CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ANESTHETIC and LIFE SUPPORT DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 09/17/97

SLIDES (FDA PRESENTATION)

PHARMACOKINETICS

ACTIQ™ (NDA 20-747)

Suresh Doddapaneni, Ph.D
Reviewing Pharmacokineticist
Food and Drug Administration

ACTIQ™ PHARMACOKINETICS

Fentanyl Delivery Characteristics of Actiq™:

- Designed to be released in the mouth and absorbed through the oral mucosa.

ACTIQ™ PHARMACOKINETICS

Fentanyl Delivery Characteristics of Actiq™:

- Potential advantages over oral solution are;
  - Higher bioavailability
  - Higher peak concentrations
  - Quicker peak concentrations
  - Faster onset of action

ACTIQ™ PHARMACOKINETICS

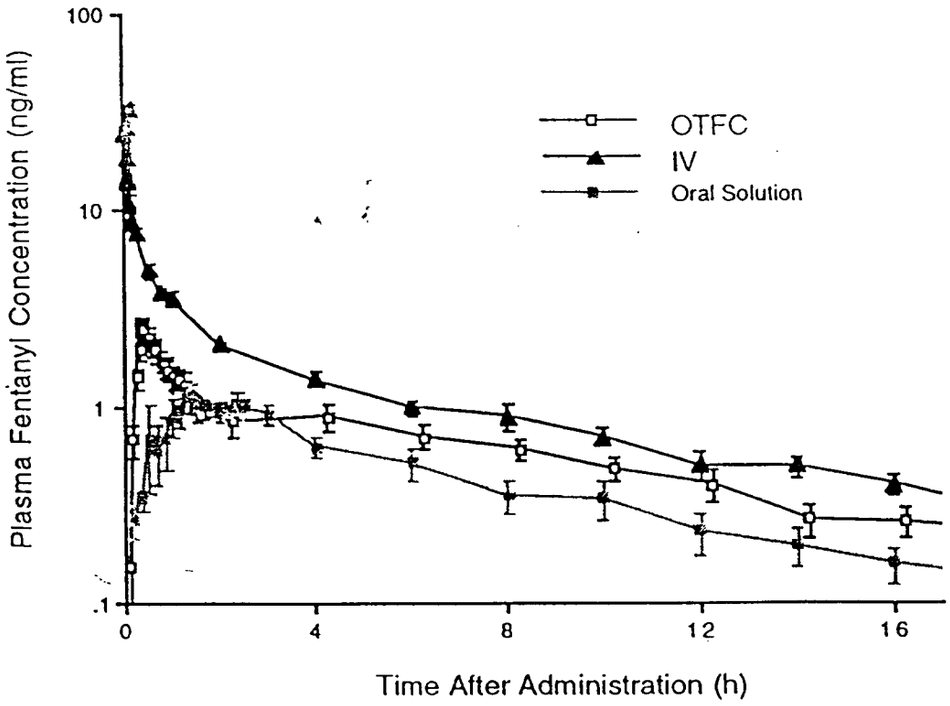
Fentanyl Delivery Characteristics of Actiq™:

- In practice, some of the fentanyl in the saliva is swallowed and as such the systemic fentanyl level profile and the bioavailability will vary depending on the fraction of the dose that is absorbed through the oral mucosa and the fraction swallowed.

ACTIQ™ PHARMACOKINETICS

Fentanyl Delivery Characteristics of Actiq™:

Figure 1. Plasma concentrations of fentanyl (mean±SEM) after intravenous (n=10), OTFC (n=10), or oral (n=8) administration of fentanyl 15 µg/kg.



ACTIQ™ PHARMACOKINETICS

Fentanyl Delivery Characteristics of Actiq™:

- It is important that the patients use the right consumption technique to minimize both the inter-patient and intra-patient variability in pharmacokinetics. Rapid or shorter consumption times than 15 minutes may be result in less efficacy.

ACTIQ™ PHARMACOKINETICS

Dose-Proportionality at Single Doses of Actiq™ between 200-1600 µg in 12 healthy volunteers (protocol AC200/009):

Table 1. Pharmacokinetic parameter values of fentanyl (mean (% Coefficient of variation)).

Pharmacokinetic Parameter	200 µg	400 µg	800 µg	1600 µg
Dose (µg/kg)	2.61 (13)	5.24 (13)	10.5 (13)	20.9 (12)
T_{max}, minute	61 (70)	55 (118)	44 (89)	61 (216)
C_{max}, ng/mL	0.39 (23)	0.75 (33)	1.6 (30)	2.5 (23)
AUC_{0-1440}, ng/mL minute	102 (65)	243 (67)	573 (64)	1026 (67)

ACTIQ™ PHARMACOKINETICS

Pharmacokinetics of Repeated Doses of Actiq™ in Cancer Patients (protocol AC200/015):

- Repeated administration of Actiq™ (upto 1200 μg strength) at short intervals (every 4-8 hours) when used as around the clock medication for treating breakthrough pain did not result in any unexpected accumulation of fentanyl.

Efficacy

Curtis Wright MD
HFD-170

The Portfolio

200/015- PK in cancer pain patients

200/006- Efficacy against placebo in postop pain

200/010- Potency against morphine/postop pain

200/013-Efficacy against placebo/cancer pain

200/011- Safety & dose ranging/oral morphines

200/012- Safety & dose ranging/Duragesic

200/013

Design- Randomized, placebo-controlled, placebo substitution design in 89 patients already titrated to adequate analgesia using individualized doses of Actiq

Strategy-Patients were enrolled, titrated to a "one-unit" dose, given ten units, three of which were placebo, and rated their pain for each episode. Additional rescue medication was available and used after 30 minutes.

Outcomes- Pain Intensity,Pain Relief, Patient Globals

Patient Disposition

Entered Titration Phase- 130 Completed-92

Withdrew due to SAE (possible)- 2

Withdrew due to SAE (unlikely)- 6

Withdrew due to other AE (possible)- 14

Patient preferred regular rescue- 4

Breakthrough pain ceased - 4

Unable/unwilling to participate- 4

Other reason- 4

Evaluable Episodes (ITT)

92 patients should have 7x92 = 644 active

3x92 = 276 placebo

7 patients withdrew early due to AEs

8 patients did not use all 10 units in 14 days

2 patients were still running at study closure

1 patient preferred regular rescue

1 patient entered radiotherapy

1 patient declined to participate

Evaluable Episodes

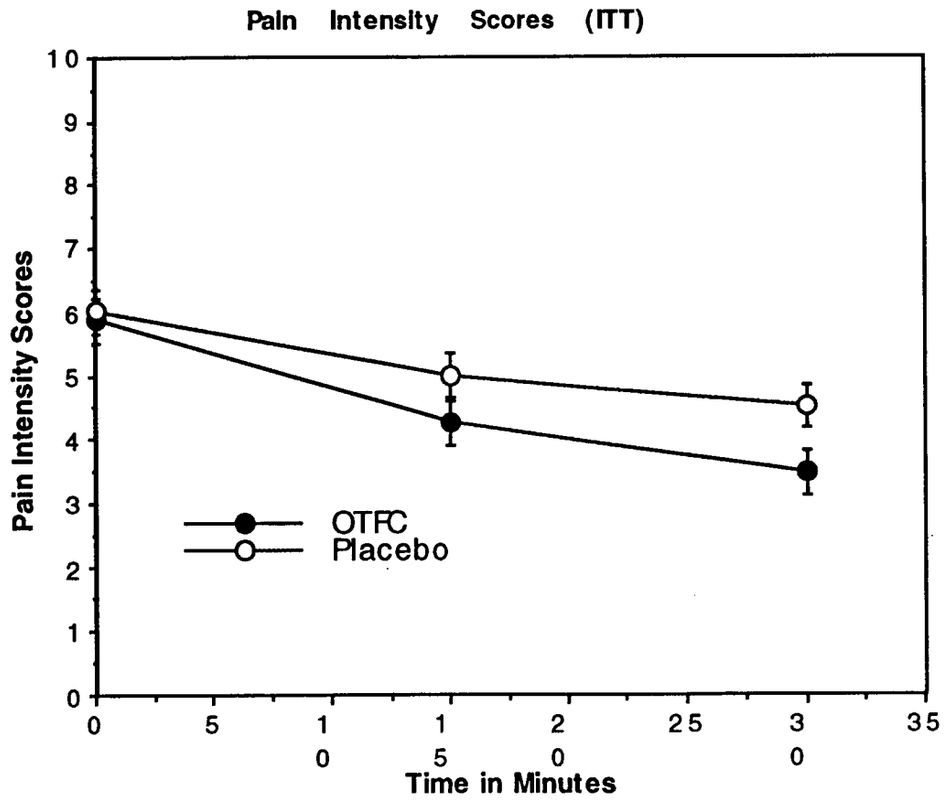
9 % of placebo episodes (22/247)
9 % of OTFC episodes (52/557)
were thus unevaluable for all time periods.

So the ITT evaluation was based on 227 placebo and 505 active treatment observations.

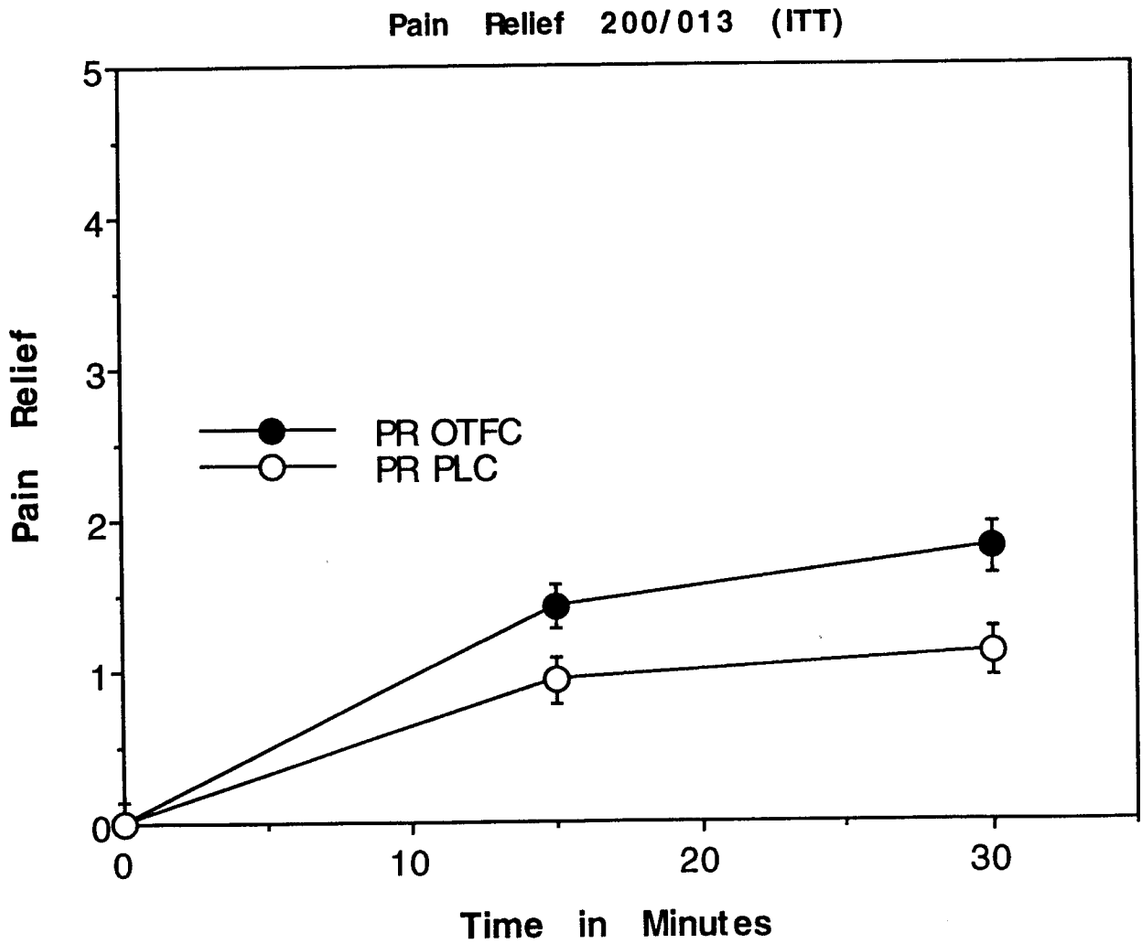
Evaluable Periods

Most breakthough pain lasts thirty minutes or less, and the claimed advantage for this product is fast onset and short duration.
In addition, patients could use rescue after 30 minutes, so the review concentrated on the 15 minute and 30 minute results.

Results


Pain Intensity Scores (ITT)
Pain Intensity Scores
10
9
8
7
6
5
4
3
2
1
0
0
5
10
15
20
25
30
35
Time in Minutes
OTFC
Placebo

Results


Pain Relief 200/013 (ITT)
Pain Relief
5
4
3
2
1
0
PR OTFC
PR PLC
0
10
20
30
Time in Minutes

Global Performance & Rescue

Globals (Scale of 0=poor, 4=excellent)

Mean Global OTFC = 1.98

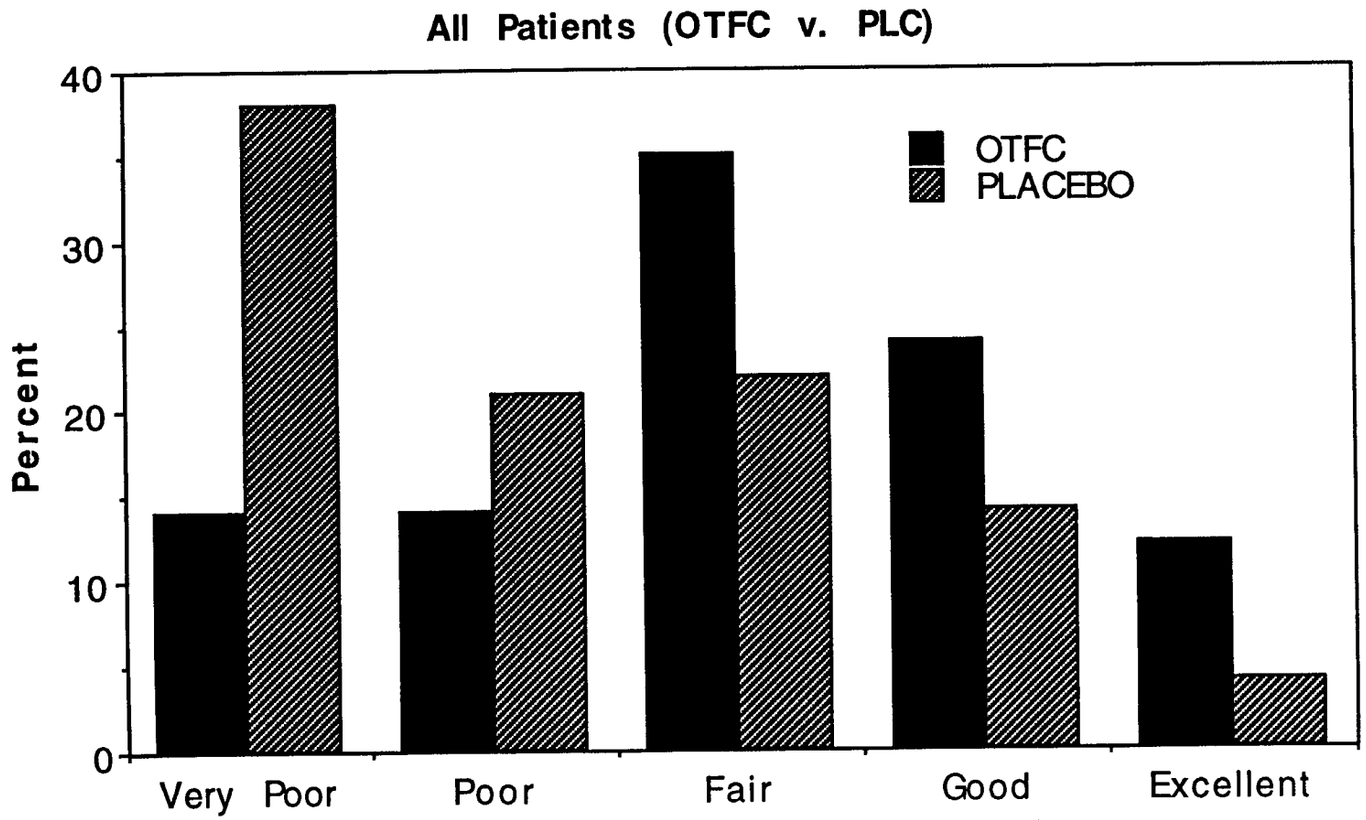
Mean Global Placebo = 1.19

Rescue (% of episodes needing rescue)

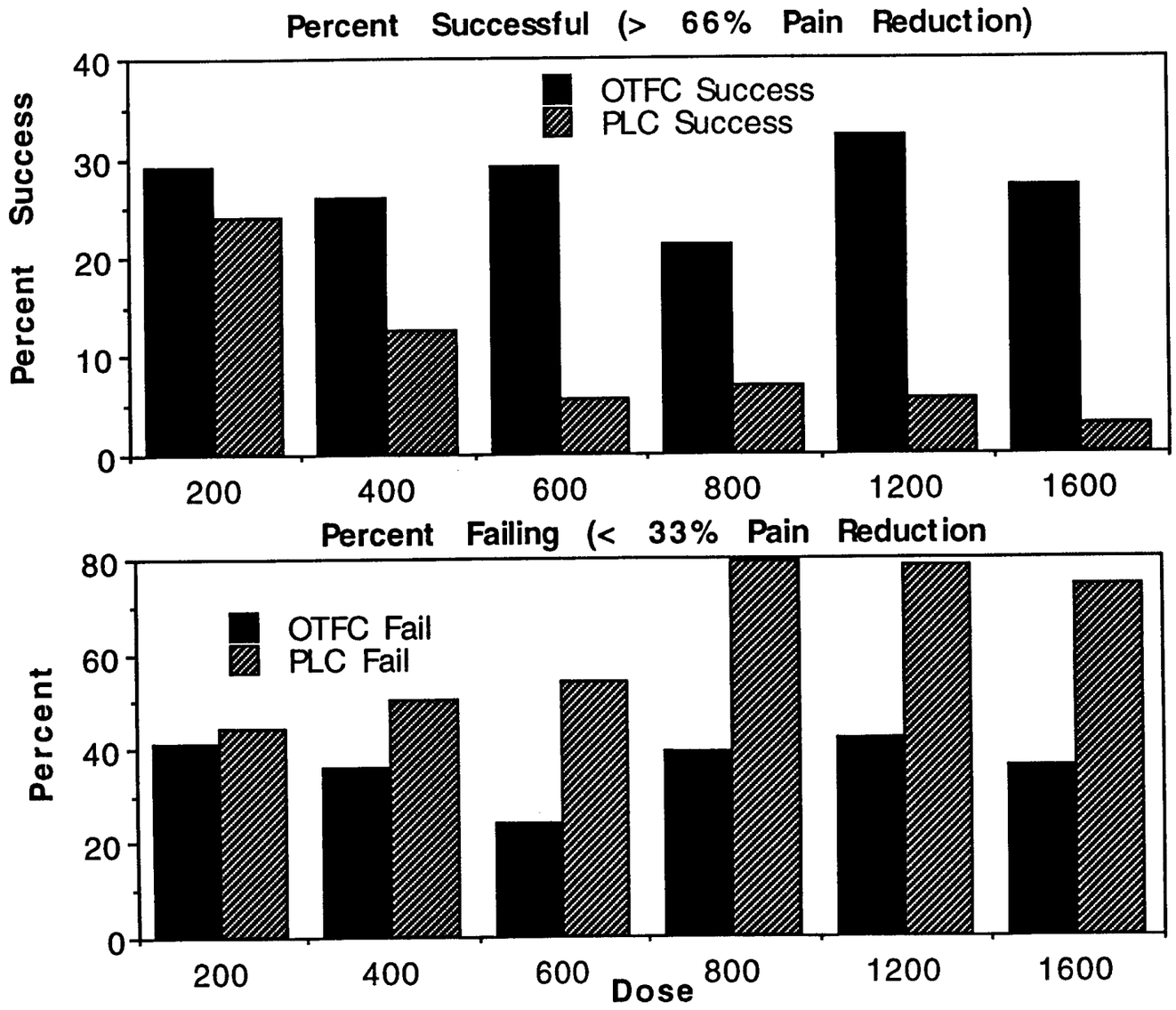
OTFC = 15%

Placebo = 35%

Exploration
OTFC Outcomes



Exploration by Dose



Conclusion-Trial 200/013

In the 2/3 of the patients who completed the titration phase, there was an unequivocal treatment effect against placebo,with most patients experiencing fair to good pain relief (25%-75% reduction in pain). The trial was sensitive to dose variation, with most of the outcome determined by doses of 600-1200 mcg/unit.

Caveat

What happened to the other patients?

The major limitation of this study was that it was descriptive titration, rather than a prescriptive titration. Sites were provided all strengths, and titrated each patient as they saw fit.

Significant Question

Will a clinical practioner using the "start low and advance slowly" paradigm achieve similar efficacy and safety results in clinical practice?

To examine this, we turn to 200/011 & 200/012

Trial 200/011

This was an open-label, historical control, blinded dose, titration study in which patients collected 2 days of pain ratings on their usual medication, then were "blind" titrated in 200 to 400 mcg steps from different starting strengths to a final dose where one OTFC was effective for two days of breakthrough episodes. Patients could take multiple units, and doses ranged from 200-7200 mcg/episode.

Disposition

65 patients started the study

17 withdrew due to an adverse event or other reason

- 5 were unrelated to OTFC (intercurrent illness)
- 5 were for uncontrolled pain on OTFC
- 3 were for AE's possibly related to OTFC
- 4 were for other reasons

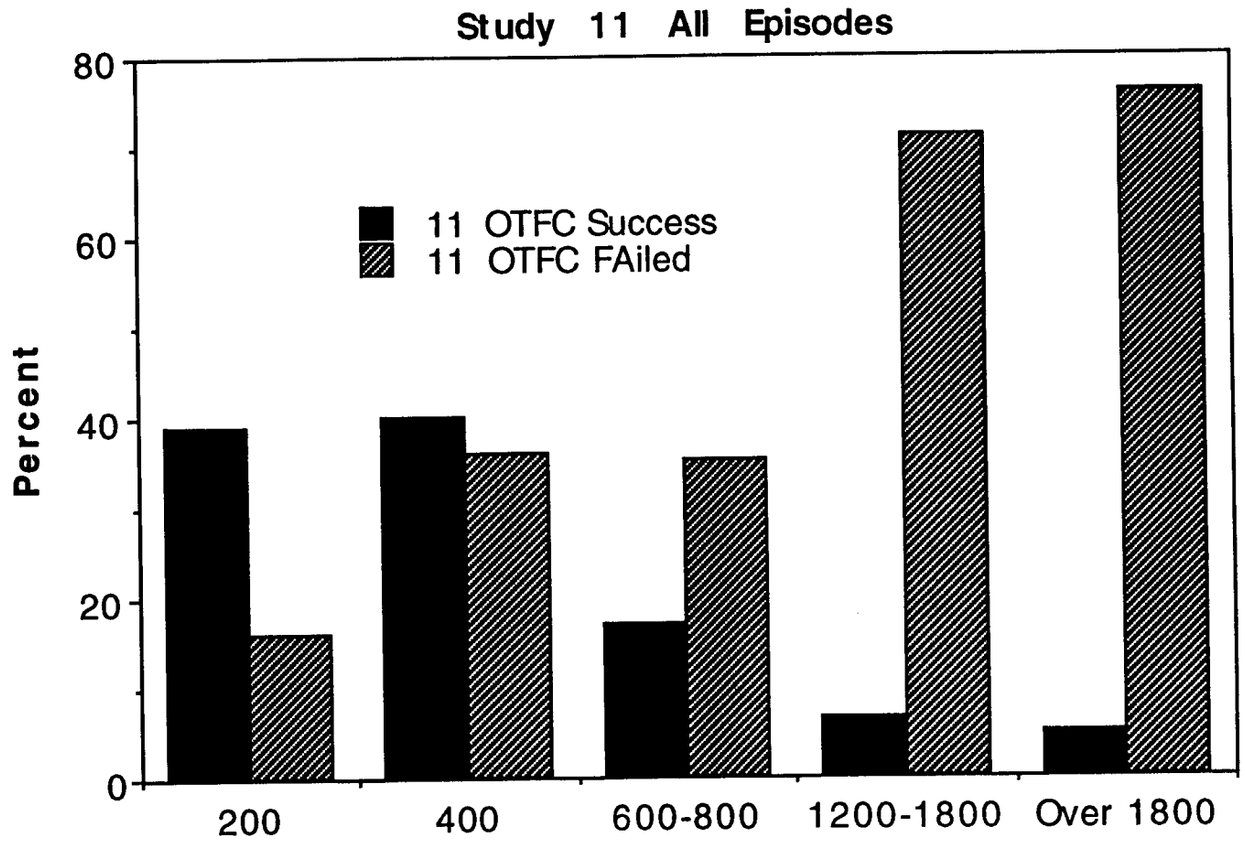
48 patients (74%) were successful for at least 2 days

Results Study 200/011

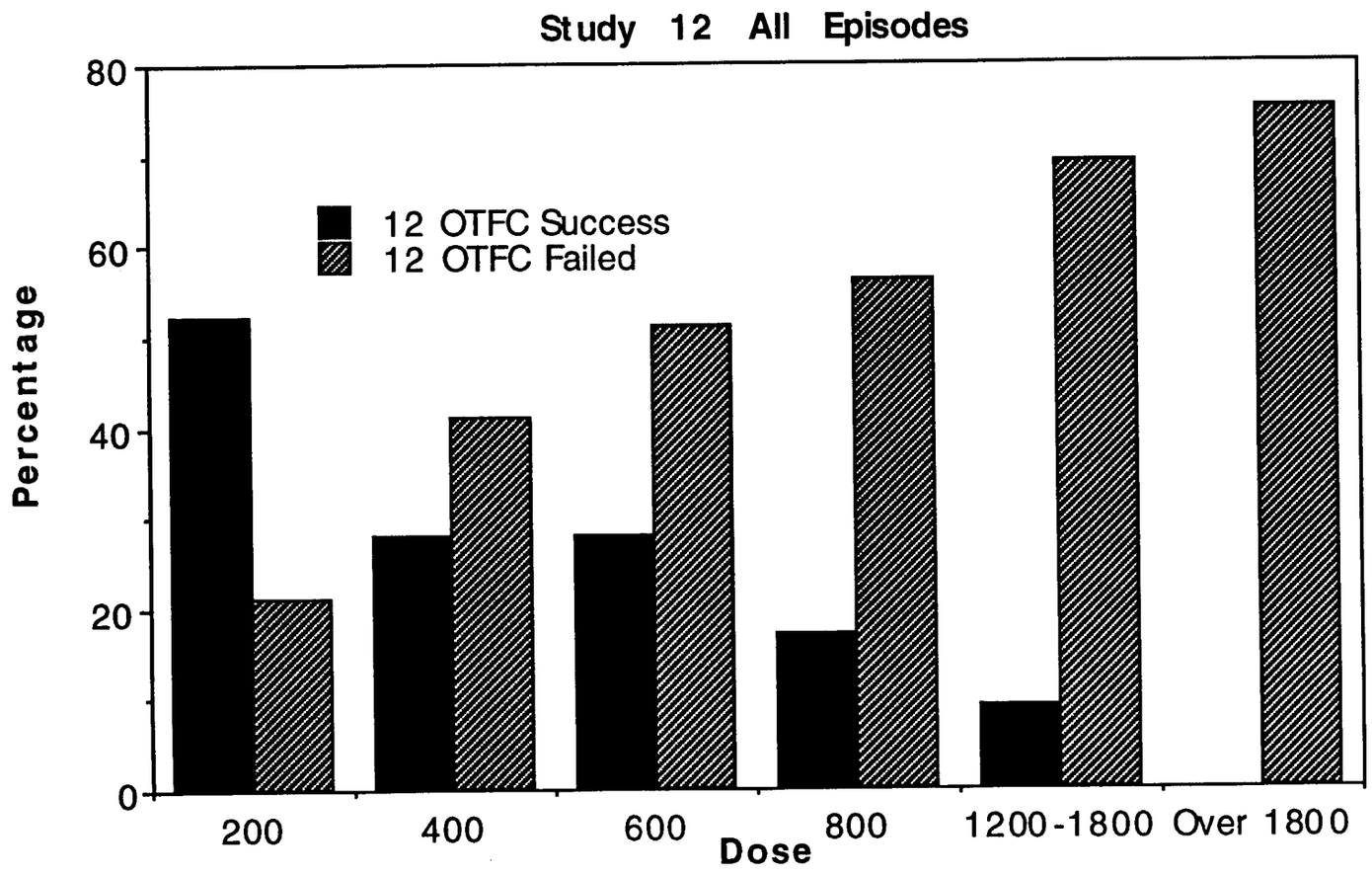
Final dose of OTFC 596 (305) mcg units

	Regular Rescue	OTFC
PID @ 30 minutes	2.53	3.49
Pain Relief @ 30 min.	1.83	2.52

Exploratory Analysis



Study 12 was similar



Discussion

No absolute conclusion about dose can be gleaned from the titration trials, since there was a systematic dropout of patients as they achieved good analgesia. Thus, the patients who reached the higher doses were guaranteed to have poorer results due to the design.

The trial does give some information, however, since it reveals that the prior probability of a satisfactory outcome from a dosage increase falls as the dose rises, and suggests that pushing the dose becomes unprofitable for the patient above 1600 mcg.

Efficacy Conclusions

OTFC showed an effect in the target population regardless of type of ATC opioid analgesic. The usual effective dose was 600-1200 mcg/unit, with smaller and larger doses being useful for titration and tolerance, respectively. 1/4 to 1/3 of the patients failed to acheive adequate analgesia regardless of dose.

Safety Experience-Adverse Events in Non-Opioid Tolerant Patients

- Studies AC 200/005, 200/008, 200/009, 200/006, 400/001.
  - Adverse effects characteristic of potent opioids: somnolence, nausea, pruritis, vomiting, dizziness, headache.
  - Monitoring of respiratory depression conducted in these studies only (resp rate, SpO2).
  - Hypoventilation defined as **sustained SpO2 < 85%, and resp rate < 6** (009: SpO2 < 80% on O2).

Respiratory Depression in Opioid-Naïve Subjects

Volunteers n of subjects	Desaturation	Hypercarbia (AC200/005)	Dose
12	4	9	800
24	0	--	800
12	12	--	200-1600
Totals and %	16 /48 (33%)	9 /12 (75%)	
Postop n of subjects			
77	17		400, 800
15	4		7-10 mcg/kg
Totals and %	21/92 (23%)		

Respiratory Effects in Opioid Naïve Subjects

- Respiratory depression was treated with verbal stimulation prior to administration of O2. Subjects who were identified by AE: "hypoventilation" had sustained desaturation and were unresponsive to verbal stimulation.
- *Actiq* in all dosage strengths was associated with the risk of respiratory depression, based on incidences of hypoxemia of 33% in healthy volunteers, and 23% in acute postoperative patients concurrently receiving PCA morphine.

Respiratory Depression- *Fentanyl Oralet* Experience (NDA 27,428)

- 730 patients opioid-naïve subjects
  - Apnea: 2 cases
    - ▼age 3; 12 kg; 361 mcg (30 mcg/kg)
    - ▼age 3; 14 kg; 300 mcg (22 mcg/kg)
  - Desaturation: 42 cases
    - ▼18 cases: ages 2- 9; dosage range 12-23 mcg/kg
    - ▼21 cases: ages 22-54; dosage range 7-15 mcg/kg
    - ▼ 3 cases: ages 59-78; dosage range 7.5-13 mcg/kg
  - Hypoventilation: 5 cases
    - ▼ages 5-7; 200-600 mcg (14-25 mcg/kg)

Respiratory Depression- *Fentanyl Oralet*- cont'd

	Cmax (mean, ng/ml)
Apnea	4.35
Hypoventilation	3.33
Desaturation*	2.87

*12/23 patients whose blood fentanyl Cmax was measured : range 0.7-2.8 ng/ml

Safety- Patient Demographics

AC 200/011, 012, 013: short-term exposure to *Actiq*.
AC 200/014: long-term safety study, 4 month blocks.

- AC 200/011, 012, 013
  - 72% ages 36-65
  - 22% age > 65
  - 56% female
  - 89% Caucasian
- Types of pain:
  - nociceptive: 80%
  - neuropathic:19%

- AC 200/014
  - 72% ages 36-65
  - 21% age > 65
  - 56% female
  - 93% Caucasian
- Types of pain:
  - nociceptive: 78%
  - neuropathic: 21.3%

Most Common Drug-related Adverse Events in Short- Duration Trials (n=257)

Somnolence	42
Dizziness	37
Nausea	29
Vomiting	11
Confusion	7
Hallucination	6
Asthenia	6
Abn. gait/ vertigo	4

2 accidental injuries related to *Actiq* use.

Most Common Adverse Drug-related Events in Chronic Use Patients (n=155)

Somnolence	14
Dizziness	13 (neuropathic: 7)
Nausea	12
Vomiting	8
Asthenia	4
Dyspnea	4
Myoclonus	2
Confusion	1
Headache	1

Adverse Events -by Body Systems (n =257)

	All Causality	Attributed (+)
Cardiovascular	27 (10.5%)	1 (0.4%)
Digestive	183 (70.4%)	73 (28.4%)
Metabolic	82 (31.9%)	1 (0.4%)
CNS	153 (59.5%)	82 (31.9%)
Respiratory	88 (34.2%)	5 (1.9%)
Skin/Appendages	50 (19.5%)	9 (3.5%)
Special Senses	24 (9.3%)	3 (1.2%)
Urogenital	41 (16%)	1 (0.4%)

Adverse Events in Long-Term Safety Trial AC 200/014 (n=155)

	All Causality	Treatment Related
Number with adverse events (%)	149 (96.1)	53 (34.2)
Number with moderate/severe adverse events (%)	143 (92.3)	30 (19.4)
Number with severe adverse events (%)	86 (55.5)	5 (3.2)

Overdose (AC 200/014)- #41206

An 85 kg, 75 year old male, prescribed for 200 mcg/unit dose, also using transdermal fentanyl 75-100 mcg/day. He received the 1600 mcg/unit dose due to pharmacy error, and used these units for 9 days.

The patient was reported to have behavioral changes, considered by the investigator to be *unrelated* to *Actiq,* and no other adverse events were reported during this usage time.

Deaths in Trial AC200/014

- Deaths (n =62) seen at all doses of Actiq in use; ascribed to progression of disease.
- One patient in study AC200/ 013 (#32204): a 62 year old male with metastatic lung CA, expired with progressive dyspnea en route to hospital 1 1/2 hours after using a 1200 mcg unit of *Actiq*. Temporal relationship suggested possible treatment-related death.

Respiratory Depression in the Chronic Population

- No monitoring in chronic studies. Hypoxia and hypoventilation cannot be self-monitored.
- Somnolence is associated with respiratory depression; therapeutic serum levels of fentanyl are associated with 50% reduction in PCO2- response.
- Tolerance to the respiratory depressant effect of fentanyl with chronic use has not been established.
- No episodes of apnea were reported in this series, significant proportion of patients with respiratory involvement.

Safety-Related Usage Considerations

- Risk of respiratory depression established in non-tolerant population. Risk and nature of respiratory depression not specifically ruled out in current data.
- Other adverse effects- nausea, vomiting, urinary retention, pruritis, etc.- are characteristic of this class.
- Somnolence, dizziness, confusion warrant special consideration in an at-home, unmonitored environment.
- Risks associated with accidental exposures.

ACTIQ™
(Oral Transmucosal Fentanyl Citrate)

NDA 20-747

ABUSE LIABILITY

ALSAC MEETING
September 17, 1997

Michael Klein, Ph.D.
CDER/ODEIII/
DACCADP

Schedule II Narcotic

1. DEA Registration

2. Separate Recordkeeping

3. Distribution Restrictions - Order forms required.

4. Manufacturing Security - Vault/safe

5. Import/Export Permit Required.

6. Reports to DEA by Manufacturers & Distributors.

7. Dispensing Limits : Rx: Written; No Refills

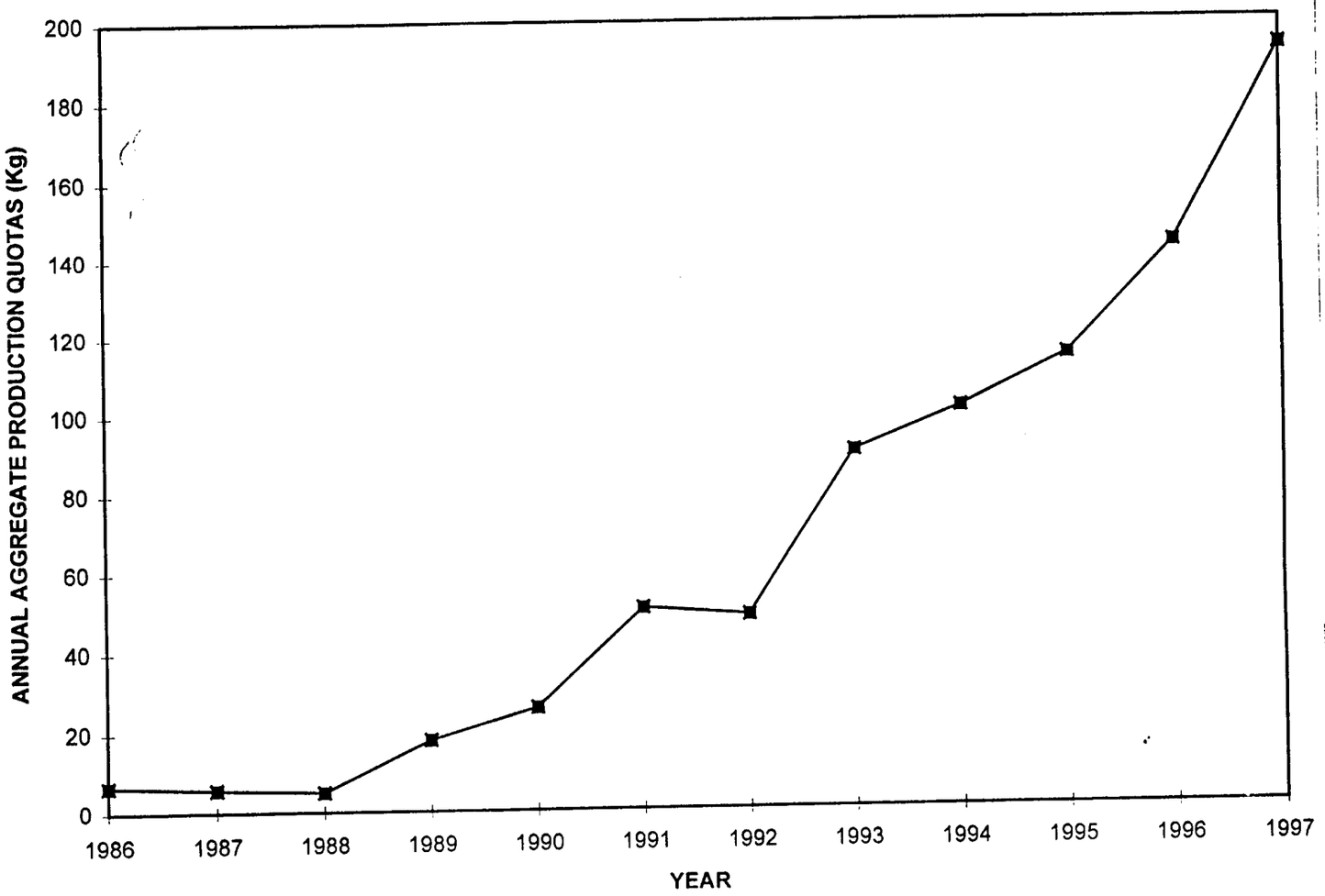
8. Manufacturing Quotas

ANNUAL AGGREGATE PRODUCTION QUOTAS

FENTANYL

1997	193 KG
1996	143 KG
1995	114.2 KG
1994	101 KG
1993	90 KG
1992	48.5 KG
1991	50.5 KG
1990	25.9 KG
1989	18 KG
1988	5 KG
1987	5.8 KG
1986	6.7 KG

ANNUAL AGGREGATE PRODUCTION QUOTAS
-FENTANYL-



NERABUSE COSTARTS (DURAGESIC, FENTANYL)

OVERDOSE INTENTIONAL	10
OVERDOSE	34
DRUG DEPENDENCE	35
WITHDRAWAL SYNDROME	51
SUICIDE ATTEMPT	15
OVERDOSE ACCIDENTAL	10
TOLERANCE INCREASED	59
DRUG DEPENDENCE/ADDICTION	7
TOTAL	221

NERABUSE COSTARTS (FENTANYL CITRATE, INNOVAR, SUBLIMAZE)

OVERDOSE INTENTIONAL	34
OVERDOSE	14
DRUG DEPENDENCE	5
WITHDRAWAL SYNDROME	4
SUICIDE ATTEMPT	3
OVERDOSE ACCIDENTAL	2
TOLERANCE INCREASED	0
DRUG DEPENDENCE/ADDICTION	0
TOTAL	62

FENTANYL MEDWATCH

NUMBER OF CASES PER SERIOUS OUTCOME, BY DRUG PRODUCT
(FROM 2ND QTR 1973 THRU 1ST QTR 1997)

DRUG	TOTAL CASES	TOTAL SERIOUS	TOTAL DIED	TOTAL HOSPITALIZED	TOTAL DISAB	TOTAL CONGENITAL ANOM.	TOTAL LIFE-THREATND
DURAGESIC	2252	291	157	135	7	0	20
FENTANYL	667	312	59	221	17	1	66
FENTANYL CITRATE	149	36	3	34	1	0	2
INNOVAR	18	4	2	1	1	0	0
SUBLIMAZE	287	128	64	57	13	0	6

EXAMPLES OF ABUSE & MISUSE CASE REPORTS OF FENTANYL TRANSDERMAL PATCH:

1. INDIVIDUALS WHO CHEWED THE PATCH AND DIED

2. EXTRACTED & RECRYSTALLIZED FENTANYL FROM DOSAGE FORM AND "SMOKED IT".

3. INDIVIDUALS WITH DRUG ABUSE HISTORIES WHO USED THE PRODUCT TO SUSTAIN AN OPIOID DEPENDENCE OR FOR ABUSE.

4. OBTAINED FROM FRIENDS (DRUG ABUSERS) .

5. DRUG PRODUCT STILL CONTAINING DRUG RESERVOIR PLACED IN TRASH AND RETRIEVED AND ABUSED, RESULTING IN DEATH.

6. ABUSE OF PARENT'S DRUG BY A MINOR

7. PIECES OF PATCHES FOUND IN GASTRIC CONTENTS AT AUTOPSY.

8. MISTAKEN DOSAGE AND SUBSEQUENT OVERDOSE.

9. SIMULTANEOUS USE OF MULTIPLE PATCHES TO ENHANCE PAIN RELIEF, RESULTING IN OVERDOSAGE.

10. MANIPULATION OR ADULTERATION FO DRUG PRODUCT TO INCREASE PAIN RELIEF.

SUMMARY

PRIOR TO APPROVAL OF PRESCRIPTIVE FENTANYL PRODUCT, DEATHS FROM ABUSE AND MISUSE WERE LIMITED TO HEALTH CARE PROVIDERS.

WHEN FENTANYL BECAME PRESCRIPTIVE, INCREASE IN REPORTS OF MISUSE, ABUSE AND DEATHS RESULTED.

Risk Management

Curtis Wright MD
HFD-170

The Problem

Actiq is potent opioid analgesic which appears to be of acceptable risk in the targeted clinical population.

It also looks sufficiently like a lollypop to be mistaken for one by a young child who might be injured or killed by an accidental ingestion.

Risk Hierarchy

Cyanotic child-

Child with unwrapped unit-

Child with wrapped unit-

Abuser with unit-

Rx for non-tolerant acute pain patient-

Rx for unselected chronic pain patient-

Rx for unselected opioid tolerant cancer patient-

Rx for opioid tolerant cancer patient on ATC opioid-

Dispensed to patient under medical observation-

Pre-operative use by anesthesiologist-

Question

Can the risk of accidental or iatrogenic toxicity be reduced to a level where the benefits to the intended users outweigh the risk to the public?

Control Plan

Control of Promotion, Prescription, Distribution

Warnings to all parties

Instructions

Surveillance

Intervention

Control

Restricted Promotion (Pain and Oncology)

Restricted Indications (Second Line Drug)

Restricted Distribution (Limited Wholesalers)

Restricted Prescribing (Package Insert)

Restricted Dispensing (Pharmacy Program)

Restricted Reimbursement (Third Party Payer)

Warnings

Negative Detailing (Quality Detailing Program)
Box Warning in Labeling
Carton Warning to Pharmacists
Software Warning to Pharmacists
Pouch Warning to all parties
Patient Package Insert
Caregiver Warnings

Instructions

"Keep Them Pouched" Instructions

"Destruction Instructions" in PPI & on pouch

"Poisoning Prevention" instructions in PPI & on pouch

"Emergency Care" instructions in PPI & on pouch

Surveillance

Abuse by the addict community

Abuse by Health Care Professionals

Off Label Sales

Adverse Events

"Mis-Promotion" in Media/Internet

Intervention

Targeted Physician Intervention Materials

Phone Calls to "outlier" prescribers

Targeted Educational Programs for State Boards & Professional Societies

General Comments

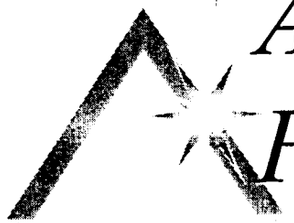
Need for specific performance parameters

Need for reporting requirements

Need for "a-priori" triggers to next action
(Absolute or Relative rates)

Question

Does this plan lower the risk to a level where the potential benefit to the patients outweighs the risk of iatrogenic misuse and accidental toxicity?



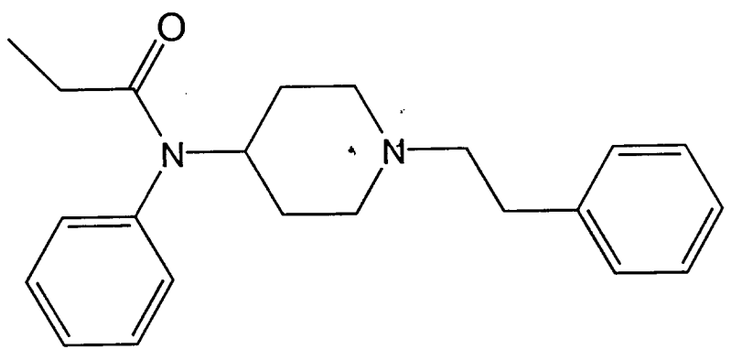
Actiq (Oral Transmucosal Fentanyl Citrate)

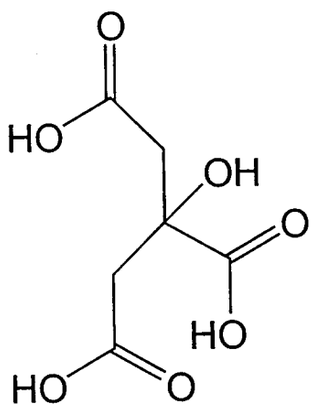
Pramoda Maturu, Ph.D., MBA,
Regulatory Review, Chemistry
FDA.CDER

Anesthetic and Life Support Advisory Committee Meeting-
September 17, 1997

Brief Chemistry Overview

- Fentanyl citrate is a 4-phenylpiperdine derivative with potent analgesic properties. Currently scheduled as CII.
- It is an almost white color powder, with bitter taste and has an aqueous solubility of 1g/40 mL. The free base has a pKa of 8.4 and an octanol/water partition coefficient of 860/1.
- It should be stored in a well closed container protected from light.





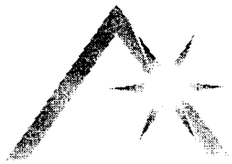
Fentanyl Citrate

Molecular weight = 528.6

pKa = 7.3 and 8.4

Proposed Dosage Strengths

- The VISUAL CUE for the overwrap is as follows:
- gray background color 200 µg,
- blue background color 400 µg,
- orange background color 600 µg,
- purple background color 800 µg,
- green background color 1200 µg,
- burgundy background color 1600 µg



Similarities and differences between Oralet and Actiq

	Oralet	Actiq
Strengths	100, 200, 300, 400, 600, and 800 mcg/unit--each unit weighs 2.38 g	200, 400, 600, 800, 1200 and 1600 mcg/unit--each unit weighs 2.38 g
Drug Candy matrix	Red Color (FD&C Blue #2 and Carmine red lake)	White Color (Titanium Oxide)
Inactive Ingredients	Raspberry Flavor	Raspberry Flavor
	Corn Syrup Solids and Sucrose	Corn Syrup Solids and Sucrose
	The drug to excipient ratios are not constant for all strengths	**The drug to excipient ratios are not constant for all strengths**
Stick	Provided with paddle with color specific printing for each strength	No paddle is provided. In tiny print, the strength is printed on the stick. The end of the stick has a screw end.

Similarities and differences between Oralet and Actiq

	Oralet	Actiq
Packaging (Overcap) Polypropylene	Provided, so the candy matrix does not directly come in contact with the foil pouch	**Not provided**, the candy matrix directly comes in contact with the foil pouch
Foil pouch material	PET Foil Polypropylene	PET Valeron Foil Polyethylene
Foil pouch	Not tested for child resistance	Requires a scissor to open the package, Consumer tested for child resistance with valeron coat half as thick as in the market package
End use	Hospital	Home use or hospital/nursing home