Analysis of the impact of FDA labeling revisions: The Fentora case study

By

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Abstract

The post marketing surveillance programs initiated by FDA are striving hard to safeguard and protect public health from drugs and biological products present in the market. Among the FDA's post marketing surveillance programs, updating the labeling information of the drugs showing adverse effects is part of surveillance. The purpose of this Fentora case study was to measure the effectiveness of FDA's labeling revisions to minimize the medication errors occurred due to prescribing, dispensing or administration of drugs. To measure the effectiveness of FDA's labeling changes drug Fentora was selected because drug Fentora was showing many medication errors. An FAERS detailed medication error report of drug Fentora from 2006-2012 was obtained. The obtained FAERS report was analyzed in contrast with FDA's labeling changes on drug Fentora. The obtained results from Fentora case study show that the measures taken by FDA's labeling revisions did not work to minimize the medication errors occurred due to prescribing, dispensing and administration of drug Fentora.

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Introduction

The drug development process is long and expensive. The Food and Drug Administration (FDA) is the organization which is responsible for the oversight of the drug development process in the United States and aims to protect and promote the public health by assuring only safe and effective drugs are allowed in the US market. The Center for Drug Evaluation and Research (CDER) is the part of the FDA with oversight for the clinical adverse events and post- market surveillance of drugs in the marketplace[1]. The post-market surveillance has become a crucial part in the drug development process as it is very difficult to anticipate all the adverse effects that are likely to be associated with an investigational drug during clinical trials involving only several hundreds to thousands of patients. It is common for newly approved drugs to exhibit different adverse effects when used by the patients. To find post marketing adverse effects of new drugs, FDA has initiated a system for post marketing surveillance and risk assessment. These FDA initiated programs identify adverse effects which did not appear during the drug development process but occurred during marketing[1]. The agency takes appropriate actions, which might include recalling the drugs from market or changing the labeling of the drugs, if the safety profile of a new drug changes.

CDER'S Risk Assessment Programs

The adverse event reporting system (AERS), part of the CDER's risk assessment program, is a computerized database used to assist the FDA's post marketing surveillance program[2]. The AERS computerized database is used to store the adverse events reports for all the drug and biologic products. The AERS system stores and allows analysis of the safety reports. The safety reports submitted to AERS are evaluated by scientists. Based on the evaluation

reports, FDA may take appropriate action. These actions include labeling changes as well as recalling the drug from market[2.]

The AERS system has evolved in the FDA Adverse Event Reporting System (FAERS) [2]. FAERS works similar to AERS, using a computerized database which has the information about adverse events and medication errors reported by consumer. According to the FDA, the only difference between the AERS reporting system and FAERS is that FAERS has included the ICH guidelines for adverse event reporting[2]. The structure of FAERS is designed on terminology based on the MEDRA dictionary for adverse events.

According to FDA, the FAERS system has over 7 million records of adverse events reported since 1969[3]. FAERS classifies the reports based on where and from whom the reports were received, which include:

domestic or international reports,
reports by healthcare professionals,
reports of patient outcomes.

Med Watch

CDER also initiated a Med Watch program for voluntarily reporting by health care professionals and public of any type of adverse events that occurred that may have been due to drugs or medical devices[1]. CDER created the Med Watch page that consists of safety information on drugs and how to report an adverse event voluntarily. All the reports submitted to Med Watch are stored into the FAERS database so- that they may be used for safety analyses. Med Watch publishes safety information about marketed drugs present.

To assure the post marketing safety of a drug, FDA conducts regular unscheduled inspections of manufacturers to confirm that they are adhering to the terms and conditions as specified in the drug approval application, FDA also verifies that standard operating procedures are being employed by the manufacturer[1].

As part of post-marketing surveillance, FDA receives reports on medication errors that occurred with either prescription drugs or over-the-counter drugs. These medication error reports are analyzed by The National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP), an independent body that aim to increase the awareness of medication errors. Medication error is defined as "any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the healthcare professional, patient, or consumer[4]". These errors could be associated with the practices of health care professionals or related to procedures such as dispensing, distribution and administration of drugs. Most of the medication errors occur as a result of misinterpretation of drug orders due to poor handwriting, confusion between the drugs with similar names, confusion between the metrics and dosing of drugs. Drug prescribing errors are made when an inappropriate drug is selected for a patient. Lack of proper knowledge about the prescribed drug, patient history and/or not knowing the recommended dose for a drug are the factors contributing to prescription errors. Dispensing errors arise at any stage starting from issuance of a prescription through dispensing of the drug by the pharmacist. These errors account for 1-24% of the medication errors. Administration errors may occur due discrepancies between the intended dose and the administered dose to the patient[4].

According to the Institute of Medicine (IOM), of the annual total of approximately 9800 deaths due to medication errors in the United States, 7000 deaths occur due to illegible

handwriting[5]. According to a report by IOM in July 2006, a majority of the medications errors occur due to improper labeling and packaging and accounts for 33% of medication errors including 30% of fatalities[5].

In 2000 the FDA received over 95,000 reports of medication errors[6]. Carol Holquist, R. Ph., Director of the Division of Medication Errors Prevention and Analysis (DMEPA) in FDA's Center for Drug Evaluation and Research stated that the number of actual events might be higher as these reports are only the voluntary ones submitted to Med Watch. The medication error reports on the marketed drugs including generic drugs, prescription drugs and over-the-counter drugs are reviewed by DMEPA. Division of Medication Errors Prevention and Analysis has established a medication error prevention program staffed with health care professionals who analyze the adverse events reports sent to Med Watch and provide possible solutions to minimize the risks occurring through these medication errors. To prevent medication errors, DPMEA also reviews the proprietary names of drugs and their labeling prior to drug approval[7]. DPMEA also works with the Institute of Safe Medication Practices (ISMP) and United States Pharmacopeia (USP).

Since the last two decades, FDA is striving hard to increase the safe use of drugs by minimizing the errors caused by unclear proprietary names, labeling and poor product design[8].

Purpose

Research Questions

- Are the measures taken by FDA for labeling revision to minimize the medication errors caused due to labeling, prescribing and administration are effective?
- Were the FDA strategies adequate in case of drug Fentora?

Background

The Food and Drug Administration stated that approximately 30,000 medication reports were voluntarily reported since 1992[1]. FDA estimates that the actual number of medication errors might be much higher compared to the voluntarily received reports.

Examples of Medication Errors

FDA enumerates the typical examples of medication errors such as a prescriber gave a prescription of 260 milligrams of Taxol for a cancer patient but the drug dispensed to the patient was Taxotere 260 milligrams, another cancer drug resulting in the death of the patient. This example comes under the dispensing error which was the mistake of the pharmacist.

A physician prescribed 20 units of insulin which, was abbreviated as 20 U in the prescription- "U" stands for zero in medical terminology, so the patient was administered 200 units of insulin leading to the patient's death. This is an example of medication error which occurred due to lack of proper communication[15].

In another incident, a woman applied six patches of the opioid Fentanyl, by mistake to her husband; he died of an overdose[15]. FDA has reported a medication error caused by the drug

methadone, drug used to treat opiate dependence which was similar to that of metadata, that is used in treating attention deficient hyperactive syndrome leading to death of the patient[15]. The error occurred as both the drugs sound similar.

These are few examples of how medication errors occur as reported to the FDA. The other reported medication errors occur due to lack of proper knowledge about the drug labeling, poor communication, confusion between the drug labels and ignorance of patients. According to Paul Seligman, Director of the Pharmacoepidemilogy and Statistical Sciences at the FDA, it is important to recognize the cause for the medication errors from the multiple factors responsible for it[15].

Regulatory approach by FDA to minimize the medication errors

In 2000, the United States Health and Human Services issued an action plan to minimize medication errors. According to Jerry Philips the former director of FDA for Medication Errors Prevention and Control announced in 2002[15] a new division in the safety field called patient safety task force to monitor medication errors.

Bar coding Label Rule

FDA proposed a new rule at the public meeting which was held in 2002 stating that drugs and biological products would require a bar code[15]. The physicians should use that bar code on the drugs while prescribing drugs, so that they prescribe suitable drugs to the suitable patients in order to avoid the medication errors caused while dispensing drugs.

According to Robert Krawisz former Director of the National Patient Safety Foundation, states that the Veteran's Administration is using bar code technology nationwide in there,

hospitals and achieved 86% reduction in medication errors over a period of 9 years[15]. Bar code rule has immensely decreased the number of medication errors caused by prescribing and dispensing errors in hospitals. FDA finalized the bar code rule on February 26, 2004 it became effective on April 26, 2004[15]. All prescription drugs, over-the-counter drugs and biological products must now contain a bar code labeling on them to minimize medication errors caused by confusion between drugs due to labeling, dosing and similarity in name.

Drug Name Confusion

To avoid confusion between drug names, FDA reviews approximately 300 drug name proposals every month. Among the reviewed names, it rejects about 200 drug names proposed by the pharmaceutical companies because they sound similar to existing drugs[15]. FDA has a 120 member health care council to review drug names assisted by a computerized technology which identifies the drug names that sound similar[15].FDA also maintains records of the drugs after their approval, and in case the approved drugs cause any errors, it distributes alerts to physicians and consumers.

Drug Labeling

The Harris interactive market research poll conducted on January 2002 for the National Council on Patient Information and Education claimed that people do not read the labeling of OTC drugs before using them. FDA has created a regulation to standardize the drug facts on the OTC drugs. Over 100,000 drugs were monitored in order to facilitate appropriate use of OTC drugs by consumers[15].

Summary of Measures to Minimize the Medications Errors

- FDA reviews over 300 drug names a month to avoid confusion between the drug names and to minimize the medication errors that arise due to similarity in name of the drugs[12].
- It also ensures that all drugs are labeled according to FDA regulations in order to minimize medication errors caused by the health care professionals.
- FDA also works with drug companies to ensure that their product design is appropriate.
- Though the Bar Code rule has been in effect since 2004, FDA ensures that every drug or biologics products has a computerized bar code[13], so that the patients would receive the correct drug and dose. It minimizes medication errors that occur during administration of drugs.
- FDA reviews approximately 1,400 reports on medication errors annually to identify the cause and tries to prevent such types of medication errors from occurring in the future.

Fentora

Fentora is one among the many drugs available in market that can cause medication errors when improperly used. Fentora was chosen as the case study to investigate the effectiveness of measures taken by FDA in terms of labeling changes aimed at minimizing medication errors.

There are many drugs used in the management of breakthrough pain in cancer. However, Fentora, an analgesic opioid is the most potent among all the drugs used. Fentora (fentanyl citrate) is used in the management of breakthrough pain in adult cancer patients[10]. It is a

prescription drug which contains fentanyl citrate as the active ingredient and is available in tablet dosage forms in doses of 100, 200, 400, 600, and 800mcg; the route of administration is through the buccal cavity and it is designed to be placed in the buccal cavity to allow maximum drug disintegration[9]. Modern oravescent technology is used in the Fentora drug delivery system to enhance the absorption of the drug in the oral cavity. Fentora, manufactured by Cephalon, was approved by FDA on September 25, 2006[14].

The patient should be above 18 years of age to use Fentora and it should be kept away from the reach of children. Fentora tablets should be used as single dose. While administering, it should be kept under the tongue or in between the teeth and gums. It should not be swallowed, chewed or sucked. Fentora is indicated only for those cancer patients who are already on opioid medicines for the management of cancer pain. It is very important to note that Fentora should be prescribed for patients who are opioid tolerant as it may cause serious adverse events or even death, if used in non-opioid tolerant patients[10].

Indications and Usage

Fentora is indicated only in the patients who are already using opioid therapy for alleviation of breakthrough pain caused by cancer[10]. It should not be used in the patients who are intolerant to opioid medications.

Dose Limitations

Only 1 dose of Fentora must be used for a single episode of breakthrough cancer pain[10].If the breakthrough pain still exists then the second dose could be used maintaining at

least a gap of 4 hours. Patients should take round-the-clock opioids while they are on treatment with Fentora[10]. Patients should not take multiple doses of Fentora at a time.

Contraindications

Fentora should not be taken along with alcohol as it causes serious adverse events[10]. It should not be taken by the patients who are not opioid tolerant as it causes serious respiratory problems. It should not be used for occasional short pain such as dental pain, headaches, and post-operative surgical pains and migraines[10].

Adverse events

The most common adverse event associated with Fentora is breathing problem which can be a life threatening if not attended by a physician[10]. It can cause pain or sores at the site of application of drug. There is a chance of drug addiction and abuse with the use of Fentora. The common side effects with Fentora are nausea, vomiting, headache and dizziness[10].

Major Factors Responsible for Causing Medication Errors with Fentora

- Lack of knowledge among physicians about the drug labeling. Often they prescribe it to the patients who are not opioid tolerant[11].
- Pharmacists dispense Fentora as a substitute to fentanyl products[11].
- Pharmacists dispense different doses of fentanyl products instead of Fentora[11].
- Physicians and pharmacists are not aware of either misuse or abuse of Fentora or addiction to Fentora by the patients[11].

Methodology

A FOIA request was sent to FDA to obtain information about medication errors associated with Fentora between 2006 and 2013. A detailed report from FDA was obtained regarding the medication errors reported to the FDA from 01-Jan-2003 to 02-Feb-2013. The FDA report consisted of medication errors reported worldwide. Errors analysis was limited to United States in this study as the scope of the research concerns reviewing strategies employed by FDA to minimize medications errors associated with drug Fentora in USA.

For the completion of this research project, an extensive literature search regarding strategies taken by FDA to minimize the medication errors associated with Fentora was performed. The data was collected from the FDA, NABP websites and search tools such as CINAHL, Pub Med were accessed through Eastern Michigan University library resources to obtain additional published research articles.

Results

FDA has revised the labeling of Fentora due to reported medication errors on a number of occasions. Fentora was approved on September 25, 2006 by FDA for the management of breakthrough pain in cancer patients who are already on the opioid therapy[16]. Fentora was initially approved with a risk minimizing action plan (Risk MAP) by FDA of concern for the post marketing safety of the drug. The goals of the RiskMAP were to avoid the use of Fentora by the non opioid users and to minimize the drug abuse and misuse[16].

Fentora Risk MAP

- The manufacturers should educate the physician, pharmacists and patients about the risks and benefits associated with the drug.
- They should implement a standard plan to avoid the use of Fentora by non opioid users and also to minimize the drug abuse and misuse.

Fentora was approved on the basis of Risk MAP strategy initiated by FDA to minimize the drug abuse and misuse[17]. FDA also insisted the manufacturers to follow the components of Risk MAP and market the product according to regulations of FDA[18]. The manufacturers started marketing Fentora with the medication guide and package insert with the indication of management of breakthrough pain due to cancer. The safety alert issued on September 13, 2007 by FDA states that the healthcare professionals and physicians should strictly abide by the labeling information mentioned in the package insert and they should not prescribe Fentora for minor pains such as headache or regular pain[20]. The FDA also issued another safety alert in January 2008 stating that Fentora might cause death and injuries[22]. Cephalon, the manufacturer of Fentora also issued Dear Healthcare Professional letters to the physicians and pharmacists on

September 10, 2007 informing them about the safety information of Fentora[21]. The letters issued by Cephalon clearly explains the usage, indication, proper dosing and avoiding substitution of Fentora with other fentanyl products and emphasized proper patient selection, dosing and administration.

Risk Evaluation and Mitigation Strategy

To ensure the safe use of drugs, FDA had introduced a new program called Risk Evaluation and Mitigation Strategy. The Food and Drug administration Amendments Act of 2007 permitted the FDA to ask for REMS from the manufacturers of the drugs to outweigh the risks and benefits of drugs to ensure the safety of the consumers[25]. FDA approved a Risk Evaluation and Mitigation Strategy for the class of transmucosal immediate release fentanyl prescription medicines (TIRF) - on December 28, 2011[26]. This was the FDA's first REMS approved for opioid drugs. The TIRF REMS program impacted the distribution of opioid products to minimize the misuse, abuse and overdosing of the drugs[26]. To ensure the safety of patients, FDA revised the label of Fentora and included Fentora into the TIRF REMS program. FDA also updated the usage and indications, precaution and warning section of the labeling of Fentora in 2011. The TIRF REMS program also requires the enrollment of physicians, pharmacists, inpatient pharmacies and outpatient pharmacies to prescribe or dispense the drug.

The TIRF REMS program has been in effect since March 2012. The TIRF REMS is designed to inform the patients about the risks associated with using Fentora products prior to the start of the treatment. This program requires patients to register the TIRF REMS program and these programs attempt to safeguard patients from misuse, abuse, overdosing of the drugs and avoid the sharing of the drugs to avoid the risk of medication errors associated with Fentora[27].

The goals of the TIRF REMS program is to minimize the risk of misuse, abuse, overdose and other associated medication errors with Fentora and ensure the safety of the patients. The medication errors caused because of the drug can be reduced by taking the following steps as mentioned in the TIRF REMS access program:

- The physicians and pharmacist dispensing the drug should make sure that it is prescribed and dispensed only to the eligible patients who are already on the round-the-clock therapy of opioids.
- They should avoid the substitution of Fentora for other fentanly products and vice versa.
- They should prevent the sharing of the fentanyl products with the patients who are not eligible to receive the drug and/or not prescribed.
- The physicians and pharmacists should be made aware of and educated about the misuse, abuse and overdosing of the drug.

FDA's Transmucosal Immediate Release Fentanyl (TIRF) REMS program started in 2012. Its aims are: educating physicians and pharmacists about the misuse, abuse and overdosing of the drug. Fentora is now available only to the registered patients in the TIRF REMS program, to prevent misuse, abuse and overdosing of Fentora and hence provide a safe course of palliative therapy for cancer patients for the management of breakthrough pain. Fentora is now available only through the TIRF REMS program to the patients who are enrolled in this program and are eligible to take this drug.

FDA has frequently revised the labeling of the drug Fentora because of its medication errors. The FDA's labeling changes are presented in chronological order in Table 1.

Date of labelling change	FDA's labelling changes
April 27, 2007[21].	Boxed warning in the labelling section is updated with the concomitant use of Fentora may cause fatal respiratory depression[21].
February 7, 2008[23]	The revised sections of the Fentora labelling include package insert, medication guide and carton containing label to enhance the safety information.
December 2, 2009	The FDA revised sections include package insert. FDA had added a language about the suicidal tendency with drug and they also updated the dosage to avoid the side effects associated with overdose of Fentora[24]
December28, 2011[26]	FDA had approved Risk Evaluation and Mitigation Strategy for the class of transmucosal immediate release fentanly prescription medicines (TIRF)
June 05, 2012	FDA again revised the labelling of Fentora and updated the boxed warning with warning of respiratory depression, medications errors and abuse potential[28]

Table1. FDA's labeling revisions on Fentora. Data obtained from FDA[26].

The medication error reports of the drug Fentora were evaluated from 2006 to 2013 to check the prime cause for medication errors. The obtained reports from the FDA were analyzed and the reports were tabulated in chronological order.

This study analyzed in detail the FOIA reports obtained from the FDA and tabulated the medication errors in chronological order (Table 2; Appendix 1)[29]

Year	No. of Fentora cases
2006	1
2007	12
2008	91
2009	99
2010	74
2011	39
2012	9
2013	1

Table2. Number of Fentora cases reported from 2006-2013. Data obtained from FOIA report from the FDA[29].

Figure 1 indicates the total number of Fentora cases from 2006-2012. The X-axis represents the years from 2006-2012 and Y-axis represents the total number of Fentora cases from 2006-2012. There is a polynomial trend line plotted on the graph, slope and R2 values are displayed on the graph.

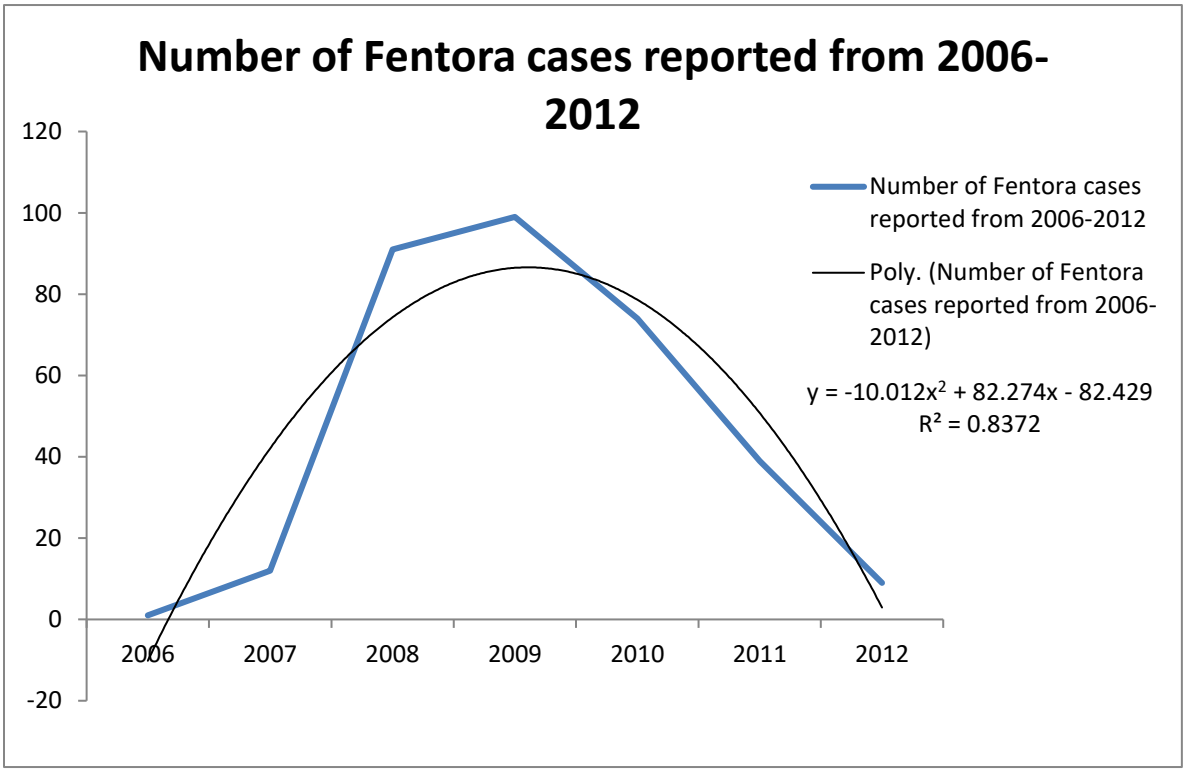

Figure1. Number of Fentora cases reported from 2006-2012[29]

Table 3 represents the Regression Analysis for the graph in Figure 1.

	df	SS	MS	F	Significance F
Regression	1	132.8928571	132.8929	0.065901	0.807630224
Residual	5	10082.82143	2016.564		
Total	6	10215.71429			

Table 3 Regression Analysis for medication errors showing slope, Ss, Ms and Significance F (P-value). Note: P=0.05 (Standard p value generally used to calculate the Significance)

Regression Analysis was performed on the number of Fentora cases reported from 2006-2012. The obtained values SS indicates the sum of the squares value and MS indicates the mean of the squares and P values indicates the significance. The obtained P value 0.807630224 indicates that there is no significance in the change of the number of cases reported from 2006-2012.

Medication errors of Fentora were plotted by month from 2006-2013. Figure 2 contains same data as Figure 1 with reports grouped by month rather than year.

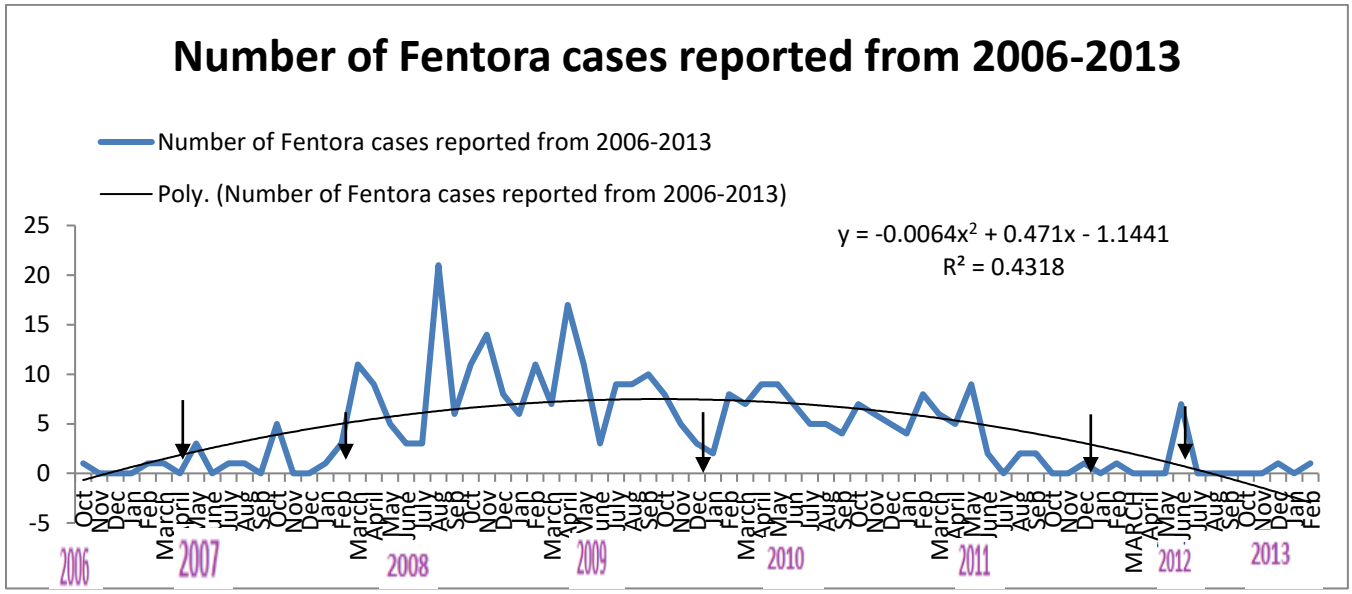

Figure2. Number of medication errors from 2006-2013 with FDA's labeling changes[29] indicated by black arrows on the following years 2007, 2008, 2009, 2011 and 2012.

Table 4 represents the Regression Analysis for Figure 2.

	df	SS	MS	F	Significance F(P - value)
Regression	1	33.9862506	33.9862506	1.722593	0.193362031
Residual	75	1479.72804	19.7297071		
Total	76	1513.71429			

Table 4 Regression Analysis for medication errors showing slope, SS, MS and Significance F (P-value). Note: P=0.05 (Standard p value generally used to calculate the Significance)

Regression Analysis was performed on the number of Fentora cases reported by months from 2006-2012. The obtained values SS indicates the sum of the squares value and MS

indicates the mean of the squares and P values indicates the significance. The obtained P value 0.193362031 indicates that there is no significance in the change in number of cases reported by month from 2006-2012.

The medication errors cases were analyzed by type, i.e., prescription errors, dispensing errors and administration errors[29]. Prescription errors occur when a patient doesn't receive right amount of medication as prescribed by a physician. Dispensing errors occur because of improper dispensing of drugs by a pharmacist. Administration errors occur due to the wrong route of administration of the correct drug. The medication errors associated with Fentora are sub-divided into prescription, dispensing and administration errors and listed in Table 5.

Year	month	Medication error	Administration error	Prescribing error	Dispensing error	Total for month	Total for Year
2006	Oct	0	0	1	0	1	
	Nov	0	0	0	0	0	
	Dec	0	0	0	0	0	1
2007	Jan	0	0	0	0	0	
	Feb	0	0	1	0	1	
	March	0	0	1	0	1	
	April	0	0	0	0	0	
	May	2	0	1	0	3	
	June	0	0	0	0	0	
	July	0	0	0	1	1	
	Aug	0	0	1	0	1	
	Sep	0	0	0	0	0	
	Oct	5	0	0	0	5	
	Nov	0	0	0	0	0	
	Dec	0	0	0	0	0	12
2008	Jan	1	0	0	0	1	
	Feb	0	0	3	0	3	
	March	3	0	8	0	11	
	April	6	0	3	0	9	
	May	0	0	5	0	5	
	June	1	0	2	0	3	
	July	0	0	3	0	3	
	Aug	8	1	12	0	21	

Year	month	Medication error	Administration error	Prescribing error	Dispensing error	Total for month	Total for Year
	Sep	1	0	5	0	6	
	0ct	5	0	5	1	11	
	Nov	8	1	5	0	14	
	Dec	0	0	7	1	8	91
	Year	month	Medication error	Administration error	Prescribing error	Dispensing error	Total for month
2009	Jan	1	0	5	0	6	
	Feb	0	1	10	0	11	
	March	0	0	6	1	7	
	April	7	0	10	0	17	
	May	2	0	9	0	11	
	June	0	0	3	0	3	
	July	2	1	6	0	9	
	Aug	3	0	6	0	9	
	Sep	2	1	7	0	10	
	Oct	4	0	4	0	8	
	Nov	0	0	5	0	5	
	Dec	1	0	2	0	3	99
2010	Jan	0	0	2	0	2	
	Feb	0	0	8	0	8	
	March	0	0	6	1	7	
	April	0	1	8	0	9	
	May	0	0	9	0	9	
	Jun	0	0	7	0	7	
	July	0	1	4	0	5	
	Aug	0	0	5	0	5	
	Sep	0	2	2	0	4	
	Oct	0	0	7	0	7	
	Nov	0	1	5	0	6	
	Dec	0	0	5	0	5	74
2011	Jan	0	1	3	0	4	
	Feb	0	1	7	0	8	
	March	0	0	6	0	6	
	April	0	1	4	0	5	
	May	0	2	7	0	9	
	June	0	0	2	0	2	
	July	0	0	0	0	0	
	Aug	0	1	1	0	2	
	Sep	0	0	2	0	2	
	Oct	0	0	0	0	0	
	Nov	0	0	0	0	0	
	Dec	0	0	1	0	1	39

Year	month	Medication error	Administration error	Prescribing error	Dispensing error	Total for month	Total for Year
2012	Jan	0	0	0	0	0	
	Feb	0	0	1	0	1	
	MARCH	0	0	0	0	0	
	April	0	0	0	0	0	
	May	0	0	0	0	0	
	June	0	3	4	0	7	
	July	0	0	0	0	0	
	Aug	0	0	0	0	0	
	Sep	0	0	0	0	0	
	Oct	0	0	0	0	0	
	Nov	0	0	0	0	0	
	Dec	0	0	1	0	1	9
2013	Jan	0	0	0	0	0	
	Feb	0	0	1	0	1	1

Table5. Fentora medication error cases by type[29].

Based on the data in Table 5, graphs were plotted for three different types of errors. The graphs are plotted based on the total number of prescription errors, dispensing errors and administration errors from 2006-2012 (Figures 3-5).

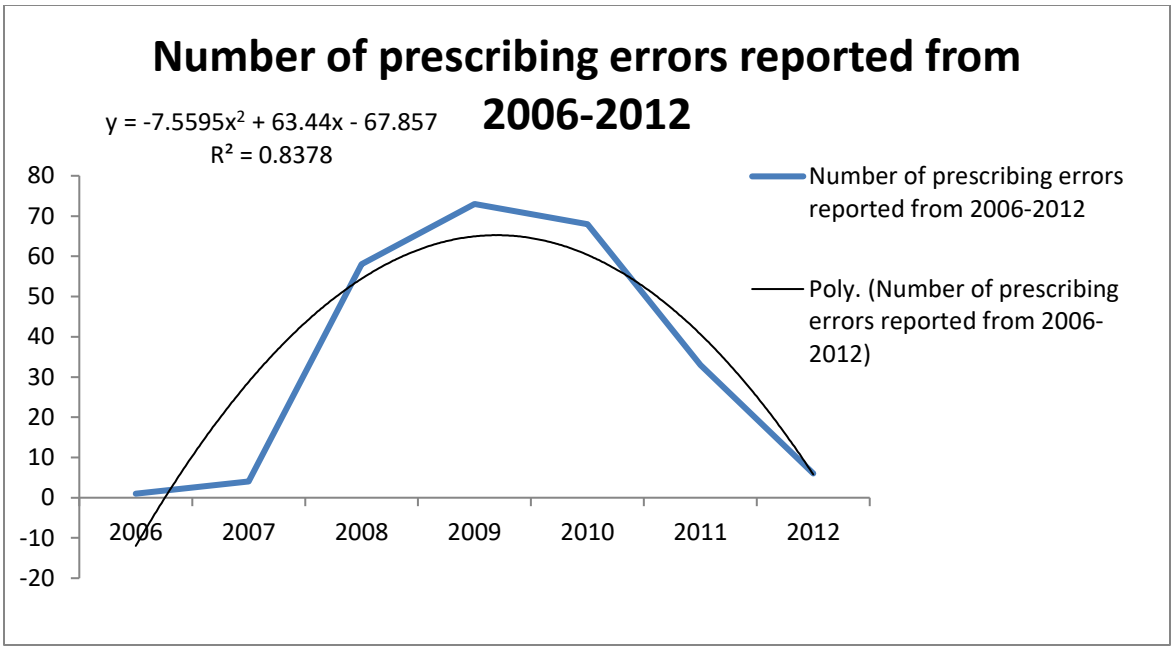

Figure3 Number of prescription errors reported from 2006-2012[29].

Table 6 contains the Regression Analysis for Figure 3.

	df	*SS*	*MS*	*F*	*Significance F*
Regression	1	246.0357	246.0357	0.21293	0.663859939
Residual	5	5777.393	1155.479		
Total	6	6023.429			

Table 6 Regression Analysis for prescription errors showing slope, SS, MS and Significance F (P-value). Note: P=0.05 (Standard p value generally used to calculate the Significance)

Regression Analysis was performed on the number of Fentora cases reported by months from 2006-2012. The obtained values SS indicates the sum of the squares value and MS indicates the mean of the squares and P values indicates the significance. The obtained P value

0.663859939 indicates that there is no significance in the total number of cases reported from 2006-2012.

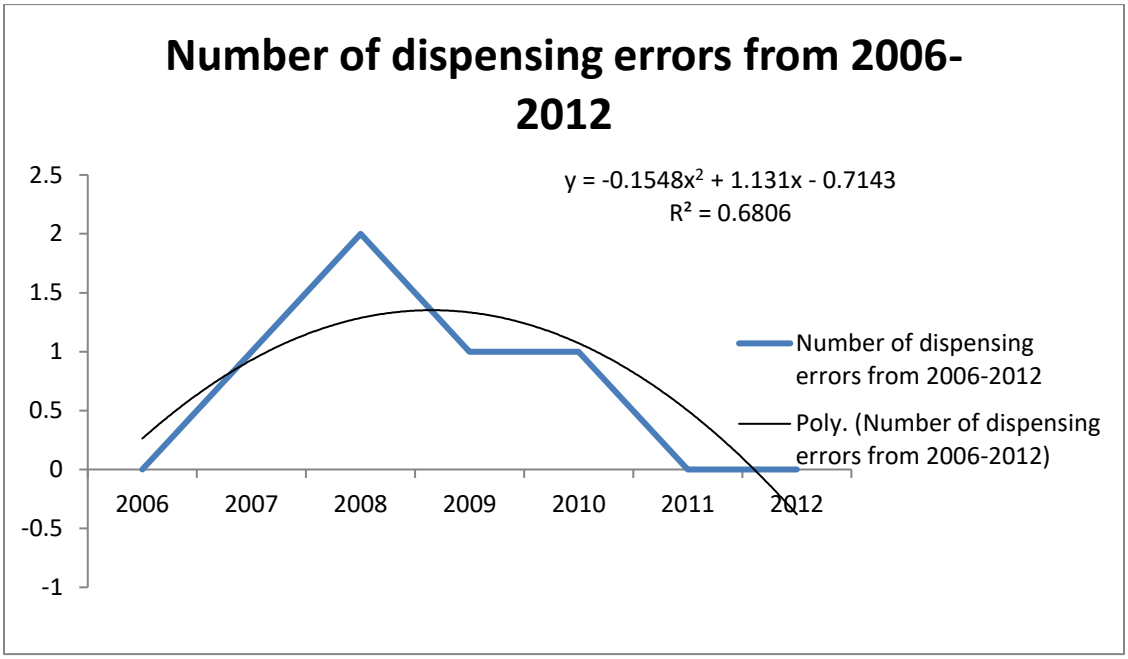

Figure4. Number of dispensing errors reported from 2006-2012[29]

Table 7 represents the Regression Analysis for Figure 4.

	df	SS	MS	F	Significance F
Regression	1	0.321429	0.321429	0.517241	0.504221085
Residual	5	3.107143	0.621429		
Total	6	3.428571			

Table 7 Regression Analysis for dispensing errors showing slope, SS, MS and Significance F (P-value). Note: P=0.05 (Standard p value generally used to calculate the Significance)

Regression Analysis was performed on the number of Fentora cases reported by months from 2006-2012. The obtained values SS indicates the sum of the squares value and MS indicates the mean of the squares and P values indicates the significance. The obtained P value 0.504221085 indicates that there is no significance in the total number of cases reported from 2006-2012.

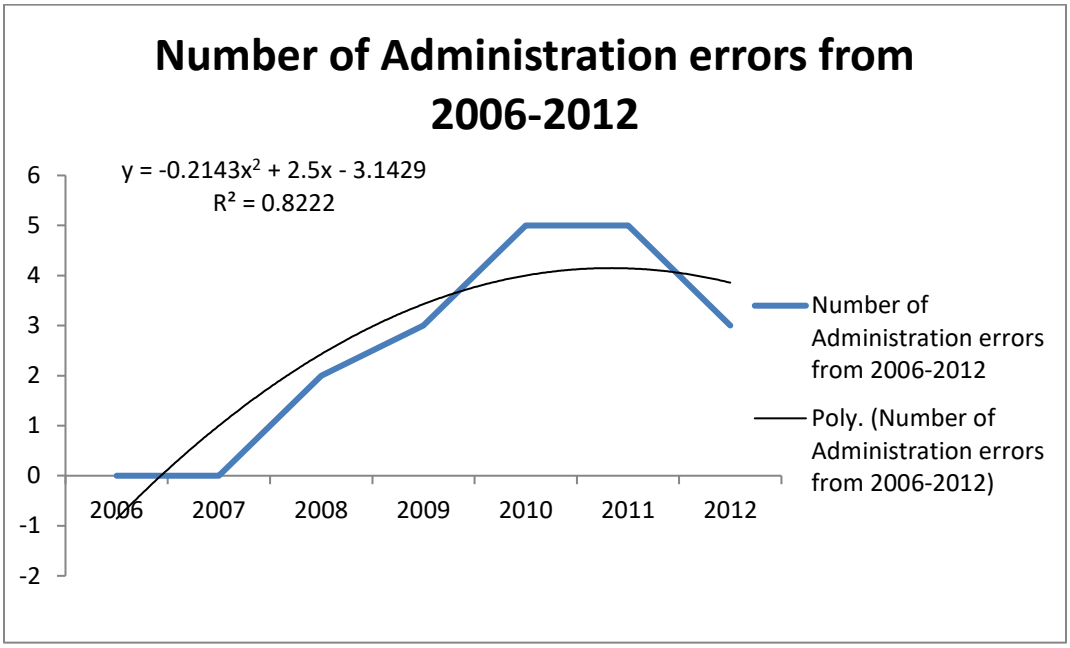

Figure5. Number of administrative errors reported from 2006-2012[29]

Table 8 represents the Regression Analysis for the Figure 5.

	df	*SS*	*MS*	*F*	*Significance F*
Regression	1	17.28571	17.28571	10.25424	0.023935637
Residual	5	8.428571	1.685714		
Total	6	25.71429			

Table 8 Regression Analysis for administration errors showing slope, Ss, Ms and Significance F (P-value). Note: P=0.05 (Standard p value generally used to calculate the Significance)

Regression Analysis was performed on the number of Fentora cases reported by months from 2006-2012. The obtained values SS indicates the sum of the squares value and MS indicates the mean of the squares and P values indicates the significance. The obtained P value 0.023935637 indicates that there is a significant increase in the total number of administration cases reported from 2006-2012.

Discussion

Based on the reports submitted to FAERS related to Fentora, FDA took regulatory action by having the manufacturer update its labeling information. FDA has periodically revised the labeling of Fentora since it was approved in 2006. As shown in table 2, the number of medication errors reported to FAERS in 2007 was 9. According to the safety alert issued by FDA on Fentora in 2007, it states that there were some deaths reported in 2007. FDA updated the labeling of Fentora in 2007 because of the deaths reported due to improper dose selection, administration to ineligible patients and improper substitution of fetanyl products for Fentora. In 2008, in spite FDA's labeling updates on Fentora, i.e., revisions to the medication guide, package insert and carton to enhance the safety information, 91 medication errors were reported. In 2009, the number of cases reported on Fentora increased to 99, resulting in additional updates to the package insert consisting of data on the suicidal risk of Fentora with instructions to physicians and pharmacists to avoid overdose. These cases occurred primarily to due to the drug misuse, abuse, overdosing and improper patient selection. As shown in Figure 1, the number of Fentora medication errors reported in 2010, 2011 and 2012 declined. According to the safety alerts issued by FDA in 2007 and 2008, majority of the medication errors caused by Fentora were associated with prescription errors made by physicians and pharmacists lacking proper knowledge about the drug.

Figure 2 shows variations during of 7 years of marketing of the medication errors reported on Fentora. The medication errors gradually increased from 12 to 99 from 2007 to 2010 in spite of FDA labeling revisions. From the above results we can infer that FDA's labeling revisions did not work in decreasing the medications errors from 2011 to 2012.

In Figure 3, a gradual increase in prescription errors occurred since drug approval in 2006 to 2010. Then there was gradual decrease in the number of prescription errors reported from 2011-2012. As shown in Table 6, P-value was not statistically significant and there was no trend seen in the number of prescription errors reported from 2006-2012. Table 7 shows no trend in the number of dispensing errors reported from 2006-2012. From the regression analysis done on the data in Table 8, the obtained P value shows there was significant trend in the increase in the total number administration errors from 2006-2012. Based on the statistics performed on all types of errors, i.e. prescription errors, dispensing errors and administration errors, only administration errors showed a significant increase from 2006-2012.

Conclusion

To measure the effectiveness of FDA mandated labeling changes on reports of medication errors, Fentora was selected as a case study. Based on reports obtained from 2006 to 2013, the FDA's regulatory actions taken on Fentora produced inconsistent results. Evaluation of Fentora medication error reports from 2006 to 2013 and FDA's labeling revisions during this period lead to the following conclusions:

- There is no significant trend in the decrease of any types of medication errors, e.g., prescription and dispensing errors.
- There was a significant increasing trend observed in case of administration errors from 2006 to 2012.
- The FDA's strategies taken to minimize the medication errors; such as updating labeling information of Fentora, were not successful.

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Appendix 1

US Medication Errors Reported from 2006 to2013 on Fentora to FAERS.
All reports were received from US and the route of administration was Buccal.

FDA received date	Preferred term	Product	Dosage	No. Of. Cases
27-oct-2006	**Drug prescribing error**	**Fentora**	**1600 UG BUCCAL**	**1**
20-Feb-2007	**Drug prescribing error**	**Fentora**	**1600 UG BID BUCCAL**	**1**
28-Mar-2007	**Drug Dispensing error**	**Fentora**	**400 UG UNK BUCCAL**	**1**
14-may-2007	**CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR**	**Fentora**	**QID BUCCAL**	**1**
24-may-2007	**Drug prescribing error**	**Fentora**	**100 UG BUCCAL**	**1**
11-july-2007	**DRUG DISPENSING ERROR**	**Fentora**	**600 UG ONCE BUCCAL**	**1**
27-aug-2007	**Drug prescribing error**	**Fentora**	**BUCCAL**	**1**
17-SEP-2007	• **INCORRECT ROUTE OF DRUG** • **INCORRECT ROUTE OF DRUG ADMINISTERED**	**Fentora**	**BUCCAL** **BUCCAL**	**2**
9-OCT-2007	**MEDICATION ERROR**	**Fentora**	**200 UG BUCCAL**	**1**
10-OCT-2007	**MEDICATION ERROR**	**Fentora**	**200 UG BID BUCCAL**	**1**
27-JAN-2008	• **MEDICATION ERROR**	**Fentora**	**400 UG UP TO FIVE TIMES DAILY BUCCAL**	**1**
4-FEB-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**800 UG Q4HR BUCCAL**	**1**
14-FEB-2008	**DRUG INEFFECTIVE**	**Fentora**	**100 UG,BUCCAL,200 UG,BUCCAL**	**1**
19-FEB-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**PRN BUCCAL**	**1**
27-FEB-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**400 UG BUCCAL**	**1**
6-MAR-2008	**MEDICATION ERROR**	**Fentora**	**400 UG BUCCAL**	**1**
17-mar-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**200 UG BUCCAL**	**1**

18-mar-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	• **400 UG BUCCAL**	**1**
21-mar-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	• **800 UG BUCCAL**	**1**
24-mar-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**BUCCAL**	**1**
27-mar-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**800 MG, BUCCAL**	**1**
31-mar-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**200 UG QID BUCCAL**	**1**
4-april-2008	**MEDICATION ERROR**	**Fentora**	**300 UG BUCCAL**	**1**
11-apr-2008	**MEDICATION ERROR**	**Fentora**	**3200 UG EVERY SIX HOURS PRN BUCCAL**	**1**
14-apr-2008	**MEDICATION ERROR**	**Fentora**	**BUCCAL**	**1**
24-apr-2008	• **MEDICATION ERROR** • **DRUG PRESCRIBING ERROR**	**Fentora**	• **BUCCAL** • **600 UG Q 1-2 HOURS BUCCAL**	**2**
28-apr-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**800 UG UNK BUCCAL**	**1**
1-may-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**200 UG BUCCAL** **400 UG BUCCAL**	**2**
7-may-2008	**CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR**	**Fentora**	**BUCCAL**	**1**
16-may-2008	**INCORRECT ROUTE OF DRUG ADMINISTRATION**	**Fentora**	**600 UG FIVE TIMES A DAY BUCCAL**	**1**
20-may-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**BUCCAL**	**1**
27-may-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**800 UG BUCCAL** **200 UG BUCCAL**	**1**
28-may-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**800 UG BUCCAL**	**1**
3-jun-2008	**MEDICATION ERROR**	**Fentora**	**BUCCAL**	**1**
12-jun-2008	• **DRUG INEFFECTIVE** • **DRUG PRESCRIBING ERROR**	**Fentora**	• **400 UG BUCCAL** • **600 UG QD BUCCAL**	**2**
17-jun-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**UNK BUCCAL**	**1**

1-jul-2008	• **DRUG PRESCRIBING ERROR**	**Fentora**	**400 UG BUCCAL**	**2**
17-jul-2008	**CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR**	**Fentora**	**400 UG TID BUCCAL**	**1**
25-jul-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**400 UG BUCCAL**	**1**
29-jul-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**400 UG BUCCAL**	**1**
1-aug-2008	**MEDICATION ERROR**	**Fentora**	**100 UG UNK BUCCAL 200 UG UNK BUCCAL**	**2**
7-aug-2008	**CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR**	**Fentora**	**BUCCAL**	**1**
13-aug-2008	**MEDICATION ERROR**	**Fentora**	**200 UG QD BUCCAL**	**1**
14-aug-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**UNK BUCCAL**	**1**
19-aug-2008	**MEDICATION ERROR**	**Fentora**	**100 UG TID BUCCAL**	**1**
25-aug-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**BUCCAL**	**1**
27-aug-2008	**MEDICATION ERROR**	**Fentora**	**400 UG QID BUCCAL**	**1**
2-sep-2008	**MEDICATION ERROR**	**Fentora**	**200 UG BUCCAL**	**1**
4-sep-2008	**CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR**	**Fentora**	**BUCCAL**	**1**
15-sep-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**BUCCAL**	**1**
24-SEP-2008	**CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR**	**Fentora**		**1**
25-sep-2008	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
26-sep-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**400 UG**	**1**
30-sep-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**BUCCAL**	**1**

6-oct-2008	**MEDICATION ERROR**	**Fentora**	**200 - 400 UG BID BID BUCCAL**	**1**
8-oct-2008	**MEDICATION ERROR**	**Fentora**	**200 UG BUCCAL**	**1**
10-oct-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**400 UG BUCCAL**	**1**
14-oct-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**400 UG EVERY 6 HOURS BUCCAL**	**1**
16-oct-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**100 UG BUCCAL**	**1**
22-oct-2008	**MEDICATION ERROR**	**Fentora**	**200 UG QD BUCCAL**	**1**
23-oct-2008	**CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR**	**Fentora**	**800 UG BUCCAL**	**1**
27-oct-2008	**MEDICATION ERROR**	**Fentora**	**600 UG BUCCAL**	**1**
30-oct-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**BUCCAL**	**1**
3-nov-2008	**MEDICATION ERROR**	**Fentora**	**400 UG BUCCAL**	**1**
4-nov-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**600 UG QID PRN BUCCAL**	**1**
5-nov-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**800 UG Q4-6HR PRN, MAY TAKE ANOTHER 1 H LATER BUCAL**	**1**
10-nov-2008	**MEDICATION ERROR**	**Fentora**	**1600 UG Q3HR BUCCAL**	**1**
12-nov-2008	**MEDICATION ERROR**	**Fentora**	**BUCCAL**	**1**
17-nov-2008	**DRUG DIVERSION**	**Fentora**	**400 UG, BUCCAL**	**1**
19-nov-2008	**MEDICATION ERROR**	**Fentora**	**200 UG PRN BUCCAL**	**1**
28-nov-2008	**MEDICATION ERROR**	**Fentora**	**400 UG TITRATED FROM 200-400MCG QD PRN BUCCAL**	**1**
2-dec-2008	• **DRUG PRESCRIBING ERROR** • **INCORRECT ROUTE OF DRUG ADMINISTRATION**	**Fentora**	**BUCCAL** **BUCCAL**	**2**
3-dec-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**400 UG QID BUCCAL**	**1**
4-dec-2008	**DRUG DISPENSING ERROR**	**Fentora**	**BUCCAL**	**1**
11-dec-2008	**DRUG PRESCRIBING**	**Fentora**	**400 UG QID BUCCAL**	**1**

	ERROR			
12-dec-2008	**DRUG PRESCRIBING ERROR**	**Fentora**	**BUCCAL**	**1**
8-jan-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**100 UG BUCCAL**	**1**
22-jan-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**600 UG BUCCAL**	**1**
2-feb-2009	**DRUG ADMINISTRATION ERROR**	**Fentora**	**BUCCAL**	**1**
3-feb-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**800 UG QID BUCCAL**	**1**
17-feb-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**600 UG BUCCAL**	**1**
19-feb-2009	**DRUG INEFFECTIVE**	**Fentora**	**800 UG SUBLINGUAL**	**1**
23-feb-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**200 UG BUCCAL**	**1**
25-feb-2009	**INCORRECT ROUTE OF DRUG ADMINISTRATION**	**Fentora**	**1600 MCG (400 MCG, 4 IN 1 D) QD BUCCAL**	**1**
27-feb-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**300 UG BUCCAL**	**1**
6-mar-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**BUCCAL**	**1**
11-mar-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**200 UG BUCCAL**	**1**
23-mar-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**(200 MCG, QIS AS NEEDED), BU**	**1**
27-mar-2009	**INTERCEPTED DRUG DISPENSING ERROR**	**Fentora**	**(400 MCG), BU**	**1**
6-apr-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**BU**	**1**
9-apr-2009	**MEDICATION ERROR**	**Fentora**	**12000 MCG (800 MCG, 15 IN 1 D), BU**	**1**
16-apr-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**9600 MCG (600 MCG, 2 IN 3 HR), BU**	**1**
21-apr-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**BU**	**1**
22-apr-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**800 MCG, 2-3 TABLETS EVERY 6-8 HOURS, BU**	**1**
29-apr-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**BU**	**1**
30-apr-2009	**MEDICATION ERROR**	**Fentora**	**BU**	**1**
7-may-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**BU**	**1**

11-may-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**(800 MCG), BU**	**1**
12-may-2009	**MEDICATION ERROR**	**Fentora**	**(200 MCG,3-4 TABLETS DAILY AS NEEDED), BU; (400 MCG,1-2 TABLETS DAILY AS NEEDED),BU**	**1**
14-may-2009	**CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR**	**Fentora**	**BU**	**1**
18-may-2009	**CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR**	**Fentora**	**BU**	**1**
26-may-2009	**CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR**	**Fentora**	**BU**	**1**
27-may-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**BU**	**1**
9-jun-2009	**INCORRECT DOSE ADMINISTERED**	**Fentora**	**BU**	**1**
23-jun-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**400 MCG (400 MCG, 1 IN 1 AS REQUIRED), BU 600 MCG (600 MCG, 1 IN 1 AS REQUIRED) BU**	**1**
14-jul-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**(800 MCG), BU**	**1**
16-jul-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**BU**	**1**
17-jul-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**600 MCG, BUCCAL**	**1**
24-jul-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**800 MG, BU**	**1**
29-jul-2009	**MEDICATION ERROR**	**Fentora**	**(400 MCG),BU**	**1**
3-aug-2009	**MEDICATION ERROR**	**Fentora**	**BU**	**1**
6-aug-2009	**CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR**	**Fentora**	**BU**	**1**
21-aug-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**400 MCG, BU**	**1**
2-sep-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**BU**	**1**

4-sep-2009	**CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR**	**Fentora**	**(200 MCG), BU**	**1**
8-sep-2009	**CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR**	**Fentora**	**1600 MCG (400 MCG, 1 IN 6 HR), BU**	**1**
16-sep-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**600 MCG, 03-4 HRS PRN, BU; 800 MCG, Q-3-4 HRS PRN; BU**	**1**
21-sep-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**(400 MCG,TID AS NEEDED),BU**	**1**
24-sep-2009	**MEDICATION ERROR**	**Fentora**	**(400 MCG,CAN'T RECALL FREQUENCY),BU**	**1**
6-oct-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**1-2 TABLETS Q 4 PRN), BU**	**1**
8-oct-2009	**MEDICATION ERROR**	**Fentora**	**BU**	**1**
13-oct-2009	**MEDICATION ERROR**	**Fentora**	**BU**	**1**
19-oct-2009	**MEDICATION ERROR**	**Fentora**	**12800 MCG (1600 MCG, 1 IN 13 HR), BU**	**1**
26-oct-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**(200 MCG),BU**	**1**
29-oct-2009	**MEDICATION ERROR**	**Fentora**	**400 MCG, BU**	**1**
13-nov-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**BU**	**1**
16-nov-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**BU**	**1**
27-nov-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**BU**	**1**
15-dec-2009	**DRUG PRESCRIBING ERROR**	**Fentora**	**200 MCG (200 MCG, 1 IN 1 AS REQUIRED),BU**	**1**
22-dec-2009	**CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR**	**Fentora**	**BU**	**1**
11-jan-2010	**DRUG PRESCRIBING ERROR**	**Fentora**	**BU**	**1**
13-jan-2010	**DRUG PRESCRIBING ERROR**	**Fentora**	**1600 MCG (400 MCG, 4 IN 1 D), BU**	**1**
22-jan-2010	**DRUG PRESCRIBING ERROR**	**Fentora**	**(400 MCG, EVERY 4-6 HOURS PRN), BU**	**1**
4-feb-2010	**DRUG PRESCRIBING ERROR**	**Fentora**	**(200 MCG), BU**	**1**

12-feb-2010	**DRUG PRESCRIBING ERROR**	**Fentora**	**2400 MCG (800 MCG, 3 IN1 D), BU**	**1**
19-feb-2010	**DRUG PRESCRIBING ERROR**	**Fentora**	**BU**	**1**
25-feb-2010	**DRUG PRESCRIBING ERROR**	**Fentora**	**(400 MCG), B**	**1**
8-mar-2010	**INTERCEPTED DRUG DISPENSING ERROR**	**Fentora**		**1**
17-mar-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
19-mar-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
26-mar-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
16-apr-2010	• **INCORRECT ROUTE OF DRUG ADMINISTRATION** • **DRUG PRESCRIBING ERROR**	**Fentora**		**2**
20-apr-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
21-apr-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
22-apr-2010	• **MEDICATION ERROR** • **DRUG PRESCRIBING ERROR**	**Fentora**		**3**
28-apr-2010	**MEDICATION ERROR**	**Fentora**		**1**
30-apr-2010	**CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR**	**Fentora**		**1**
3-may-2010	**DRUG PRESCRIBING ERROR**	**Fentora**	**BI**	**2**
11-may-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**2**
13-may-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
14-may-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**2**
18-may-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
21-may-2010	**DRUG PRESCRIBING**	**Fentora**		**1**

	ERROR			
24-may-2010	**INCORRECT ROUTE OF DRUG ADMINISTRATION**	**Fentora**		**1**
28-may-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
1-jun-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
9-jun-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
10-jun-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
15-jun-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
16-jun-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
18-jun-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
28-jun-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
2-jul-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**2**
14-jul-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
15-jul-2010	• **DRUG ADMINISTRATION ERROR** • **DRUG PRESCRIBING ERROR**	**Fentora**		**2**
27-jul-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
28-jul-2010	**CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR**	**Fentora**		**1**
3-aug-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
4-aug-2010	• **DRUG PRESCRIBING ERROR** • **DRUG PRESCRIBING ERROR**	**Fentora**		**2**
6-aug-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
18-aug-2010	**CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO**	**Fentora**		**1**

	MEDICATION ERROR			
26-aug-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**2**
2-sep-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
3-sep-2010	**POOR QUALITY DRUG ADMINISTERED**	**Fentora**		**1**
8-sep-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
14-sep-2010	**CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR**	**Fentora**		**1**
30-sep -2010	**DRUG ADMINISTRATION ERROR**	**Fentora**	**100 MCG, BU**	**1**
21-oct-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
22-oct-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
25-oct-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
26-oct-2010	• **DRUG PRESCRIBING ERROR** • **DRUG PRESCRIBING ERROR**	**Fentora**	**(400 MCG) BU** **BU**	**2**
28-oct-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
29-oct-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
2-nov-2010	**DRUG PRESCRIBING ERROR** • **DRUG PRESCRIBING ERROR**	**Fentora**	**BU** **(800 MCG) BU**	**2**
16-nov-2010	**CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR**	**Fentora**		**1**
22-nov-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
24-nov-2010	**DRUG PRESCRIBING ERROR**	**Fentora**	**400 MCG, BU**	**1**
30-nov-2010	• **DRUG PRESCRIBING ERROR** • **CIRCUMSTANCE OR**	**Fentora**		**2**

	INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR			
3-dec-2010	• **DRUG PRESCRIBING ERROR** • **DRUG PRESCRIBING ERROR**	**Fentora**	**4800 MCG (800 MCG, 6 IN 1 D), BU**	**2**
7-dec-2010	**DRUG PRESCRIBING ERROR**	**Fentora**	**BU**	**1**
16-dec-2010	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
20-dec-2010	**DRUG PRESCRIBING ERROR**	**Fentora**	**(1600 MCG (400 MCG, 4 IN 1 D) BU) (800 MCG (200 MCG, 4 IN 1 D) BU)**	**1**
24-jan-2011	**CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR**	**Fentora**		**1**
28-jan-2011	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
11-feb-2011	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
9-mar-2011	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
10-mar-2011	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
11-mar-2011	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
30-mar-2011	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
15-apr-2011	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
28-apr-2011	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
3-may-2011	**CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR**	**Fentora**		**1**
5-may-2011	• **DRUG PRESCRIBING ERROR** • **POOR QUALITY DRUG ADMINISTERED**	**Fentora**		**2**
10-may-2011	**DRUG ADMINISTRATION**	**Fentora**		**2**

	ERROR			
16-may-2011	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
17-may-2011	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
18-may-2011	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
20-may-2011	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
26-may-2011	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
3-jun-2011	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
16-jun-2011	**CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR**	**Fentora**		**1**
20-jun-2011	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
25-JUN-2011	• **INCORRECT ROUTE OF DRUG ADMINISTRATION** • **CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR**	**Fentora**		**2**
11-aug-2011	**CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR**	**Fentora**		**2**
24-aug-2011	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
23-sep-2011	**DRUG PRESCRIBING ERROR**	**Fentora**		**1**
16-dec-2011	**DRUG PRESCRIBING ERROR**	**Fentora**		**2**
24-feb-2012	• **INTENTIONAL DRUG MISUSE** • **DRUG PRESCRIBING ERROR**	**Fentora**	**PRN**	**2**

19-jun-2012	**DRUG INEFFECTIVE**	**Fentora**		**1**
20-jun-2012	• **DRUG PRESCRIBING ERROR**	**Fentora**		**1**
3-dec-2012	• **Drug prescribing error** • **Hypersensitivity**	**Fentora**		**2**
27-feb-2013	**Drug prescribing error**	**Fentora**	**2400 Microgram Daily;**	**2**