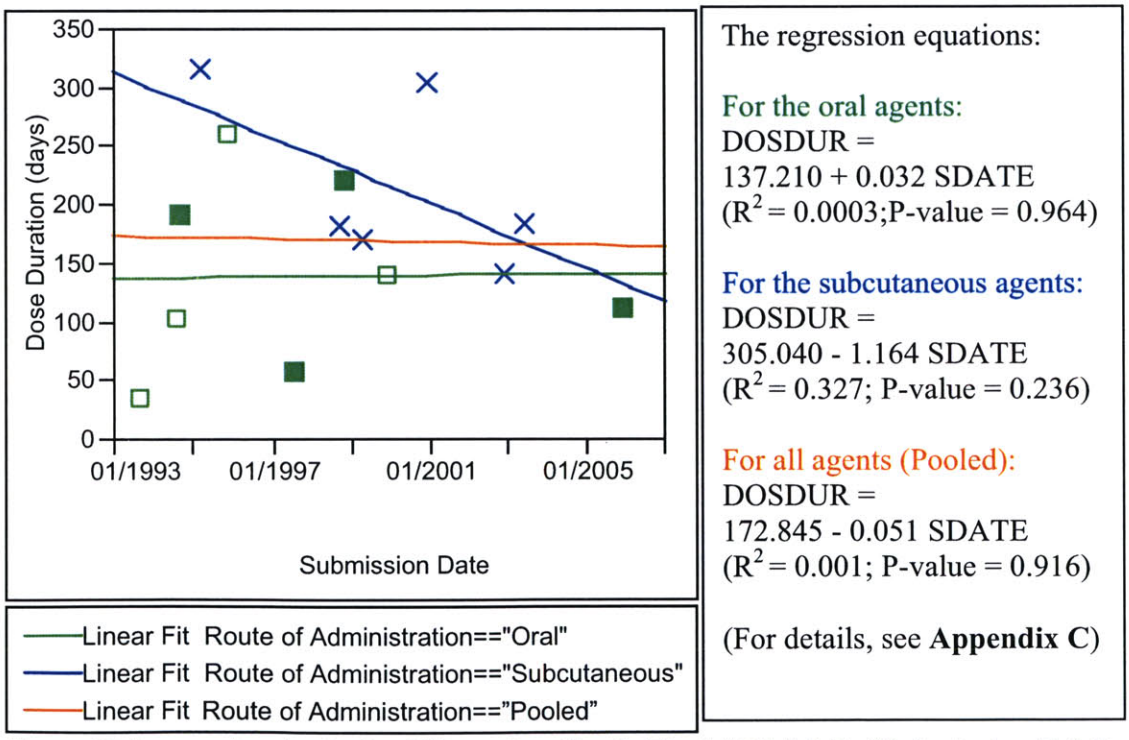


Figure 50 Regression Analysis of "Dose Duration in Pivotal Trials" By "Submission Date"

Appendix C Results from Multiple Regression Analyses

Regression Analysis 1: "Review Time" as an Indicator of Complexity over Time

Linear Fit - Route of Administration=="Oral"

REVTIME = 13.453 - 0.033 SDATE

Summary of Fit

RSquare	0.186044
RSquare Adj	0.050385
Root Mean Square Error	3.549558
Mean of Response	11.875
Observations (or Sum Wgts)	8

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	17.278847	17.2788	1.3714
Error	6	75.596153	12.5994	Prob > F
C. Total	7	92.875000		0.2860

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	13.453219	1.841504	7.31	0.0003
SDATE (Month)	-0.032625	0.027859	-1.17	0.2860

==========

Linear Fit - Route of Administration=="Subcutaneous"

REVTIME = 16.713 + 0.094 SDATE

Summary of Fit

RSquare	0.049501
RSquare Adj	-0.18812
Root Mean Square Error	16.85821
Mean of Response	24
Observations (or Sum Wgts)	6

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	59.2032	59.203	0.2083
Error	4	1136.7968	284.199	Prob > F
C. Total	5	1196.0000		0.6718

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	16.712976	17.38596	0.96	0.3908
SDATE (Month)	0.0938243	0.205568	0.46	0.6718

==========

Linear Fit - Route of Administration=="Pooled"

REVTIME = 14.531 + 0.035 SDATE

Summary of Fit

RSquare	0.021704
RSquare Adj	-0.05355
Root Mean Square Error	11.64418
Mean of Response	16.86667
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	39.1041	39.104	0.2884
Error	13	1762.6292	135.587	Prob > F
C. Total	14	1801.7333		0.6003

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	14.530998	5.287211	2.75	0.0166
SDATE (Month)	0.0354247	0.065963	0.54	0.6003

Regression Analysis 2: "Total Number of Studies for NDA" as an Indicator of Complexity over Time

Linear Fit - Route of Administration=="Oral"

NSTUDIES = 39.470 + 0.021 SDATE

Summary of Fit

RSquare	0.002541
RSquare Adj	-0.1637
Root Mean Square Error	21.93417
Mean of Response	40.5
Observations (or Sum Wgts)	8

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	7.3532	7.353	0.0153
Error	6	2886.6468	481.108	Prob > F
C. Total	7	2894.0000		0.9056

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	39.470451	11.37941	3.47	0.0133
SDATE	0.0212827	0.172151	0.12	0.9056

==========

Linear Fit - Route of Administration=="Subcutaneous"

NSTUDIES = 14.646 + 0.056 SDATE

Summary of Fit

RSquare	0.016382
RSquare Adj	-0.22952
Root Mean Square Error	17.81058
Mean of Response	19
Observations (or Sum Wgts)	6

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	21.1334	21.133	0.0666
Error	4	1268.8666	317.217	Prob > F
C. Total	5	1290.0000		0.8091

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	14.646263	18.36814	0.80	0.4699
SDATE	0.0560567	0.217181	0.26	0.8091

==========

Linear Fit - Route of Administration=="Pooled"

NSTUDIES = 32.799 - 0.004 SDATE

Summary of Fit

RSquare	0.000083
RSquare Adj	-0.07683
Root Mean Square Error	21.65326
Mean of Response	32.53333
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	0.5052	0.505	0.0011
Error	13	6095.2282	468.864	Prob > F
C. Total	14	6095.7333		0.9743

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	32.798808	9.831983	3.34	0.0054
SDATE	-0.004026	0.122664	-0.03	0.9743

Regression Analysis 3: "Total Number of Patients in Safety Database" as an Indicator of Complexity over Time

Linear Fit - Route of Administration=="Oral"

NSAFETY = 6069.688 - 28.331 SDATE

Summary of Fit

RSquare	0.345662
RSquare Adj	0.214795
Root Mean Square Error	2120.989
Mean of Response	4556
Observations (or Sum Wgts)	7

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	11882191	11882191	2.6413
Error	5	22492963	4498592.7	Prob > F
C. Total	6	34375154		0.1650

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	6069.6884	1228.871	4.94	0.0043
SDATE	-28.33107	17.43223	-1.63	0.1650

==========

Linear Fit - Route of Administration=="Subcutaneous"

NSAFETY = 1269 + 17 SDATE

Summary of Fit

RSquare	0.095511
RSquare Adj	-0.20599
Root Mean Square Error	2456.233
Mean of Response	2622.2
Observations (or Sum Wgts)	5

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	1911215	1911215	0.3168
Error	3	18099246	6033082	Prob > F
C. Total	4	20010461		0.6129

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	1269	2643.286	0.48	0.6640
SDATE	17	30.20395	0.56	0.6129

==========

Linear Fit - Route of Administration=="Pooled"

NSAFETY = 4890.805 - 16.492 SDATE

Summary of Fit

RSquare	0.117246
RSquare Adj	0.036996
Root Mean Square Error	2289.404
Mean of Response	3738.923
Observations (or Sum Wgts)	13

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	7657675	7657675	1.4610
Error	11	57655070	5241370	Prob > F
C. Total	12	65312745		0.2521

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	4890.8047	1145.14	4.27	0.0013
SDATE	-16.4917	13.64392	-1.21	0.2521

Regression Analysis 4: "Total Number of Special Studies in NDA" as an Indicator of Complexity over Time

Linear Fit - Route of Administration=="Oral"

NSPECSTD** = 2.411** + 0.030 SDATE**

Summary of Fit

RSquare	0.515089
RSquare Adj	0.43427
Root Mean Square Error	1.527624
Mean of Response	3.875
Observations (or Sum Wgts)	8

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	14.873183	14.8732	6.3734
Error	6	14.001817	2.3336	Prob > F
C. Total	7	28.875000		0.0450

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	2.4107614	0.792529	3.04	0.0227
SDATE	0.0302685	0.01199	2.52	0.0450

==========

Linear Fit - Route of Administration=="Subcutaneous"

NSPECSTD = 1.045 - 0.003 SDATE

Summary of Fit

RSquare	0.01034
RSquare Adj	-0.23707
Root Mean Square Error	1.093544
Mean of Response	0.833333
Observations (or Sum Wgts)	6

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	0.0499769	0.04998	0.0418
Error	4	4.7833565	1.19584	Prob > F
C. Total	5	4.8333333		0.8480

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	1.0450535	1.127778	0.93	0.4066
SDATE	-0.002726	0.013335	-0.20	0.8480

==========

Linear Fit - Route of Administration=="Pooled"

NSPECSTD = 2.345 + 0.002 SDATE

Summary of Fit

RSquare	0.001565
RSquare Adj	-0.07524
Root Mean Square Error	2.280812
Mean of Response	2.466667
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	0.105979	0.10598	0.0204
Error	13	67.627354	5.20210	Prob > F
C. Total	14	67.733333		0.8887

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	2.3450731	1.035636	2.26	0.0413
SDATE	0.0018442	0.012921	0.14	0.8887

Regression Analysis 5: "Number of Special Studies in Elderly Population" as an Indicator of Complexity over Time

Linear Fit - Route of Administration=="Oral"

NSPELD* = 0.360* + 0.016 SDATE*

Summary of Fit

RSquare	0.373032
RSquare Adj	0.268538
Root Mean Square Error	1.066011
Mean of Response	1.125
Observations (or Sum Wgts)	8

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	4.056726	4.05673	3.5699
Error	6	6.818274	1.13638	Prob > F
C. Total	7	10.875000		0.1077

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	0.3602883	0.553045	0.65	0.5389
SDATE	0.015808	0.008367	1.89	0.1077

==========

Linear Fit - Route of Administration=="Subcutaneous"

NSPELD = 0

Summary of Fit

RSquare	.
RSquare Adj	.
Root Mean Square Error	0
Mean of Response	0
Observations (or Sum Wgts)	6

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	0	0	.
Error	4	0	0	Prob > F
C. Total	5	0		.

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	0	0	.	.
SDATE	0	0	.	.

==========

Linear Fit - Route of Administration=="Pooled"

NSPELD = 0.310 + 0.005 SDATE

Summary of Fit

RSquare	0.05954
RSquare Adj	-0.0128
Root Mean Square Error	1.053214
Mean of Response	0.666667
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	0.912952	0.91295	0.8230
Error	13	14.420381	1.10926	Prob > F
C. Total	14	15.333333		0.3808

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	0.3097853	0.478227	0.65	0.5284
SDATE	0.0054128	0.005966	0.91	0.3808

Regression Analysis 6: "Number of Special Studies in Liver Impaired Population" as an Indicator of Complexity over Time

Linear Fit - Route of Administration=="Oral"

NSPECLIV = 0.253 + 0.003 SDATE

Summary of Fit

RSquare	0.05489
RSquare Adj	-0.10263
Root Mean Square Error	0.543458
Mean of Response	0.375
Observations (or Sum Wgts)	8

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	0.1029185	0.102918	0.3485
Error	6	1.7720815	0.295347	Prob > F
C. Total	7	1.8750000		0.5765

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	0.2531974	0.281945	0.90	0.4038
SDATE	0.0025179	0.004265	0.59	0.5765

==========

Linear Fit - Route of Administration=="Subcutaneous"

NSPECLIV = 0

Summary of Fit

RSquare	.
RSquare Adj	.
Root Mean Square Error	0
Mean of Response	0
Observations (or Sum Wgts)	6

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	0	0	.
Error	4	0	0	Prob > F
C. Total	5	0		.

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	0	0	.	.
SDATE	0	0	.	.

==========

Linear Fit - Route of Administration=="Pooled"

NSPECLIV = 0.225 - 0.0003 SDATE

Summary of Fit

RSquare	0.001862
RSquare Adj	-0.07492
Root Mean Square Error	0.429269
Mean of Response	0.2
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	0.0044684	0.004468	0.0242
Error	13	2.3955316	0.184272	Prob > F
C. Total	14	2.4000000		0.8786

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	0.2249676	0.194916	1.15	0.2692
SDATE	-0.000379	0.002432	-0.16	0.8786

Regression Analysis 7: "Number of Special Studies in Renal Impaired Population" as an Indicator of Complexity over Time

Linear Fit - Route of Administration=="Oral"

NSPECREN = 1.487 - 0.007 SDATE

Summary of Fit

RSquare	0.315645
RSquare Adj	0.201585
Root Mean Square Error	0.572643
Mean of Response	1.125
Observations (or Sum Wgts)	8

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	0.9074784	0.907478	2.7674
Error	6	1.9675216	0.327920	Prob > F
C. Total	7	2.8750000		0.1473

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	1.4866829	0.297086	5.00	0.0024
SDATE	-0.007477	0.004494	-1.66	0.1473

==========

Linear Fit - Route of Administration=="Subcutaneous"

NSPECREN = 0

Summary of Fit

RSquare	.
RSquare Adj	.
Root Mean Square Error	0
Mean of Response	0
Observations (or Sum Wgts)	6

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	0	0	.
Error	4	0	0	Prob > F
C. Total	5	0		.

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	0	0	.	.
SDATE	0	0	.	.

==========

Linear Fit - Route of Administration=="Pooled"

NSPECREN** = 1.191** - 0.009 SDATE**

Summary of Fit

RSquare	0.329632
RSquare Adj	0.278065
Root Mean Square Error	0.626025
Mean of Response	0.6
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	2.5051997	2.50520	6.3923
Error	13	5.0948003	0.39191	Prob > F
C. Total	14	7.6000000		0.0252

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	1.1911817	0.284256	4.19	0.0011
SDATE	-0.008966	0.003546	-2.53	0.0252

Regression Analysis 8: "Total Number of Drug-Drug Interaction Studies in NDA" as an Indicator of Complexity over Time

Linear Fit - Route of Administration=="Oral"

NINTERST = 5.769 + 0.007 SDATE

Summary of Fit

RSquare	0.081057
RSquare Adj	-0.0721
Root Mean Square Error	1.290575
Mean of Response	6.125
Observations (or Sum Wgts)	8

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	0.881499	0.88150	0.5292
Error	6	9.993501	1.66558	Prob > F
C. Total	7	10.875000		0.4943

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	5.7685319	0.669548	8.62	0.0001
SDATE	0.0073689	0.010129	0.73	0.4943

==========

Linear Fit - Route of Administration=="Subcutaneous"

NINTERST = 0.284 + 0.009 SDATE

Summary of Fit

RSquare	0.019052
RSquare Adj	-0.22618
Root Mean Square Error	2.712399
Mean of Response	1
Observations (or Sum Wgts)	6

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	0.571570	0.57157	0.0777
Error	4	29.428430	7.35711	Prob > F
C. Total	5	30.000000		0.7943

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	0.2840008	2.797311	0.10	0.9240
SDATE	0.0092189	0.033075	0.28	0.7943

==========

Linear Fit - Route of Administration=="Pooled"

NINTERST = 4.872 - 0.017 SDATE

Summary of Fit

RSquare	0.066923
RSquare Adj	-0.00485
Root Mean Square Error	3.157841
Mean of Response	3.733333
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	9.29789	9.29789	0.9324
Error	13	129.63544	9.97196	Prob > F
C. Total	14	138.93333		0.3519

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	4.8722503	1.433864	3.40	0.0048
SDATE	-0.017274	0.017889	-0.97	0.3519

Regression Analysis 9: "Number of Indications Proposed by Sponsor" as an Indicator of Complexity over Time

Linear Fit - Route of Administration=="Oral"

NINDSP = 2

Summary of Fit

RSquare	.
RSquare Adj	.
Root Mean Square Error	0
Mean of Response	2
Observations (or Sum Wgts)	8

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	0	0	.
Error	6	0	0	Prob > F
C. Total	7	0		.

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	2	0	.	.
SDATE	0	0	.	.

==========

Linear Fit - Route of Administration=="Subcutaneous"

NINDSP** = 0.518** + 0.013 SDATE**

Summary of Fit

RSquare	0.716197
RSquare Adj	0.645247
Root Mean Square Error	0.32623
Mean of Response	1.5
Observations (or Sum Wgts)	6

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	1.0742962	1.07430	10.0943
Error	4	0.4257038	0.10643	Prob > F
C. Total	5	1.5000000		0.0336

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	0.5183882	0.336443	1.54	0.1982
SDATE	0.0126388	0.003978	3.18	0.0336

==========

Linear Fit - Route of Administration=="Pooled"

NINDSP = 1.531 + 0.006 SDATE

Summary of Fit

RSquare	0.166974
RSquare Adj	0.102895
Root Mean Square Error	0.666544
Mean of Response	1.933333
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	1.1576890	1.15769	2.6058
Error	13	5.7756443	0.44428	Prob > F
C. Total	14	6.9333333		0.1305

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	1.5314539	0.302654	5.06	0.0002
SDATE	0.0060952	0.003776	1.61	0.1305

Regression Analysis 10: "Number of Indications Approved by FDA" as an Indicator of Complexity over Time

Linear Fit - Route of Administration=="Oral"

NINDFDA = 2 + 0 SDATE

Summary of Fit

RSquare	.
RSquare Adj	.
Root Mean Square Error	0
Mean of Response	2
Observations (or Sum Wgts)	8

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	0	0	.
Error	6	0	0	Prob > F
C. Total	7	0		.

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	2	0	.	.
SDATE	0	0	.	.

==========

Linear Fit Route of Administration=="Subcutaneous"

NINDFDA** = 0.518** + 0.013 SDATE**

Summary of Fit

RSquare	0.716197
RSquare Adj	0.645247
Root Mean Square Error	0.32623
Mean of Response	1.5
Observations (or Sum Wgts)	6

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	1.0742962	1.07430	10.0943
Error	4	0.4257038	0.10643	Prob > F
C. Total	5	1.5000000		0.0336

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	0.5183882	0.336443	1.54	0.1982
SDATE	0.0126388	0.003978	3.18	0.0336

==========

Linear Fit - Route of Administration=="Pooled"

NINDFDA = 1.531 + 0.006 SDATE

Summary of Fit

RSquare	0.166974
RSquare Adj	0.102895
Root Mean Square Error	0.666544
Mean of Response	1.933333
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	1.1576890	1.15769	2.6058
Error	13	5.7756443	0.44428	Prob > F
C. Total	14	6.9333333		0.1305

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	1.5314539	0.302654	5.06	0.0002
SDATE	0.0060952	0.003776	1.61	0.1305

Regression Analysis 11: "Number of Pivotal Trials Submitted by Sponsor" as an Indicator of Complexity over Time

Linear Fit - Route of Administration=="Oral"

NPIVSP = 5.010 + 0.018 SDATE

Summary of Fit

RSquare	0.193263
RSquare Adj	0.058806
Root Mean Square Error	1.900924
Mean of Response	5.875
Observations (or Sum Wgts)	8

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	5.193932	5.19393	1.4374
Error	6	21.681068	3.61351	Prob > F
C. Total	7	26.875000		0.2758

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	5.0097173	0.986196	5.08	0.0023
SDATE	0.017887	0.014919	1.20	0.2758

==========

Linear Fit - Route of Administration=="Subcutaneous"

NPIVSP = 5.253 + 0.016 SDATE

Summary of Fit

RSquare	0.035037
RSquare Adj	-0.2062
Root Mean Square Error	3.455635
Mean of Response	6.5
Observations (or Sum Wgts)	6

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	1.734338	1.7343	0.1452
Error	4	47.765662	11.9414	Prob > F
C. Total	5	49.500000		0.7225

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	5.2527756	3.563815	1.47	0.2145
SDATE	0.0160587	0.042138	0.38	0.7225

==========

Linear Fit - Route of Administration=="Pooled"

NPIVSP = 5.260 + 0.012 SDATE

Summary of Fit

RSquare	0.059038
RSquare Adj	-0.01334
Root Mean Square Error	2.390257
Mean of Response	6.066667
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	4.660060	4.66006	0.8156
Error	13	74.273274	5.71333	Prob > F
C. Total	14	78.933333		0.3829

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	5.2603688	1.085332	4.85	0.0003
SDATE	0.012229	0.013541	0.90	0.3829

Regression Analysis 12: "Number of Pivotal Trials for FDA to Approve NDA" as an Indicator of Complexity over Time

Linear Fit - Route of Administration=="Oral"

NPIVFDA* = 4.377* + 0.028 SDATE*

Summary of Fit

RSquare	0.415143
RSquare Adj	0.317667
Root Mean Square Error	1.752284
Mean of Response	5.75
Observations (or Sum Wgts)	8

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	13.077011	13.0770	4.2589
Error	6	18.422989	3.0705	Prob > F
C. Total	7	31.500000		0.0846

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	4.3770203	0.909082	4.81	0.0030
SDATE	0.028382	0.013753	2.06	0.0846

==========

Linear Fit - Route of Administration=="Subcutaneous"

NPIVFDA = 7.593 - 0.044 SDATE

Summary of Fit

RSquare	0.487696
RSquare Adj	0.35962
Root Mean Square Error	1.853836
Mean of Response	4.166667
Observations (or Sum Wgts)	6

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	13.086505	13.0865	3.8079
Error	4	13.746828	3.4367	Prob > F
C. Total	5	26.833333		0.1228

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	7.5926844	1.91187	3.97	0.0165
SDATE	-0.044112	0.022606	-1.95	0.1228

==========

Linear Fit - Route of Administration=="Pooled"

NPIVFDA = 5.067 + 0.000002 SDATE

Summary of Fit

RSquare	2.131e-9
RSquare Adj	-0.07692
Root Mean Square Error	2.269079
Mean of Response	5.066667
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	1.42629e-7	1.426e-7	0.0000
Error	13	66.933333	5.14872	Prob > F
C. Total	14	66.933333		0.9999

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	5.0665256	1.030309	4.92	0.0003
SDATE	0.0000021	0.012854	0.00	0.9999

Regression Analysis 13: "Number of Patients in Pivotal Trials Submitted by Sponsor" as an Indicator of Complexity over Time

Linear Fit - Route of Administration=="Oral"

NPATSP = 1796.902 + 13.090 SDATE

Summary of Fit

RSquare	0.293085
RSquare Adj	0.175266
Root Mean Square Error	1057.446
Mean of Response	2430.125
Observations (or Sum Wgts)	8

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	2781596.5	2781597	2.4876
Error	6	6709148.3	1118191	Prob > F
C. Total	7	9490744.9		0.1658

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	1796.9016	548.601	3.28	0.0169
SDATE	13.089889	8.299405	1.58	0.1658

==========

Linear Fit - Route of Administration=="Subcutaneous"

NPATSP = 1806.760 + 20.203 SDATE

Summary of Fit

RSquare	0.372524
RSquare Adj	0.215655
Root Mean Square Error	1075.12
Mean of Response	3375.833
Observations (or Sum Wgts)	6

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	2744929.6	2744930	2.3747
Error	4	4623529.3	1155882	Prob > F
C. Total	5	7368458.8		0.1982

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	1806.7596	1108.777	1.63	0.1785
SDATE	20.202667	13.10992	1.54	0.1982

==========

Linear Fit - Route of Administration=="Pooled"

NPATSP = 2021.892 + 10.795 SDATE

Summary of Fit

RSquare	0.164319
RSquare Adj	0.100036
Root Mean Square Error	1191.92
Mean of Response	2733.667
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	3631493	3631493	2.5562
Error	13	18468755	1420673	Prob > F
C. Total	14	22100247		0.1339

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	2021.8922	541.2089	3.74	0.0025
SDATE	10.795366	6.752147	1.60	0.1339

Regression Analysis 14: "Number of Patients in Pivotal Trials for FDA to Approve NDA" as an Indicator of Complexity over Time

Linear Fit - Route of Administration=="Oral"

NPATFDA*** = 1011.196*** + 20.425 SDATE***

Summary of Fit

RSquare	0.963094
RSquare Adj	0.956943
Root Mean Square Error	207.9746
Mean of Response	1999.25
Observations (or Sum Wgts)	8

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	6772390.8	6772391	156.5746
Error	6	259520.7	43253	Prob > F
C. Total	7	7031911.5		<.0001

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	1011.1955	107.8969	9.37	<.0001
SDATE	20.424899	1.632297	12.51	<.0001

==========

Linear Fit - Route of Administration=="Subcutaneous"

NPATFDA = 2878.582 - 8.173 SDATE

Summary of Fit

RSquare	0.116986
RSquare Adj	-0.10377
Root Mean Square Error	920.684
Mean of Response	2243.833
Observations (or Sum Wgts)	6

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	449208.7	449209	0.5299
Error	4	3390636.2	847659	Prob > F
C. Total	5	3839844.8		0.5070

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	2878.582	949.5062	3.03	0.0387
SDATE	-8.17273	11.22674	-0.73	0.5070

==========

Linear Fit - Route of Administration=="Pooled"

NPATFDA = 1531.686 + 7.877 SDATE

Summary of Fit

RSquare	0.165737
RSquare Adj	0.101563
Root Mean Square Error	865.2802
Mean of Response	2051.067
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	1933626	1933626	2.5826
Error	13	9733227	748710	Prob > F
C. Total	14	11666853		0.1320

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	1531.6857	392.8932	3.90	0.0018
SDATE	7.8773657	4.901754	1.61	0.1320

Regression Analysis 15: "Patients per Pivotal Trials Submitted by Sponsor" as an Indicator of Complexity over Time

Linear Fit - Route of Administration=="Oral"

AVNPATSP = 375.714 + 0.791 SDATE

Summary of Fit

RSquare	0.104838
RSquare Adj	-0.04436
Root Mean Square Error	120.1726
Mean of Response	413.9606
Observations (or Sum Wgts)	8

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	10147.932	10147.9	0.7027
Error	6	86648.766	14441.5	Prob > F
C. Total	7	96796.698		0.4340

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	375.71345	62.34536	6.03	0.0009
SDATE	0.790638	0.94318	0.84	0.4340

==========

Linear Fit - Route of Administration=="Subcutaneous"

AVNPATSP = 430.830 + 1.638 SDATE

Summary of Fit

RSquare	0.210602
RSquare Adj	0.013252
Root Mean Square Error	130.0192
Mean of Response	558.0333
Observations (or Sum Wgts)	6

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	18040.174	18040.2	1.0672
Error	4	67619.966	16905.0	Prob > F
C. Total	5	85660.141		0.3600

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	430.83011	134.0895	3.21	0.0325
SDATE	1.6378098	1.585443	1.03	0.3600

==========

Linear Fit - Route of Administration=="Pooled"

AVNPATSP = 412.079 + 0.749 SDATE

Summary of Fit

RSquare	0.058951
RSquare Adj	-0.01344
Root Mean Square Error	146.4608
Mean of Response	461.4456
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	17468.94	17468.9	0.8144
Error	13	278860.04	21450.8	Prob > F
C. Total	14	296328.97		0.3832

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	412.07906	66.5027	6.20	<.0001
SDATE	0.7487348	0.829691	0.90	0.3832

Regression Analysis 16: "Patients per Pivotal Trials for FDA to Approve NDA" as an Indicator of Complexity over Time

Linear Fit - Route of Administration=="Oral"

AVNPATFDA = 304.756 + 1.181 SDATE

Summary of Fit

RSquare	0.201088
RSquare Adj	0.067936
Root Mean Square Error	122.4485
Mean of Response	361.8882
Observations (or Sum Wgts)	8

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	22643.60	22643.6	1.5102
Error	6	89961.86	14993.6	Prob > F
C. Total	7	112605.46		0.2651

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	304.75578	63.52609	4.80	0.0030
SDATE	1.1810319	0.961042	1.23	0.2651

==========

Linear Fit - Route of Administration=="Subcutaneous"

AVNPATFDA = 400.352 + 2.305 SDATE

Summary of Fit

RSquare	0.252084
RSquare Adj	0.065105
Root Mean Square Error	162.7999
Mean of Response	579.375
Observations (or Sum Wgts)	6

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	35732.36	35732.4	1.3482
Error	4	106015.25	26503.8	Prob > F
C. Total	5	141747.61		0.3102

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	400.3521	167.8964	2.38	0.0756
SDATE	2.3050159	1.985168	1.16	0.3102

==========

Linear Fit - Route of Administration=="Pooled"

AVNPATFDA = 351.284 + 1.379 SDATE

Summary of Fit

RSquare	0.131286
RSquare Adj	0.064462
Root Mean Square Error	173.6789
Mean of Response	442.2104
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	59262.49	59262.5	1.9647
Error	13	392136.52	30164.3	Prob > F
C. Total	14	451399.00		0.1844

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	351.28402	78.86145	4.45	0.0006
SDATE	1.3790649	0.983879	1.40	0.1844

Regression Analysis 17: "Average Number of Patients to Support Each Indication Proposed by Sponsor" as an Indicator of Complexity over Time

Linear Fit - Route of Administration=="Oral"

AVNPINDSP = 898.451 + 6.545 SDATE

Summary of Fit

RSquare	0.293085
RSquare Adj	0.175266
Root Mean Square Error	528.7228
Mean of Response	1215.063
Observations (or Sum Wgts)	8

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	695399.1	695399	2.4876
Error	6	1677287.1	279548	Prob > F
C. Total	7	2372686.2		0.1658

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	898.45081	274.3005	3.28	0.0169
SDATE	6.5449446	4.149703	1.58	0.1658

==========

Linear Fit - Route of Administration=="Subcutaneous"

AVNPINDSP = 2879.571 - 6.954 SDATE

Summary of Fit

RSquare	0.199499
RSquare Adj	-0.00063
Root Mean Square Error	571.155
Mean of Response	2339.5
Observations (or Sum Wgts)	6

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	325197.1	325197	0.9969
Error	4	1304871.9	326218	Prob > F
C. Total	5	1630069.0		0.3746

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	2879.5713	589.0351	4.89	0.0081
SDATE	-6.953707	6.964614	-1.00	0.3746

==========

Linear Fit - Route of Administration=="Pooled"

AVNPINDSP = 1443.915 + 2.453 SDATE

Summary of Fit

RSquare	0.018585
RSquare Adj	-0.05691
Root Mean Square Error	872.7164
Mean of Response	1605.65
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	187504	187504	0.2462
Error	13	9901242	761634	Prob > F
C. Total	14	10088745		0.6281

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	1443.9147	396.2698	3.64	0.0030
SDATE	2.4530122	4.94388	0.50	0.6281

Regression Analysis 18: "Average Number of Patients to Support Each Indication Approved by FDA" as an Indicator of Complexity over Time

Linear Fit - Route of Administration=="Oral"

AVNPINDFDA*** = 505.598*** + 10.212 SDATE***

Summary of Fit

RSquare	0.963094
RSquare Adj	0.956943
Root Mean Square Error	103.9873
Mean of Response	999.625
Observations (or Sum Wgts)	8

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	1693097.7	1693098	156.5746
Error	6	64880.2	10813	Prob > F
C. Total	7	1757977.9		<.0001

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	505.59777	53.94844	9.37	<.0001
SDATE	10.212449	0.816149	12.51	<.0001

==========

Linear Fit - Route of Administration=="Subcutaneous"

AVNPINDFDA*** = 3264.087*** - 20.360 SDATE***

Summary of Fit

RSquare	0.846825
RSquare Adj	0.808531
Root Mean Square Error	355.0513
Mean of Response	1682.833
Observations (or Sum Wgts)	6

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	2787709.1	2787709	22.1139
Error	4	504245.7	126061	Prob > F
C. Total	5	3291954.8		0.0093

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	3264.0868	366.1663	8.91	0.0009
SDATE	-20.35949	4.329465	-4.70	0.0093

==========

Linear Fit - Route of Administration=="Pooled"

AVNPINDFDA = 1164.924 + 0.958 SDATE

Summary of Fit

RSquare	0.003803
RSquare Adj	-0.07283
Root Mean Square Error	759.1073
Mean of Response	1228.083
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	28594.4	28594	0.0496
Error	13	7491170.1	576244	Prob > F
C. Total	14	7519764.5		0.8272

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	1164.9236	344.6839	3.38	0.0049
SDATE	0.9579329	4.300292	0.22	0.8272

Regression Analysis 19: "Average Number of Pivotal Trials to Support Each Indication Proposed by Sponsor" as an Indicator of Complexity over Time

Linear Fit - Route of Administration=="Oral"

AVNTINDSP = 2.505 + 0.009 SDATE

Summary of Fit

RSquare	0.193263
RSquare Adj	0.058806
Root Mean Square Error	0.950462
Mean of Response	2.9375
Observations (or Sum Wgts)	8

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	1.2984830	1.29848	1.4374
Error	6	5.4202670	0.90338	Prob > F
C. Total	7	6.7187500		0.2758

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	2.5048587	0.493098	5.08	0.0023
SDATE	0.0089435	0.00746	1.20	0.2758

==========

Linear Fit - Route of Administration=="Subcutaneous"

AVNTINDSP = 7.238 - 0.034 SDATE

Summary of Fit

RSquare	0.33843
RSquare Adj	0.173037
Root Mean Square Error	1.959206
Mean of Response	4.583333
Observations (or Sum Wgts)	6

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	7.854386	7.85439	2.0462
Error	4	15.353948	3.83849	Prob > F
C. Total	5	23.208333		0.2258

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	7.2375347	2.020539	3.58	0.0231
SDATE	-0.034174	0.02389	-1.43	0.2258

==========

Linear Fit - Route of Administration=="Pooled"

AVNTINDSP = 3.667 - 0.003 SDATE

Summary of Fit

RSquare	0.005453
RSquare Adj	-0.07105
Root Mean Square Error	1.846313
Mean of Response	3.483333
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	0.242993	0.24299	0.0713
Error	13	44.315340	3.40887	Prob > F
C. Total	14	44.558333		0.7937

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	3.6674517	0.838346	4.37	0.0008
SDATE	-0.002792	0.010459	-0.27	0.7937

Regression Analysis 20: "Average Number of Pivotal Trials to Support Each Indication Approved by FDA" as an Indicator of Complexity over Time

Linear Fit - Route of Administration=="Oral"

AVNTINDFDA* = 2.189* + 0.014 SDATE*

Summary of Fit

RSquare	0.415143
RSquare Adj	0.317667
Root Mean Square Error	0.876142
Mean of Response	2.875
Observations (or Sum Wgts)	8

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	3.2692528	3.26925	4.2589
Error	6	4.6057472	0.76762	Prob > F
C. Total	7	7.8750000		0.0846

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	2.1885101	0.454541	4.81	0.0030
SDATE	0.014191	0.006876	2.06	0.0846

==========

Linear Fit - Route of Administration=="Subcutaneous"

AVNTINDFDA*** = 8.129*** - 0.063 SDATE***

Summary of Fit

RSquare	0.859672
RSquare Adj	0.82459
Root Mean Square Error	1.040749
Mean of Response	3.25
Observations (or Sum Wgts)	6

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	26.542365	26.5424	24.5046
Error	4	4.332635	1.0832	Prob > F
C. Total	5	30.875000		0.0078

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	8.1291881	1.07333	7.57	0.0016
SDATE	-0.062822	0.012691	-4.95	0.0078

==========

Linear Fit - Route of Administration=="Pooled"

AVNTINDFDA = 3.508 - 0.009 SDATE

Summary of Fit

RSquare	0.059431
RSquare Adj	-0.01292
Root Mean Square Error	1.747522
Mean of Response	2.916667
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	2.508488	2.50849	0.8214
Error	13	39.699845	3.05383	Prob > F
C. Total	14	42.208333		0.3813

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	3.5082363	0.793488	4.42	0.0007
SDATE	-0.008972	0.0099	-0.91	0.3813

Regression Analysis 21: "Number of Arms in Pivotal Trials" as an Indicator of Complexity over Time

Linear Fit - Route of Administration=="Oral"

NARM = 3.287 - 0.003 SDATE

Summary of Fit

RSquare	0.063349
RSquare Adj	-0.09276
Root Mean Square Error	0.669934
Mean of Response	3.125
Observations (or Sum Wgts)	8

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	0.1821278	0.182128	0.4058
Error	6	2.6928722	0.448812	Prob > F
C. Total	7	2.8750000		0.5476

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	3.287031	0.347561	9.46	<.0001
SDATE	-0.003349	0.005258	-0.64	0.5476

==========

Linear Fit - Route of Administration=="Subcutaneous"

NARM = 1.865 + 0.008 SDATE

Summary of Fit

RSquare	0.128512
RSquare Adj	-0.08936
Root Mean Square Error	0.873242
Mean of Response	2.5
Observations (or Sum Wgts)	6

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	0.4497918	0.449792	0.5899
Error	4	3.0502082	0.762552	Prob > F
C. Total	5	3.5000000		0.4853

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	1.8648394	0.900579	2.07	0.1071
SDATE	0.008178	0.010648	0.77	0.4853

==========

Linear Fit - Route of Administration=="Pooled"

NARM = 3.059 - 0.004 SDATE

Summary of Fit

RSquare	0.05705
RSquare Adj	-0.01549
Root Mean Square Error	0.780571
Mean of Response	2.8
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	0.4792167	0.479217	0.7865
Error	13	7.9207833	0.609291	Prob > F
C. Total	14	8.4000000		0.3913

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	3.0585626	0.35443	8.63	<.0001
SDATE	-0.003922	0.004422	-0.89	0.3913

Regression Analysis 22: "Length of Follow-up Period in Pivotal Trials" as an Indicator of Complexity over Time

Linear Fit - Route of Administration=="Oral"

FOLTM* = 51.753* + 1.966 SDATE*

Summary of Fit

RSquare	0.40344
RSquare Adj	0.304014
Root Mean Square Error	124.3748
Mean of Response	146.875
Observations (or Sum Wgts)	8

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	62768.39	62768.4	4.0577
Error	6	92814.49	15469.1	Prob > F
C. Total	7	155582.88		0.0906

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	51.753132	64.52542	0.80	0.4531
SDATE	1.9663435	0.97616	2.01	0.0906

==========

Linear Fit - Route of Administration=="Subcutaneous"

FOLTM = -54.439 + 1.091 SDATE

Summary of Fit

RSquare	0.290266
RSquare Adj	0.112832
Root Mean Square Error	69.98399
Mean of Response	30.33333
Observations (or Sum Wgts)	6

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	8012.300	8012.30	1.6359
Error	4	19591.034	4897.76	Prob > F
C. Total	5	27603.333		0.2700

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	-54.43943	72.17485	-0.75	0.4927
SDATE	1.0914948	0.853379	1.28	0.2700

==========

Linear Fit - Route of Administration=="Pooled"

FOLTM = 46.527 + 0.666 SDATE

Summary of Fit

RSquare	0.058021
RSquare Adj	-0.01444
Root Mean Square Error	131.4658
Mean of Response	90.46667
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	13839.32	13839.3	0.8007
Error	13	224682.41	17283.3	Prob > F
C. Total	14	238521.73		0.3871

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	46.526957	59.694	0.78	0.4497
SDATE	0.6664263	0.744745	0.89	0.3871

Regression Analysis 23: "Number of Primary Endpoints in Pivotal Trials" as an Indicator of Complexity over Time

Linear Fit - Route of Administration=="Oral"

NPEND = 1.725 - 0.005 SDATE

Summary of Fit

RSquare	0.058522
RSquare Adj	-0.09839
Root Mean Square Error	0.970298
Mean of Response	1.5
Observations (or Sum Wgts)	8

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	0.3511330	0.351133	0.3730
Error	6	5.6488670	0.941478	Prob > F
C. Total	7	6.0000000		0.5638

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	1.7249809	0.503389	3.43	0.0140
SDATE	-0.004651	0.007615	-0.61	0.5638

==========

Linear Fit - Route of Administration=="Subcutaneous"

NPEND* = 3.533* - 0.026 SDATE*

Summary of Fit

RSquare	0.614116
RSquare Adj	0.517645
Root Mean Square Error	0.850607
Mean of Response	1.5
Observations (or Sum Wgts)	6

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	4.6058684	4.60587	6.3658
Error	4	2.8941316	0.72353	Prob > F
C. Total	5	7.5000000		0.0651

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	3.5325139	0.877236	4.03	0.0158
SDATE	-0.02617	0.010372	-2.52	0.0651

==========

Linear Fit - Route of Administration=="Pooled"

NPEND* = 2.073* - 0.009 SDATE*

Summary of Fit

RSquare	0.191851
RSquare Adj	0.129686
Root Mean Square Error	0.923979
Mean of Response	1.466667
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	2.634753	2.63475	3.0861
Error	13	11.098581	0.85374	Prob > F
C. Total	14	13.733333		0.1025

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	2.0729418	0.419546	4.94	0.0003
SDATE	-0.009195	0.005234	-1.76	0.1025

Regression Analysis 24: "Number of Secondary Endpoints in Pivotal Trials" as an Indicator of Complexity over Time

Linear Fit - Route of Administration=="Oral"

NSEND = 4.674 - 0.022 SDATE

Summary of Fit

RSquare	0.141569
RSquare Adj	-0.0015
Root Mean Square Error	2.776328
Mean of Response	3.625
Observations (or Sum Wgts)	8

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	7.627015	7.62702	0.9895
Error	6	46.247985	7.70800	Prob > F
C. Total	7	53.875000		0.3583

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	4.6735453	1.440354	3.24	0.0176
SDATE	-0.021675	0.02179	-0.99	0.3583

==========

Linear Fit - Route of Administration=="Subcutaneous"

NSEND = 4.369 - 0.028 SDATE

Summary of Fit

RSquare	0.498969
RSquare Adj	0.373711
Root Mean Square Error	1.164886
Mean of Response	2.166667
Observations (or Sum Wgts)	6

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	5.405498	5.40550	3.9835
Error	4	5.427835	1.35696	Prob > F
C. Total	5	10.833333		0.1167

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	4.3685567	1.201353	3.64	0.0220
SDATE	-0.028351	0.014205	-2.00	0.1167

==========

Linear Fit - Route of Administration=="Pooled"

NSEND = 4.295 - 0.018 SDATE

Summary of Fit

RSquare	0.127655
RSquare Adj	0.060551
Root Mean Square Error	2.254323
Mean of Response	3.133333
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	9.667702	9.66770	1.9024
Error	13	66.065631	5.08197	Prob > F
C. Total	14	75.733333		0.1911

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	4.2946788	1.023609	4.20	0.0010
SDATE	-0.017614	0.012771	-1.38	0.1911

Regression Analysis 24: "Number of Secondary Endpoints in Pivotal Trials" as an Indicator of Complexity over Time

Linear Fit Route of Administration=="Oral"

DOSDUR = 137.21015 + 0.0318316 SDATE

Summary of Fit

RSquare	0.000378
RSquare Adj	-0.16623
Root Mean Square Error	85.19492
Mean of Response	138.75
Observations (or Sum Wgts)	8

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	16.449	16.45	0.0023
Error	6	43549.051	7258.18	Prob > F
C. Total	7	43565.500		0.9636

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	137.21015	44.19898	3.10	0.0210
SDATE	0.0318316	0.668656	0.05	0.9636

==========

Linear Fit Route of Administration=="Subcutaneous"

DOSDUR = 305.04039 - 1.1636102 SDATE

Summary of Fit

RSquare	0.326482
RSquare Adj	0.158103
Root Mean Square Error	68.52975
Mean of Response	214.6667
Observations (or Sum Wgts)	6

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	9106.026	9106.03	1.9390
Error	4	18785.308	4696.33	Prob > F
C. Total	5	27891.333		0.2362

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	305.04039	70.67509	4.32	0.0125
SDATE	-1.16361	0.835646	-1.39	0.2362

==========

Linear Fit=="Pooled"

DOSDUR = 172.84477 - 0.0512351 SDATE

Summary of Fit

RSquare	0.00089
RSquare Adj	-0.07596
Root Mean Square Error	84.04666
Mean of Response	169.4667
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	81.799	81.80	0.0116
Error	13	91829.935	7063.84	Prob > F
C. Total	14	91911.733		0.9159

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	172.84477	38.16263	4.53	0.0006
SDATE	-0.051235	0.476119	-0.11	0.9159

Appendix D Prescription Drug User Fees Act

Prescription Drug User Fees Act (PDUFA)

The Prescription Drug User Fees Act (The Act), PDUFA, was first passed in 1992 (PDUFA I) for five years by the Congress as to supplement Congressional appropriations for strengthening the functions and capabilities of the CDER (Center for Drug Evaluation and Research) offices in FDA, who are responsible for drug review; in other words, expediting CDER's drug approval process. The Act was renewed and revised in 1997 (PDUFA II, Title I of the Food and Drug and Administration Modernization Act) for another five years and 2002 (PDUFA III, Title V of the Public Health Security and Bioterrorism Preparedness and Response Act) for another five years, and is under consideration for reauthorization in 2007.

Under this Act, FDA can collect three types of user fees-application fees, establishment fees, and product fees from the applicant drug company. The application fee is paid to FDA upon submission of a New Drug Application. The product fees are paid annually for products that have previously received marketing approval. The establishment fees are charged annually on approved manufacturing facilities, yet multiple products manufactured in the same facility can share on establishment fee.

Congressional Findings

The congressional findings that introduced PDUFA include: ...the *prompt approval* of safe and effective new drugs is critical to the improvement of the public health...the user fee revenue were to *supplement the FDA's review activity resources*...the fees authorized...will be dedicated toward expediting the review of

human drug applications as *set forth in the goals identified in the [September 14 Letters and [September 21 Letter]...*

Evaluation of the Implementation of PDUFA

According to Philipson et al.'s findings,[2] even though there was a decline in review times of 2% a year prior to PDUFA, passage and implementation of PDUFA I and II accelerated the decline by 6-7% and 3-4% a year respectively.

PDUFA as a Solution to Correct Market Failure of Externalities

The goal of PDUFA is to correct the market failure of external costs including the delay in access of new treatment for patients leading to loss in social welfare and delay in product launch for the industry leading to higher R&D cost.

According Philipson's same study mentioned above, the researchers have found that PDUFA raised the combined social surplus between $18 to $31 billions, which consisted of the producer surplus and the consumer surplus. PDUFA raised the private surplus of producers, as well as innovative returns as consequence by about $11 to $13 billion. PDUFA raised the consumer surplus between $5 to $19 billion-dependent on the market power of the producers while having patent protection. In this research, the authors converted these economic gains into equivalent health benefits, the more rapid access of drugs on the market enabled by PDUFA saved equivalent of 180 to 310 thousand life-years.

1. Economic Rationale-Internalizing Externalities

The economic rationale behind the user fee mechanism suggests that those who benefit from a government service should also pay for it. Hence, a well-defined and

[2] Tomas Philipson, Ernst R. Berndt, Adrian H. B. Gottschalk, and Matthew W. Strobeck, Assessing the Safety and Efficacy of the FDA: the Case of the Prescription Drug User Fee Acts

identifiable group of beneficiaries, who require the service, should exist. In this case, we can consider the industry and the consumers both as the beneficiaries. Collection of user fees can also be considered as internalizing the external cost of acquiring more resources to facilitate the drug review by asking the beneficiaries to pay for the cost. In the PDUFA's case, due to the strong market power the industry has, the industry captures all the welfare gains before the expiration of the patent-which might be at the expense of product liability in the worst scenario.

2. Increase on the Producers' Surplus

PDUFA has increased the incentives in R&D innovation for the pharmaceutical industry. On average, it takes 14 years for a drug from discovery to product launch. From the moment the drug company files the patent for the new molecular entity (NME), the patent expiration typically takes place about 12 years after product launch, a.k.a. effective patent life. Another factor affecting the innovation return is that the Hatch-Waxman Act, which gives a drug 14 years as a maximum amount of time to enjoy market exclusivity (with possible 6-month extensions for sponsors providing efficacy in the pediatric population). Thus, given the fact that PDUFA decreased the drug approval time, PDUFA has effectively increased the innovative returns for the industry.

3. Increase on the Consumers' Surplus

On the social welfare side, through PDUFA, it may be possible to internalize the external cost of expediting the drug review process by collecting the user fees. However, due to the market power of the producers, no evidence has shown any decrease in the drug price though the profitability for the drug company gets improved after PDUFA. The consumers still benefit from the PDUFA with a faster access to drugs.

Appendix E System Dynamics Models for Diabetes Management

(1) **Figure 1** shows the basic stocks and flows structure in the diabetes management.

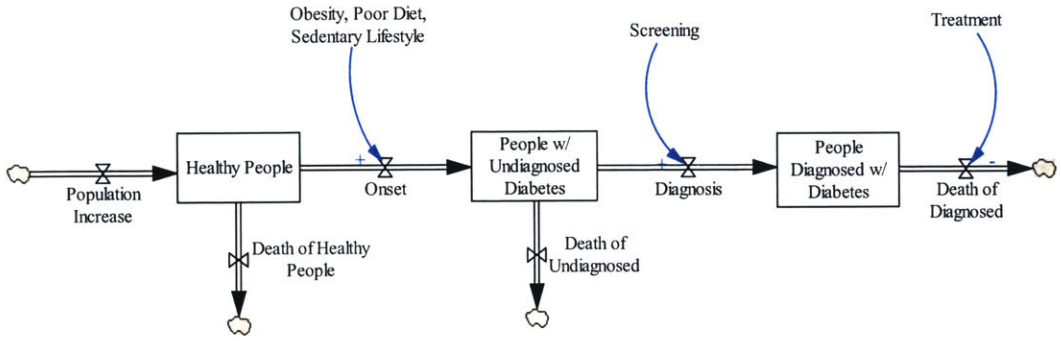


Figure 1 Stocks and Flows Structure in Diabetes Management

(2) **Figure 2** shows policy of the Center for Disease Control (CDC) on the diabetes management, National Diabetes Prevention and Control Program (NDPCP), which focuses on the downstream management of the system: (a) improving quality, availability and accessibility of treatment; and (b) earlier and broader screening.

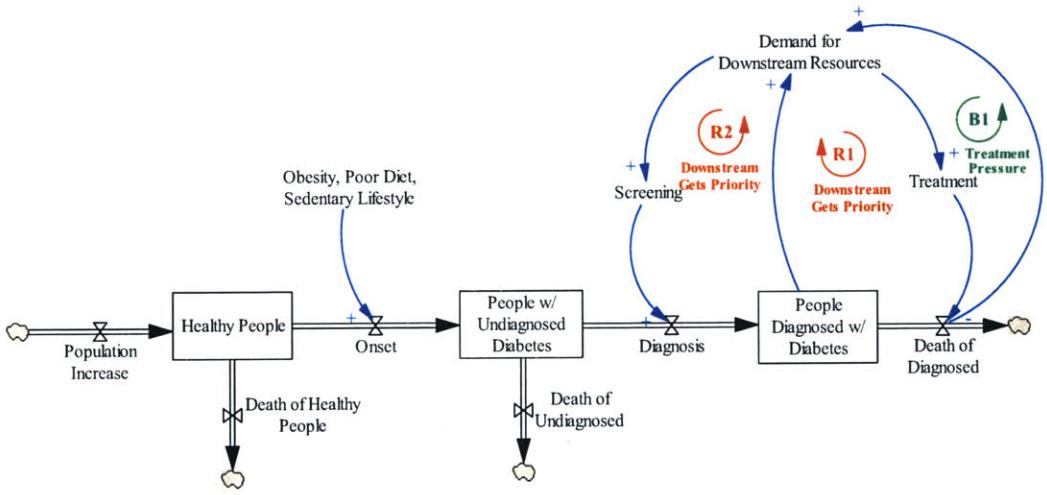


Figure 2 CDC's National Diabetes Prevention and Control Program (NDPCP)

(3) **Figure 3** demonstrates the side effect from the policy of NDPCP. Because the policy focuses on the downstream management (e.g. screening and treatment), the downstream management competes for the resources with the upstream management (e.g. prevention by changing people's lifestyle). This results in more prevalence of diabetes.

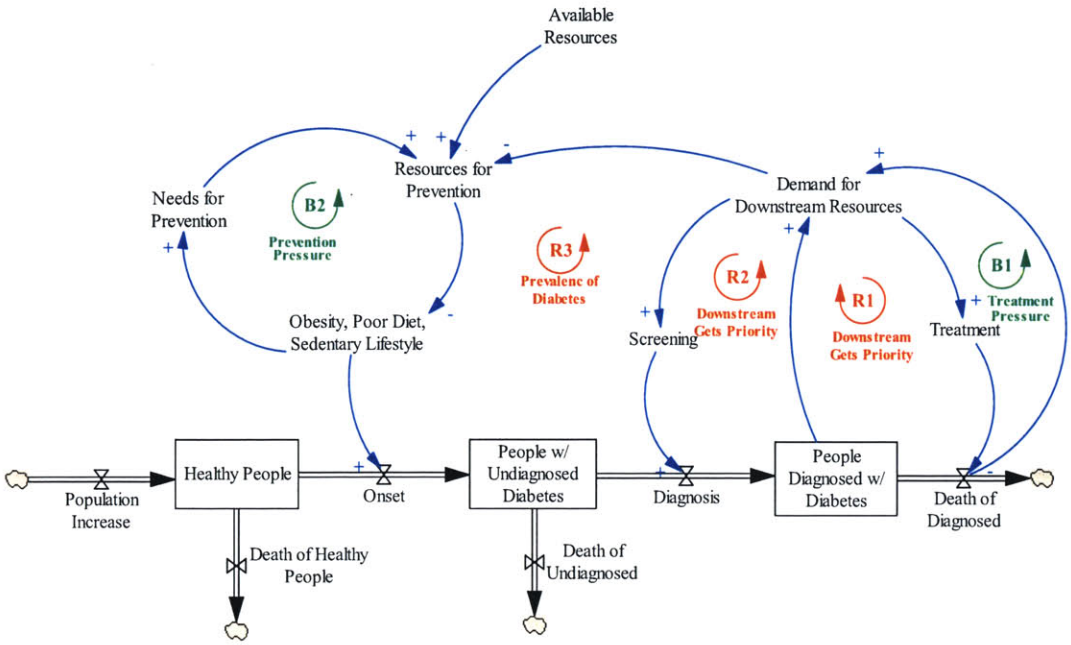


Figure 3 Side Effect of NDPCP

(Source: Based on Sterman J., *Dynamics of the Diabetes Epidemic*; Jones A.P. et al., *Understanding Diabetes Population Dynamics through Simulation Modeling and Experimentation*; Homer J.B. et al., *System Dynamics Modeling for Public Health: Background and Opportunities*)