#1319

Public Citizen

Buyers Up • Congress Watch • Critical Mass • Health Research Group • Litigation Group

Joan Claybrook, President

January 25, 1994

Dr. David Kessler
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville MD 20857

Dear Dr. Kessler:

As you are aware, the FDA recently approved a narcotic lollipop (Oralet-Abbott) containing the extremely potent (20-30 times more powerful than morphine) and widely-abused narcotic, fentanyl, as a premedication for children who are about to undergo anesthesia. We urge you immediately to reverse this dangerous and ill-conceived decision by the FDA's Center for Drug Evaluation and Research before any of these narcotic lollipops are used by children and before the first child is killed by this potentially deadly drug/candy. This will inevitably happen if you do not act to prevent sales of this product.

This drug, if marketed, would be the second non-injectable dosage form of fentanyl to be approved and used in the last several years in the United States. The first, Duragesic, a fentanyl patch made by the originator of fentanyl, Janssen Pharmaceutica, has already been associated with 58 deaths in the three years since it came onto the market for treatment of chronic pain in patients requiring opioid (narcotic) pain relief. Although some of these deaths were in older patients with cancer, other deaths, according to our analysis of FDA adverse reaction reports, have occurred in perfectly healthy younger people who were prescribed the drug for unapproved uses such as the relief of post-operative pain. One such example was a 17-year-old young man from Florida who went to an oral surgeon in January, 1993, for wisdom teeth extractions, was given the fentanyl patch, and was found dead by his mother the next morning. In addition, according to FDA information, there were deaths in a 9-year-old who girl from New Jersey who had a tonsillectomy, a 29-year-old North Carolina man with sickle cell anemia, and a 33-year-old California man with chronic back pain.

Just last week, ironically, the FDA announced that Janssen was strengthening the warnings on Duragesic "[b]ecause of serious or life-threatening breathing problems" and that, heretofore,

2000 P Street NW • Washington, D.C. 20036 • (202) 833-3000

the patch was "not to be used by children under age 12 or by patients under age 18 who weigh less than 110 pounds, except in research settings." It was also stated that "the patch should be used only by patients who are already on and tolerant to opioid [narcotic] therapy...".

The fentanyl lollipop, however, will be used mainly by children under the age of 12 who are not tolerant of narcotics. Whereas the patch, especially for cancer patients with overwhelming pain who have not responded to non-narcotic painkillers, offers an important advantage over other drugs (if it can be used safely), the use of or any unique advantage of the lollipop is highly questionable at best.

In many other respects, the patch and the lollipop are similar: both contain the same potent narcotic, fentanyl, with its potentially serious complication of respiratory depression; both show wide variation in the blood fentanyl levels delivered; both drug delivery forms are attractive for unapproved ("off-label") use. As predicted, the fentanyl patch (Duragesic) has already found its way into unapproved uses and has caused death due to respiratory depression. Despite warnings that Duragesic was not approved and potentially unsafe for post-operative pain control, death has resulted in previously healthy people when it was used for just that reason. We can be sure that similar off-label use of the fentanyl lollipop, away from the safety of the operating room with its trained anesthesiology personnel, will indeed occur causing respiratory depression and death.

The FDA has an obligation to protect the American public against the use of potent, potentially dangerous drugs when used for off-label indications. Putting warnings on package inserts is not enough; the experience with Duragesic should tell us that. Nor is it enough for the FDA to simply instruct the sponsoring drug company to develop a restricted marketing and detailing campaign. The risks associated with predictable off-label use should be factored into any risk/benefit consideration before a new drug's approval. Public Citizen believes that the predictable off-label risks associated with fentanyl lollipops are far too great and the potential benefits far too few. By hiding behind the warnings inserted on the label, the FDA is neglecting its responsibility and needlessly risking the lives of American children.

Background

Almost nine years ago, at a closed April, 1985 meeting of an FDA Advisory Committee on Anesthetic and Life Support Drugs, there was a presentation by anesthesiologist Dr. Ted Stanley about research being done involving the use of fentanyl "lollipops" as a "premedicant to anesthesia". After the presentation, according to cryptic minutes from this otherwise secret meeting, "it was suggested [by the Advisory Committee] to Dr. Stanley that a drug other than fentanyl be looked into because fentanyl has too long of a duration and a slow onset of action."

Public Citizen Health Research Group became involved in the issue of fentanyl lollipops five years ago, thanks to a concerned call and correspondence from the patent-holder and major manufacturer of the drug, Janssen. Stating that the company had been approached by Dr. Stanley and his colleagues to consider the licensing and marketing of fentanyl lollipops, Janssen wanted

to know what we thought about the idea and subsequently sent information from the clinical trials which had been completed as of then.

In a December 7, 1988 Janssen letter to Dr. Sidney Wolfe, after discussing some of the possible advantages of the new dosage form, the company concluded that **"There is also the question of a controlled substance in a candy matrix. This is the issue that most concerns us at Janssen Pharmaceutica. The real question here is whether the potential advantages and benefits of the OTFC [oral transmucosal fentanyl citrate] for pediatric patients outweigh the possible negative connotation of an abusable substance in candy."**

On the safety side, the company added that there were also some areas of potential concern, including "the need to schedule sufficient time for this premedication" (the time of peak effect for OTFC is approximately 15-30 minutes). **"There is also a potential for delayed post operative recovery as well as a possible increase in nausea and vomiting. There is need to monitor oxygen saturation and vital signs and a significant degree of facial pruritus [itching]."**

After reviewing the published literature and the information the company had sent as well as discussing the issue with a DEA official who told me that the agency was more concerned about detecting the diversion of fentanyl in lollipop form than in the existing approved dosage forms, we advised Janssen that the idea of marketing fentanyl lollipops was a dangerous idea and hoped the company would turn down the offer. We subsequently learned that for the reasons stated above and for "business" reasons, they said no. Unfortunately, although Janssen said "no" to Dr. Stanley's request, Abbott Laboratories (under license to Anesta Corporation) said "yes" and it is that company which has slated the fentanyl lollipop for marketing.

Method

This report is based on the information supplied in the following documents and data sets:

1. The fentanyl lollipop (Oralet) package insert (FDA approved but not yet marketed)
2. The fentanyl patch (Duragesic) package insert (FDA approved 09/07/90 and marketed several months later)
3. A transcript of the 09/14/93 meeting of the FDA Anesthetic and Life Support Advisory Committee and the Drug Abuse Advisory Committee regarding the fentanyl lollipop.
4. FDA documents regarding the Duragesic NDA (new drug application) including:
   a. The Approval Letter dated 09/07/90
   b. The Medical Officer's Reviews 05/22/90 and 07/16/90
   c. The Pharmacologist's Review 03/11/88
   d. The Chemist's Review 07/17/90
   e. The Bio/Dissolution Review 07/17/90
5. Duragesic Adverse Drug Reports from 05/01/91 to 09/31/93 which were released to us by the FDA pursuant to the Freedom of Information Act.

Additional information was obtained from discussions with experts including a pediatric pharmacologist, and a pediatric anesthesiologist as well as from relatives of patients who died as a result of Duragesic.

Similarities Between the Fentanyl Patch and the Lollipop

The following are reasons why the fentanyl patch experience foreshadows future deaths associated with the fentanyl lollipop.

1. **It is the same drug with the same safety concerns.**

For more than 20 years, fentanyl has proven to be a useful and potent analgesic (painkiller) when used intravenously in the operating room. However, fentanyl can commonly slow or stop breathing (referred to as hypoventilation and apnea respectively) as well as cause itching, nausea and vomiting. Hypoventilation and apnea can be easily and safely managed in an operating room by a trained anesthesiologist with the appropriate monitors and other equipment. However, unrecognized and uncorrected apnea will quickly lead to death. The ability to quickly recognize hypoventilation and to correct it is essential for the safe use of this drug.

Hypoventilation and apnea are usually dose related; the higher the dose the more likely these dangerous side effects. When the issue was reviewed by Dr. Curtis Wright, Acting Director of the FDA Pilot Drug Evaluation Staff, in conjunction with approval of the fentanyl patch, he described a 50% reduction in ventilation at serum levels of 3-4 ng/ml. He then stated that "a reasonable Ctox [the blood level that causes significant toxic side effects] for fentanyl in the non-tolerant patient is probably 2.5 ng/ml, although the data could support a Ctox of 2.0 and a Ctox of 3.0 equally well."[1] The same issue of fentanyl-induced hypoventilation is visited in the fentanyl lollipop's package insert; it states that "hypoventilation is most frequently seen with blood levels in the range of 3-4 ng/ml" although a Ctox is not specified. Even though fentanyl-induced hypoventilation is usually dose dependent, as the patch's package insert warns, "Hypoventilation can occur throughout the therapeutic range of fentanyl serum concentrations."[2]

When reviewing the patch, Dr. Wright estimated that the minimum effective concentration (MEC) for fentanyl is about 0.5-0.75 ng/ml for its analgesic properties.[3] This means that a serum concentration at this level provides the desired analgesic effect in 50% of patients. The lollipop's package insert states that "fentanyl provides effects ranging from analgesia at blood levels of 1-2 ng/ml ..." which is more that twice the MEC which Dr. Wright indicated is associated with the fentanyl patch.[4] The main effect intended for the lollipop is, however, not analgesia but rather anxiolysis (reduction in anxiety) and sedation in children about to undergo anesthesia. For this purpose, the lollipop's insert does not mention any MEC nor does it compare the MEC needed for anxiolysis with that needed for analgesia. One can only assume from the data provided that anxiolysis carries a MEC in the range of 0.5-2.0 ng/ml.

It is very apparent that, for fentanyl, there is only a small difference in serum concentration between a level of 0.6 ng /ml that is required for adequate analgesia (and

presumably anxiolysis) and a level of 2.0-3.0 ng/ml in which range there is a significant risk of hypoventilation. (According to FDA documents, 17% of adults using the patch developed hypoventilation at blood levels of 2.0-2.5 ng/ml.) It is obvious that for any fentanyl drug delivery system to be considered safe, it has to **reliably** deliver serum fentanyl concentrations between 0.6 and 2.0 ng/ml.

2. **Both products are marketed in drug delivery forms which are attractive to patients and easy to use by doctors.**

Both the lollipop and the patch are easy to administer and readily accepted by patients. Neither are associated with the unpleasantries of suppositories or painful intramuscular or intravenous injections.

3. **The patch and the lollipop are both new, previously untried narcotic delivery systems.**

The fentanyl patch was the first product approved to deliver a narcotic by way of an extended release skin patch. Similarly, the fentanyl lollipop is the first product ever planned for marketing to deliver a narcotic by the oral transmucosal route.

4. **Both products produce inconsistent and frequently dangerously high blood fentanyl levels.**

In clinical trials, both the patch and the lollipop have shown a wide variation between patients in both the maximum serum fentanyl concentration (Cmax) and the time of maximum concentration (Tmax). The lollipop (Figure 2 of the package insert) has an average Cmax of 2.7 ng/ml in adults and 2.0 ng/ml in children (standard deviation approximately 0.8 ng/ml).[3] Similarly, the FDA medical officer's review of the fentanyl patch (the 75 ug/hr strength) revealed a Cmax of 1.84 ng/ml (standard deviation 0.85 ng/ml).[4] The variation of Tmax for the lollipop (mean 23 minutes, range 13-30 minutes) is considerable; the Tmax seen with the patch is also very variable (mean 23 hours, range 12-72 hours). Moreover, the coefficients of variation (CV) for Cmax, a relative measure of variability, are very high at 30% and 40% for the 75 ug/hr patch and the lollipop respectively. (Please see Table I for a summary of the pharmacokinetic studies of the fentanyl patch which were available to us. Similar comprehensive data on the fentanyl lollipop has not been made available by either the FDA or its sponsor, Abbott Laboratories.) Dr. Curtis Wright commented in 1990 that, with the patch, "there is a large variation in the blood level of the drug supplied by the system in clinical trials and that not all of this variation is due to individual variation in clearance."[3]

One can see from this data that a significant proportion of individuals given these products will develop serum fentanyl levels in excess of the level associated with toxic side effects namely hypoventilation. These variations in serum concentration, therefore, make both the patch and the lollipop unreliable in providing therapeutic but not toxic fentanyl levels.

Table I

Summary of Pharmacokinetic Studies of Duragesic[a]

Patch Dosage	50 ug/hr[b]	75 ug/hr[c]	100 ug/hr[d]
Studies (no.)	4	5	4[e]
N (total)	33	58	50
Cmax[f] - Range	0.87-1.59	1.28-1.88	2.01-3.13
- C.V.[g]	30-50%	36-65%	34-56%
Tmax[h] - Range	16-24	22-35	20-56
- C.V.[g]	20-40%	22-58%	25-82%

[a] only studies from the FDA documents are included where summary data is available
[b] studies 85-005-3, 85-038-01, 85-038-02, 86-046-01
[c] studies 85-052-02, 89-006, 86-042-02, 87-046-02, 85-052-01
[d] studies 89-006, 88-032, 85-005-02, 85-042-02
[e] study 85-030-02 omitted as Tmax and Cmax not included in FDA documents
[f] mean maximum serum concentration in ug/ml
[g] the range of the Coefficients of Variation {C.V. = (Mean/SD) X 100}
[h] mean time to maximum concentration in hours

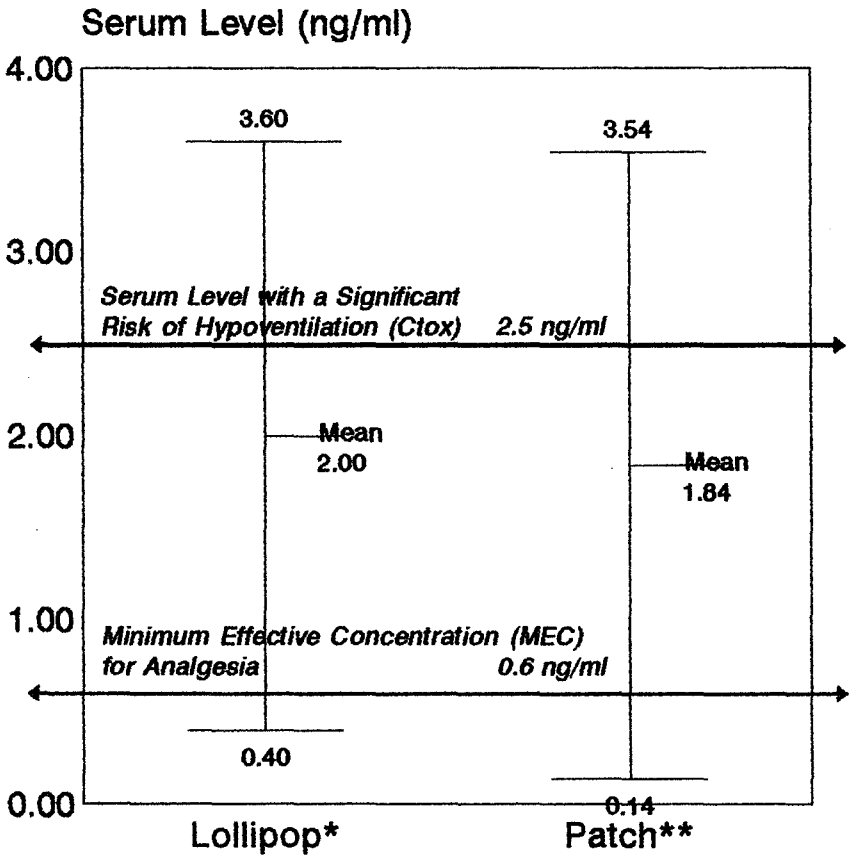
Figure I, on the following page, compares the mean maximum serum fentanyl concentration (Cmax) for the Duragesic patch (the 75 ug/hr dose) and the mean Cmax for the lollipop (as well as their respective 95% confidence limits). (The established minimum effective serum concentration (MEC) for analgesia and the serum level associated with a significant risk of hypoventilation (Ctox) are also displayed for comparison.) It is clear that many patients using the lollipop will have maximum serum concentrations of over 3 ng/ml with the highest level recorded in a clinical trial being 4.6 ng/ml. As the lollipop package insert states, "Hypoventilation is most frequently seen with blood levels in the range of 3-4 ng/ml." As mentioned above, with the patch, there was a 50% reduction in ventilation with serum levels of 3-4 ng/ml.

5. **Both the lollipop and the patch have a similar rate of hypoventilation.**

In clinical trials with the patch, 13 out of 357 patients (3.6%) had hypoventilatory episodes.[8] The lollipop package insert states that 6% of patients had slowed or arrested respirations.[9] However, when Dr. Laura McNicholas, Assistant Professor at the Philadelphia VA Medical Center, reviewed the data for the FDA Anesthetic and Life Support Advisory Committee meeting on August 24, 1993, she described an alarming hypoventilatory rate of 16% with the lowest lollipop dose when used in non-O.R. settings.[10] Anesta Corporation, the lollipop's sponsor, along with Abbott Laboratories, has refused to provide us with the raw data to which Dr. McNicholas was referring. (As

Figure I

DANGEROUS SIMILARITIES BETWEEN PATCH AND LOLLIPOP SERUM FENTANYL LEVELS



Mean Max. Serum Level (Cmax) with 95% CI

*in children
**75 ug/hr strength

mentioned above, FDA documents report that 17% of patients participating in the clinical trials of the patch with blood levels between 2.0 and 2.5 ng/ml were reported to have had hypoventilatory episodes.)

6. **Both the lollipop and the patch are attractive for off-label use.**

With the patch, one of the most "useful" (albeit unsafe) indications is in post-operative pain management. The patch can provide adequate pain control throughout the night, permitting the patient to sleep uninterrupted. At present, there is a scarcity of preparations which provide this type of relief. Hypoventilation following surgery, however, cannot be reliably detected and managed at a patient's bedside at home (or often at the hospital in the absence of monitoring).

A product which provides easily delivered analgesia and sedation to children (such as the fentanyl lollipop) is likely to be found most useful in sedating children prior to painful procedures. Providers skilled at providing care to children often complain that there is a real paucity of products which serve this function. It is for this reason that Dr. Max Schneider states that the lollipop "is a very appealing technique of pacifying people."[11] Unfortunately, the locations where these painful procedures are often performed are poorly equipped with the equipment or personnel needed to adequately detect and manage hypoventilation and apnea. Despite warnings on the label that "the patient should be attended at all times by a health care professional skilled in airway management and resuscitative measures" and "some means of measuring respiratory function is recommended, such as pulse oximetry", off-label use will inevitably occur if the marketing of the lollipop is allowed.

7. **Prior to approval, the FDA and some of the members of its advisory committee had serious concerns about the safety of the lollipop. Similar concerns were expressed by the FDA prior to approval of the patch.**

Dr. Marilyn Harper, Clinical Professor of Anesthesiology at the University of California, San Francisco and a member of the FDA Anesthetic and Life Support Advisory Committee which studied the lollipop, stated, at an August 24, 1993 FDA Advisory Committee meeting, that she had a "high degree of nervousness about having it used all over the hospital" because of concerns about unrecognized hypoventilation.[12] Dr. McNicholas echoed this sentiment when she stated that there is probably no safe setting for the lollipop's use other than in the OR where there is adequate monitoring, support, and capacity for intervention.[13] Dr. Max Schneider, a gastroenterologist and another member of the Committee, paralleled this comment when he said that "...there is a myriad of areas where this product should not be used..."[14] Similarly, Dr. Curtis Wright commented that "I have serious concerns about this product outside of its use under direct observation of an anesthesiologist."[15]

Similar sentiments were echoed in the Medical Officer's Review which was conducted before the fentanyl patch approval in 1990. In this review, Dr. Wright stated "one of the factors which has prolonged the review process for TTS fentanyl [the fentanyl

patch] was a nearly universal concern about safety on the part of the regulatory staff who reviewed the original submission."[16]

8. **For both the lollipop and the patch, the FDA is relying on package insert warnings and restricted detailing to prevent unsafe off-label use.**

In its 1990 approval of the patch, the FDA stated that they would require obligations "to be placed on the sponsor to ensure that the introduction of the system into clinical practice is not accompanied by extensive improper use and consequent mortality and morbidity."[17] Obviously, this approach has been unsuccessful.

In marked similarity, the FDA has issued obligations be placed on the lollipop's sponsor, Abbott. Dr. Wright pointed out at the August 24, 1993 advisory committee meeting that "...a careless detail person can do some real damage with this."[18]

The Fentanyl Patch Experience

Public Citizen believes that the similarities between the fentanyl patch and the fentanyl lollipop are ominous. If the approval of the lollipop is not reversed and it is widely used by American physicians, we can expect a replay of the fentanyl patch experience. The following is an accounting of that experience to date.

1. What is the fentanyl patch?

The fentanyl patch is an extended release system to be worn on the skin and intended to deliver a narcotic analgesic (fentanyl) at a near constant rate for use as a supplemental painkiller in cancer pain. Fentanyl, the parent drug, is a potent narcotic (20-30 times more potent than morphine)[19] which has been used as an intravenous anesthetic agent for many years and its toxicities are well described. The patch was the first fentanyl dosage form which could be used without injections and is effective in reducing the pain of cancer. After gaining approval for clinical trials for the patch in 1985, Alza Corporation completed numerous clinical trials, including pharmacokinetic, safety, and efficacy studies for both post-operative and chronic cancer pain. The initial NDA proposed Duragesic for use in chronic pain management and post-operative use; this NDA was not approved by the FDA because of safety concerns. The patch ultimately gained FDA approval for chronic pain management only on August 7, 1990. The patch was marketed in 3 different strengths: 50ug/hr, 75ug/hr, and 100ug/hr.

2. Adverse events

Since its approval, the fentanyl patch has resulted in 676 adverse drug reports to the FDA. In these reports, 58 (9%) patients died, an additional 28 (4%) were hospitalized for a prolonged period, and another 59 (9%) required medical treatment for a suspected complication of Duragesic use. The patient age distribution for <u>all</u> reported adverse events is included in Table II. It is of note that 35.5% of all reported adverse events in which age is listed have occurred in persons less than or equal to 50 years of age.

Table II

Age Distribution of Adverse Drug Reports

AGE	FREQUENCY*	CUMULATIVE PERCENT
<10	3	0.6
10-19	5	1.5
20-29	16	4.4
30-39	77	18.6
40-49	92	35.5
50-59	82	50.6
60-69	122	73.1
≥70	146	100.0

*age not specified in 133 adverse event reports

a. Deaths

Included in the 58 deaths where Duragesic was suspected to have contributed, was a healthy 17-year-old youth from Florida. He had routine, uncomplicated, out-patient wisdom teeth extraction performed on January 14, 1993. Postoperatively, his oral surgeon prescribed a 50 ug/hr fentanyl (the lowest dosage) for pain control, which he told the boy's mother was a "low-level pain medication". When checking on him the following morning, his mother found that he had died in his sleep. Post mortem examination revealed that death was secondary to apnea (cessation of breathing) caused by an unintentional fentanyl overdose.[20] The blood fentanyl level was 8.6 ng/ml, more than 3 times the established toxic blood level of 2.5 ng/ml. Death also resulted when a healthy, 41-year-old man was prescribed a 100 ug/hr patch following elective outpatient orthopedic surgery in Arkansas. His blood level was reported to be 35 ng/ml at autopsy. **These deaths and the three others mentioned on the first page of this letter were clearly caused by unapproved off-label use.**

The FDA adverse reporting system gives several clues as to the circumstances surrounding many of the other deaths and the indications for Duragesic use in those patients. Descriptions listed in the FDA reports are found in Table III. Death secondary to duragesic-induced apnea may be suspected in those patients where hypoventilation, apnea, coma, stupor, and somnolence is described since these descriptors refer to, commonly precede, or accompany respiratory depression. Similarly, confusion, anxiety and hallucinations are recognized signs of fentanyl toxicity and thus, these deaths may also be fentanyl-related. The term "overdose" was used to describe 7 deaths (all in patients less than 50 years old). This term likely refers to both intentional and unintentional overdoses. For instance, suicide may be suspected in 4 of the 7

"overdoses" since alcohol-use and other drug dependencies are listed as co-factors; contrastingly, the clearly unintentional death of this 17-year-old young man is also listed as an "overdose". Six deaths have no descriptors and therefore cannot be characterized. It is likely that the 6 adverse effects reports of ongoing pain represented poor efficacy of the delivery system and thus fentanyl overdose was not likely a contributing cause of death.

Although the indication for Duragesic use is not reported by the FDA, chronic cancer or other pain management can be deduced from 24 out of 58 deaths since carcinoma, anti-cancer drugs, or other drugs commonly used to treat chronic pain are listed as descriptors. The majority of these deaths occurred, as expected, in those 50 years of age and older. Of the 16 reported deaths of persons less than 50, only 2 (12.5%) had carcinoma, anti-cancer drugs, or cancer-related analgesics listed as descriptors. Three of the deaths in patients under 50 (18.8%) are most certainly related to the post-operative use of the fentanyl patch since various anesthetic agents had been given to these patients. Of the remaining deaths, no information is available to deduce whether the fentanyl patch was being used as an analgesic post-operatively, for cancer, or for some other undefined use.

Table III

Descriptions of Reported Deaths[a]

DESCRIPTION	FREQUENCY	PERCENT (of all death reports)
Respiratory	5	8.6%
Reduced Mental Status[b]	9	15.5%
Psychiatric[c]	13	22.4%
Cardiovascular	3	5.1%
Gastrointestinal	1	1.7%
Dermatologic	5	8.6%
Lab Abnormalities	1	1.7%
Overdose[d]	7	12.1%
Ongoing Pain	6	10.3%
No Description	6	10.3%
Other[e]	2	3.4%
TOTAL	**58**	**100.0%**

[a] most serious description reported to the FDA
[b] somnolence, stupor, coma, and confusion
[c] hallucinations, psychosis, and insomnia
[d] intentionality not described
[e] sepsis and anisocoria

b. Hospitalizations

Duragesic was associated in 28 reported instances where patients required prolonged hospitalization. Again, fentanyl-induced hypoventilation and apnea can be directly suspected to be the cause of 10. Two reports of intentional overdose were made. Four hospitalizations were associated with agitation or confusion. The remainder of hospitalizations were associated with unrelated conditions ranging from intestinal obstruction to hematuria (blood in the urine).

Concerns of Experts Regarding the Safety of the Lollipop

From within the FDA and its Anesthetic and Life Support & Drug Abuse Advisory Committees:

The final vote of the August 24th meeting of the FDA Anesthetic and Life Support Advisory Committee and the Drug Abuse Advisory Committee was for approval; 12 were in favor and 3 were against. The following are the concerns raised by those voting against:

Marilyn Harper M.D., Clinical Professor of Anesthesiology, University of California, San Francisco

> "I think that's my biggest problem with this drug [the fentanyl lollipop], the fact that I think it is going to be used in settings where it's going to be dangerous and that the proper personnel may not be there."[21]
>
> "I really don't want to see the drug [the fentanyl lollipop] approved."[22]
>
> "It seems to me that during the course of the day, we've had a real plethora of problems associated with this and a real paucity of advantages."[23]
>
> "My concern is really outside the operating room itself. That is my concern that I have expressed earlier today and I still continue to express a high degree of nervousness about having it used all over the hospital."[12]

Max Schneider M.D., President Max A. Schneider, Inc. and gastroenterologist, Orange County, California

> "This is a very potent, excellent narcotic, requiring massive supervision which is not going to take place in the average dentist's or "minor surgery" office, including endoscopy. Once this drug is released in this form, it will be utilized massively in spite of what recommendations may or may not be put into the label. ...we will find that the comfort that they [medical residents] may have gained during their training will indeed become a routine that one has to look at with a jaundiced eye."[24]
>
> "My experience says that doctors in private practice, be they physicians or dentists, will come to involve themselves in the use of this product with minimal precaution because

it will become, I believe, a very appealing technique of pacifying people."[11]

"...there is a myriad of areas where this product should not be used..."[14]

Rolley Johnson, Pharm. D., Associate Professor, Department of Psychiatry, Johns Hopkins University School of Medicine (It is not clear whether Dr. Johnson voted for or against.)

"But it concerns me in that it looks like we are studying it [the fentanyl lollipop] for preop [use] where all these things [appropriate monitoring and personnel] are available, but really what everybody is directing it to is all of the off-label uses of it where we are saying it can't be used or shouldn't be used unless we have these particular safety measures in place."[25]

"...this is a medication that can be very -- not 'can be' -- is very dangerous when used inappropriately, and there is a limited number of people who really need it."[26]

"But in anesthetic practice, morbidity due to simple hypoventilation is rare. In settings less able to detect and manage hypoventilation, the rate of morbidity due to pediatric premedication is 50-500 times greater. I think that 50-500 times greater brings it home much more than we thought that it did than the figures that were given that we're talking about what would occur in a setting such as the O.R. versus a setting where they didn't have this type of equipment or personnel to observe."[27]

"...there are other medications which are much safer that could be delivered by this route other than fentanyl, that possibly, I would think, could have similar effects for preop anxiety and for analgesia."[28]

The following comments were made by those voting in favor of the patch:

Laura McNicholas M.D. Ph.D., Assistant Professor, Philadelphia VA Medical Center

"...in non-OR settings at 5 ug/kg, which was really the lowest dose studied, there were still 16% of the patients who had hypoventilatory incidences. Furthermore, in the study that looked at painful operating procedures, minor operating procedures, in patients greater that 50 years of age at a dose of 5 ug/kg [the lowest dose recommended], 43% had hypoventilatory episodes."[10]

"The short answer is probably no." (Dr. McNicholas was responding to the question "Is there an effective dose of OTFC [the fentanyl lollipop] which is safe to use in settings where there is less monitoring, support and capacity for intervention than in the OR?")[13]

Andrea Grubb Barthwell M.D., Medical Director, Interventions, Chicago

"We know that it [the fentanyl lollipop] seems to be most efficacious among the age

groups 2 to 7 based upon the studies, which should therefore be smaller children, and that we would expect a high level of off-label use patterns."[29]

Theodore Cicero Ph.D., Professor of Neuropharmacology, Department of Psychiatry, Washington University School of Medicine and Chairman, Joint Meeting of the FDA Anesthetic and Life Support Advisory Committee and Drug Abuse Advisory Committee

"...there seems to also be a recognition that we are likely to have this compound [the fentanyl lollipop] used off the label. No matter what we put on the label, some would like to be using it."[30]

Other attendees at the meeting:

Curtis Wright M.D. M.P.H., Acting Director, FDA Pilot Drug Evaluation Staff

"The result of all this activity [by the FDA since the 1930s] has been the presumption that it is in the public interest that the risks associated with the introduction of a new medicine be clearly defined not only for the indication on conditions of use sought by the sponsor, but for such off-label indications where drugs of that class are commonly employed."[31]

"I think in fact one of the recommendations that you [the Joint Committee] might make which lies within your power is that benzodiazepines might be more appropriate to investigate in this indication."[32]

"This is not just another lozenge. This is something that you have to treat with respect and you can injure people with it."[33]

"I have serious concerns about this product outside of its use under the direct observation of an anesthesiologist."[15]

"...a careless detail person can do some real damage with this."[18]

Theodore Stanley M.D., Anesta Corporation

"Certainly in this dosage form the incidence almost irrespective of the doses, of pruritus [itching] is 60 to 80 to 90%. This may be a candy, but it is a candy that causes you to itch, to puke, and to feel sick."[34]

From the Drug Enforcement Administration (DEA):

Gene Hayslip, Director of the DEA Office of Diversion Control, in a letter to Dr. John Harter, Medical Officer, FDA Pilot Drug Evaluation Staff, read at the Advisory Committee meeting on August 24, 1993

"The proposed introduction of this new dosage form of fentanyl [the lollipop] is the cause of serious concern to the DEA. Fentanyl is a potent narcotic analgesic, currently available in the injectable and patch dosage forms. Diversion and abuse of both injectable fentanyl and fentanyl patches have been documented. Abusers using the patch either hold it under their tongue until the drug is absorbed or moisten the patch and extract the fentanyl with a syringe. Fentanyl has also been clandestinely manufactured in the United States and is sold in elicit [sic] traffic as heroin, resulting in over 120 deaths last year. Given the existing elicit market for this drug and the immediate attention at the introduction of this new, easily abusable dosage form received in the elicit traffic, DEA has serious concerns about the significant abuse potential of this drug."[35]

From other experts:

Allen Hinkle M.D., Associate Professor of Pediatrics and Anesthesiology, Dartmouth University School of Medicine

"Since the lollipop has to be administered 30 to 45 minutes preoperatively, most of these children, during the consumption of the lollipop need to be monitored for the occurrence of respiratory depression and arterial oxygen desaturation, requiring increased monitoring and nursing care."[36]

"Looking at the history of drug abuse in this country, it is hard to imagine that the inclusion of narcotics in lollipops won't find a route out of hospitals and into the streets."[36]

"In addition to our societal obligation, let's look for a moment into our own medical profession at the issue of narcotic control. I think it is true that physicians in general, and anesthesiologists perhaps more so than other physicians, have been attracted to drug abuse. We can argue ad infinitum about the reasons for this occurrence but clearly even within the hospital environment we have been unable to guarantee the ability to totally control narcotic availability. I believe that until we can control our own narcotic problems it makes little sense for us to develop easier drug delivery systems that will allow younger children to potentially enter into a drug abuse culture needing little or no sophistication in order to deliver narcotics into their bloodstream."[36]

Leon Eisenberg M.D., Professor of Child Psychiatry, Harvard University School of Medicine

"The idea of putting a drug which has already demonstrated its abuse potential into a lollipop form makes no sense. It is a bad idea."[37]

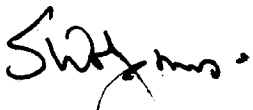
Jeffery Blumer M.D. Ph.D., Case Western Reserve University School of Medicine, has told us that he is opposed to the approval of the fentanyl lollipop for safety reasons including the fact that it is difficult to adequately control administration, there is a very low margin of safety and the occurrence of frequent adverse effects such as vomiting, both pre- and post-operatively.[38]

Conclusion

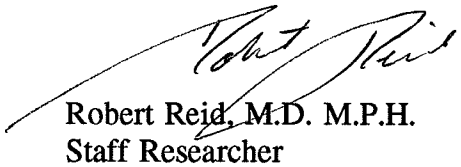
Drug approval comes down to weighing the potential benefits of a new drug (or a new drug delivery form) with the risks of both approved and unapproved use. The major benefit of the fentanyl lollipop would be to reduce anxiety and provide for a pleasant anesthetic induction in a minority of children undergoing surgery. The vast majority of patients need no anesthetic pre-medication; it has been estimated that this drug is potentially indicated in only 10% of children undergoing surgery.[39] There is an undisputed risk of morbidity associated with the lollipop's approved use but if an anesthesiologist were present, patients would not suffer. The FDA therefore believes that the risk associated with operating room use is acceptable. However, we believe that the FDA failed to give enough merit to the risks associated with use outside of the operating room. The fentanyl lollipop delivers variable blood levels and causes hypoventilation in significant numbers of children and adults. In the operating room with monitors and trained personnel, this may be of low risk; outside of the safety of the operating room, it is certainly not. The FDA feels that package label warnings and restricted detailing will prevent unsafe off-label use without proper monitoring of the patient. The FDA is putting its collective heads in the sand; one only has to look at the experience with the fentanyl patch. The risks associated with off-label use outweigh the benefits by a wide margin. The use of safe, acceptable, and efficacious methods of reducing anxiety for children undergoing surgery is certainly a laudable goal. Much more needs to be done to increase the involvement and psychological support of parents and health professionals prior to surgery and in the operating room. The fentanyl lollipop clearly does not fill this bill. The FDA has been over-zealous in approving the fentanyl lollipop and consequently, children (and adults) affected by off-label use will pay the ultimate price of death from a questionable and unnecessary drug.

We look forward to a prompt response to this urgent matter.

Sincerely,



Sidney Wolfe, M.D.
Director
Public Citizen's Health Research Group



Robert Reid, M.D. M.P.H.
Staff Researcher

REFERENCES

1. Food and Drug Administration. NDA # 19,813: Medical Officer's Review, Volume 3 - Meta-analysis and Cross-Study Comparisons. Unpublished, p.16.
2. Janssen Pharmaceutica. Package insert for Duragesic. New Jersey: June 1991.
3. Food and Drug Administration, op. cit.
4. Abbott Laboratories. Package insert for Fentanyl Oralet (Oral Transmucosal Fentanyl Citrate). Chicago: October 1993.
5. Ibid.
6. Food and Drug Administration. NDA # 19,813: Medical Officer's Review, Volume 2 - Pharmacokinetics and Pharmacodynamics. Unpublished, p.13.
7. Ibid, p.1.
8. Food and Drug Administration. NDA # 19,813: Approval Letter. Unpublished, p.18.
9. Abbott Laboratories. op. cit.
10. Transcript of the FDA Anesthetic and Life Support Advisory Committee and the Drug Abuse Advisory Committee meeting on August 24, 1993, Washington, D.C. p.36.
11. Ibid, p.51.
12. Ibid, p.187.
13. Ibid, p.36.
14. Ibid, p.51.
15. Ibid, p.180.
16. Food and Drug Administration. op. cit., volume 2, p.2.
17. Food and Drug Administration. NDA # 19,813: Medical Officer's Review, Volume 1 - Clinical Efficacy Studies. Unpublished, p.2.
18. Transcript, op. cit., p.181.
19. Gilman AG, Rall TW, Nies AS, Taylor P (eds.) Goodman and Gilman's The Pharmacological Basis of Therapeutics. Eighth edition.Elmsford, NY: Pergamon Press, 1990; 305-306.
20. Autopsy Report, April 9, 1993.
21. Transcript, op. cit., p.157.
22. Ibid, p.158.
23. Ibid, p.169.
24. Ibid, p.50.
25. Ibid, p.57.
26. Ibid, p.160.
27. Ibid, p.154.
28. Ibid, p.62.
29. Ibid, p.90.
30. Ibid, p.66.
31. Ibid, p.31.
32. Ibid, p.63.
33. Ibid, p.133.
34. Ibid, p.134.
35. Ibid, p.35.
36. Hinkle A. Personal communication. Letter to Frederic Barry MD dated March 1, 1989.
37. Eisenberg L. Personal communication. August 22, 1993.
38. Blumer J. Personal communication. August 23, 1994
39. Transcript, op. cit., p.58.