General Hospital and Personal Use Medical Devices Panel

Insulin Infusion Pumps

Panel Information

March 5, 2010

Table of Contents

PART 1: Diabetes Mellitus

Overview

The purpose of this panel meeting is to consider problems that occur with the use of insulin infusion pumps, and recommend actions that may help mitigate the risks associated with these devices in recall situations. Post-market issues and concerns with the use of insulin infusion pumps will be discussed in this meeting, along with an overview of the regulatory actions available to FDA. The Center for Devices and Radiological Health (CDRH) hopes this panel will provide insight into the relative risks and benefits of various approaches to post market safety issues.

Diabetes mellitus, commonly referred to as "diabetes", is a group of diseases characterized by high levels of blood glucose. Diabetes occurs when 1) the pancreas does not produce enough insulin, or 2) when the body cannot effectively use the insulin produced in the pancreas. Insulin and glucagon are the two major hormones that regulate blood glucose. Both insulin and glucagon are produced in the pancreas and have antagonistic (opposite) effects on blood glucose levels; insulin lowers the blood glucose by facilitating tissue uptake of glucose, whereas glucagon increases blood glucose primarily by increasing the release of glucose from the liver. When working in concert, insulin and glucagon are able to maintain normal blood glucose levels within a narrow range. Blood glucose levels range from 70 to 110 mg/dL under normal conditions.

Although glucose levels can be effectively controlled, diabetes is a life-long disease and can lead to multiple chronic life-threatening complications (morbidity) and mortality. Morbidity and mortality can also occur from treatment-related complications either due to patient error or use of defective insulin delivery devices.

It is generally thought that early diagnosis and treatment of diabetes may delay many of the complications associated with this disease. Data collected in the Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications and Pittsburgh Epidemiology of Diabetes Complications Experience (EDC) indicates that, "After 30 years of diabetes, the cumulative incidences of proliferative retinopathy, nephropathy, and cardiovascular disease were 50%, 25%, and 14%, respectively, in the DCCT conventional treatment group, and 47%, 17%, and 14%, respectively, in the EDC cohort. The DCCT intensive therapy group had substantially lower cumulative incidences (21%, 9%, and 9%) and fewer than 1% became blind, required kidney replacement, or had an amputation because of diabetes during that time."

Epidemiology

There are two major types of diabetes, Type 1 and Type 2. Type 1 diabetes mellitus (often called 'insulin-dependent' or 'juvenile-onset' diabetes) is characterized by deficient insulin production in the pancreas, and requires the administration of insulin to affected patients on a daily (or multiple times per day) basis. Approximately 5 to 10% of patients with diabetes suffer from Type 1 diabetes.

Type 2 diabetes (often called 'non-insulin dependent' or 'adult onset' diabetes) is characterized by the body's ineffective use of insulin that is produced normally in the pancreas. Elevated glucose levels may not occur until later in life. Approximately 90 to 95% of diabetics have Type 2 diabetes.

Another type of diabetes is gestational diabetes, which occurs during pregnancy, and is often diagnosed during routine prenatal screenings rather than by symptoms.

There are also an estimated 57 million adults 20 year and older who have prediabetes, a condition where blood glucose levels are higher than normal, but not reaching the hyperglycemia levels to be considered diabetes.

Diabetes affects approximately 23.6 million people (7.8% of the population) in the US, and this number is steadily increasing. Of these 23.6 million people, 17.9 million have been diagnosed with diabetes, and 5.7 million people with diabetes have not yet been diagnosed with their disease. Estimates of the prevalence of diagnosed and undiagnosed diabetes among adults in the US are:

- Ages 20 years or older: 23.5 million people, or 10.7% of this population
- Ages 60 years or older: 12.2 million people, or 23.1% of this population
- Men: 12 million, or 11.2%, of all men 20 years of age or older
- Women: 11.5 million, or 10.2% of all women 20 years of age or older
- Asian Americans: 7.5% of Asian Americans 20 years of age or older
- Hispanics: 10.4% of Hispanics 20 years of age or older
- Non-Hispanic Blacks: 11.8% of Non-Hispanic Blacks 20 years of age or older

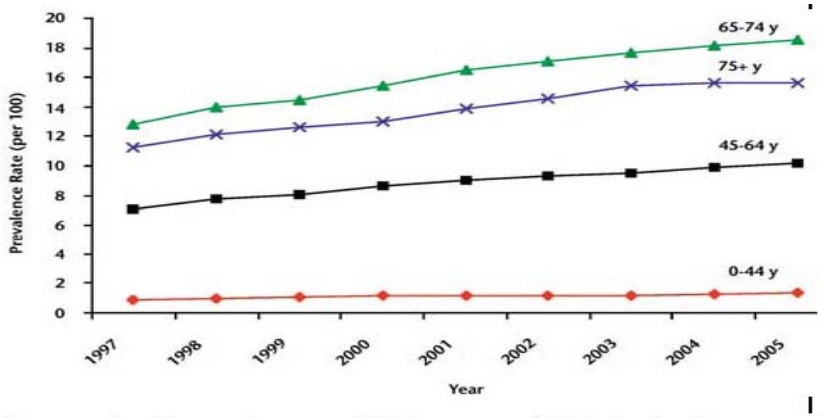


Figure 1. Prevalence of diagnosed diabetes by age in the United States. National Health Interview Survey, 1997–2005.[6]

The American Diabetes Association estimated that the national cost of diabetes in the US in 2002 was $132 billion and projected that the annual cost would reach $192 billion by the year 2020.

Clinical Course

Diabetes is a chronic, systemic disease that, over time, can lead to multiple organ deterioration and failure. The long-term clinical course of a diabetic patient is, in great part, influenced by the success in controlling their blood glucose levels over months to years. Chronic hyperglycemia leads to damage of small blood vessels, and is an important factor in accelerating the development of atherosclerosis, retinopathy, kidney failure, stroke, heart disease, and peripheral vascular disease. The most common complications are heart disease and stroke, peripheral artery disease, nephropathy, retinopathy (blindness), peripheral neuropathy, and lower limb amputation. Diabetes is associated with a reduced life expectancy, and is the seventh leading cause of death in the United States..

Chronic adverse health effects of diabetes:

Cardiovascular Disease: Cardiovascular disease is responsible for about 65% - 68% of all deaths in Type 1 and Type 2 diabetic patients. Diabetics are also 2-4 times more likely to suffer a stroke than the normal population. About 70% of diabetics also have hypertension. Risk factors are similar to the non-diabetic population, namely smoking, high blood pressure, and elevated blood lipids; however these factors appear to lead to a poorer outcome in diabetic patients. Lower extremity amputations are necessary in up to 15% of diabetics as a result of the secondary effects of peripheral vascular disease.

Diabetic Retinopathy: Diabetic retinopathy is a leading cause of blindness that results from damage to the walls of small blood vessels in the eye. It accounts for more than 10,000 new cases of blindness per year. After 15 years of diabetes, approximately 2% of patients have become blind, and 10% have developed severe visual impairment. Diabetic retinopathy and blindness can often be prevented if diagnosed in the early stages.

Diabetic Neuropathy: Diabetes can also lead to nerve damage. Diabetic neuropathy affects between 30 to 50% of both Type 1 and Type 2 diabetic patients. The cause is unclear, but once it is present, there appears to be an increase in the risk of other diabetic complications such as retinopathy. Neuropathy affecting the lower extremities, combined with reduced blood flow due to vascular and cardiac disease, increases the likelihood that patients will develop foot ulcers and the need for limb amputation.

Diabetic Nephropathy: Between 10-20% of diabetics die of kidney failure. Diabetic nephropathy appears usually after 10 or 15 years in Type 2 diabetics, and 20-40 % of all diabetics will develop end-stage renal disease requiring dialysis.

Other adverse health effects of diabetes:
Uncontrolled diabetes typically leads to biochemical imbalances that can cause diabetic ketoacidosis, coma and death. People with diabetes are often at increased risk for acquiring other illnesses than people without diabetes. The prognosis for these coexisting illnesses is often worse in people with diabetes than in people without the disease.

Treatment

Treatment of diabetes is centered on maintaining blood glucose levels as close to normal as possible. A mainstay in the treatment of patients with Type 1 diabetes is insulin therapy. Patients with Type 1 diabetes require reliable and precise delivery of insulin to prevent hypoglycemia or hyperglycemia in the short term, and poor glycemic control in the long term.

Patients with Type 2 diabetes can usually be managed with oral medications. Some patients with Type 2 diabetes also require insulin. In the United States, 14 % of adults diagnosed with diabetes require insulin treatment alone and 13 percent take both insulin and oral medication. Patients with diabetes often require other interventions including treatment of high blood pressure, high cholesterol and the known complications of diabetes.

Standard insulin regimes typically include one or more daily insulin injections (basal and meal time), one or more daily blood sugar tests, and visits to the health care team on a regular basis. The most common method for insulin administration is injecting subcutaneously using an insulin syringe and needle. Other methods to administer insulin subcutaneously include needle-free jet injectors, disposable or re-usable prefilled pens/dosers, and insulin pumps. The ability of a patient to successfully administer insulin depends on their ability to understand and use the insulin adminstration device. Misuse of insulin delivery devices, including insulin infusion pumps, have been associated with morbidity and mortality in patients with diabetes. Treatment failures have also be associated with defective pumps.

PART 2: Insulin Infusion Pumps

Overview

Insulin infusion pumps are small, lightweight devices that are indicated for the management of diabetes mellitus in adults and children requiring insulin therapy. These devices administer insulin continuously and/or intermittently to patients in the home and other clinical settings to control blood glucose levels. Insulin infusion pumps allow users to perform all types of jobs and participate in most activities they desire.

The first insulin pump to be manufactured was introduced in 1974 by Los Angeles doctor Arnold Kadish. It was the size of a large backpack and filled with metal receptacles and tubing (Fig.1). It was known as the “big blue brick” because of its size and appearance. It sparked interest among healthcare professionals who saw it as a device that would render syringes obsolete for people who have daily insulin injection needs. While the technology was promising, the first commercial pump lacked the controls and interface to make it a safe

alternative to manual injections. It was only in the beginnings of the 90's that that more user friendly and smaller models were introduced.

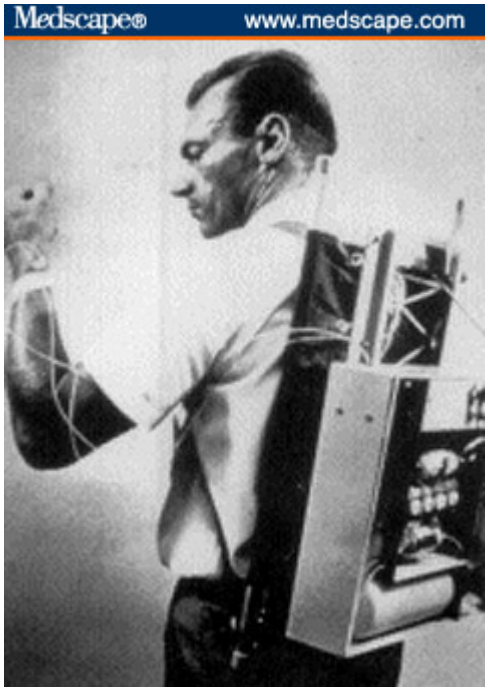


Figure 1 The first insulin pump introduced in 1974 by Dr.Arnold Kadish

Modern pumps now weigh less than four ounces, are the size of a pager or cell phone and are powered by batteries. Each pump comes with several alarms to prevent inadvertent insulin delivery and to warn the patient when the batteries are running low or when the infusion set has become clogged or dysfunctional. Insulin pumps use a special small syringe, which resides in the pump and is connected to the wearer via a small cannula. The newer pumps also have features which make it easier to track trends in lifestyle. They store huge quantities of data such as when and how much insulin the user has taken or when alarms have gone off and for what reason. New pumps also use lighted screens (for sighted users in dark locations) or audio cues for users who have visual impairment. Insulin pumps allow users to program different basal rates to allow for variation in lifestyle. In addition, the user can program the pump to deliver a bolus (large dose of insulin) during meals to cover the excess demands of carbohydrate ingestion.

The popularity of insulin pump therapy, or continuous subcutaneous insulin infusion, is increasing. Approximately 130,000 adult Type 1 diabetics used external insulin infusion pumps in 2002 as compared to 375,000 in 2007. Insulin pump therapy offers several potential advantages over standard injections including discreet and instant insulin adjustments, fewer hypoglycemic episodes, greater dietary freedom, ease of insulin administration during illness, and convenience during exercise and travel. It may also decrease the need for needle stick injections while improving overall blood glucose control.

Figure 2 shows some of the insulin pumps available commercially in 2008. New models have sophisticated electronics and complex algorithms capable of calculating insulin bolus

doses necessary to supplement continuous infusion. Some concerns have been raised regarding the safety of those algorithms, more particularly the accuracy of calculations and delivery of insulin therapy.

Figure 2

There are several newer therapeutic approaches under development for the treatment of insulin-dependent diabetics. While promising, many are several years away from being ready for wide-spread clinical use.

Use of Infusion Pumps in Diabetes

Insulin infusion pumps are used to administer continuous subcutaneous insulin infusion (CSII). The most common indication for CSII therapy is in children with Type 1 diabetes. When correctly used, CSII allows for a better control and decreased fluctuations of blood glucose, which should reduce the development of micro- and macrovascular complications. Available data suggest that CSII reduces the evolution of diabetic retinopathy, and possibly decreases the risk of cardiovascular complications. Still, while the severity of complications seems to decrease, there are conflicting results regarding to the quality of life of those patients in CSII versus multi insulin injection therapy.

The preponderance of published data suggests that CSII therapy may provide advantages over MDI (multiple daily injections) in managing children with Type 1 diabetes. However, this mode of therapy may not be appropriate for everyone. Insulin pump therapy requires parental motivation, ability to understand pump technology, frequent blood glucose monitoring, and willingness to work closely with the health care team. In addition, there are many other circumstances that contribute to poor glycemic control in children, including unpredictable food intake and physical activity, imprecise administration of small doses of insulin by injection, and

frequent viral infections. Furthermore, the use of CSII in small children has been limited due to concerns about hypoglycemia occurring unrecognized by parents. Still, CSII seems to reduce the occurrence of hypoglycemic episodes and diabetic ketoacidosis in children as a result of a more steady control of blood glucose.

Although insulin therapy may at times be indicated in Type 2 diabetics, much of the available data does not support the use of CSII in Type 2 diabetics, even those with poor glycemic control. Studies have not been able to demonstrate significant improvement in the control of hypoglycemic episodes in patients with Type 2 diabetes using CSII. Use in treatment of Type 2 diabetics is often limited to patients with frequent nocturnal hypoglycemia and/or uncontrollable morning hyperglycemia.

Problems With the Use of Insulin Infusion Pumps

Use of insulin infusion pumps may introduce new potential challenges into patient care, and candidates should be carefully selected. Difficulties with pump use, programming and maintenance can cause failure of therapy. Patient errors especially when beginning treatment or upgrading to newer pump models are possible, and intensive training of the patient and any other person that will help with treatment is usually necessary. A number of technical problems have also been reported with the use of insulin infusion pumps. These are summarized in a later section.

PART 3: PREMARKET REGULATORY OVERVIEW

Device Classification

Medical devices are grouped into three classes for regulation in the United States:

Class I devices are subject to the least regulatory control. They present minimal potential for harm to the user and are often simpler in design than Class II or III devices. Class I devices are subject to General Controls. General Controls apply to all devices and include provisions such as registration of facilities, listing of products with the FDA, manufacturing devices in accordance with Good Manufacturing Practices and labeling devices in accordance with FDA regulations. Most Class I devices (93%) are exempt from premarket review.

Examples of Class I devices include surgeon's gloves, mechanical wheelchairs, oxygen masks, hand-held surgical instruments, elastic bandages and non-powered breast pumps.

Class II devices need more than general controls to assure reasonable safety and effectiveness but existing methods are available to provide such assurance. Class II devices are subject to Special Controls. **Special Controls** may include special labeling requirements, use of a guidance document, patient registries, or postmarket surveillance. Most Class II devices, require pre-

market FDA review through the 510(k) process. The firm must demonstrate equivalence to a legally marketed device, which is referred to as the predicate device.

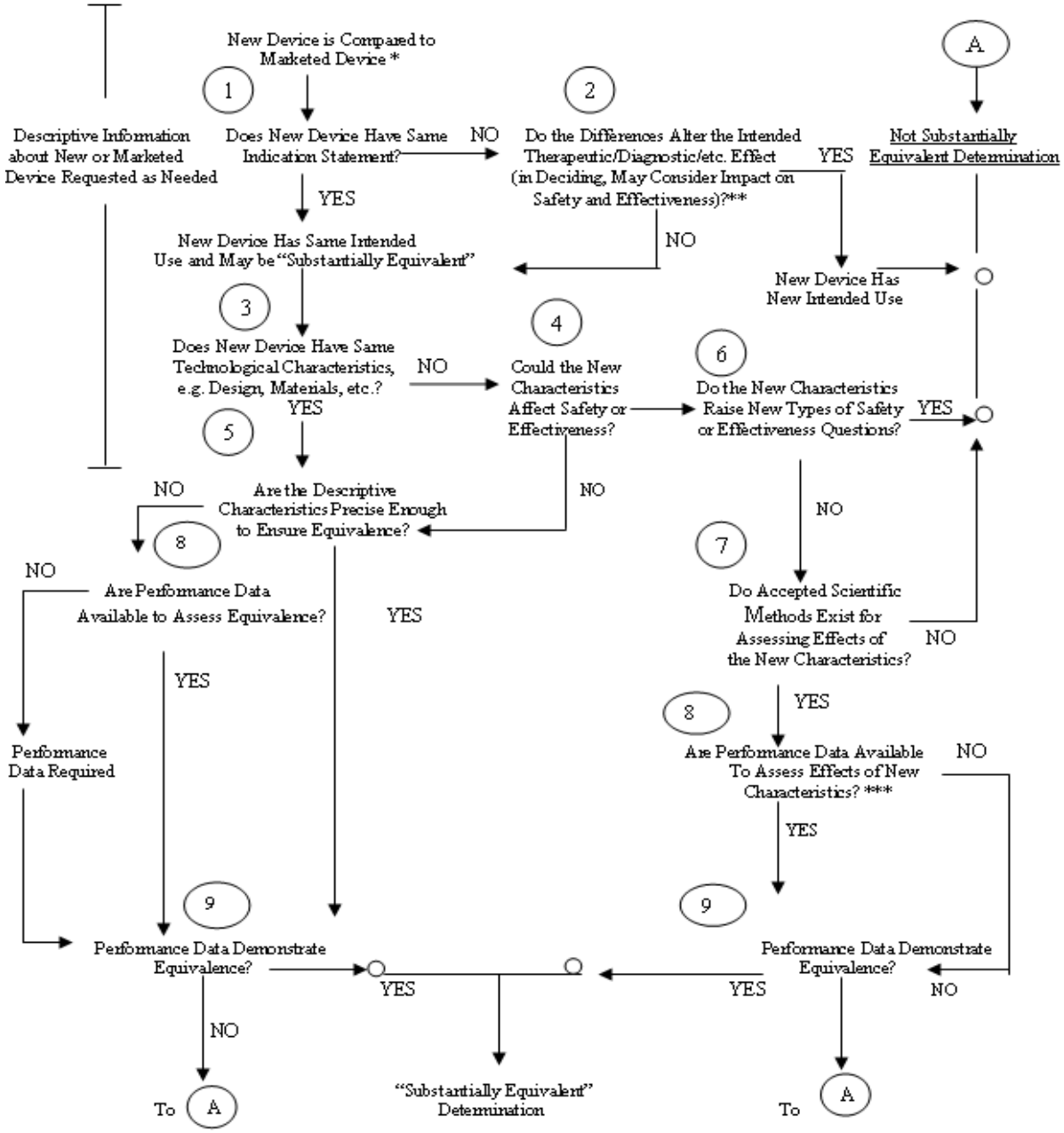
Examples of Class II devices include apnea monitors, blood pressure cuffs, surgical drapes, condoms, and powered wheelchairs.

Class III devices are subject to the most stringent regulatory control. These include inherently high risk devices as well as products with new a technology about which little is yet known. Class III devices include devices that are life sustaining or life supporting, have substantial importance in preventing impairment of human health, or present unreasonable risk of illness or injury**.** Premarket Approval (PMA) submissions are required for Class III devices. The PMA process involves a scientific review to ensure the safety & effectiveness of the specific device, without comparison to a predicate product.

The 510(k) Process

The majority of currently marketed insulin infusion pumps in the United States are Class II devices subject to pre-market review through the 510(k) process. This review determines if a device is "substantially equivalent" to a predicate device. The reviewed product must have the same intended use as the predicate device. The technological characteristics of the review product and predicate are then compared. If they are different, the firm must provide information to FDA demonstrating that the device under review does not raise new questions of safety and effectiveness and that it is at least as safe and effective as the legally marketed device.

A determination of substantial equivalence does not mean that the new and predicate devices must be identical. Substantial equivalence is established with respect to intended use, design, energy used or delivered, materials, chemical composition, manufacturing process, performance, safety, effectiveness, labeling, biocompatibility, standards, and other characteristics, as applicable. Most 510(k) submissions include some type of performance data, such as bench / laboratory testing to demonstrate substantial equivalence to the predicate product. For infusion pumps, pre-market review focuses on a range of factors including biocompatibility of materials, sterilization, software, human factors, electrical and mechanical safety, and insulin stability / compatibility.



The 510(k) "Substantial Equivalence" Decision-Making Process

PART 4: POSTMARKET REGULATORY OVERVIEW

Medical Device Reporting (MDR)

Many malfunctions and adverse events that occur with marketed medical devices must be reported to the FDA through the Medical Device Reporting (MDR) process. FDA uses this information to identify problems that are developing with marketed devices and to oversee recalls when necessary. This information also helps prioritize work within CDRH.

The regulations in Part 21 of the Code of Federal Regulations Section 803 define the medical device report requirements for user facilities, manufacturers, importers and distributors. These regulations include definitions and explanations of when and how to submit reportable events, along with requirements for files and recordkeeping.

Individual Medical Device Reports or MDRs are provided to the Agency via two forms: FDA 3500A, which is the form for use by user facilities and manufacturers for mandatory reporting; and, FDA 3500, which is the Voluntary User's Report Form for reports of adverse events product errors and product use problems.

MDR's often act as a "signal" to CDRH that that a specific device or group of devices may not be safe and/or performing as intended. The typical MDR contains information regarding a death or serious injury that was or may have been related to use of a medical device. A reportable device malfunction is defined as a failure of a device to meet its performance specifications or otherwise perform as intended and, it is likely to cause or contribute to a death or serious injury if the malfunction were to recur.

For purposes of MDR regulation, a reportable serious injury is defined as an injury or illness that is:

- life-threatening; or
- results in permanent impairment or damage to a body function or structure; or
- requires medical or surgical intervention to preclude permanent impairment or damage to a body function or structure

Sometimes adverse events that should have been reported to FDA by the manufacturer or user facility are not reported, and information contained in many reports is incomplete. These factors often delay recognition of problematic medical devices and present an obstacle to protecting public health.

The Recall Process

A recall is a firm's correction or removal of a marketed product that the Food and Drug Administration considers to be in violation of the laws it administers and against which the Agency would initiate legal action, e.g., seizure. Almost all recalls are voluntary. Corrections

address a problem without removing the device from the point of use (i.e., repair, modification, adjustment, relabeling, destruction or increased patient monitoring). Removals involve sending the device to the firm or another site for repair, modification, adjustment, relabeling, inspection or destruction.

When the only action that a firm takes to address a safety concern about a marketed device is a communication to users, this is referred to as a Safety Alert and is not considered a recall.

Device manufacturers are required to report to FDA many actions related to device recalls, and to maintain records of all corrections and removals regardless of whether they must be reported to FDA. The FDA regulations that implement this requirement are in 21, Code of Federal Regulations (CFR) Chapter 806 *Medical Devices; Reports of Corrections and Removals*. Chapter 7 in 21 CFR also addresses Enforcement Policy for regulated products including medical devices.

In addition to reporting, under rules for Good Manufacturing Practice and Quality Systems Regulations, a manufacturer that becomes aware of a potential problem is required to (among other things) initiate an investigation into complaints and returned product, and to work to identify the root cause.

Occasionally a firm does not inform the FDA of problems in marketed devices, or of a correction or removal. The FDA may instead become aware of the situation via inspections, consumer complaints, etc. FDA may inform the firm that product in question violates the law, and the firm may then choose to inform the FDA that it is conducting a voluntary recall.

The FDA has District offices across the U.S. that conduct inspections of manufacturers, regulate importing of products, and coordinate many local interactions with firms. The District Office coordinates oversight of recalls and sends information to the Center for scientific input, risk assessment and recall classification.

Classifying Recalls

Recalls are classified based on the level of risk to health the defect exposes to users. The level of risk determines the level of FDA oversight necessary to protect the public. Recalls are classified according to the following criteria:

- Class I – highest risk recall - a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death.
- Class II - situation in which use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.
- Class III - a situation in which use of, or exposure to, a violative product is not likely to cause adverse health consequences.

(Please note that recall classifications use the numbers in reverse order from medical device classifications for premarket review.)

Recalls can be classified by three different methods: (1) policy, (2) precedent; or (3) a new Health Hazard Evaluation (HHE) or risk assessment.

Policy: The Center has determined that sufficient historical precedent exists to directly classify certain recalls as Class II in the absence of serious injury or death reports. Examples include latex gloves failing a leak test, products marketed without an appropriate 510(k) or PMA, and devices labeled as latex free but containing latex. Because new information may affect these polices, a Compliance Medical Officer reviews the use of policy for each specific recall.

Precedent: Class II and Class III recalls may also classified by selecting an appropriate precedent, a predicate recall, and assigning the same classification. The precedent must have a similar overall risk level, and the devices should be of a similar type, used for a similar purpose and be recalled for a similar malfunction. A Compliance Medical Officer reviews predicates chosen to assure that hey are appropriate..

Health Hazard Evaluation (HHE): The Health Hazard Evaluation (HHE) is a risk assessment process specifically tailored to align with the regulations, guiding the Center in classifying recalls and determining what actions are necessary to protect the public health. An HHE assessing the particular device and defect is necessary for all likely Class I recall situations and many high-risk Class II recalls. An HHE is also conducted for lower risk situations that involve unique scientific or public health issues and for any recall where no appropriate policy or precedent can be found to classify.

- HHE's are based on a technical assessment of the device and defect, predicting the types and likelihood of device failures that might result. Medical experts then consider how these failures might affect patients. The number of death and injury reports received does not dictate the risk results or recall classification.
- The HHE process distinguishes serious adverse health consequences from injuries that are temporary or medically reversible. Examples of serious injuries include a fractured bone, hepatitis infection, chronic pain, and abnormal blood levels requiring hospitalization. Examples of temporary or reversible injuries include sprains and bruises, electric shock without permanent injury, and headaches that resolve with routine treatment.
- The risk is also based on the likelihood of injury or death resulting from the device defect. This is often a best estimate based on limited information available.

FDA Oversight of Recalls

CDRH will strongly encourage a firm to conduct a voluntary recall if a public health risk comes to our attention and the firm is slow to act. The Center and the Districts also advise firms on specific actions to take, and on the wording of communications such as Dear Doctor letters, press releases, Safety Alerts, and other recall communication.

In certain high risk situations, FDA can require or mandate a medical device recall. FDA has the authority to request that a firm initiate a recall under Section 518(e) of the Act and according to 21 CFR 7.45. When rapid FDA response is needed, other tools have usually proven effective. FDA has rarely needed to require a medical device recall due to lack of appropriate action by a manufacturer.

CDRH provides regulatory oversight of recalls, and the scope of these oversight actions includes the following:

- Comment on firm's recall strategy
- Review firm's communications, including the firm's "Dear Dr." letters, Press Releases and other communications; editing and revising the firm's communications when appropriate
- Prepare FDA press releases and public health notices, if applicable
- Provide scientific and regulatory input to district and firm
- Assess risk of defect/device failure, and then classify the recall based on the level of risk
- Conduct Health Hazard Evaluations (HHE) or Health Risk Assessments (HRA) where appropriate
- Audit effectiveness of recall, and notify firm of termination that the recall has been effective
- Witness product destruction or approve reconditioning plan

CDRH and FDA utilize various mechanisms to notify the public about recalled products, including:

- CDRH Internet provides a public database to search for all recalls at FDA > *Medical Devices > Medical Device Database > Recalls of Medical Devices.* This database is updated nightly with the most recent information about a recall that has been classified.
- The FDA Internet contains recall information at FDA > *Medical Devices > Medical Device Safety > Medical Device Recalls*. This site includes Class I recalls and some Class II and III recalls.
- The *Enforcement Report*, a weekly public report that includes recall information.
- The MedWatch page posts recall information at FDA > Safety > MedWatch The FDA Safety Information and Adverse Event Reporting Program > Safety Information. The recalls at this site are mainly Class I and significant Class II.

- Press releases are common for Class I recalls, generated by either FDA or the firm. Press releases are often issued for Class II recalls where devices are in the possession of the general public.
- Foreign countries receive notification.
- Additional communications can be made if FDA is unsatisfied with the public notification by the firm. These messages usually include information on mitigating risk. Examples include Public Health Notifications to health care providers and Patient Safety News.

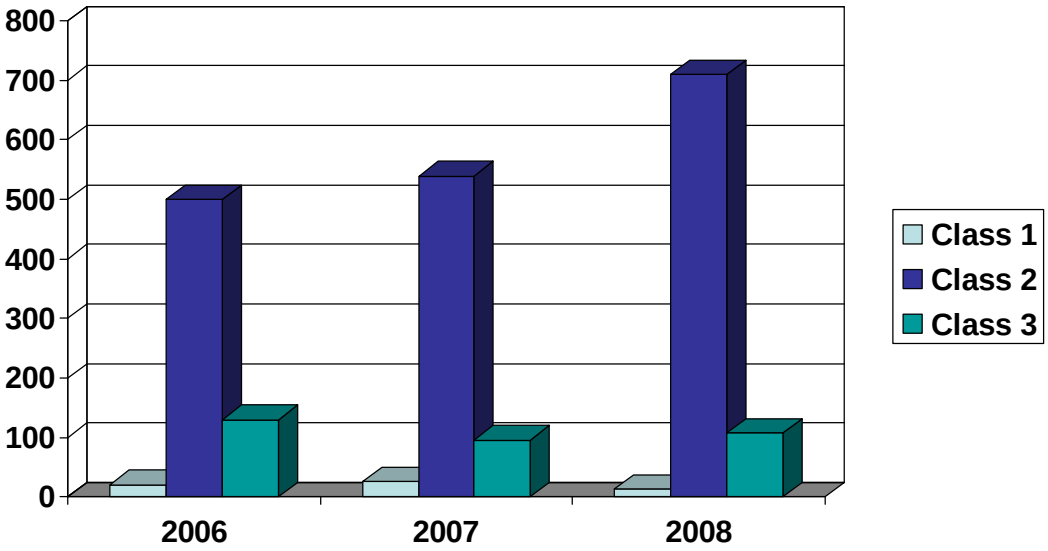
Manufacturer Responsibility

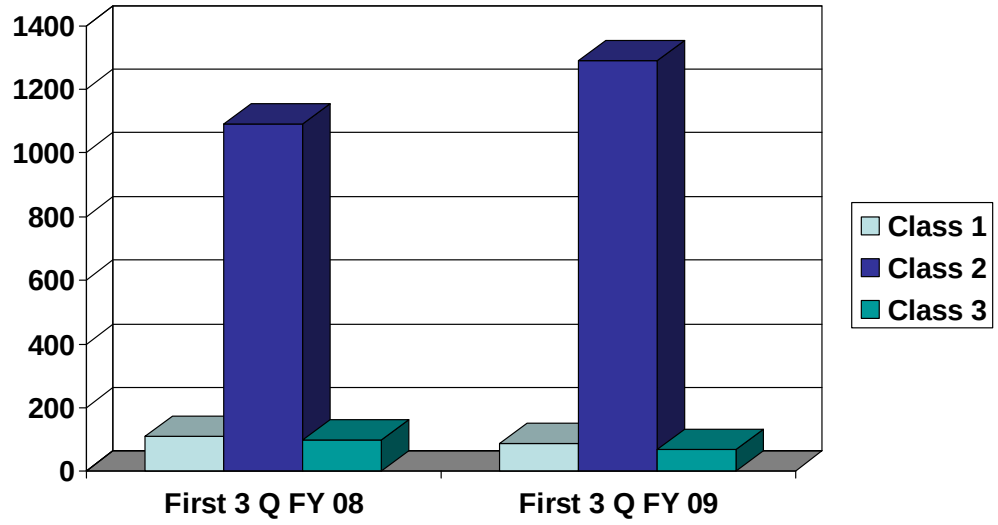
Manufacturers are responsible for performing specific actions when conducting a recall. These actions include:

- Determine need for recall, and notify the FDA District Office
- Determine root cause of the defect and then assess the risk associated with use of the defective device
- Execute appropriate recall actions aimed at improving product quality for the future (i.e.- implementing corrections to the device)
- Measure the effectiveness of the recall
- Mitigation of risk to users as a result of use of the affected device. Firm actions may include notification to users, utilizing the following methods to communicate their message:
    - Direct Mailings to Users
    - Mailings to Healthcare Practitioners
    - Direct Phone Calls
    - Personal Visits by the Firm's Representatives
    - Fax
    - Email
    - Electronic Newsgroups
    - Websites
    - Press Releases

CDRH seeks to understand how effective each of the above-mentioned communication methods is in providing critical information to clinicians and patients, and explore other post-market options that can be performed by the FDA and/or firm to mitigate risk associated with use of insulin infusion pumps.

CDRH Recall Actions by Fiscal Year





CDRH Recall Actions Comparison

PART 5: PROBLEMS ASSOCIATED WITH INSULIN PUMPS

Medical Device Reports

The members of the Product Evaluation Branches (PEB I and PEB II) in the Office of Surveillance and Biometrics (OSB), Center for Devices and Radiological Health, FDA, review MDRs as part of

the Agency's ongoing device surveillance program. PEB I and PEB II combined receive approximately 175,000 MDRs a year. Each analyst is a specialist in a particular device area and is called upon to prepare in-depth analyses of problems, trends and other abnormalities related to device function for particular devices. An in-depth analysis was prepared for insulin pumps for the past three years for this panel meeting. This section provides an analysis of the types of MDRs received by OSB regarding infusion pumps.

Methods

The MAUDE (Manufacturer and User Facility Device Experience) data base was queried using product code LZG and date entered October 1, 2006 through September 30, 2009. The reports found in MAUDE are called MDRs or Manufacturer Device Reports. Each MDR contains a variety of information including a device description, manufacturer location, type of event such as death or injury, a group of codes that are given unique identifying numbers called Device and Patient problem codes and finally a manufacturer narrative. The MDR contains a number of other data fields but the above mentioned ones are sufficient for this narrative. In addition to the MAUDE database, Insulin Pump recalls and Manufacturer Registration and Listings from FDA databases were reviewed. A second modified search was conducted in MAUDE using product code LZG, event type 'death' and date entered January 1, 2005 through September 30, 2009, with a text search using search terms accident, car, driving, and vehicle to capture the number of motor vehicle accidents associated with insulin pump users for the period reviewed.

Due to the large numbers of reports, the data analysis selected for review will focus primarily on the Top five Reporting Manufacturers and reported deaths (n=310) (Table 2).

Results

The search yielded 16,849 adverse event reports including 310 deaths, 12,093 injuries, 4,294 malfunctions, 119 'other', and 33 'invalid' reports. Reports designated as 'other' and 'invalid' are events not coded as D, IN, or M, and/ or report field left blank. Manufacturer, User Facility, and Voluntary reports are summarized in (Table 1). Of these 16,849 reports 16,640 were identified with 5 top manufacturers.

Another search yielded 431 adverse event reports, which revealed that 29 of the 431 reports were associated with motor vehicle accidents and patients wearing insulin pumps.

Table1. Report Source of Adverse Event Reports October1, 2006 – September 30, 2009

Report Source	Death	Injury	Malfunction	Other	Invalid	Total
Distributor	***0***	***15***	***1***	***0***	***0***	***16***
Manufacturer	***303***	***12,014***	***4,262***	***108***	***25***	***16,712***
User Facility	***1***	***1***	***3***	***0***	***0***	***5***
Voluntary	***6***	***63***	***28***	***11***	***8***	***116***

Total	***310***	***12,093***	***4,294***	***119***	***33***	***16,849***

Device Problems

The most frequently reported device problem in MDR's related to insulin infusion pumps was 'unknown,' and the top five reporters identified "unknown" in 5421 of 16640 reports (19.7% of reports). The second most frequent device problem reported was "replace," which accounted for 2385 entries (9% of reports). The remaining top ten device problems reported were:

- Audible Alarm (6% of reports)
- Use of device issue (5% of reports)
- Device Displays error message (4.8% of reports)
- Not Applicable (4% of reports)
- Failure to deliver (3% of reports)
- No information (3% of reports)
- Repair (3% of reports)
- Self Activation or keying (1.8% of reports)

Although the following device problems reported by all manufacturers may not have made it to any of the manufacturers' top 10 list of device problems, these problems also serve as critical signals for safety and effectiveness of insulin pumps:

- Inaudible alarm
- Device alarm issue
- Failure to prime
- Failure to infuse
- Suspected Electro Magnetic Interference
- Battery failure
- Blank screen
- Incorrect software programming calculation
- Motor failure
- Defective components
- Magnetic interference
- Loss of power
- Inaccurate delivery
- Incorrect test results
- Sensor problems
- Software issues
- Intermittent failures
- Computer hardware errors
- Dose calculation errors
- Programming issues

- Inadequate training

(Note: each MDR may contain more than one Device Problem Code)

Patient Problems

The most frequently reported patient problems were 1) hospitalization, and 2) blood glucose high. Of the 16640 MDRs from the top five manufacturers, hospitalization was identified in 7967 reports (21% of reports) while blood glucose was identified in 6236 reports (16.6% of reports). The other most frequently reported patient problems reported were:

- Diabetic Ketoacidosis (8% of reports)
- Hyperglycemia (8% of reports)
- Treatment with medication (6% of reports)
- Blood glucose low (4.7% of reports)
- Therapy/non-surgical treatment (4% of reports)
- No consequences to the patient (4% of reports)
- Unknown (3% of reports).

Other patient problems of concern associated with insulin pump therapy include:

- Hypoglycemia
- Low blood glucose
- Loss of consciousness
- Hyperglycemia
- Overdose
- Under dose
- Over infusion
- Over delivery
- Under infusion
- Death

(Note: each MDR may contain more than one Patient Problem Code)

Manufacturer Evaluation Conclusions

The most frequent manufacturer narrative or conclusion was 'no conclusion could be drawn.' Other common evaluation conclusions made by manufacturers include device failure due to user handling, device failure with no further explanation, device failure occurred but not related to event, device failure related to maintenance, device failure indirectly contributed to event and "device not returned no evaluation was performed." The failure to determine the cause of the failure limits the ability of FDA to determine the cause of the adverse event and

may affect the ability of FDA to accurately characterize the risk associated with device failures, and oversee recalls that occur.

Deaths Reported by the Manufacturer A (n=310)

The information provided by the manufacturers in MDR's in which a death occurred was typically incomplete. For example, in 225 of the 310 reported deaths, the device problem was unknown and limited details of the event were provided and the root cause of the device failure was not confirmed by the manufacturer; the device was not returned for evaluation; or there was no documentation of any investigation or follow-up by the manufacturer.

In 41 death reports, an appropriate device problem could not be identified, however described patient problems include, diabetic coma, hypoglycemia, hyperglycemia, diabetic ketoacidosis and unresponsiveness. In these event narratives, the root cause of the device failure was not determined by manufacturer. In 17 death reports in which an appropriate device problem could not be identified, respiratory infection and alcohol consumption were the documented patient problems in these events

In 5 of the 310 deaths reported in which a device problem was not identified by the manufacturer, the infusion set was implicated in 4 deaths. In one event resulting in a patient death, it was reported that the user lost control while driving a car and crashed. Information provided in MDR's for the additional 4 deaths indicate that one patient suffered a hypoglycemic episode that caused him to fall and crack his skull in the shower; one patient experienced high blood glucose levels and suffered a heart attack; in one patient, the reported cause of death was hyperglycemia, and the user's wife stated that an issue with the infusion set caused the event; and in one report, the user was in a car accident while wearing the insulin pump and the patient burned to death.

In 4 of the 310 reports resulting in a death, the manufacturer reported the following device problems: disconnection, device issue, pump alarming, and no information.

In 29 of the 310 deaths reported, a variety of patient and device problems were reported, including overdose, over infusion, hypoglycemia, bent cannulas, suicide attempts, diabetes complications, high blood glucose readings, pump not working properly, diabetic ketoacidosis, failure to deliver, suspect EMI, inadequate training issues, display failures, diabetic coma, and issues with infusion sets. No conclusions were drawn by manufacturer in their evaluation of the root causes of these events.

In one MDR, the manufacturer reported that a patient experienced two occlusions with the device within a twelve hour period, resulting in elevated blood glucose levels and caused the patient to experienced hypoxia, brain damage, sepsis, and subsequently death. This device was not returned to the manufacturer, and no conclusion could be determined regarding the cause of the device failure. In another report, the health care professional reported the patient was

hospitalized in a comatose state and subsequently passed away. The cause of the death could not be determined as the device was not returned to the firm for evaluation.

In one report, a 30 yr- old female with Type 1 Diabetes who was approximately 18 weeks pregnant died. The deceased had been trained in using the device at her home earlier that morning and was found unresponsive later that afternoon. The manufacturer was unable to confirm any product malfunction as the device was not returned and the firm did not provide FDA with information demonstrating that the pump did not cause or contribute to this death.

Patient Age Distribution (n=310)

Of the 310 MDR's submitted to FDA, 244 reports did not identify the patient's age. Of the remaining 66 patients in which age was reported, patient age ranged from 16–106 years. The age distribution of these 66 patients is provided in Tables 4 and 5 below.

Table 4: Patient Age

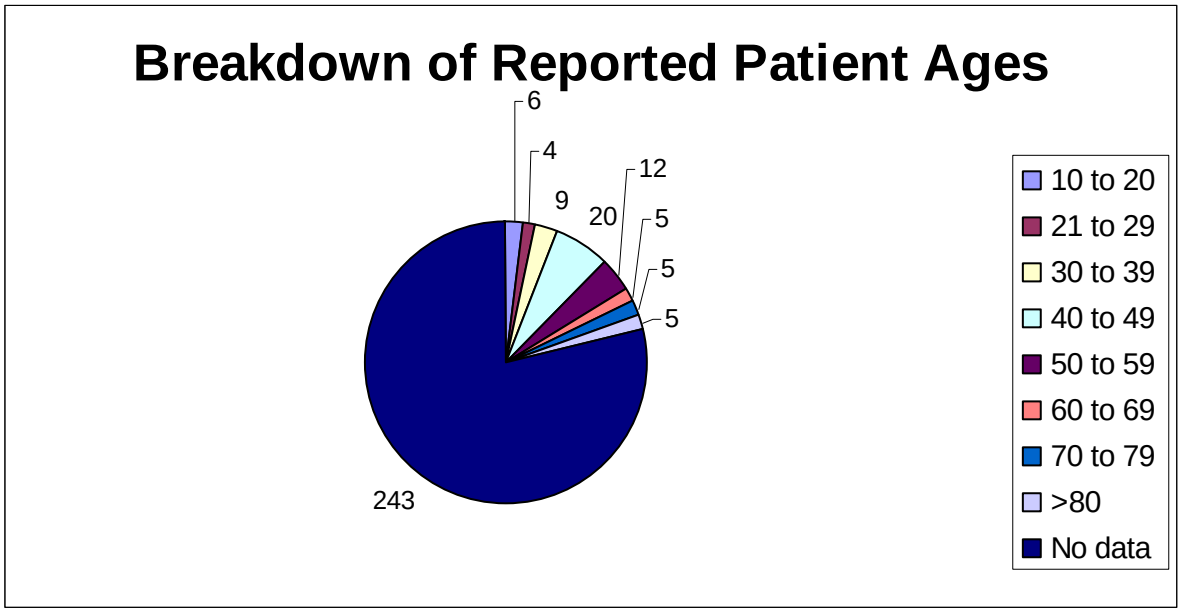
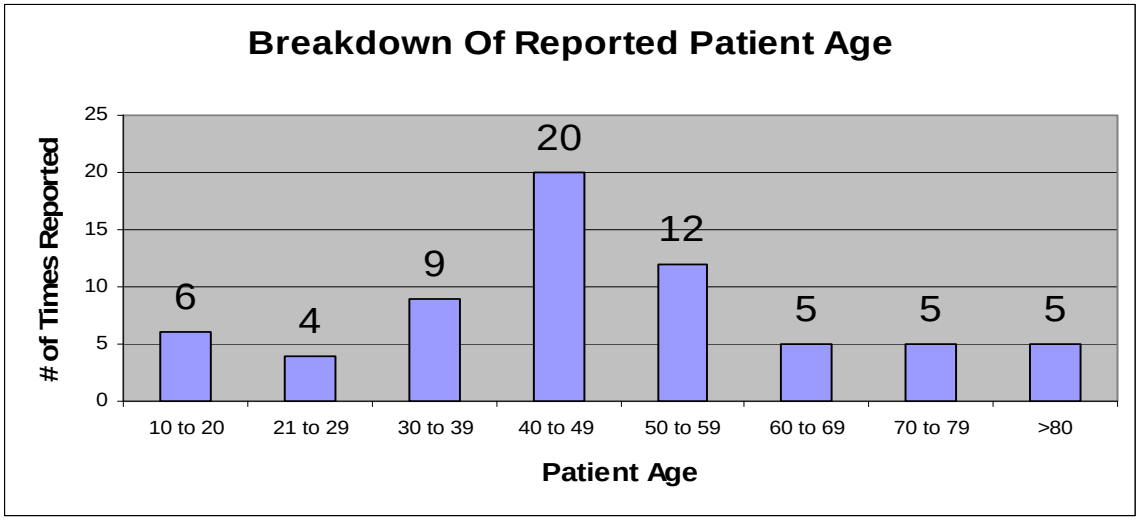


Table 5: Patient Age



Deaths Associated with Motor Vehicle Accidents and Users Wearing Insulin Pumps (n=29)

An increasing trend in motor vehicle accidents and patients wearing insulin pumps was noted in this review (Table 4). Twenty-nine adverse event reports were reviewed individually. The following is a list of auto related deaths/injuries associated with adverse event reports to FDA:

- pump user died instantly after being hit by a truck when he lost consciousness
- another user lost consciousness and hit a tree while wearing the pump
- user drowned after driving into a lake
- user experienced high blood glucose that resulted in car accident
- user experienced a hypoglycemic episode and passed away in a car accident
- user was found unconscious in a car and taken to the hospital in a coma, lost control while driving and crashed
- user passed away in a head on collision with another vehicle while wearing an insulin pump
- user burned to death in a car accident while wearing an insulin pump
- user involved in an auto accident, cause of death was hypoglycemia
- user passed away in a car accident while driving, had experienced low blood glucose levels and exposed to MRI Scans prior to user's death
- user felt blood sugar was low, felt she could make it home but passed away in a car accident
- User passed away in a car accident after crashing into a building at 55m.p.h, and was wearing an insulin pump at time of death.

In the majority of these deaths, hypoglycemia or low blood glucose experienced by the user may have caused or contributed to the event. In other reports, hyperglycemia and diabetic ketoacidosis may have caused or contributed to the adverse event. In the majority of these adverse events, the pumps were not returned to the manufacturer for further evaluation and testing, and in those cases where they were returned, the devices passed the displacement test, which indicated that the pump was delivering accurately.

Table 6: Number of motor vehicle accidents associated with patients wearing insulin pumps

Date of event-- by Year	*# of Deaths*
2004	**2**
2005	**4**
2006	**5**
2007	**6**
2008	**5**
2009	**7**

Insulin Infusion Pump MDR's- General Observations

A review of the insulin infusion pump data has identified hypoglycemia as the most common and dangerous complication caused by both insulin therapy and insulin pump therapy. Injuries resulting from pump failures including hyperglycemia, hypoglycemia, hypoglycemia unawareness are often difficult to distinguish from the therapeutic complications of the disease, especially when data in the reports are incomplete.. Other observations include the following:

- Device problems critical to insulin pumps exist across manufacturers.
- Device problems have not been identified in a large majority of reports submitted, and in a large number of reports, no evaluation was performed. Potentially reportable events may not have been appropriately investigated to insure proper follow-up in determining causality and device failure and reportability.
- In a large number of reports no evaluation was performed because the device was not returned, preventing manufacturers from performing failure analysis.
- Cause of deaths associated with insulin pumps have not been thoroughly investigated and evaluated by manufacturers in determining causality and device failure.
- Patient age was not reported in 78% of the MDRs submitted by manufacturers.
- Hypoglycemia, diabetic ketoacidosis, and hyperglycemia are the most frequently reported patient complications associated with insulin pump therapy; these complications are life threatening, and have resulted in death.
- An emerging trend in motor vehicle accidents has been identified in insulin pump users, and may also be due to hypoglycemic unawareness.
- There is an increasing trend in software and hardware device problems across manufacturers.
- Low blood sugars could result in seizures from a malfunctioning pump or from hypoglycemic unawareness when the user can lose consciousness without ever knowing their blood sugar level has dropped or without showing other symptoms of hypoglycemia.
- Hyperglycemia, if untreated, can result in diabetic ketoacidosis and death

- Extreme caution should be used in prescribing pumps for individuals with psychiatric illnesses, such as drug and alcohol abuse, eating disorders as well as those who are unwilling to perform blood glucose monitoring.

Recalls

The Recall database was searched, and 18 recalls for insulin pumps were identified from October 2004 to May 2009.

Recall Class	***Number of Recalls***
Class I Recall	***3***
Class II Recall	***13***
Class III Recall	***2***

In some cases the recalls involved multiple products and/or models, and were associated with the following failure modes:

Failure Mode	**Number of Recalls**	**Number of Products/Models**
Device Design	4	36
Labeling False & Misleading	1	1
Manufacturing	4	8
Other	1	1
Process Control	1	4
Software Design	6	7
Unavailable/Pending	1	1
Total Number of Recalls/Cases	**18**	**58**

The total quantity of product distributed for each identified root cause of failure can be seen in the table below:

Root Cause of Failure	Quantity Distributed	% Distributed
Device Design	3,896,320	88%
Unavailable/Pending	334,000	8%
Manufacturing	115,669	2%
Software Design	42,252	1%
Other	14,929	0.3%
Labeling False & Misleading	14,560	0.3%
Process Control	32	0.001%
Total	**4,417,762**	

Examples of Recalls

Example 1:

Problem: Defective medication cartridge; the tubing connector prevents medication cartridge from equalizing pressure with surrounding atmosphere.

Hazard: Over or under delivery of insulin may occur when there is a change in atmospheric pressure. The amount of over/under-delivery of insulin is independent of the amount of change in atmospheric pressure; users unaware that their pump failed.

Confounding Factors: Over 4 million defective products in distribution; the firm was unable to individually contact all affected patients to inform them of this issue.

Clinical Implications: Users not aware that they received too much or too little insulin, causing severe hyperglycemia and hypoglycemia along with the complications of hyperglycemia (e.g.- DKA) and hypoglycemia.

Recall Classification: Class I Recall

Example 2:

Problem: The battery may disconnect, turning the pump off without warning/alarm.

Hazard: Under-delivery of insulin may occur without knowledge of patient.

Clinical Implications: Users not aware that they received too little insulin, causing severe hyperglycemia and complications associated with severe hyperglycemia.

Recall Classification: Class I Recall

Example 3:

Problem: The luer tube may break at the connection to the pump.

Hazard: Under-delivery of insulin may occur without knowledge of patient.

Clinical Implications: Users may not be aware that they did not receive enough insulin, causing severe hyperglycemia and complications associated with severe hyperglycemia.

Recall Classification: Class I Recall

Example 4:

Problem: A software code caused a logic error that can report old inaccurate information.

Hazard: User may be confused as to the amount of insulin they have been administered by the pump.

Clinical Implications: User confusion introduces the potential for over or under delivery of insulin.

Confounding Factors: User has ability to be avoid over or under delivery of insulin.

Recall Classification: Class II Recall

Example 5:

Problem: Loss of communication between pump and remote meter

Hazard: The pump may display inaccurate bolus values in the remote meter.

Clinical Implications: User confusion has potential for over or under delivery of insulin.

Confounding Factors: The bolus value is correctly displayed in the pump, and user has ability to avoid over or under delivery of insulin.

Recall Classification: Class II Recall

Example 6:

Problem: Device labeling did not adequately warn patients against exposing the pump to an MRI.

Hazard: Exposing device to MRI may damage the pump and cause an over delivery of insulin.

Clinical Implications: User may receive an over delivery of insulin.

Recall Classification: Class II Recall

Example 7:

Problem: An error in the Instructions for Use was included with the insulin pumps related to performing insulin sensitivity testing

Hazard: Patients may not know how to perform insulin sensitivity testing.

Clinical Implications: User may not be able to use their pump and/or may not administer the correct amount of insulin when using it.

Recall Classification: Class III Recall

A description of other insulin pump related recalls is provided below:

Date	Reason for Recall
2009	Approximately 2% of the infusion sets in the affected lots may not allow the insulin pump to vent properly. Venting is necessary to equalize the pressure in the syringe compartment with the surrounding atmosphere. If the vent does not work properly this could potentially result in too much or too little insulin being delivered.
2009	The up and down buttons which are used for changing the program in the menu or to administer additional insulin through a bolus delivery may experience intermittent failure or completely cease to operate.

2009	Manufacturer E has become aware of a display irregularity with their Insulin Pumps containing Model XXXX software. There have been adverse events reported that the amount of Extended Bolus delivered was not accurately displayed by the Pump. The amount of extended Bolus displayed on the Pump Home Screen 2 and in the Bolus Summary Report is less than what w
2008	Unintentional rebooting: Pump products exhibit an intermittent loss of power due intermittent loss of contact between battery cap and battery canister resulting in the device resetting. The failure of the battery cap may result in failure of the device to administer insulin therapy which may result in hyperglycemia.
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2008	display old inaccurate values for bolus amount delivered and amount of planned bolus totals.
2008	Manufacturer E has received reports of Insulin Pumps powering down without an alarm. Investigation concluded that if the battery cap is not fully tightened the Pump may power down and a brief chirp will sound. This may occur if the user has not sufficiently tightened the battery cap or if the battery cap is damaged. If a patient is asleep or does not regularly check their blood glucose levels, they may be exposed to the risks associated with severe hyper- or hypo- glycemia.
2008	Manufacturer E discovered an issue with a motor component in specific serial numbers of their Insulin Pump. This issue affects how the motor operates and may cause an over-delivery of insulin which could result in injury to the user.
2006	The battery may turn the pump off without warning due to a design change in the battery.

PART 6: QUESTIONS FOR THE PANEL

1. What factors should be taken into account when assessing the level of risk associated with an insulin pump failure?

2. What are the short term and long term risks associated with a patient changing their mode of insulin adminstration from an insulin infusion pump to an alternative mode of insulin?
3. Describe and compare the relative risks associated with continued use of a defective insulin infusion pump to the risks associated with switching to an alternative method of insulin administration. Consider the following scenarios:
    a. A pump failure that results in an interruption or under-infusion of insulin therapy
    b. A pump failure that results in an over-infusion of insulin
    c. A pump failure that results in over- and under-infusion of insulin
    d. A pump failure in which the appropriate audio and/or visual alerts and warnings are not issued.
4. Please comment on the risks for the above pump failures for children, adolescents and adults.
5. For patients using an insulin pump with a remote control, what features are critical for successful patient/pump interface?
6. What information should users and manufacturers include in their reports to FDA in order to understand the cause and severity of adverse outcomes associated with use of insulin pumps?
7. Please suggest how device manufacturers and users may be encouraged to improve and provide investigation, evaluation and follow-up when reporting device problems to FDA.

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