Prior to challenge #4, an irritation screening using animals from Group V was conducted to evaluate the irritation potential of 4% and 1% fentanyl base in 50% alcohol/water. After a 24 hour passive application, an irritation index of 0.3 and 0 was calculated for the 4% fentanyl and 1% fentanyl, respectively. No clinical observations were seen during the screening.
All four groups were challenged with passive 4% and 1% fentanyl base in alcohol. This was with an in vitro flux rate of 12 ug/cm^2 hour and 0.86 ug/cm^2 hour, respectively for a total of 12.86 ug/cm^2/h (dose of 0.1 mg/kg/8 h) based on 0.75 kg animal. The only group with a positive response to 4% fentanyl base was Group II (1/8), placing it in the mild category.

Challenge #5

Subsequent challenges with ETS fentanyl were at a lower current density of 0.060 mA/cm^2 and total current of 42 uA to reduce irritation possibly related to high flux of approximately 100 /ug/cm^2 hour (dose of 0.7 mg/kg/8 h). For Challenges #1 and #2 versus 60 ug/ cm^2 hour (dose of 0.4 mg/kg/8 h) for Challenge #5.
Groups V (DNCB) and VI (naive) which had previously not been exposed to ETS (fentanyl) were included in this challenge. Corrected for irritation responses in Groups I,III, IV, V, and VI, the % responders in Group II are 25, 64, 37, 75, and 65, respectively, placing ETS (fentanyl) in the mild to moderate sensitizer category. Statistical analysis showed a significant difference for scores at the 72 hour observation ($p < 0.01$) only between Group II (induced with fentanyl/current) and Group VI (naive) when challenged with ETS (fentanyl). In no case did the irritation exceed a 2 for erythema. No induration was recorded.

Challenge #6

A saline/current challenge was applied to Groups I-IV and VI. Systems were set at current density 0.06 mA/cm^2. Positive responders at 72 hours ranged from 0-28% (weak-mild), which if applied, as a baseline control to data in Challenge #5 would place ETS (fentanyl) responders for Group II at approximately 50% (moderate sensitizer category).

Summary and result

The continuous administration of fentanyl via electrotransport used 70 uA total current (current density 0.1 mA/cm^2) for 8 hours during inductions (Group II) and challenges 01, #2 and 42 mA total current (current density 0.06 mA/ cm^2) for challenge #5. The total maximum dose was 1.1 mg/kg/8 h. This dose was associated with clinical observed systemic effects in hairless guinea pigs which can be attributed to the analgesic and pharmacological activity of the drug. In a clinical situation, a series of bolus doses (not continuous delivery) would be administered where a maximum of six consecutive

10-minute bolus doses (25 Ag/bolus) per hour may be delivered. This results in an intended maximum dose of 3.6 mg/day or a dose of 0.051 mg/kg/day for a 70 kg human. Thus, the animals received a dose about 64 times the human daily dose.

For challenge #1, the anode responses to fentanyl gel and current might reflect cumulative irritation, which was seen in all four groups. However, comparing fentanyl and current (Group II) to saline and current (Group 1), the passive (Group III), or sham (Group IV) would place it in the mild to moderate sensitizer category. For challenge #2, the number of responders increased in all groups, most likely indicative of irritation. Challenge #3 with saline and current suggests that animals induced with current (Groups I and II) are more hyperreactive since similar responses are seen in these groups and not seen in Groups III & IV. This occurrence may be explainable as "excited skin syndrome". Subsequent challenges to Group II at a lower current density (0.06 mA/cm^2) categorized fentanyl as a mild-moderate sensitizer.

The results of this study in hairless guinea pigs indicate that electrically-assisted delivery of fentanyl (anode) at a maximum dose of 1.1 mg/kg/8 h and the maximum current density of 0.1 mA/cm^2 be placed in the mild to moderate sensitizer category.

Study title: Visual (Macroscopic) and Histological Evaluation of Guinea Pig Skin Sites Following Single and Multiple Applications of Electrotransport Therapeutic Systems

Key study findings: Histopathologically, increasing the current density did not result in an enhancement of inflammation. For the cathode, the lower current density (0. 1 mA/cm^2) resulted in a higher irritation score. The mean cathode scores were 3.5 and 2.8 for Groups A and A', respectively.

Study no.: TR-92-9999-014

Volume #, 1 and page #: 1-176
Conducting laboratory and location: ALZA CORPORATION. Palo Alto, Ca
Date of study initiation: July 20, 1992
GLP compliance: Yes
QA reports: yes (x) no ()
Drug, lot #, and % purity: Electrotransport Therapeutic Systems (ETS)

Code Name: Gel Based Electrotransport Delivery Platform Code Number. —

Lot Numbers: 500018, 500020, 500021, 500022
An electrotransport platform having two electrodes — , and associated electrolyte compartments was used. Each gel reservoir had an electrode area of 2 crn^2 with a volume capacity approximately 0.2 mL. The platform contained the power source set to 0.1

mA/cm^2 current density for a total current of about 200 uA (electrode area 2.0 cm^2) or 100 uA (electrode area masked to 1.0 cm2) and current density of 0.2 uA/ for total current of about 200 uA (electrode area masked to 1.0 cm^2).

Test Article for Cathode
Code Name: Cathode Gel Code Number: Lot Number: 500016

Test Article for Anode Code Name: Anode
Code Number: Lot Number: 500019

Formulation/vehicle:

formulation was purified water, sodium chloride, citric acid, polyvinyl alcohol . The cathode hydrogel was 1/16 in x 2cm^2.

The anode hydrogel was 1/16 in x 2 cm^2 .

Methods

Doses:

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Quantitative Hydrogel Composition

Component	Toxicology Formulation TR-92-9999-014		Clinical Formulation C-93-019		Clinical Formulation C-95-003	
	Percent (%)		Percent (%)		Percent (%)	
	Anode	Cathode	Anode	Cathode	Anode	Cathode
Purified Water						
Polyvinyl Alcohol						
Citric Acid, USP,						
Sodium Chloride, USP						
Drug	--	--	1.4	--	1.74	--
Polarcrillin						

Treatment Regimen

Group	Total Current (μA)	Current Density (μA/cm^2)	Electrode Area (cm^2)	Number of Applications	Number of Days Between Applications
H	200	0.1	2.0	1	NA
A	200	0.1	2.0	2	1
A'	200	0.2	1.0	2	1
B	200	0.1	2.0	2	3
C	200	0.1	2.0	2	5
D	200	0.1	2.0	3	1
D'	200	0.2	1.0	3	1
E	200	0.1	2.0	3	1 day between first and second application; days between second and third application
F	200	0.1	2.0	3	3 days between first and second application day between second and third application
G	200	0.1	2.0	4	1
I	100	0.1	1.0	7	1

Site Orientation

HEAD

I (cathode) II (anode) (odd number applications)
IV (cathode) III (anode) (even number applications)

Study design:

Prior to application of ETS, the cathode hydrogel formulation was placed in the cathode gel and the anode hydrogel formulation was placed in the anode gel cup. Both gel reservoirs had a double thickness of foam (1/16") and a release liner. For Group IV, some of the anode gels were masked to 1.0 cm^2electrode area using a — release liner. The animals (24 male guinea pigs) were treated with the occluded topical application of the respective hydrogels in the anode and cathode gel cup of an active electro- transport therapeutic system and worn for 24 hours. The skin sites were wiped with an alcohol swab. The release liner was removed from the adhesive and the electrotransport therapeutic was system placed on the dorsal area of the animal. The electrotransport therapeutic system was secured with — 1 bandage and bandaging tape. Observations for retention of systems were made periodically during the wearing period.

In the study design, the animals were placed in six different groups, Groups IV - VI were to be evaluated for durations of 7, 14 and 21 days (applications alternated sites between two sites such that the 7 days equals 3 applications to one site and 4 applications to the second site on alternating days and 14 days equals 7 applications to each of 2 sites,) at current density 0.1 mA/cm^2, total current 200 uA. Group IV and Group IV (M) was to be similar in applications (7) and current density (0.1 mA/cm^2) but differs in total current, 200 uA and 100 uA, respectively. However, when applying the 1.0 cm^2 mask (M) to the anode electrode area to Group IV (M) the total current remained at 200 uA and was not adjusted to 100 uA resulting in a current density of 0.2 mA/cm^2 not 0. 1 mA/cm^2 . Group VIII was added to evaluate 14 days of application to alternate sites, at the planned current density 0.1 mA/cm^2, total current 100 uA.

Cumulative irritation seen at some of the anode and cathode sites resulted in an alternation in treatment: some animals completed less than the intended treatments. For data analysis, the sites were organized into groupings that reflected similar number of applications to sites. This resulted in a total of eleven site treatment groups.

Results:

All guinea pigs appeared normal and healthy prior to application of the electrotransport therapeutic systems. During the course of the study, the animals exhibited a mean weight loss that may be attributed to the handling and wrapping procedures of the repeated ETS applications.

Various repeat applications for days 1-14 alternated between sites were scored and skin irritation scores were calculated according to Draize scale in a range of 1-8.

The skin irritation scores categorized the cathode as mild to moderate irritant (1.7-4.4) and the anode as mild to moderate irritant (2.1-5.2). Additional observations after the 48-hour observation, made to follow the resolution of the irritated skin sites, showed mild irritation (1.0-2.0) for the cathode and mild to low moderate irritation (1.2-3.4) for the anode. Some animals scratched their site after system removal, usually after the second

application to the same site, and this self-inflicted injury resulted in eschar formation and contributed to the high irritation scores (4.3). In some instances, the eschar formation had healed within 24 hour post removal and was no longer present on the site. It is unknown whether a skin sensation encouraged the animals to scratch the applied site. Papules were seen at both the cathode and anode sites periodically for all groups except Group F (three applications: 3 days between first and second application; 1 day between second and third application) and flaky epidermis was also seen in all groups.

As the number of applications increased from one to four, with one day between applications to the same site for Groups H, A, D, and G at a current density of 0. 1 mA/cm^2, there was no increase in irritation at the anode and cathode sites with the exception for the Group H having a single application. Groups with a one to five day rest period between the next application to the same site (Groups B, C, E, F) was categorized as moderate irritants (3.0-5.2) for the anode and cathode at current density 0.1 mA/cm^2. There was no consistent decrease in irritation as the number of days between applications increased.

Comparison between the two current densities for Groups A (0.1 mA/cm^2) and Group A (0.2 mA/cm^2) for two applications (one day between applications) showed that the higher current density resulted in higher anode mean scores of 2.3 and 3.3 for Groups A and A', respectively at 48 hour post removal.

However, since the eschar formation from the scratched sites was seen in both groups, it appeared the increase in current density did not attribute to the eschar formation resulting in the moderate irritation. By 72 hours, the eschar formation had healed and was categorized as a mild irritant.

Histopathologically, increasing the current density did not result in an enhancement of inflammation. For the cathode, the lower current density (0. 1 mA/cm^2) resulted in a higher irritation score. The mean cathode scores were 3.5 and 2.8 for Groups A and A', respectively.

Comparison between the two current densities for Groups D (0.1 mA/cm^2) and Group D(0.2 mA/cm^2) for three applications, one day between applications, showed no difference in irritation at the anode site however histopathologically, there was a difference between the current densities. The cathode site at 0.1 mA/cm^2 resulted in a higher irritation score (3.0) than the current density at 0.2 mA/cm^2

There was no consistent decrease in irritation as the number of days between applications increased. The groups that had a one to five day rest period between the next application to the same site (Groups B, C, E, F) were categorized as moderate irritants (3.0-5.2) for the anode and cathode at current density 0.1 mA/ cm^2.

Summary of Skin Irritation Scores
(0.1 mA/cm^2)

Total Current	Group	n	Number of Application (s)	Number of Days Between Application	Application No.	Skin Irritation Score Anode (≤48h)	Anode (≥72h)	Cathode (≤48h)	Cathode (≥72h)
200 µA	H	2	1	0	2	4.3[a]	4.4[a]	2.3	1.8
200 µA	A	3	2	1	1, 3	2.4[a]	1.4	4.3[a]	2.0
		9	2	1	2, 4	2.2	1.2	2.7	1.6
					Mean	**2.3**	**1.3**	**3.5**	**1.8**
200 µA	A[b]	4	2	1	1, 3	3.3[a]	1.9	3.0[a]	1.6
		1	2	1	2, 4	3.2[a]	2.0	2.6	1.0
					Mean	**3.3**	**2.0**	**2.8**	**1.3**
200 µA	B	2	2	3	1	3.5	2.0	2.5	2.0
					5	3.0	1.3	3.7[a]	1.5
		3	2	3	2	2.8	2.3	2.0	2.0
					6	4.4[a]	--	3.7	--
					Mean	**3.4**	**1.9**	**3.0**	**1.8**
200 µA	C	3	2	5	1	4.1[a]	3.4[a]	2.7	1.6
					7	5.2[a]	--	4.4[a]	

[a] Scratched sites self inflicted by animal (24 hours post application) resulting in eschar formation.
[b] Current density 0.2 mA/cm^2.

Histological assessment by light microscopy indicated that the topical applications of the ETS containing saline hydrogels to intact hairless guinea pig skin sites, resulted in biologically meaningful increases in incidence and severity of dermatitis. This includes (lymphohistiocytic (LHC) and polymorphonuclear (PMN) cellular infiltrates), parakeratosis, acanthosis, hyperkeratosis, inflammatory crusts (serocellular crusts), and epidermal necroses (ulceration) when compared to the respective untreated control sites.

Summary of Histopathology for Lymphohistiocytic (LHC)
Cellular Infiltrates, Acanthosis (AC), Hyperkeratosis (HK), and Parakeratosis (PK)

	Parameters				
Sites for All Groups	Increase in Applications Did Not Result in Increase Severity	More Time Between Applications Resulted in Less Severe Reaction	More Time Between Applications Did Not Result in Less Severe Reaction	Related to Increase of Current Density	Not Related to Increase in Current Density
CATHODE					
LHC	X	X		X	
AC	X		X		X
HK	X		X		X
PK	X		X	X	
ANODE					
LHC	X		X		X
AC	X		X		X
HK	X		X		X
PK	X		X	X	

LHC cellular infiltrates, acanthosis, and hyperkeratosis by incidence were the three major changes or lesions that were observed in 100% of the animals in all eleven groups of cathode and anode treatment sites. The only exceptions were 50% incidence of hyperkeratosis at the cathode sites, 0% incidence of LHC cellular infiltrates, acanthosis, and hyperkeratosis at the anode sites of Group H (one application), and 83% incidence of hyperkeratosis at the anode sites for Group A. All the skin lesions described in this study ranged from minimal to marked in severity, and would be expected to be reversible following cessation of treatment.

Study title: Evaluation of Polacrilin Resin — Extract Dilutions for Delayed Contact Hypersensitivity in Guinea Pigs

Key study findings: Polacriline was found to cause dermal irritation (mild to moderate) and do have a contact sensitivity potential of category I (mild).

Study no.: TR-96-1561-048

Volume # 1, and page #: 1-155
Conducting laboratory and location:
Date of study initiation: July 10, 1996
GLP compliance: Yes
QA reports: yes (x) no ()
Drug, lot #, and % purity:
Formulation/vehicle:

Methods

Doses: Intradermal induction: 1% polacrilin extract
Topical induction: undiluted polacrilin extract
Intradermal challenge: 0.1, 1, & 50% polacrilin extract

Study design: Route of administration was intradermal injections and topical applications (under occlusion for 24 hr) during induction, and intradermal injections during challenge exposures. The study length was 47 days. Following is the experimental plan

Group Number	No. of Animals	Induction Treatment	Challenge Treatment
1 (Control)	20	50:50 water in FCA	polacrilin resin saline extract and saline
2 (Vehicle Control)	20	Saline	polacrilin resin saline extract and saline
3 (Polacrilin Extract)	20	50:50 2% polacrilin resin aqueous extract: FCA	polacrilin resin saline extract and saline
4 (Polacrilin Extract)	20	1% polacrilin resin saline extract	polacrilin resin saline extract and saline

Induction Dose Administration:

Group No.	Intradermal Injections on Days 1, 3, 5, 8, and 10	Topical Applications to Abraded Skin on Days 3 and 8 (0.1 ml/application)
1[a]	50% water: 50% FCA	Sterile water
2[b]	Sterile saline	Sterile water
3[a]	50% of a 2% polacrilin resin aqueous extract: 50% FCA	Undiluted polacrilin resin aqueous extract
4[b]	1% polacrilin resin saline extract	Undiluted polacrilin resin aqueous extract

[a] Administered as two 0.05 ml injections/dose.
[b] Administered as one 0.1 ml injection/dose.

Challenge Dose Administration:

Group No.	Intradermal Injection Challenge 1; Day 22 (0.1 ml/injection)	Intradermal Injection Challenge 2; Day 36 (0.1 ml/injection)
1	0.1% and 1% polacrilin resin saline extract, and saline vehicle	1% and 50% polacrilin resin saline extract, and saline vehicle
2	0.1% and 1% polacrilin resin saline extract, and saline vehicle	1% and 50% polacrilin resin saline extract, and saline vehicle
3	0.1% and 1% polacrilin resin saline extract, and saline vehicle	1% and 50% polacrilin resin saline extract, and saline vehicle
4	0.1% and 1% polacrilin resin saline extract, and saline vehicle	1% and 50% polacrilin resin saline extract, and saline vehicle

Results:

Induction with 1%Polacrilin resin extract: Polacrilin resin extract at a concentration of 0. 1% was nonirritating to control animals. There were no positive responders (0/20) in the polacrilin resin extract/FCA-induced group to intradermal challenge with the 0.1% polacrilin resin extract, placing it in the weak sensitizer category (Category I).
Polacrilin resin extract at a concentration of 1% was nonirritating to control animals at Challenge # 1. None of the animals in the test group (Group 2) had a positive skin response at 72 hr (0/20 or 0%) following Challenge #1; however, following Challenge #2 there were 1/20 (5%) positive responders in the control group (considered to be due to irritation) and 2120 (10%) positive responders in the test group. The 1% polacrilin resin extract was classified as a mild sensitizer (Category I) under these conditions.
When polacrilin resin extract at a concentration of 50% was intradermally injected to the control animals (Group 1; water/FCA-induced) at Challenge #2, 2/20 (10%) of the animals had a total score of 2 at 72 hr. This positive skin response to the 50% concentration was considered to be due to irritation, since total scores of 0 or 1 were observed at the same site at 24 and/or 48 hr after injection. Thus the responses in these two animals did not persist throughout the 72-hr post injection evaluation period. The 2/20 (10%) positive responses of the test group (Group 3; polacrilin resin extract/FCA-induced) to polacrilin resin extract at a concentration of 50% at Challenge # 2 were considered to be allergic reactions due to the pattern of response (i.e., the skin responses persisted throughout the 72 hr period following challenge).

Therefore, when polacrilin resin extract at a concentration of 50% was intradermally injected to the test animals at Challenge #2, 2/20 (10%) had a total score of 2 or greater at 72 hr, classifying the 50% polacrilin resin extract as a mild sensitizer (Category I) under these conditions.

Percent Positive Skin Reactions (Mean Irritation Score) Following Intradermal Challenge on Day 22

Group	Induction Treatment	Challenge Treatment	2 hr	24 hr	48 hr	72 hr
1	50:50 Water:FCA	Polacrilin Saline Extract				
		0 %	100% (2.0)	0% (0.1)	0% (0)	0% (0)
		0.1%	100% (2.3)	0% (0.3)	0% (0)	0% (0)
		1%	100% (2.5)	0% (0.4)	0% (0)	0% (0)
3	50:50 2% Polacrilin Aqueous Extract/FCA	Polacrilin Saline Extract				
		0 %	95% (2.0)	0% (0.2)	0% (0)	0% (0)
		0.1%	100% (2.8)	10% (0.8)	0% (0.1)	0% (0)
		1%	100% (2.8)	25% (1.1)	5% (0.2)	0% (0)
2	Saline	Polacrilin Saline Extract				
		0 %	100% (2.0)	0% (0.1)	0% (0.1)	0% (0)
		0.1%	100% (2.3)	0% (0.2)	0% (0)	0% (0)
		1%	100% (2.4)	5% (0.4)	0% (0.1)	0% (0)
4	1% Polacrilin Saline Extract	Polacrilin Saline Extract				
		0 %	100% (2.0)	0% (0)	0% (0)	0% (0)
		0.1%	100% (2.0)	0% (0)	0% (0)	0% (0)
		1%	100% (2.2)	0% (0.5)	0% (0)	0% (0)

Percent Positive Skin Reactions (Mean Irritation Score) Following Intradermal Challenge on Day 36

Group	Induction Treatment	Challenge Treatment	2 hr	24 hr	48 hr	72 hr
1	50:50 Water/FCA	Polacrilin Saline Extract				
		0 %	100% (2.0)	0% (0.1)	0% (0)	0% (0)
		1%	100% (2.2)	5% (0.7)	5% (0.2)	5% (0.2)
		50%	100% (2.3)	20% (1.3)	5% (0.6)	10% (0.5)
3	50:50 2% Polacrilin Aqueous Extract/FCA	Polacrilin Saline Extract				
		0 %	100% (2.0)	0% (0.1)	0% (0)	0% (0)
		1%	100% (2.7)	15% (1.0)	10% (0.3)	10% (0.2)
		50%	100% (3.0)	25% (1.6)	15% (0.8)	10% (0.6)
2	Saline	Polacrilin Saline Extract				
		0 %	100% (2.0)	0% (0.2)	0% (0.1)	0% (0)
		1%	100% (2.1)	0% (0.3)	0% (0.1)	0% (0)
		50%	100% (2.3)	20% (1.3)	0% (0.5)	5% (0.5)
4	1% Polacrilin Saline Extract	Polacrilin Saline Extract				
		0 %	100% (2.0)	0% (0.1)	0% (0)	0% (0)
		1%	100% (2.1)	0% (0.4)	0% (0.1)	0% (0)
		50%	100% (2.6)	20% (1.3)	5% (0.6)	0% (0.5)

Induction with 1% Polacrilin Resin Extract without FCA: There were no positive responders (0/20) in the control group (Group 2) or in the polacrilin resin extract-induced group (Group 4) to intradermal challenge with the 0.1% polacrilin resin extract, placing it in the weak sensitizer category (Category I).

There were no positive responders (0/20) in the control group (Group 2) or in the polacrilin resin extract-induced group (Group 4) to either intradermal challenge with the 1% polacrilin resin extract, placing it in the weak sensitizer category (Category I). Polacrilin resin extract at a concentration of 50% elicited a positive skin response in one control animal (Group 2; saline-induced), with a positive skin response at 72 hr of 1/20 or 5% of the animals at Challenge #2. There were no positive responders (0/20 or 0%) in the polacrilin resin extract-induced group (Group 4) to intradermal challenge with 50% polacrilin resin extract, placing it in the weak sensitizer category (Category I).

Study title: Evaluation of the Sensitization Potential of Electrotransport Systems Containing Placebo Anode Hydrogels (Histidine and Polacrilin in the Hairless Guinea Pig

Key study findings:

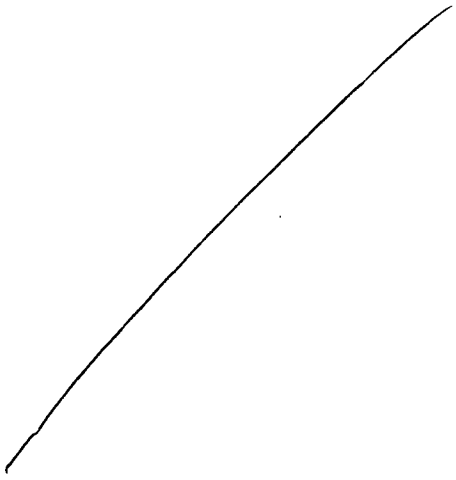
- No evidence of sensitization occurred in the animals induced and challenged with the anode placebo containing histidine with polacrilin, thereby categorizing it as a weak sensitizer.
- No evidence of sensitization occurred in the animals induced and challenged with the cathode hydrogel (at either 50-uA cm^2/or 30 uA cm^2/), thereby categorizing it as a weak sensitizer.

Study no.: TR-97-1561 -011

Volume #1 and page #: 1-144
Conducting laboratory and location: ALZA CORPORATION, Palo Alto, Ca
Date of study initiation: 05-28-98
GLP compliance: Yes
QA reports: yes (x) no ()
Drug, lot #, and % purity:

Anode Hydrogel Formulations

Group No.	Name/Code Name	Formulation Component	Wt. Percent (%)	Code/Control No.
I	Placebo Anode Hydrogel without Polacrilin, 1.4 cm^2			
II	Placebo Anode Hydrogel with Polacrilin, 1.4 cm^2			
III	Placebo Anode Hydrogel without Polacrilin, 2 cm^2			
IV	Tetracaine Anode Hydrogel, 2 cm^2			



Cathode Hydrogel Formulations

Group No.	Name/Code Name	Formulation Component	Wt. Percent (%)	Code/Control No.
I, II	Cathode Hydrogel, 1.4 cm^2			
III, IV	Cathode Hydrogel 2 cm^2			

Formulation/vehicle: Please see anode and cathode hydrogel tables above for formulations of the placebos, tetracaine was used as a positive control. System for Group I and II had areas of 1.4 cm^2, systems for Groups III and IV had areas of 2.0 cm^2.

Methods

Doses:

Clinical System (Groups II and I): E-TRANS (fentanyl) system comprised two subassemblies joined together: the electromechanical component was on top and the drug component was below. The electromechanical subassembly was composed of a protective casing which houses the electronics: printed circuit board and custom-designed integrated circuit, lithium battery, and the light emitting diode (LED). The drug component subassembly consisted of a housing with two recessed cavities, the anode and cathode cavities. The skin contact area was 1.4 cm^2. For this study, the anode cavity is filled with the placebo anode hydrogel with histidine with no polacrilin (control) or with the placebo anode hydrogel with histidine and polacrilin (test). The cathode cavity was filled with the cathode hydrogel. An adhesive, which is protected by a removable release liner, covered the bottom of the drug component housing and allowed.
Toxicology System (Groups III and IV): An , 2 cm^2) with an anode and a cathode gel cavity was used. The anode and cathode lined the bottom of the anode and cathode cavities, respectively. Each electrode had an area of 2 cm^2 with a cavity depth of 0.32 cm. The anode cavity was filled with the placebo anode hydrogel with histidine and no polacrilin or with the tetracaine hydrogel. The cathode cavity is filled with the cathode hydrogel. The backing of the and the pouches that contained the anode

hydrogels were labeled with the study number, group number, hairless guinea pig number, test or control article, and/or application number.

Controllers

Clinical Controllers: The controller had the current set to 100 uA ± 5% (95-105 uA). The current density was 71.4 uA/ cm^2 (based on a skin contact area of 1.4 cm^2). There were no electrical measurements after application and before removal since there were no measurement ports. A recessed on-demand-dosing button and red LED were located on the top surface of the E-TRANS system. For this study, the was modified to allow for continuous delivery for about 13 hours (ie, no activation of an on-demand dose is required). The system was placed on the animal with slight pressure for approximately 15 seconds to ensure good adhesion. The dosing button was pressed twice in less than 3 seconds to initiate delivery. The red LED of the system went on and a single beep could generally be heard. Confirmation of the red LED "on" was sufficient to indicate proper function of the system and was documented for each application. The light was to remain on (indicating ions were being delivered) and one beep was to be emitted every 10 minutes indicating the start of each new 10-minute dose. The system was to automatically administer 80 doses, one right after another, with one beep and two blinks every 10 minutes. The sound level of the beeps was variable therefore the number of beeps was not documented. However, an attempt was made to use the pattern of beeps to assess system function, if needed. The two blinks were not recorded since they occurred so quickly. After all 80 doses were administered (approximately 13 hours) the system was to automatically shut off permanently and the red light begins blinking (16 blinks between pauses in the blink sequence). The blinking indicated no ions were being delivered. The system was left on the animals for 3 hours (passive delivery) for ease of scheduling during normal working hours. Before removal of the system, the number of blinks were recorded (the expected number of blinks between pauses is 16). Problems encountered after application are listed in Appendix 4. The number of times the controller was inoperable was sporadic and distributed among animals and groups and was determined not to have effected the integrity of the study.

Zero-Order Disposable Controllers (Groups III and IV): attached the zero-order disposable toxicology controllers to the o supply and regulate the electrical current. The controllers contained the power source set to approximately 60 uA. For Groups III and IV, the anticipated current density was 0.03 mA/crn^2 (based on a hydrogel and electrode area of 2 cm^2). The zero order disposable toxicology controllers were stored at room temperature.

Each controller was labeled with the study number and a unique identification number (for tracking purposes). The current of Groups III and IV were set to 60 uA ± 5% (57-63 uA). The battery voltage should be >8.5 volts.

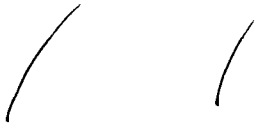
Placebo Gel

The placebo gel used for Challenge 2 was composed of:

The final pH of the gel was approximately —

Tetracaine HEC Gel

The tetracaine gel formulation was composed of



The final pH of the gel was approximately —

Study design:
Hairless guinea pigs (.GOHI-hr) were used to evaluate the sensitization potential of an E-TRANS system with placebo anode hydrogels containing histidine and polacrilin

The guinea pigs were divided into five groups:

Anode

Group I (n=10)	Negative Control for Group II
Group II (n=10)	Histidine/Polacrilin
Group III (n=5)	Negative Control for Group IV
Group IV (n=5)	Positive Control (Tetracaine)
Group V (n=5)	Naive Control Group for Challenge No. 2

The cathode hydrogel formulation was the same for all groups. Animals in Groups I and II received nine induction applications over 21 days (three applications per week) of their respective test or control articles. Each application was for 16 hours (13 hours activated and 3 hours passive). The direct current density at the anode was approximately 71.4 u-A/cm^2 (based on a total current of approximately 100 uA and an electrode area of 1.4 cm^2). The direct current density at the cathode was approximately 50 uAcm^2 (based on a total current of approximately 100 uA and an electrode and hydrogel area of 2.0 cm^2). Groups III and IV received nine induction applications over 21 days, each with a 6-hour wearing duration. The direct current density at the anode and cathode was approximately 30 uAcm^2 (based on a total current of approximately 60 uA and an electrode area of 2 cm ^{2}). Each anode and cathode application site was evaluated for primary and cumulative skin irritation after removal of the first and last induction applications, respectively, approximately 2 and 24 hours after system removal.

Approximately 10 days after the last induction application, each guinea pig in Groups I and II was challenged with E-TRANS systems with placebo anode hydrogels containing histidine and polacrilin and placebo anode hydrogels containing histidine with no polacrilin at a direct current density of 71.4 uA/cm^2 (hydrogel area of 1.4 cm^2) for 16 hours (13 hours activated and 3 hours passive). Each guinea pig in Groups III and IV was challenged with one E-TRANS system containing a placebo anode hydrogel containing histidine with no polacrilin and one E-TRANS system containing a tetracaine anode hydrogel at a direct current density of 30 uA/cm^2 (hydrogel area of 2 cm^2) for 6 hours. Approximately 15 days after the first challenge application, each guinea pig in Groups III, IV and V were challenged with an E-TRANS system with a tetracaine anode hydrogel and with HEC placebo and HEC tetracaine gels for 6 hours. For the challenge phases, all irritation scores at the anode and cathode sites were performed at 2 ± 0.5, 24 ± 1, 48 ± 1, and 72 ± 1 hours after removal of the system. The observers used a standardized scoring system (Draize scoring system).

Results:

No treatment related change in body weights or clinical conditions occurred.
Primary and Cumulative Irritation are scored according to Draize scale.
Mean irritation data are presented in Table 2.

Challenge Results:

First Challenge:
The animals induced with placebo anode hydrogel containing histidine with polacrilin showed a mild skin response upon challenge with the same formulation. The animals induced with the citrate cathode showed a mild skin response upon challenge at 50 uA/ cm^2 (Groups II and I) and at 30 uAcm^2 (Groups III and IV). These responses were similar to those observed during the induction period and, therefore, considered irritation.

Upon challenge with the tetracaine anode the animals induced with the tetracaine anode showed similar irritation to the animals not induced with the tetracaine anode. Therefore, to confirm that the animals were capable of being sensitized, these animals were challenged with both a tetracaine gel and the E-TRANS tetracaine anode.

Second Challenge:
In the animals induced with the tetracaine anode, a positive response occurred in 80% and 100% of the animals after challenge with the tetracaine anode and the tetracaine gel, respectively. The naive animals showed mild to moderate irritation (20% to 40% with scores of 2.0 or greater at 72 hours). In the animals induced with the cathode for the tetracaine anode, moderate irritation was present in 40% to 60% of the animals after challenge with the tetracaine cathode. In the naive animals, moderate irritation was also present in 60% of the animals at 72 hours post removal.

Conclusions

No evidence of sensitization occurred in the animals induced and challenged with the anode placebo containing histidine with polacrilin, thereby categorizing it as a weak sensitizer. No evidence of sensitization occurred in the animals induced and challenged with the cathode hydrogel (at either 50-uA cm^2/or 30 uA cm^2/), thereby categorizing it as a weak sensitizer.

Animals induced with tetracaine were considered to be sensitized upon electrical and passive challenge with tetracaine; these results confirmed that a sensitization reaction could be elicited in the animals. The system shows irritation as described in the table below.

Group	Hydrogel Formulation	Irritation Index	
		First Induction	Ninth Induction
	Anode		
I	Placebo anode hydrogel without polacrilin	1.8	3.9[a]
II	Placebo anode with polacrilin	1.8	2.7[a]
III	Placebo anode hydrogel without polacrilin	0.3	2.0
IV	Tetracaine anode hydrogel	1.8	3.4[a]
	Cathode[b]		
I	Buffered cathode hydrogel with CPC	1.6	3.0
II	Buffered cathode hydrogel with CPC	1.1	2.4
III	Buffered cathode hydrogel with CPC	0.9	3.0
IV	Buffered cathode hydrogel with CPC	0.9	4.6

[a] Due to irritation after repeat applications to the same site, not all inductions were applied to the same site; therefore, the irritation index is not a true representative score of all nine inductions.
[b] All groups had the same cathode formulation; Groups I,II ran at 50 $\mu A/cm^2$ for 13 h active (and 3 h passive); Groups III, IV ran at 30$\mu A/cm^2$ for 6 h

Study title: A Primary Skin Irritation Study of E-TRANS (placebo) Systems Containing Cetylpyridinium Chloride (CPC) and — and — Adhesives on Hairless Guinea Pigs and Rabbits

Key study findings:

- Cetylpyridinium Chloride (CPC) and — tested on hairless guinea pigs and rabbits did not show irritation or contact sensitivity.
- The — adhesive was a mild irritant in guinea pigs and a moderate irritant in rabbits. The histopathology supported the macroscopic evaluation.

Study no.: TR-98-1561-031

Volume # 1 and page #: 1-99
Conducting laboratory and location: ALZA CORPORATION, Palo Alto, Ca
Date of study initiation: 07-28-98
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: See the formulation
Formulation/vehicle:
The hydrogels were tested before and after testing for appearance, pH (both anode and cathode) and CPC content. The E-TRANS systems were tested for electrical current before testing. The test and control articles passed all testing parameters and were deemed stable for the duration of the study. At the initial time point one cathode gel from lot 4923-66 (0.2% CPC, — adhesive) was out of specification for cetylpyridium chloride (CPC) content. The CPC content was , and the specification wa to . This lot was accepted for use on study.
Anode Hydrogel. The test — was composed of — purified water, USP, — polyvinyl alcohol —
NAOH, — sodium chloride. — polacrilin, and —

The hydrogel area was 1.4 cm^2 and had a thickness of 0.16 cm.

Electrosubstrates
The E-TRANS (placebo) systems are comprised of two subassemblies joined together: an electromechanical component on top and a drug component. The electromechanical subassembly is composed of a protective — casing which houses the electronics: printed circuit board and custom-designed integrated circ lithium battery, and the light emitting diode (LED). The drug component subassembly consists of a — ousing with two recessed cavities, the anode and cathode cavities. The skin contact area was 1.4 cm^2 at both the anode and cathode. The anode was filled with the anode hydrogel and the cathode was filled with either the 0.08% CPC cathode gel or the 0.2% CPC cathode hydrogel. An adhesive, which is protected by a removable release liner, covers the bottom of the drug component housing and allows attachment to the skin.

There were two test articles; an E-TRANS (placebo) with the cathode hydrogel containing 0.2% CPC and the — dermal adhesive and an E-TRANS (placebo) with cathode hydrogel containing 0.2% CPC and the — dermal adhesive. The control article was an E-TRANS (placebo) with the cathode hydrogel containing 0.08% CPC and the — dermal adhesive, the current clinical system.

The controllers were set to 100 uA ±5% (95-105 uA). The current density at both the anode and cathode was approximately 71.4 uA/ cm^2 (based on a skin contact area of 1.4 cm^2) . No electrical measurements were taken since there were no measurement ports. A recessed on-demand-dosing button and red LED are located on the top surface of the E-TRANS system. For this study, the circuit board was modified to allow for continuous delivery for about 13.3 hours (ie, no activation of an on-demand dose required).

Methods

Doses:

Each E-TRANS system was applied to the animal with slight pressure for approximately 15 seconds to ensure good adhesion. The dosing button was pressed twice in less than 3 seconds to initiate delivery. The red LED of the system went "on" and this was documented. The light remained "on" (indicating that ions were being delivered). The system must have completed one dose in order to self-actuate the next 79 doses. The system automatically administered 80 10-minute doses, one right after another.

It was possible for the system to shutdown part way through the first dose due to high skin resistance and not self-actuate further dosing. The systems were checked after 1 0 minutes to assure that the systems were still activated. If the LED was illuminated, then it was highly likely that the remaining doses would be delivered. If the LED was not illuminated, it could be due to the system detecting either a low or high skin resistance. If the LED was not illuminated, the dosing button was again pressed twice to initiate delivery. If the system detected a low skin resistance, the system would not restart and the system was removed and replaced with a new system, on a new skin site. If the system detected a high skin resistance, the system would restart. The system was checked again after 10 minutes to assure that the system was working properly. If the system was not functioning correctly, then the system was removed and replaced with a new system.

All systems were secured with — bandage and — tape. Rabbits had an additional overlay of orthopedic stockinet and — tape applied over the first wrapping.

After all 80 doses were administered (approximately 13.3 hours) the system automatically shut off and the red light would blink (sixteen blinks between pauses in the blink sequence). The blinking indicated that no ions were being delivered. Before removal of the system, the number of blinks were recorded (the expected number of blinks between pauses was 16). After approximately 13.3 hours, the E-TRANS systems and associated bandaging were removed. The worn hydrogels were placed into the original foil pouches, heat sealed, and stored at the proper storage conditions. The test articles were disposed of in drug waste.

Study design:

Twelve guinea pigs and six rabbits were used to evaluate the potential degree of dermal inflammatory response produced by exposure to three different E-TRANS systems: (1) E-TRANS (placebo) with cathode hydrogel containing 0.08% CPC and [redacted] adhesive, (2) E-TRANSTM (placebo) with cathode hydrogel containing 0.2% CPC and [redacted], adhesive. and (3) E-TRANS (placebo) with cathode hydrogel containing 0.2% CPC and [redacted] adhesive. The controllers were set to 100 uA ±5% (95-105 uA). The direct current density at both the anode and cathode was approximately 71.4 uA/cm^2 (based on a skin contact area of 1.4 cm^2). Each guinea pig had one or two E-TRANS systems applied resulting in two or four intact skin application sites (one or two anode hydrogel and one or two cathode hydrogel sites). Each rabbit had three E-TRANS systems applied resulting in six intact skin application sites (three-anode hydrogel and three cathode hydrogel sites).

After the completed wearing period of 13.3 hours, the systems were removed. The anode and cathode application sites were scored for erythema and eschar formation and edema at 30 to 40 minutes, 24 ±1, and 48 ±l hours after system removal (data is presented as 0.5, 24, and 48 hours), and Primary Irritation Indexes were calculated. Histological evaluation of irritation was conducted on the sites.

Results:

All animals survived the treatment and observation periods. No change in clinical condition was observed.

Primary irritation index and irritation category for the anode and cathode test and control articles is presented below.

Primary Irritation Indices

E-TRANS™ Treatment	Primary Irritation Index (Category)					
	Guinea Pig			Rabbit		
	Anode	Cathode	Adhesive	Anode	Cathode	Adhesive
cathode hydrogel 0.08% CPC E-TRANS™ — Adhesive	1.3 (mild)	1.6 (mild)	0.8 (mild)	0.0 (none to negligible)	1.4 (mild)	2.2 (moderate)
	n = 5	n = 5	n = 6	n = 6	n = 6	n = 6
cathode hydrogel 0.2% CPC E-TRANS™ — Adhesive	0.9 (mild)	2.0 (mild)	1.0 (mild)	0.3 (none to negligible)	1.8 (mild)	2.3 (moderate)
	n = 6	n = 6	n = 6	n = 3	n = 3	n = 6
cathode hydrogel 0.2% CPC E-TRANS™ — Adhesive	1.3 (mild)	2.0 (mild)	1.0 (mild)	0.6 (none to negligible)	1.6 (mild)	2.2 (moderate)
	n = 6	n = 6	n = 6	n = 4	n = 4	n = 6

Histopathology revealed an increased incidence rate of mild to moderate acanthosis, hyperkeratosis, and dermal inflammation at all sites in guinea pigs when compared to untreated control. The anode skin sites were less affected than the cathode skin sites. Based on severity and incidence rates, treatment sites without CPC produced the least changes, while those with CPC were the most affected. Rabbits had an increased incidence of one or more of the following lesions noted at all treatment sites: dermal inflammation, epidermal necrosis, acanthosis, parakeratosis, and/or hyperkeratosis. Treatment sites without CPC produced the least changes, while those with CPC were the most affected. All changes were generally mild to moderate.

The cathode hydrogel containing 0.08% CPC and the cathode hydrogel containing 0.2% CPC were mild irritants in guinea pigs and rabbits. The corresponding anode was a mild irritant in guinea pigs and a non- to negligible irritant in rabbits. The — adhesive was a mild irritant in guinea pigs and a moderate irritant in rabbits. The — adhesive was a mild irritant in guinea pigs and a moderate irritant in rabbits. The histopathology supported the macroscopic evaluation.

Study title: USP XXII: Biological Testing of Silver Foil, Code Number 80770, Control Number 363290

Key study findings:

- [redacted], met the requirements for Class VI-50°C plastics as described in the United States Pharmacopea XXII.

Study no.: TR-90-1550-018
Volume # 1, and page #: 1-25
Conducting laboratory and location: ALZA CORPORATION, Palo Alto, and Ca

Date of study initiation: November 5, 1990

GLP compliance: Yes
QA reports: yes (x) no ()
Drug, lot #, and % purity: Code Number [redacted]
Formulation/vehicle:

Methods

Doses: 10gm/kg

Study design:

Extracts and samples of [redacted] were used in three assays: the Systemic Injection, Intracutaneous Injection, and Implantation Tests. All procedures necessary to meet Class VI requirements of the USP XXII to establish biological suitability of plastic materials were followed. Extracts of the plastic prepared at 50° C met the requirements of the Systemic Injection Test and Intracutaneous Injection Test. The Implantation Test evaluated the reaction of tissue to the plastic after implantation for 7 days and requirements of this test were met.

Results: [redacted], met the requirements for Class VI-50°C plastics as described in the United States Pharmacopoeia XXII.

Study title: USP XXII: Biological Testing of

Key study findings:

- may be used as a component in various electrotransport therapeutic systems.

Study no.: TR-93-2420-068

Volume #1, and page # 1-24
Conducting laboratory and location:
Date of study initiation: 03- 8-1994
GLP compliance: Yes
QA reports: yes (x) no ()
Drug, lot #, and % purity: Code Number 091172, Control Number 766594
Formulation/vehicle: The material was extracted in the following extraction media for the preparation of test article extracts and corresponding blanks.
Sodium Chloride Injection, USP, 1-in-20 Solution of Alcohol in Sodium Chloride Injection, USP 4.2.3.3, Polyethylene Glycol 400 (PEG 400).
Diluted with saline to about 200 mg per mL for Systemic Injection Test. Diluted to, about 120 mg per mL for intracutaneous injection test.

Doses: 10g/kg

Study design
Control Number 766594, was extracted in four different media for 72 hours at 50°C and these extracts were evaluated for biological reactivity by systemic injections in mice and intracutaneous injections in rabbits. All procedures necessary to meet Class V- 50°C requirements of the USP XXII to establish biological suitability of plastic materials were followed. The test article, met the requirement for Class V-50°C Plastics as described by the United States Pharmacopoeia XXII Ninth Supplement.

Results: may be used as a component in various electrotransport therapeutic systems.

Study title: USP XXII: Biological Testing of Lower Housing, Acute System, Code Number

Key study findings:

- All procedures necessary to meet Class VI-50°C requirements of the USP XXII to establish biological suitability of plastic materials were followed and all such requirements were met.

Study no.: TR-93-8888-059

Volume # 1, and page #: 1- 34
Conducting laboratory and location:
Date of study initiation: January 25, 1994
GLP compliance: Yes
QA reports: yes (x) no ()
Drug, lot #, and % purity: Code Number
Formulation/vehicle:

The following extraction media were used for the preparation of test article extracts and corresponding blanks. Sodium Chloride Injection, USP, 1-in-20 Solution of Alcohol in Sodium Chloride Injection, USP, Polyethylene Glycol 400 (PEG 400) Dilution for Systemic Injection Test : The PEG 400 test article extract (0.9 mL) and the corresponding control blank (0.9 mL) were each diluted with 4.1 mL of Sodium Chloride Injection, USP to obtain a solution having a concentration of about 200 mg of PEG 400 per mL .Dilution for intracutaneous Injection Test :The PEG 400 test article extract (0.9 mL) and the corresponding control blank (0.9 mL) were each diluted with 7.4 mL of Sodium Chloride Injection, USP to obtain a concentration of about 120 mg of PEG 400 per mL Cotton seed oil was used as vehicle.

Methods

Doses: 21 and 37gm

Study design: Lower Housing, Acute System, Code Numbe
may be used as a component in various electrotransport therapeutic systems. It is
The test article was extracted in four different media for 72 hours at 50°C and systemic injections in mice and intracutaneous injections in rabbits evaluated these extracts for biological reactivity. Samples of test article were also evaluated for biological reactivity after a 7-day implantation into the paravertebral muscles of rabbits. All procedures necessary to meet Class VI-50°C requirements of the USP XXII to establish biological suitability of plastic materials were followed and all such requirements were met.

Results: All procedures necessary to meet Class VI-50°C requirements of the USP XXII to establish biological suitability of plastic materials were followed and all such requirements were met.

Study title: Evaluation of Cetylpyridinium Chloride for Delayed Contact Hypersensitivity in Guinea Pigs

Key study findings:

- No animals induced with CPC were considered to be sensitized upon intradermal or topical challenge with CPC, categorizing CPC as a weak sensitizer under the conditions of this study.
- The positive control material, DNCB, was shown to be a sensitizer using the Freund's Complete Adjuvant Test (FCAT).

Study no.: TR-96-1561-017
Volume #, 1 and page #:1-88
Conducting laboratory and location: [redacted]
Date of study initiation: May 7, 1996
GLP compliance:
QA reports: yes no ( )
Drug, lot #, and % purity:
Formulation/vehicle:

Methods

Forty-five male Hartley guinea pigs were used to evaluate the sensitization potential of cetylpyridinium chloride (CPC). During induction, Group I (n = 20) received 1% w/v CPC in sterile water emulsified 1: I by volume with Freund's Complete Adjuvant (FCA). Group 2 (n = 20) received sterile water emulsified 1:1 by volume with FCA. Group 3 (n = 5) received the positive control article, 0.05% 1-chloro 2, 4-dinitrobenzene (DNCB), in 5% ethanol/95% water.

Groups 1 and 2 received two 0.05-mL intradermal injections with the respective test or control article in FCA in the shoulder region every 2 to 3 days for a total of five pairs of injections within a 10-day period. At the time of the second and fourth sets of FCA injections, topical applications to abraded skin of 0.4 mL of 0.5% w/v CPC in sterile water were administered to Group 1 and of vehicle alone was administered to Group 2. Each application was occluded for 24 hours. No treatments were made for approximately 2 weeks after the tenth induction injection

Group 3 animals received one 0.1-mL injection of 0.05% w/v DNCB in 5% v/v ethanol in sterile water every 2 to 3 days for a total of five injections. No topical induction applications were made for Group 3 animals.

For the first challenge, the vehicle control and test groups were intradermally injected (0. 1 mL) with 0.005% and 0.01 % CPC in saline and with saline alone. The DNCB group was challenged with an intradermal injection (0.1-mL) of 0.05% DNCB in 5% ethanol/95% saline and with vehicle alone. The sites were evaluated approximately 2, 24, 48 and 72 hours after injection.

For the second challenge, 2 weeks after the first challenge both the vehicle control and test group received 0.4-mL topical applications of 0. 1 % CPC in sterile water and vehicle alone to abraded skin sites. The positive control group was challenged with 0.05% w/v DNCB in acetone and with acetone alone, each applied topically to abraded skin sites occluded for 24 hours. The sites were evaluated at approximately 2, 24, 48, and 72 hours post removal.

Results: No animals induced with CPC were considered to be sensitized upon intradermal or topical challenge with CPC, categorizing CPC as a weak sensitizer under the conditions of this study.

The positive control material, DNCB, was shown to be a sensitizer using the Freund's Complete Adjuvant Test (FCAT).

Study title: USP XXII: Biological Testing of [redacted]

Key study findings: [redacted] met the requirements for Class V-50°C plastics.

Study no.: TR-94-1561-020
Volume # 1, and page #: 1-48
Conducting laboratory and location: [redacted]
Date of study initiation: 10,15, 1994

GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity:
Formulation/vehicle: The following extraction media were used for the preparation of test article extracts and corresponding blanks. Sodium Chloride Injection, USP, 1-in-20 Solution of Alcohol in Sodium Chloride Injection, USP, Polyethylene Glycol 400 (PEG 400) Dilution for Systemic Injection Test : The PEG 400 test article extract (0.9 mL) and the corresponding control blank (0.9 mL) were each diluted with 4.1 mL of Sodium Chloride Injection, USP to obtain a solution having a concentration of about 200 mg of PEG 400 per mL .Dilution for intracutaneous Injection Test :The PEG 400 test article extract (0.9 mL) and the corresponding control blank (0.9 mL) were each diluted with 7.4

mL of Sodium Chloride Injection, USP to obtain a concentration of about 120 mg of PEG 400 per mL ;Cotton seed oil, was used as vehicle.

Methods

Doses: 10 g/kg

Study design: [redacted] is extracted in four different media for 72 hours at 50°C and these extracts were evaluated for biological reactivity by systemic injections in mice and intracutaneous injections in rabbits. All procedures necessary to meet Class V-50°C requirements of the USP XXII to establish biological suitability of plastic materials were followed. Classification of the test article as Class I-V depended on the test results. Electrically Conductive Adhesive Tape (ECAT),

Results: [redacted] met the requirements for Class V-50°C plastics.

Study title: USP 23: Biological Testing of Lower Housing, Acute System, Code Number 0002083, Control Number 520301

Key study findings: All procedures necessary to meet Class VI-50"C requirements of the USP 23 to establish biological suitability of plastic materials were followed and all Class VI-50'C requirements were met.

Study no.: TR-95-1561-031
Volume # 1, and page #: 1-45
Conducting laboratory and location: [redacted]
Date of study initiation: November 11, 1995
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Code Number [redacted]

Formulation/vehicle: The following extraction media were used for the preparation of test article extracts and corresponding blanks. Sodium Chloride Injection, USP, 1-in-20 Solution of Alcohol in Sodium Chloride Injection, USP,Polyethylene Glycol 400 (PEG 400) Dilution for Systemic Injection Test : The PEG 400 test article extract (0.9 mL) and the corresponding control blank (0.9 mL) were each diluted with 4.1 mL of Sodium Chloride Injection, USP to obtain a solution having a concentration of about 200 mg of PEG 400 per mL .Dilution for Intracutaneous Injection Test :The PEG 400 test article extract (0.9 mL) and the corresponding control blank (0.9 mL) were each diluted with 7.4 mL of Sodium Chloride Injection, USP to obtain a concentration of about 120 mg of PEG 400 per mL ;Cotton seed oil, was used as vehicle.

Methods

Doses: 10g/kg

Study design: [redacted]
fabricate the lower housing in various acute electrotransport systems. [redacted] This housing, Code Number [redacted], was extracted in four different media for 72 hours at 500C and these extracts were evaluated for biological reactivity by systemic injections in mice and intracutaneous injections and intramuscular implants in rabbits.

Results: All procedures necessary to meet Class VI-50"C requirements of the USP 23 to establish biological suitability of plastic materials were followed and all Class VI-50'C requirements were met.

Study title: USP 23: Biological Testing of Film, [redacted] PIB Adhesive, Code No. 0002421, Control No. 539195

Key study findings: Film, [redacted] PIB Adhesive, Code Number [redacted], may be used as a component in [redacted] systems, which are electrotransport systems containing fentanyl.

Study no.: TR-96-1561-011
Volume # 1, and page #: 1-45
Conducting laboratory and location: [redacted]
Date of study initiation: 03, 27, 1996
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Code No. [redacted]

Formulation/vehicle:

A ratio of 120 cm^2:20 mL (surface area of test article to volume of vehicle) was used for each preparation. The surface area calculation was based on one side of the test article. The test article was extracted in SC(sodium Chloride), AS (alcohol in saline), PEG, and CSO (cotton seed oil) at 50°C for 72 hours. The extraction vehicles without test article were similarly prepared to serve as control blanks. The PEG test extract and control blank were diluted with SC after extraction to provide 120 mg of PEG.

Methods

Film, [redacted] PIB Adhesive, Code Number [redacted] was extracted in four different media for 72 hours at 50°C. These extracts were then evaluated for biological reactivity by single-dose systemic injections in mice and

intracutaneous injections in rabbits. All procedures necessary to meet Class V-50°C requirements of the USP 23 (USP/NF 1995) to establish biological suitability of plastic materials were followed.

Results: Film, [redacted] PIB Adhesive, Code Number [redacted] may be used as a component in [redacted] systems, which are electrotransport systems containing fentanyl.

Study title: Evaluation of Film, [redacted] Polyisobutylene (PIB) Adhesive (Code [redacted] xtract for Delayed Contact Hypersensitivity in Guinea Pigs

Key study findings:

- For the first challenge, Groups 1, 2 and 3 received an intradermal injection (0.1 mL) of the maximum nonirritating dose (determined by using 6 guinea pigs) of test extract and an intradermal injection (0.1 mL) of vehicle alone. The DNCB group was challenged with DNCB at a concentration of 0.05% in ETOH. The injection sites were evaluated approximately 2, 24, 48 and 72 hours after injection.

Study no.: TR-96-1563-012
Volume # 1, and page #: 1-46
Conducting laboratory and location: [redacted]
Date of study initiation: 06,05,1996
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Code No. [redacted]
Formulation/vehicle: Vehicle for Extraction ,Toxicology Code Name: 1 -in-20 alcohol-in-saline ;Positive Control Article, Toxicology Code Name: 1 -Chloro-2,4-dinitrobenzene (DNCB) [redacted] QC Inventory Number: [redacted]

Methods

Prior to the induction phase a Primary Irritation test was performed with animals pretreated with Freund's Complete Adjuvant (FCA) to determine the maximum non-irritating concentration of the test article extracts The animals (3 males and 3 females) were injected 24 hours prior to the start of the Primary Irritation test with 0.1 mL of FCA. The test article extracts were administered by intradermal injection (0. 1 mL per site) at concentrations of 1 00% and 75% (diluted in EtOH:NaCl). After 2 + 0.5 hours and 24, 48 and 72 hours, the reaction at the test article injection site was evaluated for erythema and/or edema.
Based on the results of the Primary Irritation Study, the test article was found to be non-irritating and was used full strength for the intradermal induction and challenge phases.

Four groups of Hartley guinea pigs were used to evaluate the sensitization potential of a saline/alcohol extract of Film, PIB Adhesive (Code No.). Extracts of adhesive were prepared for each administration. Group I (n = 1 0) received extract emulsified 1: 1 in Freund's Complete Adjuvant (FCA). Group 2 (n = 1 0) received the experimental extract neat. Group 3 (n = I 0) received the vehicle control article (1 -in-20 alcohol-in-saline) emulsified 1: 1 in FCA with no test article added. Group 4 (n = 5) received the positive control article, 0.05% 1-Chloro 2, 4-dinitrobenzene (DNCB) in 95% ethanol (EtOH).

For the induction phase, test article extract or control article was administered in two 0.05 mL intradermal injections to the shoulder region of the appropriate animals every 2 to 3 days for a total of IO injections within a 1 0 day period. Group 1 and 3 animals were administered test article extract in FCA and negative control in FCA, respectively. Group 2 and 4 animals received neat test article extract and positive control, respectively. Following the second and fourth set of induction injections, topical applications of Film, . PIB Adhesive were made to Group 1 and 2 animals. Group 3 animals received a topical application of Band Aid following the second and fourth set of induction injections. Each application was made over the injection sites and occluded for 24 hours. No treatments were made for approximately 2 weeks after the tenth induction injections.

For the first challenge, Groups 1, 2 and 3 received an intradermal injection (0.1 mL) of the maximum nonirritating dose (determined by using 6 guinea pigs) of test extract and an intradermal injection (0.1 mL) of vehicle alone. The DNCB group was challenged with DNCB at a concentration of 0.05% in ETOH. The injection sites were evaluated approximately 2, 24, 48 and 72 hours after injection.

Four groups of Hartley guinea pigs were used to evaluate the sensitization potential of a saline/alcohol extract of Film, PIB Adhesive (Code No.). Extracts of adhesive were prepared for each administration. Group I (n = 1 0) received extract emulsified 1: 1 in Freund's Complete Adjuvant (FCA). Group 2 (n = 1 0) received the experimental extract neat. Group 3 (n = I 0) received the vehicle control article (1 -in-20 alcohol-in-saline) emulsified 1: 1 in FCA with no test article added. Group 4 (n = 5) received the positive control article, 0.05% 1-Chloro 2, 4-dinitrobenzene (DNCB) in 95% ethanol (EtOH).

For the induction phase, test article extract or control article was administered in two 0.05 mL intradermal injections to the shoulder region of the appropriate animals every 2 to 3 days for a total of 10 injections within a 10 day period. Group 1 and 3 animals were administered test article extract in FCA and negative control in FCA, respectively. Group 2 and 4 animals received neat test article extract and positive control, respectively. Following the second and fourth set of induction injections, topical applications of Film, PIB Adhesive were made to Group 1 and 2 animals. Group 3 animals received a topical application of Band-Aid following the second and fourth set of induction injections. Each application was made over the injection sites and occluded for

24 hours. No treatments were made for approximately 2 weeks after the tenth induction injections.

Results:

For the first challenge, Groups 1, 2 and 3 received an intradermal injection (0.1 mL) of the maximum nonirritating dose (determined by using 6 guinea pigs) of test extract and an intradermal injection (0.1 mL) of vehicle alone. The DNCB group was challenged with DNCB at a concentration of 0.05% in ETOH. The injection sites were evaluated approximately 2, 24, 48 and 72 hours after injection.

Study title: Evaluation of Polacrilin Resin — Extract for Delayed Contact Hypersensitivity in Guinea Pigs

Key study findings: Polacrilin has some potential to induce sensitization, but at concentrations proposed for clinical use, the potential is reduced. Polacrilin was determined to be an acceptabl— for use in electrotransport hydrogels.

Study no.: TR-96-1561-016

Volume # 1, and page #: 1-159
Conducting laboratory and location: —
Date of study initiation: 03,29,1997
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity:
Formulation/vehicle:

Methods: Forty-five male Hartley guinea pigs were used to evaluate the intradermal sensitization potential of polacrilin resin extract. Fresh aqueous extracts of the resin were prepared for each administration. Group 1 animals (n=20) received resin extract (4 g polacrilin:20 mL vehicle) emulsified 1:1 by volume with Freund's Complete Adjuvant (FCA). Group 2 animals (n=20) received the vehicle control article, sterile water, emulsified 1: 1 by volume with FCA. Group 3 animals (n=5) received the positive control article, 0.05% 1-chlorc 2, 4-dinitrobenzene (DNCB), in 5% ethanol 95% water, emulsified 1:1 by volume with FCA. Each group received two 0.05 mL intradermal injections of the respective test/ control article in FCA in the shoulder region every two to three days for a total of five pairs of injections within a 10 day period. At the time of the second and fourth sets of FCA injections, topical applications (0.1 mL) were applied to abraded skin for Group I and Group 2 animals. Aqueous resin extract was administered to Group 1 animals and vehicle alone was applied to Group 2 animals. No topical applications were administered to Group 3 animals. No treatments were made for approximately 2 weeks after the last induction injection.

A Category V classification (extreme sensitizer - 515 positive responders) was obtained for the positive control article, DNCB, when challenged intradermally (0.05% DNCB in 5% ethanoV95% sterile saline) and topically (0-05% DNCB in acetone). These results confirmed that a skin sensitization reaction could be elicited in the animals.
For the first resin extract challenge, both the vehicle control and test group animals received four intradermal injections (0. 1 mL each) of 0% (vehicle), 25%, 50%, 1 00% saline resin extract. Injection sites were evaluated approximately 2, 24, 48 and 72 hours post injection.

For the second challenge, both the vehicle control and test group animals received 24-hour topical applications (0. 1mL) of undiluted resin extract in saline and of vehicle alone to abraded skin sites. Skin sites were evaluated at approximately 2, 24 and 48 hours post removal.

For the third challenge the vehicle and test group animals received four intradermal injections (0.1 mL each) of 0%, 1% and 50% polacrilin extract in saline and undiluted extract prepared using 0.030 mg polacrilin in 20 mL saline. Injection sites were evaluated approximately 2, 24, 48, and 72 hours postinjection. Intradermal challenge injections of 25% to 100% polacrilin extracted 4 g:20 mL saline elicited a sensitization reaction in 60% to 85% of the animals, categorizing polacrilin as having a moderate to extreme sensitization potential. Intradermal challenge injections with 1% polacrilin extracted 4 g:20 mL and polacrilin extracted 0.030 mg:20 mL in saline did not elicit a sensitization response, indicative ot a weak sensitization potential. Topical challenge with undiluted polacrilin did not elicit a positive sensitization response.

Portions of this study were repeated in another sensitization study (TR-96-1561- 048) with polacrilin extracts at more clinically relevant concentrations. The second study evaluated the potential of 1% polacrilin extract in eliciting a sensitization response with and without coadministration of FCA. Induction with 1% polacrilin extract in FCA enhanced the immune response of animals to polacrilin extract. Polacrilin extract at 1 % and 50% was classified as a mild sensitizer in the second study in animals treated with FCA and as a weak sensitizer without coadministration of FCA.

Results: Polacrilin has some potential to induce sensitization, but at concentrations proposed for clinical use, the potential is reduced. Polacrilin was determined to be an acceptable — for use in electrotransport hydrogels.

Study title: Evaluation of Cetylpyridinium Chloride for Delayed Contact Hypersensitivity in Guinea Pigs

Key study findings: At an induction concentration of 0.5%, CPC was determined to be an acceptable — t for topical formulations.

Study no.: TR-96-1561-017
Volume # 1, and page #: 1-88

Conducting laboratory and location:
Date of study initiation: 05, 7, 1996
GLP compliance: Yes
QA reports: yes ( ) no ( )
Drug, lot #, and % purity:
Formulation/vehicle:

Methods

Forty-five male Hartley guinea pigs were used to evaluate the sensitization potential of cetylpyridinium chloride (CPC). During induction, Group 1 (n = 20) received I% w/v CPC in sterile water emulsified 1: 1 by volume with Freund's Complete Adjuvant (FCA). Group 2 (n = 20) received sterile water emulsified 1:1 by volume with FCA. Group 3 (n = 5) received the positive control article, 0.05% 1-chloro 2, 4-dinitrobenzene (DNCB), in 5% ethanol/95% water.

Groups 1 and 2 received two 0.05 mL intradermal injections with the respective test or control article in FCA in the shoulder region every 2 to 3 days for a total of five pairs of injections within a 10 day period. At the time of the second and fourth sets of FCA injections, topical applications to abraded skin of 0.4 mL of 0.5% w/v CPC in sterile water were administered to Group 1 and of vehicle alone was administered to Group 2. Each application was occluded for 24 hours. No treatments were made for approximately 2 weeks after the tenth induction injection Group 3 animals received one 0.1 mL injection of 0.05% w/v DNCB in 5% v/v ethanol in sterile water every 2 to 3 days for a total of five injections. No topical induction applications were made for Group 3 animals.
For the first challenge, the vehicle control and test groups were intradermally injected (0. 1 mL) with 0.005% and 0.01 % CPC in saline and with saline alone. The DNCB group was challenged with an intradermal injection (0.1 mL) of 0.05% DNCB in 5% ethanol/95% saline and with vehicle alone. The sites were evaluated approximately 2, 24, 48 and 72 hours after injection.

For the second challenge, 2 weeks after the first challenge both the vehicle control and test group received 0.4 mL topical applications of 0. I% CPC in sterile water and vehicle alone to abraded skin sites. The positive control group was challenged with 0.05% w/v DNCB in acetone and with acetone alone, each applied topically to abraded skin sites occluded for 24 hours. The sites were evaluated at approximately 2, 24, 48, and 72 hours post removal.

No animals induced with CPC were considered to be sensitized upon intradermal or topical challenge with CPC, categorizing CPC as a weak sensitizer under the conditions of this study. The positive control material, DNCB, was shown to be a sensitizer using the Freund's Complete Adjuvant Test (FCAT).

Results: At an induction concentration of 0.5%, CPC was determined to be an acceptable for topical formulations.

Study title: USP 23: Biological Testing of

Key study findings: The c
.net the requirements of the Systemic Injection Test and Intracutaneous Injection Test, but failed the Muscle Implantation Test. The test material is therefore classified as Class V-50°C as described in the USP 23, and is suitable for use as an electrode material.

Study no.: TR-96-1561-044

Volume # 1, and page #: 1-46
Conducting laboratory and location:
Date of study initiation: 04, 22,1997
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Code Number 0002964
Formulation/vehicle: A ratio of 120 cm 1:20 mL (surface area of test article to volume of vehicle) was used for each preparation. The test article was extracted in SC, AS, PEG, and CSO at 50°C for 72 hours. The extraction vehicles without test article were similarly prepared to serve as control blanks. The PEG test extract and control blank were diluted with SC after extraction to provide 200 mg of PEG/mL.

1. 0.9% Sodium Chloride, Lot #J7A620
2. Alcohol in Saline, alcohol Lot #JFI 76
3. Chemical, Saline Lot #J7A620
3. Polyethylene Glycol, Lot #LJO219
4. Cottonseed Oil, Lot #4248224067

Methods

The electrode material,
which may be used as an electrode material for E-TRANS electrotransport technology systems was extracted in four different media for 72 hours at 50°C. These extracts were evaluated for biological reactivity by systemic injections in mice and intracutaneous injections in rabbits. Samples of the test article were also evaluated for biological reactivity following intramuscular implantation in rabbits for 7 days. All procedures necessary to meet Class VI-50°C requirements of the USP 23 (USP/NF 1995) to establish biological suitability of plastic materials were followed.

Results: The electrode material,
met the requirements of the Systemic Injection Test and Intracutaneous Injection Test, but failed the Muscle Implantation Test. The test material is therefore classified as Class V-50°C as described in the USP 23, and is suitable for use as an electrode material.

Study title: Evaluation of Polacrilin Resin —, Extract Dilutions for Delayed Contact Hypersensitivity in Guinea Pigs

Key study findings: Polacrilin has some potential to induce sensitization, but at concentrations proposed for clinical use, the potential is reduced. Polacrilin was determined to be an acceptable — for use in electrotransport hydrogels.

Study no.: TR-96-1561-048
Volume # 1, and page #: 1-155
Conducting laboratory and location: —
Date of study initiation: 07,10, 1996
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity:
Formulation/vehicle:

Methods

Eighty male Hartley guinea pigs (20 per group) were used to evaluate the intradermal sensitization potential of polacrilin resin — extract. Fresh aqueous or saline extracts of the resin (4 g resin:20 mL) were prepared for each administration. During intradermal induction, Group I animals received sterile water emulsified 1:1 by volume with Freund's Complete Adjuvant (FCA). Group 2 animals received saline. Group 3 animals received the aqueous resin extract (2%) emulsified 1: 1 by volume with FCA. Group 4 animals received the resin extract (1 %) in saline.

Each group received five injections of the respective test or control article intradermally in the shoulder region every two to three days for a total of five 0.1 mL doses within a 10 day period. For animals in Groups 1 and 3, the induction dose was administered as two 0.05 mL injections. At the time of the second and fourth injection doses, topical applications (0.1 mL) of the respective test or control article were also applied to abraded skin; sterile water to Group 1 and 2 animals and resin extract in sterile water to Group 3 and 4 animals. Each application was occluded for 24 hours. No treatments were made for approximately two weeks after the last induction dose.

For the first challenge, all groups received (0. 1 mL) intradermal injections of 0.1% and 1% resin saline extract and saline alone. Each site was evaluated at approx. 2, 24, 48 and 72 hours post injection. There were no positive responders (combined erythema and edema score >2) at 72 hours in any of the groups to the test or control articles at Challenge No. 1. For the second challenge, all groups received intradermal injections of 1% and 50% resin saline extract and saline alone. There were no sensitization responders in Groups 1, 2, or 4. Positive responders at the 72-hour observation in Groups 1 and 2 were considered to be due to irritation and not sensitization. Two animals in Group 3 had positive responses to both challenge concentrations of polacrilin extract.

This sensitization study repeated some work performed in an earlier sensitization study (TR-96-1561-016) with polacrilin extracts at more clinically relevant doses and evaluated the doses in animals with and without coadministration of FCA. Induction with 1% polacrilin extract in FCA enhanced the immune response of animals to polacrilin extract. Polacrilin extract at 1 % and 50% was classified as a mild sensitizer in this study in FCA-treated animals induced with 1% polacrilin extract and as a weak sensitizer without coadministration of FCA.

Results: Polacrilin has some potential to induce sensitization, but at concentrations proposed for clinical use, the potential is reduced. Polacrilin was determined to be an acceptable for use in electrotransport hydrogels.

Study title: USP 23: Biological Testing of Housing, Bottom, —, Red, E-TRANS (Acute), Code Number —

Key study findings: The Housing, Bottom, 2.78 cm^2, Red, Code Number 2, met the requirements of the Systemic Injection Test, Intracutaneous Injection Test, and the Muscle Implantation Test. The test material is therefore classified as Class VI-50°C as described in the USP 23, and is suitable for use as a housing material.

Study no.: TR-97-1561-009
Volume # 1, and page #: 1-46
Conducting laboratory and location: —

Date of study initiation: 10,23,1997
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Code Number
Formulation/vehicle: A ratio of 120 cm^2:20 mL (surface area of test article to volume of vehicle) was used for each preparation. The test article was extracted in SC, AS, PEG, and CSO at 50°C for 72 hours. The extraction vehicles without test article were similarly prepared to serve as control blanks. The PEG test extract and control blank were diluted with SC after extraction to provide 200 mg of PEG/mL.

1. 0.9% Sodium Chloride, Lot #J7A620
2. Alcohol in Saline, alcohol Lot #JFI 76
3. Chemical, Saline Lot #J7A620
4. Polyethylene Glycol, Lot #LJO219
5. Cottonseed Oil, Lot #4248224067

Methods

The Housing, Bottom, 2.78 cm^2, Red, Code Numbe —
which may be used as a housing material for E-TRANS electrotransport technology systems was extracted in four different media for 72 hours at 50°C. These extracts were

evaluated for biological reactivity by systemic injections in mice and intracutaneous injections in rabbits. Samples of the test article were also evaluated for biological reactivity following intramuscular implantation in rabbits for 7 days. All procedures necessary to meet Class VI-50°C requirements of the USP 23 (USP/NF 1995) to establish biological suitability of plastic materials were followed.

Results: The Housing, Bottom, 2.78 cm^2, Red, Code Number —, met the requirements of the Systemic Injection Test, Intracutaneous Injection Test, and the Muscle Implantation Test. The test material is therefore classified as Class VI-50°C as described in the USP 23, and is suitable for use as a housing material.

Study title: USP 23: Biological Testing of Housing, Bottom, —, E-TRANSTM (Acute), Code Number —

Key study findings: The Housing, Bottom, —, Code Number —, met the requirements of the Systemic Injection Test, Intracutaneous Injection Test, and the Muscle Implantation Test. The test material is therefore classified as Class VI-50°C as described in the USP 23, and is suitable for use as a housing material.

Study no.: TR-97-1561-010
Volume # 1, and page #: 1-46
Conducting laboratory and location:

Date of study initiation: 10,23,1997
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Code Number
Formulation/vehicle: A ratio of 120 cm^2:20 mL (surface area of test article to volume of vehicle) was used for each preparation. The test article was extracted in SC, AS, PEG, and CSO at 50°C for 72 hours. The extraction vehicles without test article were similarly prepared to serve as control blanks. The PEG test extract and control blank were diluted with SC after extraction to provide 200 mg of PEG/mL.

1. 0.9% Sodium Chloride, Lot #J7A620
2. Alcohol in Saline, alcohol Lot #JFI 76
3. Chemical, Saline Lot #J7A620
4. Polyethylene Glycol, Lot #LJO219
5. Cottonseed Oil, Lot #4248224067

Methods
The Housing, Bottom, —, Code Number — which may be used as a housing material for E-TRANS electrotransport technology systems was extracted in four different media for 72 hours at 50°C. These extracts were evaluated for biological reactivity by systemic injections in mice and intracutaneous injections in rabbits. Samples of the test article were also evaluated for biological

reactivity following intramuscular implantation in rabbits for 7 days. All procedures necessary to meet Class VI-50°C requirements of the USP 23 (USPINF 1995) to establish biological suitability of plastic materials were followed.

Results: The Housing, Bottom, Code Number: met the requirements of the Systemic Injection Test, Intracutaneous Injection Test, and the Muscle Implantation Test. The test material is therefore classified as Class VI-50°C as described in the USP 23, and is suitable for use as a housing material.

Study title: In Vitro Biological Testing of BH Hardener (Lot No. T790, Part No. 120301): USP Elution and MTT Assay

Key study findings: Extracts from a mixture of [redacted] were noncytotoxic in both the USP Elution test and the MTT assay.

Study no.: TR-98-1561-023

Volume # 1, and page #: 1-37
Conducting laboratory and location: Alza Inc, Ca

Date of study initiation: 05,22,1997
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Lot No. T790, Part No. [redacted] and [redacted] Lot No. LF1436037. [redacted]
Formulation/vehicle: The material was extracted according to the Sponsor SOP detail is not provided with this report .Negative Control Article: Code Name: High Density Polyethylene (HDPE) Item No.: [redacted]
Lot Number: 971796
Manufacturer: [redacted]
Positive Control Article
Code Name: Latex gloves. [redacted] (floor/exam) Code Number: [redacted]
Control Number [redacted]
Manufacturer: [redacted]

Methods

The biocompatibility of a mixture of [redacted] (Lot No. T790, Part No. [redacted] and [redacted] was evaluated using two in vitro tests: (1) the Elution test method described in United States Pharmacopoeia (USP) 23, and (2) the MTT (3-[4,5-di- methylthiazol-2-2,5-diphenyltetrazolium bromide) assay. Due to the noxious vapors emitted from the [redacted]

[redacted] 1), the USP Elution test and MTT assay were unable to be performed using the [redacted]. To test [redacted] in a state similar to the final product, a [redacted] mixture of [redacted] was used to perform the in vitro tests.

In the USP Elution test, extracts of a mixture of the test article [redacted] and extracts of the positive control (Latex) and negative control (USP Reference Standard Negative Control Plastic) articles were added to monolayers of L-929 mouse fibroblast cells in 6-well plates. Cells were examined microscopically before treatment and 24 and 48 hours after treatment. Cytopathic responses were assigned using USP Reactivity Grades ranging from None to Severe (0-4) representing responses that range from no effect to total cell lysis.

In the MTT assay, extracts of a mixture of the test article [redacted] and dilutions of the extracts or extracts of the positive and negative control articles were added to the appropriate wells of a 96-well plate containing near-confluent monolayers of L-929 cells. After the incubation period, the extracts were removed, culture medium containing MTT was added to cell monolayers, and cells were incubated for 3 to 4 hours at 37°C. Following the incubation step, MTT containing medium was aspirated and replaced with an isopropanol/HCl mixture. The 96-well plates were agitated and the resulting formazon production was measured using an ELISA Multiplate reader. A 50% decrease in formazon production (LD50) was the index used to reflect the relative cytotoxicity of the test articles.

Results: Extracts from a mixture of [redacted] and [redacted] were noncytotoxic in both the USP Elution test and the MTT assay.

Study title: ISO In Vivo Biocompatibility Testing of Housing, Top, E-TRANS (Acute), [redacted] Code Number [redacted]

Key study findings: Implantation of the test article in rabbits caused no irritation. Housing, Top, E-TRANS (Acute), [redacted] Code Number [redacted] may therefore be used as a new component of the E-TRANS technology.

Study no.: TR-99-1561-056
Volume # 1, and page #: 1-77
Conducting laboratory and location: [redacted]

Date of study initiation: 10,06,1999
GLP compliance: Yes
QA reports: yes (x) no ( )

Drug, lot #, and % purity: —— , Code Number ——
Formulation/vehicle: Based on a ratio of 60 cm^2:20 mL, a 67.2 cm^2 portion of the test article was covered with 22 mL of the vehicle. The test article was extracted in SC and CSO at SOC for 72 hours. The extraction vehicles without test article were similarly prepared to serve as reagent controls.

1. 0.9% sodium chloride (SC), Lot #J9E555,
2. Cottonseed oil, Lot #PP4/901

Methods

Housing, Top, E-TRANS (Acute), —— , Code Number —— , were processed under conditions similar to the intended use of the product and tested for biological reactivity. Extracts of the test article were prepared by placing the test article in saline or cottonseed oil (CSO), each for 72 hours at 50"C. These extracts were injected systemically (intravenously or intraperitoneally) in mice and intracutaneously in rabbits. The test article was also implanted into the paravertebral muscles of rabbits for 7 days. All procedures necessary to meet the requirements of the International Organization for Standardization (ISO) 10993: Biological Evaluation of Medical Devices, Parts 6, 10, and 11, to establish biological suitability of plastic materials were followed. Injection of the extracts of the test article resulted in no systemic toxicity in mice and no intracutaneous irritation in rabbits.

Results: Implantation of the test article in rabbits caused no irritation. Housing, Top, E-TRANS (Acute), —— ge, Code Number —— may therefore be used as a new component of the E-TRANS technology.

Study title: ISO In Vivo Biocompatibility Testing of Housing, Top, E-TRANS (Acute), —— , Code Number ——

Key study findings: No irritation and systemic toxicity was observed with the present protocol. Housing, Top, E-TRANS (Acute), —— , Code Number —— may therefore be used as a new component of the E-TRANS technology.

Study no.: TR-99-1561-057

Volume # 1, and page #: 1-78

Conducting laboratory and location: ——
Date of study initiation: 10,06,99
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: —— Code Number ——
Formulation/vehicle: Based on a ratio of 60 cm^2:20 mL, a 67.2 cm^2 portion of the test article was covered with 22 mL of the vehicle The test article was extracted in SC and

CSO at SOC for 72 hours. The extraction vehicles without test article were similarly prepared to serve as reagent controls.

Methods

Housing, Top, E-TRANS (Acute), ' — : Code Number — were processed under conditions similar to th.e intended use of the product and tested for biological reactivity. Extracts of the test article were prepared by placing the test article in saline or cottonseed oil, each for 72 hours (±2 hours) at 50'C. These extracts were injected systemically (intravenously or intraperitoneally) in mice and intracutaneously in rabbits. The test article was also implanted into the paravertebral muscles of rabbits for 7 days. All procedures necessary to meet the requirements of the International Organization for Standardization (ISO) 10993: Biological Evaluation of Medical Devices, Parts 6, 1 0, and 11, to establish biological suitability of plastic materials were followed. Injections of the test article extracts resulted in no systemic toxicity in mice and no intracutaneous irritation in rabbits. Implantation of the test article in rabbits caused no irritation.

Results: No irritation and systemic toxicity was observed with the present protocol. Housing, Top, E-TRANS (Acute), ' — :, Code Number — , may therefore be used as a new component of the E-TRANS technology.

Study title: USP XXII: Biological Testing of — , Control Number —

Key study findings: The test article, — , met the requirements for Class VI- 50°C as described in the United States Pharmacopoeia XXII Ninth Supplement.

Study no.: TR-94-1561-017

Volume # 1, and page #: 1-33

Conducting laboratory and location: —
Date of study initiation: 03,11, 1994
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Code Number
Formulation/vehicle: A ratio of 120 cm^2:20 mL (surface area of test article to volume of vehicle) was used for each preparation. The test article was extracted in SC, AS, PEG, and CSO at 50°C for 72 hours. The extraction vehicles without test article were similarly prepared to serve as control blanks. The PEG test extract and control blank were diluted with SC after extraction to provide 200 mg of PEG/mL.

4. 0.9% Sodium Chloride, Lot #J7A620
5. Alcohol in Saline, alcohol Lot #JFI 76
6. Chemical, Saline Lot #J7A620

4. Polyethylene Glycol, Lot #LJO219
5. Cottonseed Oil, Lot #4248224067.

Methods

[redacted] may be used as a component in various electrotransport therapeutic systems. The test article was extracted in four different media for 72 hours at 50°C and these extracts were evaluated for biological reactivity by systemic injections in mice and intracutaneous injections in rabbits. Samples of the test article were also evaluated for biological reactivity following intramuscular implantation in rabbits. All procedures necessary to meet Class VI-50°C requirements of the USP XXII to establish biological suitability of plastic materials were followed. Classification of the test article as Class I-VI depended on the test results.

Results: The test article. [redacted] met the requirements for Class VI- 50°C as described in the United States Pharmacopoeia XXII Ninth Supplement.

Impurity Qualification

Impurities in the fentanyl HCl are monitored by [redacted] and ALZA. Unknown impurities are also monitored routinely to ensure that their levels do not exceed the specified limits. The impurities are detectable and quantified in the drug substance by ALZA's high-performance liquid chromatography (HPLC) methods, ALZA Analytical Methods (AAMS) [redacted]. None of the impurities have been detected in the drug substance at levels close to [redacted](the specification limit). The two impurities not specifically monitored in the drug substance are [redacted] The [redacted] impurity is monitored in finished product stability, and the [redacted] impurity has been monitored by the [redacted] and reported in [redacted] Certificate of Analysis. This impurity is historically below the reporting threshold of 0.05% for drug substance as defined in the International Conference on Harmonization (ICH) Q3A. ALZA does not monitor for these two impurities specifically but reports any impurities detected above [redacted] with a limit of [redacted] Those impurities that are greater than [redacted], have been identified and are being monitored in the drug substance as discussed above.

In order to assess the potential contribution of [redacted] a potential impurity, a comparison with its parent compound fentanyl was made.
Doses of 0, 10 and 20 mg/kg were administered to mice and of 0, 1.25, 2.5 and 5 mg/kg to rats. LD50-values, calculated 14 days after the intravenous injection, were 16 mg/kg (mice) and 3.1 mg/kg (rats). Intravenous injection of [redacted] was lethal in 4 out of 5 mice at 20 mg/kg. Mortality occurred within the first hour after dosing [redacted] produced some central opioid-like actions, e.g. excitation, exophthalmos, Straub tail on arched back, corneal opacity, dyspnea and loss of righting reflex. All surviving mice completely recovered within 6 hours after injection. In rats, no mortality occurred at a dosage of 1.25 mg/kg. At a dose of 2.5 mg/kg, two out of five rats died after administration of [redacted] At a dose of 5 mg/kg, mortality occurred in four out of five animals. All deaths occurred

immediately after dosing. Apart from mortality, the following clinical observations were noted at all doses: blockade of cornea and pinna reflexes, dyspnea, loss of righting reflex, muscular rigidity, hypertonia, exophthalmos and salivation. The surviving rats recovered within 1 day after dosing. No abnormalities were found at autopsy in mice or rats. The acute intravenous toxicity of fentanyl and —— is considered to be very comparable in male mice and rats.

Tabulation of Fentanyl HCl Drug Substance Testing - Current Lots

Attribute	Specification	Lot 0117793	Lot 00121058	Lot 0123068
Identification				
IR				
HPLC				
Assay				
Total Impurities				
Specified Impurities				
Unspecified Impurities				
Appearance				
Loss on Drying				

NOTES: ne, HPLC = high-performance liquid chromatography,
IR = infrared, ND=not detected,

2.6.6.8 Discussion and Conclusions

The pharmacologic and toxicologic properties of fentanyl are well characterized. Following is a brief summary of toxicity studies done with fentanyl.

Single dose toxicity studies were performed with fentanyl following intravenous administration to adult mice, rats and dogs. Doses of 0, 10 and 20 mg/kg were administered to mice and of 0, 1.25, 2.5 and 5 mg/kg to rats (IV). LD50-values, calculated 14 days after the intravenous injection, were 12 mg/kg (mice) and 2.3 mg/kg (rats and dogs). Fentanyl produced slow, irregular pulse rates, rapid, deep ventilations, loss of righting reflex, defecation, urination and overall decreases in

activity in the dogs from 0.3 mg/kg IA administration for 7 days. Similar observations were made with rat and mice with oral dosing of 10 mg/kg.

In the 5-week toxicity study, fentanyl was administered continuously by intravenous infusion to Wistar rats. The dosing period was followed by a 4- week recovery period in order to examine the reversibility of any adverse effects. The doses were 0, 0.025, 0.1 and 0.4 mg/kg. All rats survived the study. Dosing rats up to a dose of 0.4 mg/kg did not result in ophthalmologic abnormalities, changes in hematological and urinary parameters nor in macroscopic or histological changes. Fentanyl was well tolerated and did not result in any adverse effects when animals were dosed at 0.025 mg/kg. When rats were dosed at 0.1 mg/kg, a few females became slightly excited in the last week of dosing. In addition, slight increases in serum glucose in both sexes and in serum inorganic phosphate in females was present. At a dose of 0.4 mg/kg, excitation was seen in several males and females. Decreases in food consumption, especially in males, as well as slight changes in some serum parameters were present in both sexes (increases in calcium and glucose in both sexes and increases in potassium and inorganic phosphate in females). In males, a slight decrease in body weight towards the end of the dosing period and a pronounced decrease in the first week of the recovery period were present, resulting in a slight decrease in the weight of the liver. All changes were reversible within a four-week recovery period.

Rats were given an intravenous bolus injection of fentanyl at doses of 0, 0.01, 0.02, 0.03, 0.05, 0.075 and 0.1 mg/kg during 4 weeks. Intravenous dosing in rats resulted in mortality at all doses except the lowest dosage of 0.01 mg/kg, which was determined as the no toxic effect.

4-week study - intravenous bolus injection of fentanyl, was administered to dogs intravenously by injection at doses of 0, 0.1, 0.3 and 1 mg/kg. All dogs survived the study.

All the animals receiving fentanyl were sedated immediately after the administration of the compound, resulting in occasionally exhibited hyperpnea decreased food intake and lack of defecation. Upon recovery from sedation, excitement was occasionally observed in the dogs. Convulsions were seen in all dosage groups. These effects, sedation as well as convulsions were much more pronounced at the highest dose (1 mg/kg) than in the 0.1 and 0.3 mg/kg dosage groups. In addition, emesis and loss of righting reflex were observed in the animals of the 1 mg/kg dosage group.

A slightly decreased body weight was present at 0.1 mg/kg whereas a moderately to severely decreased body weight occurred at 0.3 and 1 mg/kg. Histological changes in the liver and the kidneys were related to the test article. The liver changes included hepatocellular changes, which were only present at 1 mg/kg and, at light microscopic level, focal cholestasis, which was present at all doses. Vacuolar alterations in the kidney were noted at 0.3 and 1 mg/kg whereas

granular casts in the lumen of the collecting tubules were only present in one dog at 1 mg/kg.

A second 4-week toxicity study was performed in dogs. In this study, fentanyl was administered by an intramuscular injection. The doses were 0, 0.1 and 0.4 mg/kg. Fentanyl up to 0.4 mg/kg was well tolerated and did not lead to mortality. No effects on behavior and appearance, body weight and food consumption were noted and no alterations in hematology, organ weights and histology were seen in any dosage group.

The effects of fentanyl on male fertility were investigated in rats following intravenous infusion (continuously) to male animals, 4 weeks before mating and throughout mating with undosed females. The doses were 0.025, 0.1 and 0.4 mg/kg. Fentanyl dosed up to 0.1 mg/kg in male rats did not lead to mortality or clinical symptoms. Parental toxicity was evidenced in male rats dosed at 0.4 mg/kg, by decreases in body weight, in weight gain and in food consumption. None of the maternal or litter parameters were adversely affected in any of the groups, indicating that up to 0.4 mg/kg there was no primary adverse effect on male fertility. Histopathology of the male tract organs did not indicate drug-related changes.

The effects of fentanyl on female fertility and embryo-fetal development were investigated in rats, when administered continuously by intravenous infusion for 14 days prior to mating until day 16 of pregnancy at doses of 0.025, 0.1, 0.4mg/kg. Fentanyl dosed up to 0.4 mg/kg did not lead to mortality nor resulted in relevant clinical signs. There were no relevant adverse effects at any dosage on body weight, weight gain or food consumption during the pre- copulation period. Dosing up to 0.025 mg/kg did not affect any parameter. A decrease in body weight was seen towards the end of pregnancy period at 0.4 mg/kg and a dose-dependent decrease in corrected maternal weight gain was seen at 0.1 and 0.4 mg/kg. There was a slight decrease in food consumption towards the end of the pregnancy period in females dosed at 0.1 mg/kg. At 0.4 mg/kg, food consumption was decreased throughout the pregnancy period. These changes evidenced maternal toxicity in females dosed at 0.1 and 0.4 mg/kg. There were no adverse effects on the weight of the gravid uterus and of the ovaries, on the copulation and fertility rates as well as on the pre-coital intervals in any of the dosage groups. Additionally, there were no adverse effects on any of the litter data (number of corpora lutea, number of live and dead fetuses, mean litter size, number of implantations, number of resorptions and pre- and post-implantations). No test article related teratogenic effects were seen. It can be concluded that fentanyl, when dosed up to 0.4 mg/kg, had no adverse effects on the fertility of female rats and that embryo-fetal development was not adversely affected.

The potential effects of fentanyl on the embryo-fetal development were evaluated in rabbit by intravenous infusion of the compound administration from day 6 to day 18 of pregnancy. The doses for the developmental toxicity study in rabbits

were set at 0, 0.025, 0.1 and 0.4 mg/kg. Fentanyl dosed up to 0.1 mg/kg in pregnant female rabbits did not lead to mortality. At 0.4 mg/kg, three out of eighteen rabbits died after showing severe sedation at the beginning of the dosing period. Clinical observations consisted of dose-related sedation throughout the dosing period. Slight sedation was seen in all rabbits of the 0.025 mg/kg dosage group. The animals dosed at 0.1 mg/kg showed slight to moderate sedation while rabbits of the 0.4 mg/kg dosage group suffered from severe sedation, resulting in a dose-dependent decrease in body weight and food consumption during the dosing period and in decreased corrected mean maternal weight gain at both dosages. No adverse effects in any of the groups on weight of the gravid uterus or on other parameters studied, which included number of fetuses, resorptions, implantations and corpora lutea, pre- and post-implantation loss and sex ratio of live fetuses. In conclusion, fentanyl up to 0.4 mg/kg had no effects on the fertility of female rabbits and the embryo-fetal development was not adversely affected.

The pre- and postnatal development in rats was assessed after administration of fentanyl continuously by infusion from day 6 of pregnancy through a three-week lactation period. The doses were 0, 0.025, 0.1 and 0.4 mg/kg. All animals survived the study. At the doses of 0.025 and 0.1 mg/kg, neither maternal toxicity nor adverse effects on the litter were demonstrated. At 0.4 mg/kg, slight maternal toxicity was evidenced by a marginal decrease in body weight throughout the lactation period and a slight decrease in food consumption throughout the pregnancy and the lactation period. Fertility and gestation rate, duration of gestation and the number of implantations were comparable between all groups of the dosed females. For the F_1-generation, there were no adverse effects on any of the parameters in the 0.025- or 0.1-mg/kg dosage groups during the lactation period. The parameters studied in these periods included the number of live and dead pups, mean litter size, birth rate, fetal observations, body weight, survival rate, physical, sexual and behavioral development and an object discrimination test. At 0.4 mg/kg, a slight decrease in body weight of the pups was noted on days 4 and 7 and the survival rate was decreased at 4 days after birth. The survival rate was normalized from day 7 onwards, the body weight of the pups from day 14 onwards. In the second, undosed generation, the reproductive performance was normal and comparable between rats of the vehicle group and rats originating from the 0.025, 0.1 and 0.4 mg/kg-dosed dams. The examined parameters included: copulation and fertility rates, weight of the gravid uterus, pre-coital interval, number of corpora lutea, number of live and dead F2 fetuses, implantations and resorptions and pre-and post-implantation loss. These findings indicate that fentanyl does not result in primary effects on peri-and postnatal parameters on the F1 -generation and it is not considered to be a behavioral teratogen in rats at doses up to 0.4 mg/kg.

Fentanyl was tested in rats in fertility and developmental toxicity studies and in a 3-generation study previously with subcutaneous and intravenous administration. Based on the results from these studies fentanyl has been listed as Pregnancy Category C. The current labeling for Duragesic reads 'Fentanyl has been shown to

impair fertility and to have an embryocidal effect in rats when given in intravenous doses 0.3 times the human dose for a period of 12 days. No evidence of teratogenic effects has been observed after administration of fentanyl to rats. There are no adequate and well- controlled studies in pregnant women. DURAGESIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetuses'. Although the proposed duration for the current application is acute and no fetotoxicity was observed in the reproductive studies upto 0.4 mg/kg in the absence of the adequate and well- controlled studies in pregnant women fentanyl is recommended to be labeled as Pregnancy Category C for the current application.
The requirement for the carcinogenicity study for the present application is waved due to its acute indication of application.

Nonclinical toxicology studies in the IONSYS program evaluated the potential for skin irritation and sensitization associated with the system and its components. The durations of exposure and current densities were selected to be representative of human treatment with IONSYS.

The commercial E-TRANS anode and cathode hydrogel formulations were categorized as mild irritants in single-application skin irritation studies (anode, Study TR-96-1561-052; cathode, TR-98-1561-031). The commercial anode formulation was evaluated in New Zealand White rabbits treated for 14 hours at a current density of 0.08 mA/cm^2 (ie, 80 $uA/cm^{2)}$ resulting in a mean total fentanyl dose of 3.5 mg (0.073 mg/k/h). The commercial cathode formulation was evaluated in New Zealand White rabbits and hairless guinea pigs for approximately 13 hours at a current density of 0.07 mA/cm^2 (70 uA/cm^2).

The initial sensitization study in hairless guinea pigs evaluated an IONSYS system that had early-formulation hydrogels (TR-92-1561-022). The system was categorized as a mild to moderate sensitizer, but the findings of the study were influenced by the fact that irritation contributed to the observed responses. The systems in this study delivered fentanyl at a dose of 1. 1 mg/kg over 8 hours at a maximum current density of 0.1 mA/cm^2 (100 uA/cm^2). A second sensitization study in hairless guinea pigs evaluated placebo E-TRANS systems with hydrogel formulations that were more similar to the commercial formulation (TR-97-1561-01 1). No evidence of sensitization was found in animals induced and challenged with the anode or cathode hydrogels, categorizing them as weak sensitizers.

Additional studies found no evidence of sensitization in hairless guinea pigs induced and challenged with
(cetylpyridinium chloride) (TR-96-1561-017) or with extracts of the skin adhesive used in the E-TRANS system (TR-96-1563-012). Extracts of the
(polacrilin) had some potential to induce sensitization, but at the concentrations proposed for clinical use, the potential was low (TR-96-1561-016, TR-96-1561-048). Therefore, polacrilin was determined to be an acceptable for use in E-TRANS hydrogels.

Extracts and samples of system components in contact with the hydrogels met either USP Class V-50°C or VI-50°C requirements and were therefore judged to be safe for use in the E-TRANS system.

A single dose of 0.5 mL of fentanyl (0. 1 mg base/mL) was injected into the sacrospinalis muscle of the rabbit. Positive controls were administered 0.5 mL doses of tetracycline (125 mg/mL) and pyraigin (500 mg/mL). The rabbits were killed 72 hours later and the degree of irritation determined by gross observation of serially sectioned muscle. The irritation responses were none to slight for fentanyl, moderate to severe for pyraigin while tetracycline showed a severe

The cytotoxicity of fentanyl was evaluated in the tissue culture with human keratinocytes. Cell viability was determined by using a tetrazolium dye that is reduced to a blue formazan by living cells. The resultant color is measured with a spectrophotometer. There was no cytotoxicity at concentrations below 1 mM (0.3 mg/mL).

Impurities in the fentanyl HCl are monitored by , and ALZA. Unknown impurities are also monitored routinely to ensure that their levels do not exceed the specified limits. The impurities are detectable and quantitated in the drug substance by ALZA's high-performance liquid chromatography (HPLC) methods, ALZA Analytical Methods (AAMS) None of the impurities have been detected in the drug substance at levels close to the specification limit). The two impurities not specifically monitored in the drug substance are . The impurity is monitored in finished product stability, and the impurity has been monitored by the and reported in Certificate of Analysis. This impurity is historically below the reporting threshold of 0.05% for drug substance as defined in the International Conference on Harmonisation (ICH) Q3A. ALZA does not monitor for these two impurities specifically but reports any impurities detected above with a limit of Those impurities that are greater than have been identified and are being monitored in the drug substance as discussed above.

In order to assess the potential contribution of a potential impurity, a comparison with its parent compound fentanyl was made.
Doses of 0, 10 and 20 mg/kg were administered to mice and of 0, 1.25, 2.5 and 5 mg/kg to rats. LD50-values, calculated 14 days after the intravenous injection were 16 mg/kg (mice) and 3.1 mg/kg (rats). Intravenous injection of was lethal in 4 out of 5 mice at 20 mg/kg. Mortality occurred within the first hour after dosing. produced some central opioid-like actions, e.g. excitation, exophthalmos, Straub tail on arched back, corneal opacity, dyspnea and loss of righting reflex. All surviving mice completely recovered within 6 hours after injection. In rats, no mortality occurred at a dosage of 1.25 mg/kg. At a dose of 2.5 mg/kg, two out of five rats died after administration of At a dose of

5 mg/kg, mortality occurred in four out of five animals. All deaths occurred immediately after dosing. Apart from mortality, the following clinical observations were noted at all doses: blockade of cornea and pinna reflexes, dyspnea, loss of righting reflex, muscular rigidity, hypertonia, exophthalmos and salivation. The surviving rats recovered within 1 day after dosing. No abnormalities were found at autopsy in mice or rats. The acute intravenous toxicity of fentanyl and — is considered to be very comparable in male mice and rats.

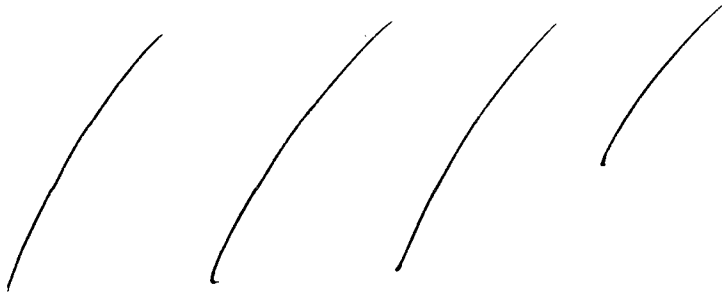
The amount of fentanyl absorbed systemically in human from a 10-minute dose from the E-TRANS system increased proportionally with the applied current. The desired nominal 40 ug E-TRANS dose was delivered systemically by a 170 uA current and a 2.75 cm^2 anode surface area at Hour 23 following a standard dosing regimen of 2 sequential doses every hour for 23 hours. A nominal 25-ug dose was delivered by a 100-uA current and a 1.40-cm^2 anode surface area at 23 hours following the standard regimen. Mild to moderate irritation was observed with the current formulation in hairless guinea pig local tolerance studies with 70-230 uA current and comparable anode surface. The irritation is characterized by erythema. Similar local toxicity is expected in human population. Although no hypersensitivity was observed with fentanyl, polacrilin extract at a concentration of 50% administered intradermally induced some hypersensitivity characterized by irritation and allergic reaction. So, it is concluded that the polacrilin has some potential to induce sensitization, but at concentrations proposed for clinical use .g), the potential is reduced. Fentanyl HCl is used in the clinical formulation, although fentanyl HCl is used for most of the non-clinical studies. Due to the pH lowering capability of the HCl formulation of the fentanyl, absorption is expected to be higher than that of the citrate formulation. However, the toxicity data discussed in this review is mainly via intravenous route of administration. Considering sufficient safety margin exists in the toxicity studies, safety data for the current formulation is expected to be adequate.

Polacriline and cetylpyridinium chloride has not been used previously for transdermal use. So, the toxicity of the excipient is not adequately qualified in the relevant toxicity studies. The absorption of the above mentioned excipients are expected to be minimum. However, to comply with the current excipient draft guidance, the toxicity should be one month toxicity study in the most appropriate species is recommended. Alternatively Sponsor should generate the data to illustrate no dermal absorption of the excipients

Impurities of the drug substance are adequatelv evaluated for the drug product. However, the specification for the impurity — should be adequately maintained (IV dosing caused mortality in rat and mice over 1.25 mg/kg).

Impurity qualification in the drug substance and drug product:

In the Approvable Action letter dated July 23, 2004 it was noted that ALZA, Corp. has provided adequate data to support the nonclinical safety of their E-TRANS system. However, it was also recommended that the Sponsor should reduce the specifications for the following impurities in the drug substance to NMT — , or provide adequate qualification of their safety:

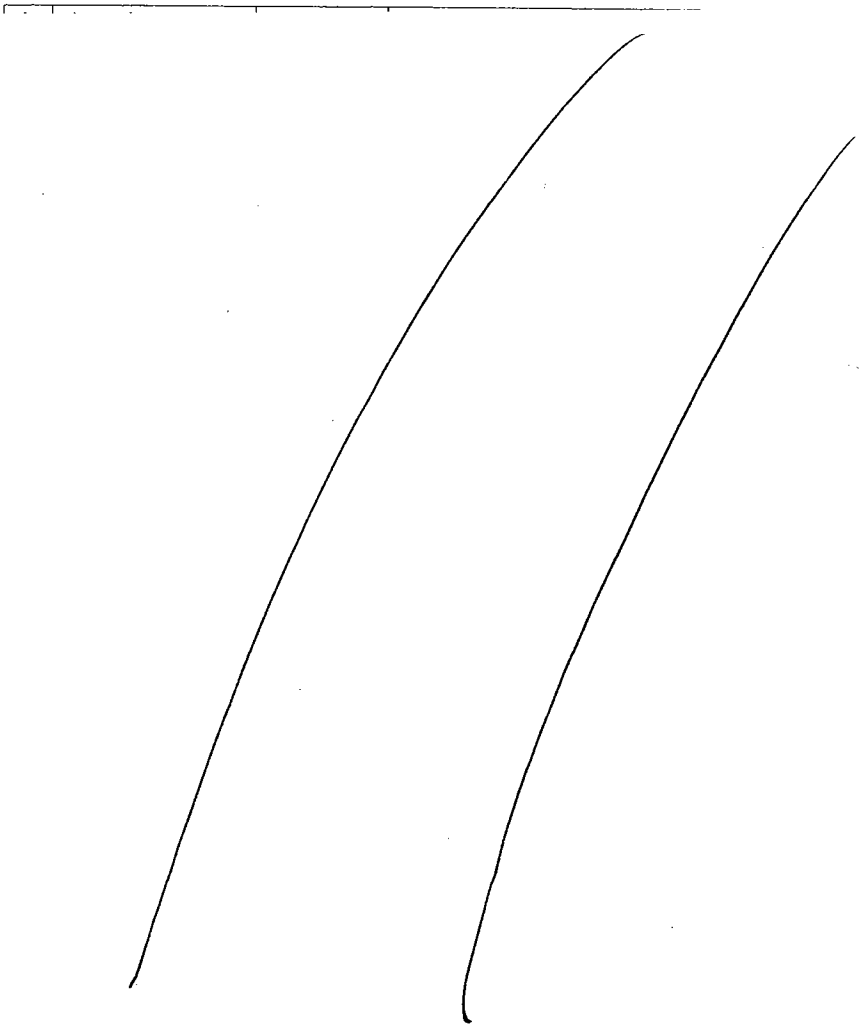


It was also recommended that the Sponsor should provide a limit of NMT — % for — This is due to the fact that these impurities are — and are structural alerts for mutagenicity.

Alternatively, the Sponsor may support the currently proposed levels for these impurities by demonstration that they are significant human metabolites, or by performing mutagenicity studies that support adequate qualification of their safety. In the resubmission dated March 27, 2006, the Sponsor provided the following list of fentanyl related substances.

List of Fentanyl Related Substances in the Drug Substance and Drug Product:

	Name	Ph Eur Name	CA Index	Structure
1				
2				
3				



In the drug substance specification, an acceptance criterion of — was established for — These three impurities are structural alerts and considered as potential genotoxic impurities for mutagenicity. According to the draft guidance for the qualification of genotoxic impurities the level of individual genotoxic impurity in the drug substance should be limited to 1.5 µg.

The current drug formulation contains 10.8 mg of fentanyl HCl/ unit of the IONSYS product. According to the dosing schedule the patient can get a maximum amount of 3200 µg/ day (40 µg/10 min, maximum of 80 doses allowed /24 hrs). The amount of individual genotoxic impurities in the drug substance is calculated to be —

— , of 3200 µg). Therefore, the genotoxic impurities are qualified in the drug substance level.

The acceptance criteria for the total and the individual non genotoxic impurities in the drug substance and drug product are specified as — and — respectively. These acceptance criteria are within the limit specified by the ICH Q3A guidance for drug substance. Therefore the non genotoxic impurities in the drug substance and drug product are determined to be qualified.

The acceptance criteria for the genotoxic — ; has been set in the drug product as — as this impurity has been found as a degradant in the stability studies — , the two other genotoxic impurities did not found as degradants, there fore the specification for these impurities are still at the levels of — which is equivalent to — , each in the drug product and thus determined to be qualified in the drug product also. However, the limit of — , exceeds the limit of quantification (1.5 µg) as specified by the draft guidance for the qualification of the genotoxic impurities —, of 3200 ug= —. Also, it has been shown by the Sponsor's analysis that the fentanyl related substances travel quicker than the fentanyl through the skin during the ionophoresis, therefore, chances of accumulation or passive diffusion through the skin is minimal for these impurities. IONSYS is indicated for post operative pain in the hospital setting for 72 hrs only. Although the system might be used intermittently, the clinical experience with fentanyl assures that fentanyl could not be used chronically throughout the life span of the patient. The limit of genotoxic impurity is specified as 1.5 µg/day based on the life time exposure, considering the clinical application of fentanyl, it seems quite unlikely that the duration of the fentanyl used from the ETRANS system would be of chronic. Also, the mutagenic potential of the — . is not experimentally determined. It is predicted to be potential structural alert based on the computer generated model. Considering the fact that the genotoxic qualification

Type of study	Species	Route	Duration of observation	Doses in mg/kg/day	GLP yes/no	Ref.
Part III - A	mouse	i.v.	14 days	0, 10, 20	yes	A 1
Single dose toxicity		i.v.	3 days	unknown	no	A 3

Type of study	Species	Route	Duration of observation	Doses in mg/kg/day	GLP yes/no	Ref.
		i.m.	7 days	15, 25, 30, 40	no	A 6
		i.m.	7 days	0.35	no	A 9
		s.c.	5 days	0.04, 0.08, 0.16, 1.25	no	A 10
		i.a.	7 days	0.3	no	A 11
	cat	i.v.	5 days	0.04, 0.08, 0.16	no	A 10
	hamster	i.m.	5 days	8, 12, 25	no	A 6
	guinea pig	i.v.	0 days	3 a)	no	A 10
		i.m.	5 days	18, 24, 25, 30, 35, 50, 55, 65, 75, 85, 100	no	A 6
	monkey	i.v.	1 day	0.0316	no	A 10

a) LD_{100}

Toxicology Summary Table: Overview of Toxicology Studies with Fentanyl contd.:

Type of study	Species	Route	Duration of treatment	Doses in mg/kg/day	GLP yes/no	Ref.
Part III - A	Rat	i.v. (infusion)	DRF	0.025, 0.1, 0.2, 0.4, 0.5, 1, 2[a)]	no	A 12
Repeated dose toxicity		i.v. (infusion)	5 weeks	0, 0.025, 0.1, 0.4	yes	A 13
		i.v. (bolus)	4 weeks	0, 0.01, 0.02, 0.03, 0.05, 0.075, 0.1	no	A 14
		oral (diet)	2 weeks	0, 5, 10, 20, 40, 80, 160, 320	no	A 10
		i.m.	4 weeks	0, 0.1, 0.4	no	A 15
	Dog	i.v.	4 weeks	0, 0.1, 0.3, 1	yes	A 16
		i.m.	4 weeks	0, 0.1, 0.4	no	A 15
Part III - B						
reproductive function						
male fertility	Rat	i.v. (infusion)		0, 0.025, 0.1, 0.4	yes	B 1
fertility and		i.v. (infusion)		0, 0.025, 0.1, 0.4	yes	B 2
embryotoxicity		s.c. (infusion)		0, 0.01, 0.1, 0.5	no	B 3
Part III - C						
developmental toxicity						
embryotoxicity and	Rabbit	i.v. (infusion)	3-days DRF	0, 0.025, 0.1, 0.4	no	C 1
teratogenicity		i.v. (infusion)		0, 0.025, 0.1, 0.4	yes	C 2
	Rat	i.v. (bolus)		0, 0.01, 0.03	no	C 4
		s.c. (infusion)		0, 0.5	no	C 5
		s.c. (bolus)		0, 0.16, 0.31, 0.64, 1.25	no	C 6
		s.c. (bolus)		0, 0.16, 0.31, 0.64, 1.25	no	C 7

Type of study	Species	Route	Duration of treatment	Doses in mg/kg/day	GLP yes/no	Ref.
pre/postnatal toxicity	Rat	i.v. (infusion)		0, 0.025, 0.1, 0.4	yes	C 3
fertilisation study	Sea urchin	*in vitro*		3.3, 33, 66 nM/ml	no	C 8

a) Dose Range Finding study up to a dose of 2 mg/kg. The effects of two doses, 0.025 and 0.4 mg/kg, were evaluated after continuous infusion for five days.

Toxicology Summary Table: Overview of Toxicology Studies with Fentanyl contd.:

Type of study	Test system	Route	Duration of observation	Doses in mg/kg/day	GLP yes/ no	Ref.
Part III - D						
Point and/or gene mutations						
Ames	S. typhimurium	*in vitro*		25 up to 2500 µg/plate +/- S9	yes	D 1
				25 up to 2500 µg/plate +/- S9	yes	D 2
				8.4 up to 2100 µg/plate +/- S9	yes	D 3
Mouse lymphoma	mouse lymphoma cells	*in vitro*		13 up to 126 µg/ml +/- S9	yes	D 4
				-S9: 200 up to 500 µg/ml +S9: 100 up to 600 µg/ml	yes	D 5
Chromosome aberrations						
Micronucleus test	mouse	*in vivo*		0.63, 2.5, 10 mg/kg	yes	D 6
CAT	Chinese hamster ovary cells	*in vitro*		-S9: 0.06 up to 2050 µg/ml +S9: 0.062 up to 2050 µg/ml	yes	D 7
	human peripheral lymphocytes	*in vitro*		-S9; 1.1×10^{-6} - 7.5×10^{-6} mol/l	no	D 8
Mammalian Cells Transformations						
Transformation	BALB/C-3T$_3$ cells	*in vitro*		25 up to 250 µg/ml +/- S9	yes	D 9
Primary DNA damage						
Unscheduled DNA synthesis	rat hepatocytes	*in vitro*		0.4 up to 84 µg/ml +/- S9	yes	D 10

Toxicology Summary Table: Overview of Toxicology Studies with Fentanyl contd.:

Type of study	Test system	Route	Duration of observation	Doses in mg/kg/day	GLP yes/ no	Ref.
Part III - Q						
Special studies						
Muscle irritation	rabbit	i.m.	once	0.157 mg/ml	-	Q 1
Cytotoxicity	human keratocytes	*in vitro*		188.562 and 827 mM	yes	Q 2
Impurity study	mouse	i.v.	14 days	0, 10, 20 [a)]	yes	Q 3
	rat	i.v.	14 days	0, 1.25, 2.5, 5 [a)]	yes	Q 4

a) Study was conducted with — a potential impurity of fentanyl

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Summary of E-Trans Dermal Toxicity Study:

Study Number/Type	Species/ Strain	Group Size/Sex	Treatment	Formulation[a]	Duration	Finding/Irritation[b]
TR-96-1561-052 Primary irritation of fentanyl-containing systems	New Zealand White Rabbit	6 females	Current density 0.08 mA/cm^2	Cathode: C3 Anode: A4	14 hours	anode PII=1.5 (mild) cathode PII=1.6 (mild)
TR-98-1561-031 Primary irritation of non fentanyl-containing systems	[redacted]:GOHI-hr) Guinea pigs New Zealand White Rabbit	12 females 6 females	Current density 0.07 mA/cm^2	Cathode: C3,C4 Anode: A6	15.3 hours	adhesive/0.2% CPC cathode PII=2.0 in guinea pig and 1.9 in rabbit (mild) Anode PII=0.9 - 1.3 in guinea pig and 0 - 0.4 in rabbit
TR-92-1561-021 Primary irritation of fentanyl-containing systems	IAF/HA-HO Guinea Pig	6 males	Current density 0.1 mA/cm^2; estimated drug release 111 µg/cm^2/h; estimated dose 2.24 mg/kg	Cathode: C2 Anode: A2	16 hours	anode PII=1.9 (mild) cathode PII=0.7 (mild)
TR-92-1561-053 Primary irritation of fentanyl-containing systems	New Zealand White Rabbits	3 females	Current density 0.1 mA/cm^2	Cathode: C2 Anode: A2	16 hours	anode PII=1.2 (mild) cathode PII=0.2 (negligible)
TR-93-1561-048 Primary irritation of placebo anode hydrogels with and without polacrilin	IAF/HA-HO Guinea Pig	6 males	Current density 0.1 mA/cm^2 no drug	Cathode: C2 Anode: A1 Anode: A3	8 hours; 24 hours	placebo anode with or without [redacted] PII=1.7 and 0.7 respectively (mild) cathode PII=0.8 (mild) placebo anode with or without [redacted] PII=2.3 (moderate) and 1.8 (mild) respectively cathode PII=1.0 (mild)

a) Different formulations are presented on the following page.

b) PII = Primary Irritation Index (0-8); PSI = Primary Skin Irritation (Irritation Scale: 0-0.5 negligible; 0.6-2.0 mild; 2.1-5.0 moderate; 5.1-8.0 severe).

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Summary of E-TRANS Dermal Toxicity Study contd:

Study Number/Type	Species/ Strain	Group Size/Sex	Treatment	Formulation[a)]	Duration	Finding/Irritation[b)]
TR-96-1561-052 Primary Irritation of fentanyl-containing systems	New Zealand White Rabbit	6 females	Current density 0.08 mA/cm^2	Cathode: C3 Anode: A4	14 hours	anode PII=1.5 (mild) cathode PII=1.6 (mild)
TR-98-1561-031 Primary Irritation of non fentanyl-containing systems	GOHI-hr) Guinea pigs New Zealand White Rabbit	12 females 6 females	Current density 0.07 mA/cm^2	Cathode: C3,C4 Anode: A6	13.3 hours	adhesive/0.2% CPC cathode PII=2.0 in guinea pig and 1.9 in rabbit (mild) Anode PII=0.9 - 1.3 in guinea pig and 0 - 0.4 in rabbit
TR-92-1561-021 Primary Irritation of fentanyl-containing systems	IAF/HA-HO Guinea Pig	6 males	Current density 0.1 mA/cm^2; estimated drug release 111 µg/cm^2/h; estimated dose 2.24 mg/kg	Cathode: C2 Anode: A2	16 hours	anode PII=1.9 (mild) cathode PII=0.7 (mild)
TR-92-1561-053 Primary Irritation of fentanyl-containing systems	New Zealand White Rabbits	3 females	Current density 0.1 mA/cm^2	Cathode: C2 Anode: A2	16 hours	anode PII=1.2 (mild) cathode PII=0.2 (negligible)
TR-93-1561-048 Primary Irritation of placebo anode hydrogels with and without polacrilin	IAF/HA-HO Guinea Pig	6 males	Current density 0.1 mA/cm^2 no drug	Cathode: C2 Anode: A1 Anode: A3	8 hours; 24 hours	placebo anode with or without [redacted] PII=1.7 and 0.7 respectively (mild) cathode PII=0.8 (mild) placebo anode with or without [redacted] PII=2.3 (moderate) and 1.8 (mild) respectively cathode PII=1.0 (mild)

a) Different formulations are presented on the following page.

b) PII = Primary Irritation Index (0-8); PSI = Primary Skin Irritation (Irritation Scale: 0-0.5 negligible; 0.6-2.0 mild; 2.1-5.0 moderate; 5.1-8.0 severe).

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Summary of E-TRANS Dermal Toxicity Study contd:

Study Number/Type	Species/ Strain	Group Size/Sex	Treatment	Formulation[a]	Duration	Finding/Irritation[b]	Ref.
TR-92-1561-023 Subchronic irritation of fentanyl-containing systems	IAF/HA-HO Guinea Pig	10 males	Current density 0.1 mA/cm²; estimated drug release 110 µg/cm²/h; estimated dose 1.21 mg/kg/8 h	Cathode: C2 Anode: A2	14 days; fourteen 8 h exposures	anode CII=1.9 (mild) cathode CII=0.6 (mild)	H 6
TR-92-9999-014 Visual and histologic evaluation of skin after single and multiple applications of placebo systems	IAF/HA-HO Guinea Pig	35 males	Current density 100µA/cm² no drug delivered	Cathode: C1 Anode: A1	6 hours 24 hours 7 days	Irritation increased from mild (1.7) to moderate (3.6) with increased duration from 1-7 days	H 7
TR-92-1561-022 Sensitisation study of fentanyl-containing systems	IAF/HA-HO Guinea Pig	55 males 1 female	Current density 0.1 mA/cm²; estimated induction dose 110 µg/cm²/h	Cathode: C2 Anode: A2	9 induction applications over 3 weeks; 8 hours per induction	anode CII = 2.1 (moderate) mild to moderate sensitizer; irritation contributed to responses	H 8
TR-97-1561-011 Sensitisation study of non fentanyl-containing systems	.GOHI-hr) Guinea Pig	35 females	Current density 0.07 mA/cm²	Cathode: C3 Anode: A5, A6	9 induction applications over 3 weeks; 13 hours activated and 3 hours passive	anode (histidine + polacrilin) CII = 2.7 (moderate) mild sensitizer	H 9

a) Different formulations are presented on the following page.

b) PII = Primary Irritation Index (0-8); PSI = Primary Skin Irritation (Irritation Scale: 0-0.5 negligible; 0.6-2.0 mild; 2.1-5.0 moderate; 5.1-8.0 severe); CII = Cumulative Irritation Indexes.

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_ § 552(b)(5) Deliberative Process

_ § 552(b)(4) Draft Labeling

Summary of E-TRANS Delayed Contact Hypersensitivity Studies in Guinea pigs-Study Design continued:

Study Number	Test Article/ Route of administration for Induction/Challenge 1/Challenge 2	Induction	Challenge 1	Challenge 2
TR-92-1561-022	E-TRANS™ (fentanyl HCl)/ Topical/Topical/Topical	E-TRANS™ (placebo)	E-TRANS™ (fentanyl HCl)	E-TRANS™ (fentanyl HCl)
		E-TRANS™ (fentanyl HCl)	E-TRANS™ (fentanyl HCl)	E-TRANS™ (fentanyl HCl)
		E-TRANS™ (fentanyl HCl) without current	E-TRANS™ (fentanyl HCl)	E-TRANS™ (fentanyl HCl)
		DNCB	DNCB	DNCB
TR-97-1561-011	E-TRANS™ (placebo)/ Topical/Topical/NA	E-TRANS™ (placebo) without polacrilin	E-TRANS™ (placebo) with and without polacrilin	NA
		E-TRANS™ (placebo) with polacrilin	E-TRANS™ (placebo) with and without polacrilin	NA
		E-TRANS™ (tetracaine)	E-TRANS™ (tetracaine)	NA
TR-98-1561-017	Cetylpyridinium chloride (CPC)/ Intradermal/Intradermal/Topical	1% CPC in FCA	0.005% CPC, 0.01% CPC, water	0.1% CPC, water
		water in FCA	0.005% CPC, 0.01% CPC, water	0.1% CPC, water
		0.05% DNCB	0.05% DNCB	0.05% DNCB

NA = not applicable.

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Summary of E-TRANS Summary of ETRANS Delayed Contact Hypersensitivity Studies in Guinea pigs-Study Design contd:

Study Number	Test Article/Route of administration for Induction/ Challenge 1/Challenge 2	Induction	Challenge 1	Challenge 2	Ref.
TR-96-1561-018	Polacrilin resin ([redacted]) aqueous extract (4g resin:20ml saline)/ Intradermal/ Intradermal/Topical	polacrilin extract in FCA	0% (vehicle), 25%, 50%, 100% extract	0%, 100% (undiluted) extract	H 11
		water in FCA	0% (vehicle), 25%, 50%, 100% extract	0%, 100% (undiluted) extract	
		0.05% DNCB	0.05% DNCB	0.05% DNCB	
TR-96-1561-048	Polacrilin resin aqueous extract (4g resin:20ml saline)	water in FCA	0.1% extract, 1% extract, saline	1% and 50% extract, saline	H 12
	Intradermal/Intradermal/ Intradermal	saline	0.1% extract, 1% extract, saline	1% and 50% extract, saline	
		2% extract in FCA	0.1% extract, 1% extract, saline	1% and 50% extract, saline	
		1% extract in saline	0.1% extract, 1% extract, saline	1% and 50% extract, saline	
TR-96-1563-012	Polyisobutylene adhesive extracts/ Intradermal/ Intradermal/Topical	adhesive extract in FCA	adhesive extract, vehicle	adhesive, [redacted]	H 13
		adhesive extract	adhesive extract, vehicle	adhesive. [redacted]	
		vehicle (1:20 alcohol in saline) in FCA	adhesive extract, vehicle	adhesive, [redacted]	
		0.05% DNCB	0.05% DNCB		

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The pharmacology and toxicology of the IONSYS system has been well characterized. The main toxicological finding, other than expected opioid effects, include mild to moderate skin irritation with one minor component demonstrating the potential to induce sensitization following exposures in excess of what would be obtained from proper use of the IONSYS system.

In the original submission dated September, 2003 impurities of the drug substance were found to be inadequately evaluated. The Sponsor was advised to reduce the specification for the drug substance impurities to NMT or to provide adequate qualification of the impurities via repeat-dose toxicity study in a single species and a minimal genetic toxicology screen. With the current submission dated November, 2005, the Sponsor provided acceptable specification criteria for the drug substance with the non genotoxic and genotoxic impurities. There were three potential genotoxic impurities in the drug substance namely [redacted]. The limit of each of these

impurities were set as — in the drug substance which is equivalent to — g (considering the maximal daily dose of fentanyl as 3.2 mg), the total of these potential genotoxic impurities thus results into — day (<1.5 µg/day, a limit set by the current draft guidance for qualification of the genotoxic impurities). Therefore these three potential impurities are collectively below considered qualified in the drug substance. Among these three potential genotoxic impurities only one of them — was found as degradant. In the drug product the acceptability criteria for — is set as which is —µg/day. In the opinion of this reviewer the limit of specification is acceptable because the actual genotoxic potential of this impurity is not known (predicted based on chemical structure). Further, the specification in the draft guidance is based on the risk of developing cancer following exposure to the compound over the entire life time, which is in contrast to what is proposed for fentanyl under the current formulation. Although this product might be used more than 72 hrs intermittently (under this submission the duration of the administration of fentanyl is 72 hrs only), chronic use of fentanyl with this formulation is highly unlikely. The other two potential genotoxic impurities are under the 1.5 µg limit in the drug product. The draft EMEA guidance for genotoxic impurity qualification is still in the draft stage and the proposed limit of NMT 1.5 µg/day is based on the theoretical values of toxicological threshold concern which is still under discussion in the scientific community. — slightly exceeds 1.5 µg/day, the proposed limit in the draft guidance for genotoxic qualification. — and predicted to be structural alert with genotoxic potential. No studies were done under this submission to find out whether the compound is actually genotoxic or not. So, attempt could be made for qualifying — as a non genotoxic impurity. The amount of fentanyl/unit in this product is 10.8 mg. Therefore, with a — specification, the amount of — will account for a maximum of — %, this is acceptable as per ICH Q3BR guidance. According to the Sponsor, fentanyl related product passes through the skin faster in this IONOSYS system. Therefore, chances of passive diffusion resulting in the depot formation in skin for the impurities are minimal. From the previous experience with fentanyl (which has similar impurities) products, clearance of fentanyl after systemic absorption was quick. Therefore, fentanyl related product in the IONOSYS system seem to pose minimal toxicological concern.

Unresolved toxicology issues (if any): None

Recommendations: From the nonclinical pharmacology toxicology perspective, NDA 21-338 may be approved.

Suggested labeling:

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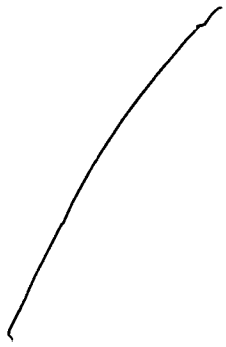
_ § 552(b)(4) Trade Secret / Confidential

_ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling



Signatures (optional):

Reviewer Signature Mamata De, Ph.D.

Supervisor Signature R. Daniel Mellon, Ph.D. Concurrence Yes X No

APPENDIX/ATTACHMENTS

REFERENCES

References:

A 1 A comparison of the acute intravenous toxicity of the narcotic analgesic fentanyl (R4263) and its potential impurity R4380 in male mice. A. The toxicity of fentanyl (R4263). Janssen Research Foundation, November 1993. Toxicological Research Report, Experiment No. 3107.

A 2 A comparison of the acute intravenous toxicity of the narcotic analgesic fentanyl (R4263) and its potential impurity in male rats. A. The toxicity of fentanyl (R4263). Janssen Research Foundation, November 1993; Toxicological Research Report, Experiment No. 3105.

A 3 Gardocki JF, Yeinosky J. A study of some of the pharmacologic actions of fentanyl citrate. Toxicology and Applied Pharm6cology 6 (1): 48-62 (January 1964).

A 4 The pharmacology of R4263 (Phentanyl), a potent, short acting analgesic agent for IV use in anesthesiology. (January 1962).

A 5 . The acute oral toxicity of McN-JR-4263-49 in rats and mice. McNeil Laboratories, Inc., Toxicological Research Report No. 127 (650927).

A 6 The acute intramuscular toxicity of McN-JR-4263-49 in guinea pigs, hamsters, rats and dogs. McNeil Laboratories, Inc., Toxicological Research Report No. 124 (650922).

A 7 [redacted] Acute toxicity of McN-JR-4263-49 administered intragastrically to newborn rat pups. McNeil laboratories, Inc., Toxicological Research Report No. 104 (650719).
A 8 [redacted]. Acute intravenous toxicity of McN-JR-4263-49 in dogs. McNeil Laboratories, Inc., Toxicological Research Report N. 110 (650803).
A 9 [redacted]. Acute toxicity of INNOVAR in dogs and rats. McNeil Laboratories, Inc., Toxicological Research Report No. 54 (640415).
A10 [redacted] ummary of toxicological data on SUBLIMAZEO, fentanyl (McN-JR-4263-49, R-4263, and Phentanyl). McNeil Laboratory, Inc., Toxicological Research Report No. 139 (651124).
A11 [redacted]. The effect of McN-JR-4263-49 administered intra-arterially to dogs. McNeil Laboratories, Inc., Toxicological Research Report No. 143 (651029).
A12 [redacted]. R005240. Dose-range-finding study in SPF Wistar rats. Janssen Research Foundation, August 1996; Toxicological Research Report, Experiment No. 3777.
A 13 [redacted]. R004263. Evaluation of the subchronic toxicity potential in SPF Wistar rats. Janssen Research Foundation, July 1997; Toxicological Research Report, Experiment No. 3831.
A 14 [redacted] Safety evaluation of McN-JR-4263-49 given intravenously to rats for thirty days. McNeil Laboratories, Inc., Toxicological Research Report No.126 (650922).
A 15 [redacted]. Toxicity study of McN-JR-4263 in rats and dogs. McNeil Laboratories, Inc., Toxicological Research Report No. 9 (630529).
A 16 [redacted] Safety evaluation of McN-JR-4263 administered intravenously to dogs for thirty days. McNeil Laboratories, Inc., Toxicological Research Report No. 108 (650802).
B 1 [redacted].RO04263. Male fertility in SPF Wistar rats. (Segment 1). Janssen Research Foundation, October 1997; Toxicological research Report, Experiment No 3899.
B 2 [redacted] R004263. Intravenous female fertility and developmental toxicity study in the Wistar rat. Janssen Research Foundation, November 1997; Toxicological Research Report No. 3972.
B 3 Fujinaga M, et al. Reproductive and teratogenic effects of fentanyl in Sprague-Dawley rats. Teratology 34: 51-7 (1986)
C 1 [redacted]. R004263. 3-day repeated dose intravenous toxicity in the rabbit. Janssen Research Foundation, March 1998; Toxicological Research Report No. 4159.
C 2 [redacted] R004263. Intravenous developmental toxicity study in the rabbit. Janssen Research Foundation, March 1998; Toxicological Research Report No. 4397.
C 3 [redacted]. R004263. Intravenous pre-and postnatal developmental toxicity in the Wistar rat. Janssen research Foundation, March 1998; Toxicological Research Report No. 4055.
C 4 [redacted]. Teratologic study of intravenous McN-JR-4263-49 in inbred rats. McNeil Laboratories, Inc., Toxicological Research Report No. III (650812) Revised (680611).
C 5 Mazze RI, et al. Reproductive and teratogenic effects of nitrous oxide, fentanyl and their combination in Sprague-Dawley rats. British Journal Anaesthesia. 59: 1291-7 (1987).
C 6 [redacted] Teratological data in rats receiving R4263 subcutaneously. Janssen Pharmaceutica: Toxicological Research Report on fentanyl (R4263), No. 45 (651020).
C 7 [redacted] Teratological data in rats receiving R4263 subcutaneously. Janssen Pharmaceutica; Toxicological Research Report on fentanyl (R4263), No. 44 (651020).
C 8 Bruce DL, et al. Fentanyl does not inhibit fertilization or early development of sea urchin eggs. Anesthesia and Analgesia 64: 498-500 (1985).
C9 Letter to the editor: Fentanyl and fertilization. Anesthesia and Analgesia 65: 103 (1986).

D 1 [redacted] al. R004263. Salmonella typhimurium gene reverse mutation test (Ames test). Janssen Research Foundation, February 1991; Toxicological Research Report No. 2345.
D 2 [redacted]. R004263. Salmonella typhimurium gene reverse mutation assay Janssen Research Foundation. July 1997; Toxicological Research Report No. 3942
D 3 [redacted] In vitro microbiological mutagenicity assays with fentanyl for ALZA Corporation. ALZA Final Report TR-85-1772-068 [redacted]. Report No. LSC-1 499-1), January 1986.

D 4 . Mouse lymphoma cell mutagenesis assay (TK+/--@TK-/-) with fentanyl for ALZA Corporation. ALZA Final Report TR-85-1772-067 (Report No. LSC-1 499-3), April 1986

D 5 . Evaluation of the mutagenic activity of fentanyl in an in vitro mammalian cell gene mutation test with L5178Y mouse lymphoma cells (with independent repeat). Final Report 073823 August 1992.

D 6 . R004263. Micronucleus test in mice. Janssen Research Foundation, April 1991; Toxicological Research Report No. 2338.

D 7 . In vitro chromosomal aberration assay on fentanyl.ALZA Final Report TR-87-1772-015 (Reference 55789-01)); September 1987.

D 8 Wagner M. The effects of some commonly used piperidine derivates on human chromosomes in vitro. Arzneimiftel.-Forschung. 21 (7): 1017-24 (1971).

D 9 Evaluation of 80285 in the Balb/c-3T3 in vitro cell transformation assay in the absence and presence of S9 metabolic activation. ALZA Final Report TR-86-1772-014), October 1986.

D 10 In vitro hepatocyte DNA repair assay with fentanyl for ALZA Corporation. ALZAFinalReportTR-85-1772-066(eportNo.LSC-1393-2),April 1986.

Fl harmacokinetics of fentanyl. Proceedings of a workshop on transdermal fentanyl, . In: Transdermal fentanyl. a new approach to prolonged pain control.

F 2 ransdermal permeation: physiological and physicochemical aspects. Proceedings of a workshop on transdermal fentanyl, In: Transdermal fentanyl a new approach to prolonged pain control

F 3 Lehmann KA, Zech D. Transdermal fentanyl: Clinical pharmacology. Journal of Pain and Symptom Management 7 (3) (suppi.): S8-SI 6 (1992).

F 4 Scholz J, et a[. Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil. An update. Clinical Pharmacokinetics 31 (4): 275-92 (1996).

F 5 Fentanyl. In: Drug discovery: A casebook and analysis, Ed. RA Maxwell and SB Eckhardt, Human Press, Clifton, New Jersey, USA: 307-18 (1990).

F 6 Moldenhauer CC, Hug CC. Use of narcotic analgesics as anaesthetics. Clinics in Anaesthesiology 2 (1): 107-38 (1984).

F 7 Andrews CJH, Prys-Roberts C. Fentanyl - A review. Clinics in Anaesthesiology 1 (1): 97-122 (1983).

F 8 Meert TF. Pharmacotherapy of opioids: present and future developments. Pharmacy NI14314 World & Science 18 (1): 1-15 (1996).

F 9 Willens JS, Myslinski NR. Pharmacodynamics, pharmacokinetics, and clinical uses of fentanyl, sufentanil, and alfentanil. Heart & Lung 22 (3): 239-51 (1993).

F 10 Soudijn W. The pharmacology and the pharmacokinetics of fentanyl. In: Stress-free anaesthesia. Royal society of medicine international congress and symposium series No-3, Ed. Wood C., The royal society of medicine and academic press: 3-10 (1978).

F 1 1 . Nonclinical expert report on the toxicological, pharmacodynamic and pharmacokinetic documentation related to fentanyl TTS. Janssen Research Foundation, October 1992; Expert Report on

F 12 Hermans B, et al. Interaction of peptides and morphine-like narcotic analgesics with specifically labelled mu- and delta-opiate receptor binding sites. Archives Internationales de Pharmacodynamie et de Therapie 263: 317-9 (1983).

F 13 Leysen JE, et al. (3H) Sufentanil, a superior ligand for mu-opiate receptors: binding properties and regional distribution in rat brain and spinal cord. European Journal of Pharmacology 87: 209-25 (1983).

F 14 Maguire P, et al. Pharmacological profiles of fentanyl analogs at mu, delta and kappa opiate receptors. European Journal of Pharmacology 213: 219-25 (1992).

F 15 Thysman S, Preat V. In vivo iontophoresis of fentanyl and sufentanil in rats: pharmacokinetics and acute antinociceptive effects. Anesthesia and Analgesia 77: 61-6 (1993).

F 16 Roy SD, Flynn GL: Transdermal delivery of narcotic analgesics: pH, anatomical, and subject influences on cutaneous permeability of fentanyl and sufentanil. Pharmaceutical Research 7 (8): 842-7 (1990).

F 17 Gardocki JF, Yelnosky J. A study of some of the pharmacologic actions of fentanyl citrate. Toxicology and Applied Pharmacology 6: 48-62 (1964).
F 18 McNeil Laboratories. Injection letter to Dr. Kelsey. McN-JR-4263 (1963 letter) August 23, 1963.
F 19 Niemegeers C.J.E., et al. Sufentanil, a very potent and extremely safe intravenous morphine-like compound in mice, rats and dogs. Arzneimittel-Forschung (Drug Res.) 26 (8): 1551-6 (1976)
F 20 De Castro J, et al. Comparative study of cardiovascular, neurological and metabolic side-effects of eight narcotics in dogs. Acta Anaesthesiologica Beigica 30: 5-99 (1979).
F 21 Bushnell TG, Justins DM. Choosing the right analgesic. A guide to selection. Drugs 46 (3): 394-408 (1993).
F 22 Niemegeers CJE. 13. Pharmacology of antidiarrheal agents in vivo. Clinical Research Reviews 1 (Suppl. 1): 125-39 (1981).
F 23 Megens AAHP, et al. Comparison of the analgesic and intestinal effects of fentanyl and morphine in rats. Journal of Pain and Symptom Management 15 (4): 253-7 (1998).
F 24 Tammisto T, et al. A comparison of the circulatory effects in man of the analgesic fentanyl, pentazoeine and pethidine. British Journal of Anaesthesia 42: 317-24 (1970).
F 25 Graves CL, et al. Cardiovascular effects of minimal analgesic quantities of innovar, fentanyl, and droperidol in man. Anesthesia and Analgesia 54 (1): 15-23 (1975).
F 26 Hill HF, et al. Steady-state infusions of opioids in human: II. Concentration-effect relationships and therapeutic margins. Pain 43: 69-79 (1990).
F 27 Prys-Roberts C, Kelman GR. The influence of drugs used in neuroleptanalgesia on cardiovascular and ventilatory function. British Journal of Anaesthesia 39: 134-45 (1967).
F 28 Cartwright P, et al. Ventilatory depression related to plasma fentanyl concentrations during and after anesthesia in humans. Anesthesia and Analgesia 62: 966-74 (1983).
F 29 Janssen Research Foundation. TTS-fentanyl. Investigator's Brochure, Third Edition, October 1995.
F 30 Stephen GW, Cooper LV. The role of analgesics in respiratory depression: a rabbit model. Anaesthesia 32: 324-7 (1977).
F 31 Brown JH, et al. Respiratory effects of a new opiate analgesic, R39209, in the rabbit: comparison with fentanyl. British Journal of Anaesthesia 52: 1101-6 (1980).
F 32 Jeal W, Benfield P. Transdermal fentanyl. A review of its pharmacological properties and therapeutic efficacy in pain control. Drugs 53 (1): 109-38 (1997).
F 33 Van den Hoogen RHWM, et al. Respiratory effects of epidural and subcutaneous morphine, meperidine, fentanyl and sufentanil in the rat. Anesthesia and Analgesia 67: 1071-8 (1988).
F 34 . Expert report on the preclinical (pharmacological, pharmacokinetic, toxicological) documentation on epidural sufentanil. Janssen Research Foundation, November 1989; Preclinical Expert Report No. 30 (R33800).
F 35 Meert TF, et al. Pharmacological validation of ritanserin and risperidone in the drug discrimination test procedure in the rat. Drug Development Research 19: 353-73 (1990).
F 36 [redacted] . Abuse potential of alfentanil and sufentanil: preclinical evaluation using the fentanyl drug discrimination test procedure in the rat. Janssen Research Foundation, December 1988; Preclinical Research Report No. 42 (R39209) and No. 28 (R33800).
F 37 Negus SS, et al. Interactions between the discriminative stimulus effects of mu and kappa opioid agonists in the squirrel monkey. The Journal of Pharmacology and Experimental Therapeutics 256 (1): 149-158 (1990).
F 38 McNeil Laboratories. Pharmacologist review of NDA 16-619. (1967b letter) July 19, 1967.
F 39 De Kock M, Meert TF. Can alpha2-adrenoceptor agonists reverse or prevent tolerance to the antinociceptive activity of opioids in rats? Acta Anaesthesiologica Beigica 46 (3- 4): 141-52 (1995).
F 40 Colpaert FC, et al. The effects of prior fentanyl administration and of pain on fentanyl analgesia: tolerance to and enhancement of narcotic analgesia. The Journal of Pharmacology and Experimental Therapeutics 213 (2): 418-24 (1980).
F 41 Schneider E, Brune K. Opioid activity and distribution of fentanyl metabolites. Naunyn-Schmiedeberg's Archives of Pharmacology 334: 267-74 (1986).
F 42 Lehmann KA, et al. Biotransformation von Fentanyl III. Einfluesse chronischer N30913 Arzneimittelexposition auf Verteilung, Metabolismus und Ausscheidung bei der Ratte. Der Anaesthesist 32: 165-73 (1983).

F43 Meert TF, DeKock M. Interactions between the lipophilic opioid sufentanil and clonidine in N I 26209 rats after spinal application, Acta Anasthesiologica Scandinavica 39:527-34 (1995)
F 44 Verborgh C, et al. Effects of chlordiazepoxide on opioid-induced antinociception and respiratory depression in restrained rats. Pharmacology Biochemistry and Behavior 59 (3): 663-70 (1998).
F 45 Meert TF, De Kock M. Interactions between the lipophilic opioid sufentanil and clonidine in rats after spinal application. Acta Anaesthesiologica Scandinavica 39: 527-34 (1995).
F 46 Vereauteren M, et al. Spinal sufentanil in rats: Part II: Effect of adding bupivacaine to epidural sufentanil. Acta Anaesthesiologica Scandinavica 36: 245-9 (1992).
GI — non-clinical pharmacokinetics. Review of literature available March 1998. Janssen Research Foundation, September 1998; Non-clinical Pharmacokineties Report R004263/FK2963.
G 2 Michiels M, et al. A sensitive radioimmunoassay for fentanyl. Plasma level in dogs and man. European Journal of Clinical Pharmacology 12: 153-8 (1977).
G 3 Woestenborghs RJH, et al. Assay methods for fentanyl in serum: gas-liquid chromatography versus radioimmunoassay. Anesthesiology 67: 85-90 (1987).
G 4 Jadoul A, et al. Quantification and localization of fentanyl and TRH delivered by iontophoresis in the skin. International Journal of Pharmacology 120: 221-8 (1995).
G 5 Thysman S, et al. Transdermal iontophoresis of fentanyl: delivery and mechanistic analysis. International Journal of Pharmacology 101: 105-13 (1994).
G 6 Vanbever R, et al. Transdermal delivery of fentanyl by electroporation. I. Influence of electrical factors. Pharmaceutical Research 13: 559-65 (1996).
G 7 Vanbever R, et al. Transdermal delivery of fentanyl by electroporation. II. Mechanisms involved in drug transport. Pharmaceutical Research 13: 1360-6 (1996).
G 8 Thysman S, Pr6at V: In vivo iontophoresis of fentanyl and sufentanil in rats: pharmacokinetics and acute antinociceptive effects. Anesthesia and Analgesia 77: 61-6 (1993).
G 9 Vanbever R, et al. Transdermal delivery of fentanyl: rapid onset of analgesia using skin electroporation. Journal of Controlled Release 50: 225-35 (1998).
GIO — An in vitro study on the interaction of ketamine, meperidine, midazolam andpromethazine with the metabolism of fentanyl in human liver microsomes. Janssen Research Foundation, March 1998; Non-Clinical Pharmacokinetics Report R004263/FK16968.
G 11 — The in-vitro metabolism of fentanyl in human hepatocytes. Janssen Research Foundation, March 1998; Non-Clinical Pharmacokinetics Report R004263/FKI 698.
G 12 — . An in-vitro study on the metabolism of fentanyl in human liver microsomes and on the interaction potential of fentanyl towards possible co-medication. Janssen Research Foundation, June 1995; Non-Clinical Pharmacokinetics Report R004263/FK1872.
G 13 — In-vitro determination of the drug-drug interaction potential of fentanyl in human liver microsomes: effects of possible co-medication on the metabolism of fentanyl. Janssen Research Foundation, March 1998; Non-Clinical Pharmacokinetics Report R004263/FK2428.
G 14 Palkama VJ, et al. The effect of oral itraconazole on the pharmacokinetics and pharmacodynamics of intravenous fentanyl in healthy volunteers. January 1998. Manuscript submitted for publication. Presented in part (abstract) at the Annual Meeting of the American Society of Anesthesiologists, San Diego, CA, October 18-22, 1997.
G 15 — Toxicokinetics of fentanyl in a single-dose Dose Range Finding toxicity study (Exp. No. 3777) in female SPF Wistar rats after single intravenous administration of fentanyl citrate (ROO5240) by 24-hour infusion at 0.01, 0.02, 0.05, 0.1, 0.2, 0.5, 1 and 2 mg fentanyl/kg and a 5-day (120 h) infusion at 0.025 and 0.4 mg/kg/day. Janssen Research Foundation, March 1998; Non-clinical Pharmacokinetics Report R004263/FK2145, Addendum to the Toxicity Report Exp. No. 3777.Preclinical Summary on E-TRANSTM (fentanyl HCL)
G 16 — Toxicokinetics of fentanyl (ROO4263) in the SPF Wistar rat in a 5-week continuous infusion toxicity study (Exp. No. 3831) of fentanyl at 0.025, 0.1 and 0.4 mg/kg/day, followed by a 4-week recovery period. Janssen Research Foundation, April 1997; Non-clinical Pharmacokinetics Report R004263/FK2224 Addendum' to the Toxicity Report Exp. No. 3831.
G 17 — . Toxicokinetics of fentanyl in a combined intravenous segment I and II reproduction study on the effects on fertility and embryo-foetal development of aqueous solutions of fentanyl at 0.025, 0.1 and 0.4 mg/kg/day, given as a continuous infusion. to the SPF Wistar rat (Exp. No. 3972). Janssen

Research Foundation, March 1998; Non- clinical Pharmacokinetics Report R004263/FK2362, Addendum to the Toxicity Report Exp. No. 3972.
G 18 — Toxicokinetics of fentanyl in pregnant SPF albino rabbits in a 3-day intravenous Dose Range Finding toxicity study (Exp. No. 4159) on aqueous solutions of fentanyl at 0.2, 0.4, 0.8 and 1.6 mg/kg, given as a daily 4-hour infusion. Janssen Research Foundation, March 1998; Non-clinical Pharmacokinetics Report R004263/FK2467, Addendum to the Toxicity Report Exp. No. 4159.
G 19 — Toxicokinetics of fentanyl in an intravenous segment II study on the effects of aqueous solutions of fentanyl at 0.025, 0.1 and 0.4 mg/kg/day, given as a daily 4-hour infusion, on the embryo-foetal development in the albino rabbit (Exp. No. 4397). Janssen Research Foundation, March 1998; Non-clinical Pharmacokinetics Report R004263/FK2686, Addendum to the Toxicity Report Exp. No. 4397
G 20 — The pharmacokinetics of frequent and infrequent fentanyl bolus doses in healthy volunteers ALZA Corporation Final Report, March 1993; Protocol C-92-029-01 (FEN-USA-14).
G 21 — Effects of formulation variables on the pharmacokinetics of fentanyl delivered from two new ETS (fentanyl) formulations. ALZA Corporation Final Report, April 1995; Protocol C-94-055-05 (FEN-USA-31).
G 22 — (Fentanyl) pilot efficacy and safety study in the treatment of postoperative pain. ALZA Corporation Final Report, January 1996; Protocol C-93-023-00 (FEN-INT-2).

H 1 — Primary skin irritation study of E-TRANSTII systems with anode hydrogels containing fentanyl on rabbits, ALZA Study No. TR-96-1561-052, November 1996.
H 2 — A Primary Skin Irritation Study of E-TRANSTM (placebo) systems containing Cetylpyridinium chloride (CPC) and — and — Adhesives on Hairless Guinea Pigs and Rabbits. ALZA Study No. TR-98-1561-031, December 1998.
H 3 — . Primary skin irritation study of E-TRANSTM (fentanyl) in guinea pigs, ALZA Study No. TR-92-1561-021, January 1993.
H 4 — Primary skin irritation study of electrotransport therapeutic systems containing fentanyl in rabbits, ALZA Study No. TR-92-1561-053, December 1992.
H 5 — rimary skin irritation study of electrotransport therapeutic systems placebo anode hydrogels in the hairless guinea pig, ALZA Study No. TR-93-1561-048, December 1993.

H 6 — . Fourteen-day subchronic skin irritation study in guinea pigs of electrotransport [ET] fentanyl, ALZA Study No. TR-92-1561-023, January 1993.
H 7 — Visual (macroscopic) and histological evaluation of guinea pig skin sites following single and multiple applications of electrotransport therapeutic systems, ALZA Study No. TR-92-9999-014, December 1992.
H 8 — . Experimental sensitisation evaluation of fentanyl using electrotransport therapeutic systems in the hairless guinea pig, ALZA Study No. TR-92-1561-022, October 1992.
H 9 — Evaluation of the sensitization potential of electrotransport systems containing placebo anode hydrogels (histidine and polacrilin —), in the hairless guinea pig, ALZA Study No. TR-97-1561-011, May 1998
H 10 — . Evaluation of cetypyridinium chloride for delayed contact hypersensitivity in guinea pigs, ALZA Study No. TR-96-1561-017, January 1997
H 11 — . Evaluation of Polacrilin Resin —) Extract for Delayed Contact Hypersensitivity in guinea pigs, ALZA Study No. TR-96-1561-016, October 1997.
H 12 — Evaluation of polacrilin resin) extract dilutions for delayed contact hypersensitivity in guinea pigs, ALZA Study No. TR-96-1561-048, October 1997.
H 13 Quigley P. Evaluation of film, — . polyisobutylene — adhesive (code no. —, —) extract for delayed contact hypersensitivity in guinea pigs, ALZA Study No. TR-96-1563-012, January 1997.
H 14 Bagdadi D. USP XXII: Biological testing of — ALZA Study No. TR-90-1550-018, April 1991.
H 15 Johnson P. USP XXII: Biological testing of. — ALZA Study No. TR-94-1561-017, June 1994.

H 16 , ...) In Vivo Biocompatibility Testing of Housing, Top, E- TRANS™ (acute). [redacted] code number [redacted] ALZA Study No. TR-99- 1561-057, February 2000

H17 . . .) In Vivo Biocompatibility Testing of Housing, Top, E- TRANS™ (acute). [redacted] code number [redacted] , ALZA Study No. TR-99- 1561-056, February 2000

H 1' . USP 23: Biological testing of Housing, Bottom. [redacted] , red, E-TRANS™ (acute). code number [redacted] ALZA Study No. TR-97-1561-009. April 1998.

H 19 . . . . . USP 23: Biological testing of Housing, Bottom. [redacted] , E-TRANS™ (acute), code number [redacted] , ALZA Study No. TR-97-1561-010, April 1998

H 20 USP XXII: Biological testing of [redacted] ALZA Study No. TR-94-1561-020, December 1996.

H 21 3: Biological testing of [redacted] [redacted] ALZA Study No. TR-96-1561-044, May 1998.

H 22 . USP 23: Biological testing of film, [redacted] PIB adhesive, code no. [redacted] ALZA Study No. TR-96-1561-011, January 1997.

H 23 . . . . LISP XXII: Biological testing of [redacted] , ALZA Study No. TR-93-2420-068, December 1994.

H 24 . USP XXII: Biological testing of Lower Housing, acute system, code [redacted] ALZA Study No. TR-93-8888-059, April 1994.

H25 . LISP 23: Biological testing of Lower Housing, acute system, code number [redacted] 1, ALZA Study No. TR-95-1561-031, December 1996.

H 26 In vitro biological testing of [redacted] Lot No. T790, Part No [redacted] . LISP Elution and MTT Assay. ALZA Study No. TR-98-1561-023, January 1999.

Q 1 V tudies on intramuscular injections of McN-JR-4263 in rabbits. McNeil Laboratories, Inc., Toxicological Research Report No. 18 (630725).

[redacted] olorimetric assay for cytotoxicity of fentanyl. ALZA Final Report TR-86- 1772-023 [redacted]), September 1986

Q 3 [redacted] . . . A comparison of the acute intravenous toxicity of the narcotic analgesic fentanyl (R4263) and its potential impurity [redacted] n male mice. B. The toxicity of [redacted] Janssen Research Foundation, November 1993; Toxicological Research Report, Experiment No. 3108.

Q 4 [redacted] A comparison of the acute intravenous toxicity of the narcotic analgesic fentanyl (R4263) and its potential impurity [redacted] in male rats. B. The toxicity of [redacted] Janssen Research Foundation, November 1993; Toxicological Research Report, Experiment No. 3106.

L 1 Kurilenko VM, et al. Synthesis and analgesic of piperidine and decahydroquinoline derivatives. Pharmaceutical Chemical Journal 10: 1193-6 (1976).

L 2 Bianchi C, Franceschini J. Experimental observations on Haffner's method for testing analgesic drugs. British Journal of Pharmacology 9: 280-4 (1954).

L 3 Jennett S. Assessment of respiratory effects of analgesic drugs. British Journal of Anaesthesia 40: 746-56 (1968).

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/s/

Mamata De
5/19/2006 12:39:05 PM
PHARMACOLOGIST

R. Daniel Mellon
5/19/2006 12:41:58 PM
PHARMACOLOGIST
I concur with Dr. De's recommendation. From the nonclinical pharmacology toxicology perspective, NDA 21-338 may be approved.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-338**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**09/23/03**
PRODUCT:	**E-TRANS FENTANYL**
INTENDED CLINICAL POPULATION:	**Adult patients with acute pain requiring opioid analgesia**
SPONSOR:	**ALZA CORPORATION**
DOCUMENTS REVIEWED:	**EDR 000 23-SEP-2003** **EDR 000 BZ 06-APR-2004**
REVIEW DIVISION:	**Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170)**
PHARM/TOX REVIEWER:	**Mamata De, Ph.D.**
PHARM/TOX SUPERVISOR:	**R. Daniel Mellon, Ph.D.**
DIVISION DIRECTOR:	**Bob A. Rappaport, M.D.**
PROJECT MANAGER:	**Kimberly Compton**

Date of review submission to Division File System (DFS): July 22, 2004

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

From the pharmacology toxicology perspective, NDA 21-338 (E-TRANS fentanyl system should be considered approvable, upon adequate qualification of several impurities via 14-day repeat dose toxicology studies and a minimal genetic toxicology screen, as described in ICHQ3A and ICHQ3BR. Alternately, the stability specifications should be reduced to NMT [redacted]

B. Recommendation for nonclinical studies

1. The sponsor should either reduce the specifications for the following impurities in the drug substance to NMT [redacted] or provide adequate qualification for their safety:

[redacted]

2. [redacted] ontair and are structural alerts for mutagenicity. Therefore provide a limit of NMT [redacted] each for these impurities in the drug substance. Alternatively support the proposed levels by demonstration that these anilino-compounds are human metabolites, or by two genotoxicology studies; one in vitro mutation assay such as Ames bacterial mutagenicity assay and the other an in vitro cytogenetic assay. Studies should achieve the limit doses for these assays with the isolated impurities. If the impurities are mutagenic, provide a limit of [redacted] or provide an assessment of carcinogenic potential in a standard 2-year model or an appropriate alternative model. Consultation with the Agency in the design of these studies is encouraged.

2 Page(s) Withheld

_ § 552(b)(4) Trade Secret / Confidential

_ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

The pharmacologic and toxicologic properties of fentanyl are well characterized. The sponsor has right of reference to the study reports originally generated by Janssen Research Products in support of other fentanyl containing drug products. Therefore, the nonclinical development program for E-TRANS fentanyl consisted primarily of local tissue assessments of the final product and various components of the device.

Nonclinical toxicology studies in the E-TRANS fentanyl program evaluated the potential for skin irritation and sensitization associated with the system and its components. The durations of exposure and current densities were selected to be representative of human treatment with E-TRANS fentanyl.

The commercial E-TRANS anode and cathode hydrogel formulations were categorized as mild irritants in single-application skin irritation studies (anode, Study TR-96-1561-052; cathode, Study TR-98-1561-031). The commercial anode formulation was evaluated in New Zealand White rabbits treated for 14 hours at a current density of 0.08 mA/cm^2 (i.e., 80 uA/cm^2) resulting in a mean total fentanyl dose of 3.5 mg (0.073 mg/k/h). The commercial cathode formulation was evaluated in New Zealand White rabbits and hairless guinea pigs for approximately 13 hours at a current density of 0.07 mA/cm^2 (70 uA/cm^2).

The initial sensitization study in hairless guinea pigs evaluated an E-TRANS fentanyl system that had early-formulation hydrogels (TR-92-1561-022). The system was categorized as a mild to moderate sensitizer, but the findings of the study were influenced by the fact that irritation contributed to the observed responses. The systems in this study delivered fentanyl at a dose of 1.1 mg/kg over 8 hours at a maximum current density of 0.1 mA/cm^2 (100 uA/cm^2). A second sensitization study in hairless guinea pigs evaluated placebo E-TRANS systems with hydrogel formulations that were more similar to the commercial formulation (TR-97-1561-01 1). No evidence of sensitization was found in animals induced and challenged with the anode or cathode hydrogels, categorizing them as weak sensitizers.

Additional studies found no evidence of sensitization in hairless guinea pigs induced and challenged with the bactericide in the cathode hydrogel (cetylpyridinium chloride) (TR-96-1561-017) or with extracts of the skin adhesive used in the E-TRANS system (TR-96-1563-012). Extracts of the — (polacrilin) had some potential to induce sensitization, but at the concentrations proposed for clinical use, the potential was low (TR-96-1561-016, TR-96-1561-048). Therefore, polacrilin was determined to be an acceptable — for use in E-TRANS hydrogels.

Extracts and samples of system components in contact with the hydrogels met either USP Class V-50°C or VI-50°C requirements and were therefore judged to be safe for use in the E-TRANS system.

A single dose of 0.5 ml of fentanyl (0.1 mg base/ml) was injected into the sacrospinalis muscle of the rabbit to evaluate muscle irritation potential of fentanyl. Positive controls were administered 0.5 ml doses of tetracycline (125 mg/ml) and pyralgin (500 mg/ml). The rabbits were killed 72 hours later and the degree of irritation determined by gross observation of serially sectioned muscle. The irritation responses were none to slight for fentanyl, moderate to severe for pyraigin while tetracycline showed a severe response.

The cytotoxicity of fentanyl was evaluated in the tissue culture with human keratinocytes. Cell viability was determined by using a tetrazolium dye that is reduced to a blue formazan by living cells. The resultant color is measured with a spectrophotometer. There was no cytotoxicity at concentrations below 1 mM (0.3 mg/ml).

Impurities in the fentanyl HCl are monitored by , and ALZA. Unknown impurities are also monitored routinely to ensure that their levels do not exceed the specified limits. The impurities are detectable and quantified in the drug substance by ALZA via high-performance liquid chromatography (HPLC) methods, ALZA Analytical Methods (AAMS) . None of the impurities have been detected in the drug substance at levels close to (the specification limit). The two impurities not specifically monitored in the drug substance are The impurity is monitored in the finished product stability, and the impurity has been monitored by the and reported in Certificate of Analysis. This impurity is historically below the reporting threshold of 0.05% for drug substance as defined in the International Conference on Harmonisation (ICH) Q3A. ALZA does not monitor for these two impurities specifically but reports any impurities detected above , with a limit of

B. Pharmacologic activity

Fentanyl is a synthetic opioid agonist that interacts primarily with the u-opioid receptor subtype to produced analgesia and sedation. It increases the patient's tolerance for pain and decreases the perception of suffering, although the patient may still recognize the pain itself. Opioids work to relieve nociceptive pain but are not very effective for neuropathic pain. In addition to analgesia μ-opioid agonists such as fentanyl produce drowsiness, changes in mood, respiratory depression decreased gastrointestinal motility, nausea, vomiting and alterations in the endocrine and autonomic nervous system.

High doses of fentanyl produce muscle rigidity possibly due to effects of opioids on dopaminergic transmission in the striatum. The euphoric effects of opioids are believed to be mediated in part via interaction with opioid receptors located in the ventral tegmental area (VTA) leading to the enhancement of dopamine release in the nucleus accumbens. Opioid receptors in the locus coeruleus appear to inhibit the adrenergic neurons thought to play a role in feelings of alarm, panic, fear and anxiety. Opioids act within the hypothalamus to regulate body temperature (generally temperature decreases slightly, but at higher doses temperature may increase). Opioids inhibit neuroendocrine systems including gonadotropin-releasing hormone (GNRH) and corticotropin-releasing factor (CRF) thereby decreasing release of luteinizing hormone (LH), follicle-stimulating hormone (FSH), adrenal corticotrophic hormone (ACTH), and P-endorphin. This leads to decrease plasma levels of testosterone and cortisol. Opioids increase circulating levels of prolactin. Opioids such as fentanyl lead to constriction of the pupil (miosis) via increased parasympathetic nerve activity innervating the pupil. Pinpoint pupils are pathognomonic for toxic doses of μ-opioid agonists, however mydriasis can develop upon asphyxia.

The safety of fentanyl administration pertaining to the submitted NDA are similar to those following systemic administration of potent opioids. The major concern is respiratory depression, which can occur at plasma concentrations between 2 and 4 ng/ml. In addition, fentanyl administration may produce sedation, nausea and vomiting, bradycardia, urinary retention and constipation. Although opioids such as fentanyl can have significant safety concerns, the effects are well known. Therefore, given careful clinical monitoring, especially for respiratory depression, the proposed application does not appear to pose significant concerns regarding safety pharmacology.

Opioids are readily absorbed from the gastrointestinal tract and the rectal mucosa. More lipophilic agents are also absorbed through the nasal or buccal mucosa and those with the greatest lipophilicity can be absorbed transdernally. An increase in temperature from 32°C to 37°C has been shown to double the rate of fentanyl delivery.

Fentanyl is widely distributed in the body following administration. There is some evidence that it can accumulate in skeletal muscle and fat. Fentanyl demonstrates approximately 69-84% protein binding and an average volume of distribution of 6 L/kg. Fentanyl crosses the placenta and can also be detected in breast milk. Fentanyl is metabolized primarily in the liver by N-dealkylation and hydroxylation via cytochrome P450 3A4. In humans, the primary metabolite is norfentanyl. Fentanyl is not considered to have any active or toxic metabolites. The metabolites of fentanyl and unchanged drug are primarily eliminated via the urine with only 10% representing the unchanged drug. About 9% of the dose is eliminated in the feces, primarily as metabolites. The skin does not appear to metabolize fentanyl that is absorbed transdermally. The short duration of action of

intravenous fentanyl (30-60 minutes) is probably due to rapid redistribution into tissues and not due to metabolism. The elimination half-life is about 4 hours. Although there are always concerns regarding the potential for respiratory depression following fentanyl administration, careful clinical monitoring and co-treatment with naltrexone should prevent any unnecessary adverse events related to fentanyl administration.

Toxicokinetic data have been provided from the reproductive toxicity studies performed in rat and rabbit after intravenous administration of fentanyl. A comparison of pharmacokinetics and exposure in animals and man after intravenous dosing of fentanyl resulted in similar observations regarding the general plasma concentration-time course, the tissue distribution, the routes of metabolism and of excretion in the rat, rabbit, and man. E-TRANS (fentanyl HCl) is designed to deliver fentanyl in on-demand doses of either 25 or 40 ug over 10 min. Patients may self-administer at the highest possible dose rate, i.e. one delivery every 10 min. Fentanyl plasma levels reached with E-TRANS (fentanyl HCl) delivering one dose every 10 min, with this high dose rate specifically studied, are only available from volunteers blocked with naltrexone. In one volunteer study, a 25 ug system was applied to 9 male subjects. They were dosed 75 ug in the first 30 min of every hour for 25 h, with an estimated total fentanyl dose of 1875 ug. In a similar volunteer study in 12 subjects an E-TRANS (fentanyl HCl)-like system as applied delivering approximately 47-48 ug in 20 min with one dose delivered every hour for 25 h. Maximal fentanyl plasma levels were below 4 ng/ml in all individuals. In a pilot efficacy and safety study in 253 post-operative patients, fentanyl plasma levels were measured in subjects on either a 25 ug system (50 values) or a 40 ug system (52 values), with fentanyl i.v. supplements administered when required. The majority of subjects had plasma levels around 1-2 ng/ml. It was not reported whether and, if so, when, i.v. supplements were administered to the patients of which plasma levels were presented.

In the rabbit reproduction study, performed with fentanyl dosed via intravenous infusion, the maximal plasma fentanyl levels of on average 27.8 ng/ml (highest dose level) were markedly higher than those expected in patients using E-TRANS (fentanyl HCl). In the rat combined segment I/II study, the mean C_{max} at the highest dose level was only 6.2 ng/ml, but still higher than the peak levels expected in patients. However, a 'Dose Range Finding' study indicated that higher rat dose levels were not feasible because of increased mortality.

C. Nonclinical safety issues relevant to clinical use

The amount of fentanyl absorbed systemically in human from a 10-minute dose from the E-TRANS system increased proportionally with the applied current. The desired nominal 40 ug E-TRANS dose was delivered systemically by a 170 uA current and a 2.75 cm^2 anode surface area at Hour 23 following a standard dosing regimen of 2 sequential doses every hour for 23 hours. A nominal 25-ug dose was

delivered by a 100-uA current and a 1.40-cm^2 anode surface area at 23 hours following the standard regimen. Mild to moderate irritation was observed with the current formulation in hairless guinea pig local tolerance studies with 70-230 uA current and comparable anode surface. The irritation is characterized by erythema. Similar local toxicity is expected in human population. Although no hypersensitivity was observed with fentanyl, polacrilin [redacted] xtract at a concentration of 50% administered intradermally induced some hypersensitivity characterized by irritation and allergic reaction. These data indicate that the polacrilin has some potential to induce sensitization at high exposures, but at concentrations proposed for clinical use [redacted], the potential is reduced.

Fentanyl HCl is used in the clinical formulation, although fentanyl HCl is used for most of the non-clinical studies. Due to the pH lowering capability of the HCl formulation of the fentanyl, absorption is expected to be higher than that of the citrate formulation. However, the toxicity data discussed in this review is mainly via intravenous route of administration.

Impurities of the drug substance are not adequately evaluated. The specification for the drug substance impurities should be reduced to NMT [redacted] or the sponsor should provide adequate qualification of the impurities via repeat-dose toxicity study in a single species and a minimal genetic toxicology screen. Alternatively, the sponsor should generate the data to illustrate no dermal absorption of the excipients.

APPEARS THIS WAY
ON ORIGINAL

Pages 11 – 151 of this review are identical to pages 9 – 148 in the 5/19/06 Pharmacology / Toxicology for this NDA.

2.6.6.10 Tables and Figures

Not applicable

2.6.7 TOXICOLOGY TABULATED SUMMARY

TOXICOLOGY SUMMARY TABLE: OVERVIEW OF TOXICOLOGY STUDIES WITH FENTANYL

Type of study	Species	Route	Duration of observation	Doses in mg/kg/day	GLP yes/no	Ref.
Part III - A	mouse	i.v.	14 days	0, 10, 20	yes	A 1
Single dose toxicity		i.v.	3 days	unknown	no	A 3
		i.v.	5 days	5, 10, 20, 40, 80, 160, 320	no	A 4
		oral	7 days	30, 50, 60, 80, 100, 120, 140, 160	no	A 5
		s.c.	3 days	1, 2, 3, 4, 5, 8, 10, 50, 100, 200, 300	no	A 3
		s.c.	5 days	5, 10, 20, 40, 80, 160, 320	no	A 4
	rat	i.v.	14 days	0, 1.25, 2.5, 5	yes	A 2
		i.v.	5 days	1.25, 2.5, 5, 10, 20, 40, 80	no	A 4
		oral	7 days	5, 10, 20, 30, 40, 50	no	A 5
		i.m.	5 days	1, 2, 4, 8, 12, 16	no	A 6
		s.c.	5 days	1.25, 2.5, 5, 10, 20, 40, 80	no	A 4
	rat (neonatal)	i.g.	16 days	4, 8, 16, 32, 75, 100	no	A 7

Type of study	Species	Route	Duration of observation	Doses in mg/kg/day	GLP yes/no	Ref.
		i.m.	7 days	15, 25, 30, 40	no	A 6
		i.m.	7 days	0.35	no	A 9
		s.c.	5 days	0.04, 0.08, 0.16, 1.25	no	A 10
		i.a.	7 days	0.3	no	A 11
	cat	i.v.	5 days	0.04, 0.08, 0.16	no	A 10
	hamster	i.m.	5 days	8, 12, 25	no	A 6
	guinea pig	i.v.	0 days	3 [a)]	no	A 10
		i.m.	5 days	18, 24, 25, 30, 35, 50, 55, 65, 75, 85, 100	no	A 6
	monkey	i.v.	1 day	0.0316	no	A 10

a) LD_{100}

Toxicology Summary Table: Overview of Toxicology Studies with Fentanyl contd.:

Type of study	Species	Route	Duration of treatment	Doses in mg/kg/day	GLP yes/no	Ref.
Part III - A	Rat	i.v. (infusion)	DRF	0.025, 0.1, 0.2, 0.4, 0.5, 1, 2[a)]	no	A 12
Repeated dose toxicity		i.v. (infusion)	5 weeks	0, 0.025, 0.1, 0.4	yes	A 13
		i.v. (bolus)	4 weeks	0, 0.01, 0.02, 0.03, 0.05, 0.075, 0.1	no	A 14
		oral (diet)	2 weeks	0, 5, 10, 20, 40, 80, 160, 320	no	A 10
		i.m.	4 weeks	0, 0.1, 0.4	no	A 15
	Dog	i.v.	4 weeks	0, 0.1, 0.3, 1	yes	A 16
		i.m.	4 weeks	0, 0.1, 0.4	no	A 15
Part III - B reproductive function						
male fertility	Rat	i.v. (infusion)		0, 0.025, 0.1, 0.4	yes	B 1
fertility and		i.v. (infusion)		0, 0.025, 0.1, 0.4	yes	B 2
embryotoxicity		s.c. (infusion)		0, 0.01, 0.1, 0.5	no	B 3
Part III - C developmental toxicity						
embryotoxicity and	Rabbit	i.v. (infusion)	3-days DRF	0, 0.025, 0.1, 0.4	no	C 1
teratogenicity		i.v. (infusion)		0, 0.025, 0.1, 0.4	yes	C 2
	Rat	i.v. (bolus)		0, 0.01, 0.03	no	C 4
		s.c. (infusion)		0, 0.5	no	C 5
		s.c. (bolus)		0, 0.16, 0.31, 0.64, 1.25	no	C 6
		s.c. (bolus)		0, 0.16, 0.31, 0.64, 1.25	no	C 7
pre/postnatal toxicity	Rat	i.v. (infusion)		0, 0.025, 0.1, 0.4	yes	C 3
fertilisation study	Sea urchin	*in vitro*		3.3, 33, 66 nM/ml	no	C 8

a) Dose Range Finding study up to a dose of 2 mg/kg. The effects of two doses, 0.025 and 0.4 mg/kg, were evaluated after continuous infusion for five days.

Toxicology Summary Table: Overview of Toxicology Studies with Fentanyl contd.:

Type of study	Test system	Route	Duration of observation	Doses in mg/kg/day	GLP yes/ no	Ref.
Part III - D						
Point and/or gene mutations						
Ames	S. typhimurium	*in vitro*		25 up to 2500 µg/plate +/- S9	yes	D 1
				25 up to 2500 µg/plate +/- S9	yes	D 2
				8.4 up to 2100 µg/plate +/- S9	yes	D 3
Mouse lymphoma	mouse lymphoma cells	*in vitro*		13 up to 126 µg/ml +/- S9	yes	D 4
				-S9: 200 up to 500 µg/ml	yes	D 5
				+S9: 100 up to 600 µg/ml		
Chromosome aberrations						
Micronucleus test	mouse	*in vivo*		0.63, 2.5, 10 mg/kg	yes	D 6
CAT	Chinese hamster ovary cells	*in vitro*		-S9: 0.06 up to 2050 µg/ml	yes	D 7
				+S9: 0.062 up to 2050 µg/ml		
	human peripheral lymphocytes	*in vitro*		-S9: 1.1×10^{-6} - 7.5×10^{-6} mol/l	no	D 8
Mammalian Cells Transformations						
Transformation	BALB/C-3T$_3$ cells	*in vitro*		25 up to 250 µg/ml +/- S9	yes	D 9
Primary DNA damage						
Unscheduled DNA synthesis	rat hepatocytes	*in vitro*		0.4 up to 84 µg/ml +/- S9	yes	D 10

Toxicology Summary Table: Overview of Toxicology Studies with Fentanyl contd.:

Type of study	Test system	Route	Duration of observation	Doses in mg/kg/day	GLP yes/ no	Ref.
Part III - Q Special studies						
Muscle irritation	rabbit	i.m.	once	0.157 mg/ml	-	Q 1
Cytotoxicity	human keratocytes	*in vitro*		188.562 and 827 mM	yes	Q 2
Impurity study	mouse	i.v.	14 days	0, 10, 20 [a)]	yes	Q 3
	rat	i.v.	14 days	0, 1.25, 2.5, 5 [a)]	yes	Q 4

a) Study was conducted with R004380, a potential impurity of fentanyl

Summary of E-Trans Dermal Toxicity Study:

Study Number/Type	Species/ Strain	Group Size/Sex	Treatment	Formulation[a)]	Duration	Finding/Irritation[b)]
TR-96-1561-052 Primary irritation of fentanyl-containing systems	New Zealand White Rabbit	6 females	Current density 0.08 mA/cm^2	Cathode: C3 Anode: A4	14 hours	anode PII=1.5 (mild) cathode PII=1.6 (mild)
TR-98-1561-031 Primary irritation of non fentanyl-containing systems	(Ibm:GOHI-hr) Guinea pigs New Zealand White Rabbit	12 females 6 females	Current density 0.07 mA/cm^2	Cathode: C3,C4 Anode: A6	13.3 hours	adhesive/0.2% CPC cathode PII=2.0 in guinea pig and 1.9 in rabbit (mild) Anode PII=0.9 - 1.3 in guinea pig and 0 - 0.4 in rabbit
TR-92-1561-021 Primary irritation of fentanyl-containing systems	IAF/HA-HO Guinea Pig	6 males	Current density 0.1 mA/cm^2; estimated drug release 111 µg/cm^2/h; estimated dose 2.24 mg/kg	Cathode: C2 Anode: A2	16 hours	anode PII=1.9 (mild) cathode PII=0.7 (mild)
TR-92-1561-053 Primary irritation of fentanyl-containing systems	New Zealand White Rabbits	3 females	Current density 0.1 mA/cm^2	Cathode: C2 Anode: A2	16 hours	anode PII=1.2 (mild) cathode PII=0.2 (negligible)
TR-93-1561-048 Primary irritation of placebo anode hydrogels with and without polacrilin	IAF/HA-HO Guinea Pig	6 males	Current density 0.1 mA/cm^2 no drug	Cathode: C2 Anode: A1 Anode: A3	8 hours; 24 hours	placebo anode with or without [redacted] PII=1.7 and 0.7 respectively (mild) cathode PII=0.8 (mild) placebo anode with or without [redacted] PII=2.3 (moderate) and 1.8 (mild) respectively cathode PII=1.0 (mild)

a) Different formulations are presented on the following page.

b) PII = Primary Irritation Index (0-8); PSI = Primary Skin Irritation (Irritation Scale: 0-0.5 negligible; 0.6-2.0 mild; 2.1-5.0 moderate; 5.1-8.0 severe).

Summary of E-TRANS Dermal Toxicity Study contd:

Study Number/Type	Species/ Strain	Group Size/Sex	Treatment	Formulation[a)]	Duration	Finding/Irritation[b)]
TR-96-1561-052 Primary irritation of fentanyl-containing systems	New Zealand White Rabbit	6 females	Current density 0.08 mA/cm^2	Cathode: C3 Anode: A4	14 hours	anode PII=1.5 (mild) cathode PII=1.6 (mild)
TR-98-1561-031 Primary irritation of non fentanyl-containing systems	(Ibm:GOHI-hr) Guinea pigs New Zealand White Rabbit	12 females 6 females	Current density 0.07 mA/cm^2	Cathode: C3,C4 Anode: A6	13.3 hours	adhesive/0.2% CPC cathode PII=2.0 in guinea pig and 1.9 in rabbit (mild) Anode PII=0.9 - 1.3 in guinea pig and 0 - 0.4 in rabbit
TR-92-1561-021 Primary irritation of fentanyl-containing systems	IAF/HA-HO Guinea Pig	6 males	Current density 0.1 mA/cm^2; estimated drug release 111 µg/cm^2/h; estimated dose 2.24 mg/kg	Cathode: C2 Anode: A2	16 hours	anode PII=1.9 (mild) cathode PII=0.7 (mild)
TR-92-1561-053 Primary Irritation of fentanyl-containing systems	New Zealand White Rabbits	3 females	Current density 0.1 mA/cm^2	Cathode: C2 Anode: A2	16 hours	anode PII=1.2 (mild) cathode PII=0.2 (negligible)
TR-93-1561-048 Primary irritation of placebo anode hydrogels with and without polacrilin	IAF/HA-HO Guinea Pig	6 males	Current density 0.1 mA/cm^2 no drug	Cathode: C2 Anode: A1 Anode: A3	8 hours; 24 hours	placebo anode with or without [redacted] PII=1.7 and 0.7 respectively (mild) cathode PII=0.8 (mild) placebo anode with or without [redacted] PII=2.3 (moderate) and 1.8 (mild) respectively cathode PII=1.0 (mild)

a) Different formulations are presented on the following page.

b) PII = Primary Irritation Index (0-8); PSI = Primary Skin Irritation (Irritation Scale: 0-0.5 negligible; 0.6-2.0 mild; 2.1-5.0 moderate; 5.1-8.0 severe).

Summary of E-TRANS Dermal Toxicity Study contd:

Study Number/Type	Species/ Strain	Group Size/Sex	Treatment	Formulation[a)]	Duration	Finding/Irritation[b)]	Ref.
TR-92-1561-023 Subchronic irritation of fentanyl-containing systems	IAF/HA-HO Guinea Pig	10 males	Current density 0.1 mA/cm^2; estimated drug release 110 µg/cm^2/h; estimated dose 1.21 mg/kg/8 h	Cathode: C2 Anode: A2	14 days; fourteen 8 h exposures	anode CII=1.9 (mild) cathode CII=0.6 (mild)	H 6
TR-92-9999-014 Visual and histologic evaluation of skin after single and multiple applications of placebo systems	IAF/HA-HO Guinea Pig	35 males	Current density 100µA/cm² no drug delivered	Cathode: C1 Anode: A1	6 hours 24 hours 7 days	Irritation increased from mild (1.7) to moderate (3.6) with increased duration from 1-7 days	H 7
TR-92-1561-022 Sensitisation study of fentanyl-containing systems	IAF/HA-HO Guinea Pig	55 males 1 female	Current density 0.1 mA/cm^2; estimated induction dose 110 µg/cm^2/h	Cathode: C2 Anode: A2	9 induction applications over 3 weeks; 8 hours per induction	anode CII = 2.1 (moderate) mild to moderate sensitizer; irritation contributed to responses	H 8
TR-97-1561-011 Sensitisation study of non fentanyl-containing systems	(Ibm:GOHI-hr) Guinea Pig	35 females	Current density 0.07 mA/cm^2	Cathode: C3 Anode: A5, A6	9 induction applications over 3 weeks; 13 hours activated and 3 hours passive	anode (histidine + polacrilin) CII = 2.7 (moderate) mild sensitizer	H 9

a) Different formulations are presented on the following page.

b) PII = Primary Irritation Index (0-8); PSI = Primary Skin Irritation (Irritation Scale: 0-0.5 negligible; 0.6-2.0 mild; 2.1-5.0 moderate; 5.1-8.0 severe); CII = Cumulative Irritation Indexes.

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/ § 552(b)(4) Trade Secret / Confidential

_ § 552(b)(5) Deliberative Process

_ § 552(b)(4) Draft Labeling

Summary of E-TRANS Delayed Contact Hypersensitivity Studies in Guinea pigs-Study Design continued:

Study Number	Test Article/ Route of administration for Induction/Challenge 1/Challenge 2	Induction	Challenge 1	Challenge 2	F
TR-92-1561-022	E-TRANS™ (fentanyl HCl)/ Topical/Topical/Topical	E-TRANS™ (placebo)	E-TRANS™ (fentanyl HCl)	E-TRANS™ (fentanyl HCl)	F
		E-TRANS™ (fentanyl HCl)	E-TRANS™ (fentanyl HCl)	E-TRANS™ (fentanyl HCl)	
		E-TRANS™ (fentanyl HCl) without current	E-TRANS™ (fentanyl HCl)	E-TRANS™ (fentanyl HCl)	
		DNCB	DNCB	DNCB	
TR-97-1561-011	E-TRANS™ (placebo)/ Topical/Topical/NA	E-TRANS™ (placebo) without polacrilin	E-TRANS™ (placebo) with and without polacrilin	NA	F
		E-TRANS™ (placebo) with polacrilin	E-TRANS™ (placebo) with and without polacrilin	NA	
		E-TRANS™ (tetracaine)	E-TRANS™ (tetracaine)	NA	
TR-96-1561-017	Cetylpyridinium chloride (CPC)/ Intradermal/Intradermal/Topical	1% CPC in FCA	0.005% CPC, 0.01% CPC, water	0.1% CPC, water	F
		water in FCA	0.005% CPC, 0.01% CPC, water	0.1% CPC, water	
		0.05% DNCB	0.05% DNCB	0.05% DNCB	

NA = not applicable.

Summary of E-TRANS Summary of ETRANS Delayed Contact Hypersensitivity Studies in Guinea pigs-Study Design contd:

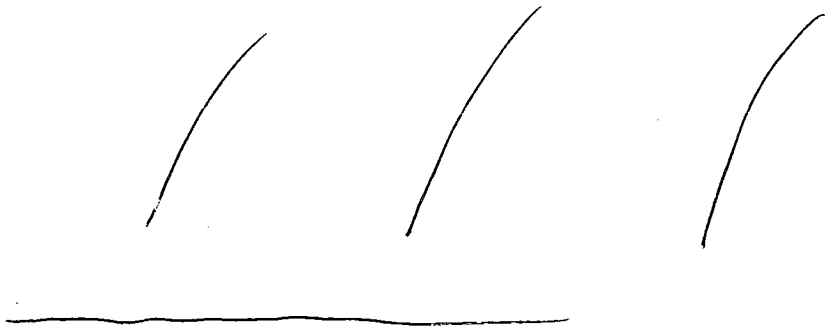
Study Number	Test Article/Route of administration for Induction/ Challenge 1/Challenge 2	Induction	Challenge 1	Challenge 2	Ref.
TR-96-1561-016	Polacrilin resin (buffer) aqueous extract (4g resin:20ml saline)/ Intradermal/ Intradermal/Topical	polacrilin extract in FCA	0% (vehicle), 25%, 50%, 100% extract	0%, 100% (undiluted) extract	H 11
		water in FCA	0% (vehicle), 25%, 50%, 100% extract	0%, 100% (undiluted) extract	
		0.05% DNCB	0.05% DNCB	0.05% DNCB	
TR-96-1561-048	Polacrilin resin aqueous extract (4g resin:20ml saline) Intradermal/Intradermal/ Intradermal	water in FCA	0.1% extract, 1% extract, saline	1% and 50% extract, saline	H 12
		saline	0.1% extract, 1% extract, saline	1% and 50% extract, saline	
		2% extract in FCA	0.1% extract, 1% extract, saline	1% and 50% extract, saline	
		1% extract in saline	0.1% extract, 1% extract, saline	1% and 50% extract, saline	
TR-96-1563-012	Polyisobutylene adhesive extracts/ Intradermal/ Intradermal/Topical	adhesive extract in FCA	adhesive extract, vehicle	adhesive —	H 13
		adhesive extract	adhesive extract, vehicle	adhesive —	
		vehicle (1:20 alcohol in saline) in FCA	adhesive extract, vehicle	adhesive —	
		0.05% DNCB	0.05% DNCB		

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The pharmacology and toxicology of the E-TRANS fentanyl system has been well characterized. The main toxicological finding, other than expected opioid effects, include mild to moderate skin irritation with one minor component demonstrating the potential to induce sensitization following exposures in excess of what would be obtained from proper use of the E-TRANS fentanyl system. Further qualification of impurities, however, will be required prior to approval.

Unresolved toxicology issues (if any): The sponsor should either reduce the specifications for the following impurities in the drug substance to NMT —, or provide adequate qualification for their safety:

—



contain and are structural alerts for mutagenicity. Therefore provide a limit of NMT each for these impurities in the drug substance. Alternatively support the proposed levels by demonstration that these anilino- compounds are human metabolites, or by two genotoxicology studies; one in vitro mutation assay such as Ames bacterial mutagenicity assay and the other an in vitro cytogenetic assay. Studies should achieve the limit doses for these assays with the isolated impurities. If the impurities are mutagenic, provide a limit of or provide an assessment of carcinogenic potential in a standard 2-year model or an appropriate alternative model. Consultation with the Agency in the design of these studies is encouraged.

Recommendations: From the pharmacology toxicology perspective, NDA 21-338 (E-TRANS fentanyl system should be considered approvable, upon adequate qualification of several impurities via 14-day repeat dose toxicology studies and a minimal genetic toxicology screen, as described in ICHQ3A and ICHQ3BR. Alternately, the stability specifications should be reduced to NMT

Suggested labeling:

Based upon three additional reproductive toxicology studies submitted to this NDA, the following labeling recommendations are proposed (recommended deletions are in blue and recommended additions are in red text):

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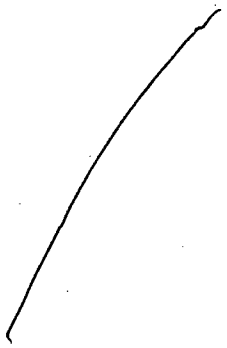
_ § 552(b)(4) Trade Secret / Confidential

_ § 552(b)(5) Deliberative Process

_ § 552(b)(4) Draft Labeling



Signatures (optional):

Reviewer Signature Mamata De, Ph.D.

Supervisor Signature R. Daniel Mellon, Ph.D. Concurrence Yes X No

APPENDIX/ATTACHMENTS

REFERENCES

References:

A 1 A comparison of the acute intravenous toxicity of the narcotic analgesic fentanyl (R4263) and its potential impurity R4380 in male mice. A. The toxicity of fentanyl (R4263). Janssen Research Foundation, November 1993. Toxicological Research Report, Experiment No. 3107.

A 2 A comparison of the acute intravenous toxicity of the narcotic analgesic fentanyl (R4263) and its potential impurity in male rats. A. The toxicity of fentanyl (R4263). Janssen Research Foundation, November 1993: Toxicological Research Report, Experiment No. 3105.

A 3 Gardocki JF, Yeinosky J. A study of some of the pharmacologic actions of fentanyl citrate. Toxicology and Applied Pharm6cology 6 (1): 48-62 (January 1964).

A 4 The pharmacology of R4263 (Phentanyl), a potent, short acting analgesic agent for IV use in anesthesiology. (January 1962).

A 5 The acute oral toxicity of McN-JR-4263-49 in rats and mice. McNeil Laboratories, Inc., Toxicological Research Report No. 127 (650927).

A 6 The acute intramuscular toxicity of McN-JR-4263-49 in guinea pigs, hamsters, rats and dogs. McNeil Laboratories, Inc., Toxicological Research Report No. 124 (650922).

A 7 — Acute toxicity of McN-JR-4263-49 administered intragastrically to newborn rat pups. McNeil laboratories, Inc., Toxicological Research Report No. 104 (650719).
A 8 — Acute intravenous toxicity of McN-JR-4263-49 in dogs. McNeil Laboratories, Inc., Toxicological Research Report N. 110 (650803).
A 9 — . Acute toxicity of INNOVAR in dogs and rats. McNeil Laboratories, Inc., Toxicological Research Report No. 54 (640415).
A10 — ummary of toxicological data on SUBLIMAZEO, fentanyl (McN-JR-4263-49, R-4263, and Phentanyl). McNeil Laboratory, Inc., Toxicological Research Report No. 139 (651124).
A11 — . The effect of McN-JR-4263-49 administered intra-arterially to dogs. McNeil Laboratories, Inc., Toxicological Research Report No. 143 (651029).
A12 — .. R005240. Dose-range-finding study in SPF Wistar rats. Janssen Research Foundation, August 1996; Toxicological Research Report, Experiment No. 3777.
A 13 — . R004263. Evaluation of the subchronic toxicity potential in SPF Wistar rats. Janssen Research Foundation, July 1997; Toxicological Research Report, Experiment No. 3831.
A 14 — Safety evaluation of McN-JR-4263-49 given intravenously to rats for thirty days. McNeil Laboratories, Inc., Toxicological Research Report No.126 (650922).
A 15 — . Toxicity study of McN-JR-4263 in rats and dogs. McNeil Laboratories, Inc., Toxicological Research Report No. 9 (630529).
A 16 — Safety evaluation of McN-JR-4263 administered intravenously to dogs for thirty days. McNeil Laboratories, Inc., Toxicological Research Report No. 108 (650802).
B 1 — .RO04263. Male fertility in SPF Wistar rats. (Segment 1). Janssen Research Foundation, October 1997; Toxicological research Report, Experiment No 3899.
B 2 — R004263. Intravenous female fertility and developmental toxicity study in the Wistar rat. Janssen Research Foundation, November 1997; Toxicological Research Report No. 3972.
B 3 Fujinaga M, et al. Reproductive and teratogenic effects of fentanyl in Sprague-Dawley rats. Teratology 34: 51-7 (1986)
C 1 — . R004263. 3-day repeated dose intravenous toxicity in the rabbit. Janssen Research Foundation, March 1998; Toxicological Research Report No. 4159.
C 2 — R004263. Intravenous developmental toxicity study in the rabbit. Janssen Research Foundation March 1998; Toxicological Research Report No. 4397.
C 3 — . R004263. Intravenous pre-and postnatal developmental toxicity in the Wistar rat. Janssen research Foundation, March 1998; Toxicological Research Report No. 4055.
C 4 — .. Teratologic study of intravenous McN-JR-4263-49 in inbred rats. McNeil Laboratories, Inc., Toxicological Research Report No. III (650812) Revised (680611).
C 5 Mazze RI, et al. Reproductive and teratogenic effects of nitrous oxide, fentanyl and their combination in Sprague-Dawley rats. British Journal Anaesthesia. 59: 1291-7 (1987).
C 6 — Teratological data in rats receiving R4263 subcutaneously. Janssen Pharmaceutica: Toxicological Research Report on fentanyl (R4263), No. 45 (651020).
C 7 — Teratological data in rats receiving R4263 subcutaneously. Janssen Pharmaceutica; Toxicological Research Report on fentanyl (R4263), No. 44 (651020).
C 8 Bruce DL, et al. Fentanyl does not inhibit fertilization or early development of sea urchin eggs. Anesthesia and Analgesia 64: 498-500 (1985).
C9 Letter to the editor: Fentanyl and fertilization. Anesthesia and Analgesia 65: 103 (1986).

D 1 — al. R004263. Salmonella typhimurium gene reverse mutation test (Ames test). Janssen Research Foundation, February 1991; Toxicological Research Report No. 2345.
D 2 — . R004263. Salmonella typhimurium gene reverse mutation assay Janssen Research Foundation. July 1997; Toxicological Research Report No. 3942
D 3 — In vitro microbiological mutagenicity assays with fentanyl for ALZA Corporation. ALZA Final Report TR-85-1772-068 — Report No. LSC-I 499-1), January 1986.

D 4 [redacted]. Mouse lymphoma cell mutagenesis assay (TK+/--@TK-/-) with fentanyl for ALZA Corporation. ALZA Final Report TR-85-1772-067 [redacted]Report No. LSC-1 499-3), April 1986.
D 5 [redacted]. Evaluation of the mutagenic activity of fentanyl in an in vitro mammalian cell gene mutation test with L5178Y mouse lymphoma cells (with independent repeat). [redacted] Final Report 073823, August 1992.
D 6 [redacted]. R004263. Micronucleus test in mice. Janssen Research Foundation, April 1991; Toxicological Research Report No. 2338.
D 7 [redacted]. In vitro chromosomal aberration assay on fentanyl.ALZA Final Report TR-87-1772-015 ([redacted]Reference 55789-01) [redacted]), September 1987.
D 8 Wagner M. The effects of some commonly used piperidine derivates on human chromosomes in vitro. Arzneimiftel.-Forschung. 21 (7): 1017-24 (1971).
D 9 [redacted] Evaluation of 80285 in the Balb/c-3T3 in vitro cell transformation assay in the absence and presence of S9 metabolic activation. ALZA Final Report TR-86-1772-014 [redacted]), October 1986.
D 10 [redacted] In vitro hepatocyte DNA repair assay with fentanyl for ALZA Corporation. ALZAFinalReportTR-85-1772-066([redacted]eportNo.LSC-1393-2),April 1986.
F1 [redacted] Pharmacokinetics of fentanyl. Proceedings of a workshop on transdermal fentanyl, [redacted]. In: Transdermal fentanyl, a new approach to prolonged pain control. [redacted]
F 2 [redacted] Transdermal permeation: physiological and physicochemical aspects. Proceedings of a workshop on transdermal fentanyl, [redacted] In: Transdermal fentanyl, a new approach to prolonged pain control [redacted]
F 3 Lehmann KA, Zech D. Transdermal fentanyl: Clinical pharmacology. Journal of Pain and Symptom Management 7 (3) (suppl.): S8-S1 6 (1992).
F 4 Scholz J, et al. Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil. An update. Clinical Pharmacokinetics 31 (4): 275-92 (1996).
F 5 Fentanyl. In: Drug discovery: A casebook and analysis, Ed. RA Maxwell and SB Eckhardt, Human Press, Clifton, New Jersey, USA: 307-18 (1990).
F 6 Moldenhauer CC, Hug CC. Use of narcotic analgesics as anaesthetics. Clinics in Anaesthesiology 2 (1): 107-38 (1984).
F 7 Andrews CJH, Prys-Roberts C. Fentanyl - A review. Clinics in Anaesthesiology 1 (1): 97-122 (1983).
F 8 Meert TF. Pharmacotherapy of opioids: present and future developments. Pharmacy N114314 World & Science 18 (1): 1-15 (1996).
F 9. Willens JS, Myslinski NR. Pharmacodynamics, pharmacokinetics, and clinical uses of fentanyl, sufentanil, and alfentanil. Heart & Lung 22 (3): 239-51 (1993).
F 10 Soudijn W. The pharmacology and the pharmacokinetics of fentanyl. In: Stress-free anaesthesia. Royal society of medicine international congress and symposium series No-3, Ed. Wood C., The royal society of medicine and academic press: 3-10 (1978).
F 11 [redacted]. Nonclinical expert report on the toxicological, pharmacodynamic and pharmacokinetic documentation related to fentanyl TTS. Janssen Research Foundation, October 1992; Expert Report on [redacted]
F 12 Hermans B, et al. Interaction of peptides and morphine-like narcotic analgesics with specifically labelled mu- and delta-opiate receptor binding sites. Archives Internationales de Pharmacodynamie et de Therapie 263: 317-9 (1983).
F 13 Leysen JE, et al. (3H) Sufentanil, a superior ligand for mu-opiate receptors: binding properties and regional distribution in rat brain and spinal cord. European Journal of Pharmacology 87: 209-25 (1983).
F 14 Maguire P, et al. Pharmacological profiles of fentanyl analogs at mu, delta and kappa opiate receptors. European Journal of Pharmacology 213: 219-25 (1992).
F.15 Thysman S, Preat V. In vivo iontophoresis of fentanyl and sufentanil in rats: pharmacokinetics and acute antinociceptive effects. Anesthesia and Analgesia 77: 61-6 (1993).
F 16 Roy SD, Flynn GL: Transdermal delivery of narcotic analgesics: pH, anatomical, and subject influences on cutaneous permeability of fentanyl and sufentanil. Pharmaceutical Research 7 (8): 842-7 (1990).

F 17 Gardocki JF, Yelnosky J. A study of some of the pharmacologic actions of fentanyl citrate. Toxicology and Applied Pharmacology 6: 48-62 (1964).
F 18 McNeil Laboratories. Injection letter to Dr. Kelsey. McN-JR-4263 (1963 letter) August 23, 1963.
F 19 Niemegeers C.J.E., et al. Sufentanil, a very potent and extremely safe intravenous morphine-like compound in mice, rats and dogs. Arzneimittel-Forschung (Drug Res.) 26 (8): 1551-6 (1976)
F 20 De Castro J, et al. Comparative study of cardiovascular, neurological and metabolic side-effects of eight narcotics in dogs. Acta Anaesthesiologica Beigica 30: 5-99 (1979).
F 21 Bushnell TG, Justins DM. Choosing the right analgesic. A guide to selection. Drugs 46 (3): 394-408 (1993).
F 22 Niemegeers CJE. 13. Pharmacology of antidiarrheal agents in vivo. Clinical Research Reviews 1 (Suppl. 1): 125-39 (1981).
F 23 Megens AAHP, et al. Comparison of the analgesic and intestinal effects of fentanyl and morphine in rats. Journal of Pain and Symptom Management 15 (4): 253-7 (1998).
F 24 Tammisto T, et al. A comparison of the circulatory effects in man of the analgesic fentanyl, pentazoeine and pethidine. British Journal of Anaesthesia 42: 317-24 (1970).
F 25 Graves CL, et al. Cardiovascular effects of minimal analgesic quantities of innovar, fentanyl, and droperidol in man. Anesthesia and Analgesia 54 (1): 15-23 (1975).
F 26 Hill HF, et al. Steady-state infusions of opioids in human: II. Concentration-effect relationships and therapeutic margins. Pain 43: 69-79 (1990).
F 27 Prys-Roberts C, Kelman GR. The influence of drugs used in neuroleptanalgesia on cardiovascular and ventilatory function. British Journal of Anaesthesia 39: 134-45 (1967).
F 28 Cartwright P, et al. Ventilatory depression related to plasma fentanyl concentrations during and after anesthesia in humans. Anesthesia and Analgesia 62: 966-74 (1983).
F 29 Janssen Research Foundation. TTS-fentanyl. Investigator's Brochure, Third Edition, October 1995.
F 30 Stephen GW, Cooper LV. The role of analgesics in respiratory depression: a rabbit model. Anaesthesia 32: 324-7 (1977).
F 31 Brown JH, et al. Respiratory effects of a new opiate analgesic, R39209, in the rabbit: comparison with fentanyl. British Journal of Anaesthesia 52: 1101-6 (1980).
F 32 Jeal W, Benfield P. Transdermal fentanyl. A review of its pharmacological properties and therapeutic efficacy in pain control. Drugs 53 (1): 109-38 (1997).
F 33 Van den Hoogen RHWM, et al. Respiratory effects of epidural and subcutaneous morphine, meperidine, fentanyl and sufentanil in the rat. Anesthesia and Analgesia 67: 1071-8 (1988).
F 34 . Expert report on the preclinical (pharmacological, pharmacokinetic, toxicological) documentation on epidural sufentanil. Janssen Research Foundation, November 1989; Preclinical Expert Report No. 30 (R33800).
F 35 Meert TF, et al. Pharmacological validation of ritanserin and risperidone in the drug discrimination test procedure in the rat. Drug Development Research 19: 353-73 (1990).
F 36 . Abuse potential of alfentanil and sufentanil: preclinical evaluation using the fentanyl drug discrimination test procedure in the rat. Janssen Research Foundation, December 1988; Preclinical Research Report No. 42 (R39209) and No. 28 (R33800).
F 37 Negus SS, et al. Interactions between the discriminative stimulus effects of mu and kappa opioid agonists in the squirrel monkey. The Journal of Pharmacology and Experimental Therapeutics 256 (1): 149-158 (1990).
F 38 McNeil Laboratories. Pharmacologist review of NDA 16-619. (1967b letter) July 19, 1967.
F 39 De Kock M, Meert TF. Can alpha2-adrenoceptor agonists reverse or prevent tolerance to the antinociceptive activity of opioids in rats? Acta Anaesthesiologica Beigica 46 (3-4): 141-52 (1995).
F 40 Colpaert FC, et al. The effects of prior fentanyl administration and of pain on fentanyl analgesia: tolerance to and enhancement of narcotic analgesia. The Journal of Pharmacology and Experimental Therapeutics 213 (2): 418-24 (1980).
F 41 Schneider E, Brune K. Opioid activity and distribution of fentanyl metabolites. Naunyn-Schmiedeberg's Archives of Pharmacology 334: 267-74 (1986).
F 42 Lehmann KA, et al. Biotransformation von Fentanyl III. Einfluesse chronischer N30913 Arzneimittelexposition auf Verteilung, Metabolismus und Ausscheidung bei der Ratte. Der Anaesthesist 32: 165-73 (1983).

F43 Meert TF, DeKock M. Interactions between the lipophilic opioid sufentanil and clonidine in N I 26209 rats after spinal application, Acta Anasthesiologica Scandinavica 39:527-34 (1995)
F 44 Verborgh C, et al. Effects of chlordiazepoxide on opioid-induced antinociception and respiratory depression in restrained rats. Pharmacology Biochemistry and Behavior 59 (3): 663-70 (1998).
F 45 Meert TF, De Kock M. Interactions between the lipophilic opioid sufentanil and clonidine in rats after spinal application. Acta Anaesthesiologica Scandinavica 39: 527-34 (1995).
F 46 Vereauteren M, et al. Spinal sufentanil in rats: Part II: Effect of adding bupivacaine to epidural sufentanil. Acta Anaesthesiologica Scandinavica 36: 245-9 (1992).
GI — non-clinical pharmacokinetics. Review of literature available March 1998. Janssen Research Foundation, September 1998; Non-clinical Pharmacokineties Report R004263/FK2963.
G 2 Michiels M, et al. A sensitive radioimmunoassay for fentanyl. Plasma level in dogs and man. European Journal of Clinical Pharmacology 12: 153-8 (1977).
G 3 Woestenborghs RJH, et al. Assay methods for fentanyl in serum: gas-liquid chromatography versus radioimmunoassay. Anesthesiology 67: 85-90 (1987).
G 4 Jadoul A, et al. Quantification and localization of fentanyl and TRH delivered by iontophoresis in the skin. International Journal of Pharmacology 120: 221-8 (1995).
G 5 Thysman S, et al. Transdermal iontophoresis of fentanyl: delivery and mechanistic analysis. International Journal of Pharmacology 101: 105-13 (1994).
G 6 Vanbever R, et al. Transdermal delivery of fentanyl by electroporation. I. Influence of electrical factors. Pharmaceutical Research 13: 559-65 (1996).
G 7 Vanbever R, et al. Transdermal delivery of fentanyl by electroporation. II. Mechanisms involved in drug transport. Pharmaceutical Research 13: 1360-6 (1996).
G 8 Thysman S, Pr6at V: In vivo iontophoresis of fentanyl and sufentanil in rats: pharmacokinetics and acute antinociceptive effects. Anesthesia and Analgesia 77: 61-6 (1993).
G 9 Vanbever R, et al. Transdermal delivery of fentanyl: rapid onset of analgesia using skin electroporation. Journal of Controlled Release 50: 225-35 (1998).
GIO — An in vitro study on the interaction of ketamine, meperidine, midazolam andprometnazine with the metabolism of fentanyl in human liver microsomes. Janssen Research Foundation, March 1998; Non-Clinical Pharmacokinetics Report R004263/FK16968.
G 11 — The in-vitro metabolism of fentanyl in human hepatocytes. Janssen Research Foundation, March 1998; Non-Clinical Pharmacokinetics Report R004263/FKI 698.
G 12 — . An in-vitro study on the metabolism of fentanyl in human liver microsomes and on the interaction potential of fentanyl towards possible co-medication. Janssen Research Foundation, June 1995; Non-Clinical Pharrnacokinetics Report R004263/FK1872.
G 13 — In-vitro determination of the drug-drug interaction potential of fentanyl in human liver microsomes: effects of possible co-medication on the metabolism of fentanyl. Janssen Research Foundation, March 1998; Non-Clinical Pharmacokinetics Report R004263/FK2428.
G 14 Palkama VJ, et al. The effect of oral itraconazole on the pharmacokinetics and pharmacodynamics of intravenous fentanyl in healthy volunteers. January 1998. Manuscript submitted for publication. Presented in part (abstract) at the Annual Meeting of the American Society of Anesthesiologists, San Diego, CA, October 18-22, 1997.
G 15 — Toxicokinetics of fentanyl in a single-dose Dose Range Finding toxicity study (Exp. No. 3777) in female SPF Wistar rats after single intravenous administration of fentanyl citrate (ROO5240) by 24-hour infusion at 0.01, 0.02, 0.05, 0.1, 0.2, 0.5, 1 and 2 mg fentanyl/kg and a 5-day (120 h) infusion at 0.025 and 0.4 mg/kg/day. Janssen Research Foundation, March 1998; Non-clinical Pharmacokinetics Report R004263/FK2145, Addendum to the Toxicity Report Exp. No. 3777.Preclinical Summary on E-TRANSTM (fentanyl HCL)
G 16 — Toxicokinetics of fentanyl (ROO4263) in the SPF Wistar rat in a 5-week continuous infusion toxicity study (Exp. No. 3831) of fentanyl at 0.025, 0.1 and 0.4 mg/kg/day, followed by a 4-week recovery period. Janssen Research Foundation, April 1997; Non-clinical Pharmacokinetics Report R004263/FK2224 Addendum' to the Toxicity Report Exp. No. 3831.
G 17 — . Toxicokinetics of fentanyl in a combined intravenous segment I and II reproduction study on the effects on fertility and embryo-foetal development of aqueous solutions of fentanyl at 0.025, 0.1 and 0.4 mg/kg/day, given as a continuous infusion, to the SPF Wistar rat (Exp. No. 3972). Janssen

Research Foundation, March 1998; Non- clinical Pharmacokinetics Report R004263/FK2362, Addendum to the Toxicity Report Exp. No. 3972.

G 18 — Toxicokinetics of fentanyl in pregnant SPF albino rabbits in a 3-day intravenous Dose Range Finding toxicity study (Exp. No. 4159) on aqueous solutions of fentanyl at 0.2, 0.4, 0.8 and 1.6 mg/kg, given as a daily 4-hour infusion. Janssen Research Foundation, March 1998; Non-clinical Pharmacokinetics Report R004263/FK2467, Addendum to the Toxicity Report Exp. No. 4159.

G 19 — Toxicokinetics of fentanyl in an intravenous segment II study on the effects of aqueous solutions of fentanyl at 0.025, 0.1 and 0.4 mg/kg/day, given as a daily 4-hour infusion, on the embryo-foetal development in the albino rabbit (Exp. No. 4397). Janssen Research Foundation, March 1998; Non-clinical Pharmacokinetics Report R004263/FK2686, Addendum to the Toxicity Report Exp. No. 4397

G 20 — The pharmacokinetics of frequent and infrequent fentanyl bolus doses in healthy volunteers ALZA Corporation Final Report, March 1993; Protocol C-92-029-01 (FEN-USA-14).

G 21 — Effects of formulation variables on the pharmacokinetics of fentanyl delivered from two new ETS (fentanyl) formulations. ALZA Corporation Final Report, April 1995; Protocol C-94-055-05 (FEN-USA-31).

G 22 — (Fentanyl) pilot efficacy and safety study in the treatment of postoperative pain. ALZA Corporation Final Report, January 1996; Protocol C-93-023-00 (FEN-INT-2).

H 1 — Primary skin irritation study of E-TRANSTH systems with anode hydrogels containing fentanyl on rabbits, ALZA Study No. TR-96-1561-052, November 1996.

H 2 — A Primary Skin Irritation Study of E-TRANSTM (placebo) systems containing Cetylpyridinium chloride (CPC) and — and — Adhesives on Hairless Guinea Pigs and Rabbits. ALZA Study No. TR-98-1561-031, December 1998.

H 3 — . Primary skin irritation study of E-TRANSTM (fentanyl) in guinea pigs, ALZA Study No. TR-92-1561-021, January 1993.

H 4 — Primary skin irritation study of electrotransport therapeutic systems containing fentanyl in rabbits, ALZA Study No. TR-92-1561-053, December 1992.

H 5 — rimary skin irritation study of electrotransport therapeutic systems placebo anode hydrogels in the hairless guinea pig, ALZA Study No. TR-93-1561-048, December 1993.

H 6 — Fourteen-day subchronic skin irritation study in guinea pigs of electrotransport [ET] fentanyl, ALZA Study No. TR-92-1561-023, January 1993.

H 7 — Visual (macroscopic) and histological evaluation of guinea pig skin sites following single and multiple applications of electrotransport therapeutic systems, ALZA Study No. TR-92-9999-014, December 1992.

H 8 — . Experimental sensitisation evaluation of fentanyl using electrotransport therapeutic systems in the hairless guinea pig, ALZA Study No. TR-92-1561-022, October 1992.

H 9 — Evaluation of the sensitization potential of electrotransport systems containing placebo anode hydrogels (histidine and polacrilin —, in the hairless guinea pig, ALZA Study No. TR-97-1561-011, May 1998

H 10 — . Evaluation of cetypyridinium chloride for delayed contact hypersensitivity in guinea pigs, ALZA Study No. TR-96-1561-017, January 1997

H 11 — . Evaluation of Polacrilin Resin —) Extract for Delayed Contact Hypersensitivity in guinea pigs, ALZA Study No. TR-96-1561-016, October 1997.

H 12 — Evaluation of polacrilin resin) extract dilutions for delayed contact hypersensitivity in guinea pigs, ALZA Study No. TR-96-1561-048, October 1997.

H 13 Quigley P. Evaluation of film, — . polyisobutylene — adhesive (code no. —, —) extract for delayed contact hypersensitivity in guinea pigs, ALZA Study No. TR-96-1563-012, January 1997.

H 14 Bagdadi D. USP XXII: Biological testing of — ALZA Study No. TR-90-1550-018, April 1991.

H 15 Johnson P. USP XXII: Biological testing of — ALZA Study No. TR-94-1561-017, June 1994.

H 16 [redacted] In Vivo Biocompatibility Testing of Housing, Top, E- TRANS™ (acute) [redacted] ALZA Study No. TR-99- 1561-057, February 2000

H17 [redacted] In Vivo Biocompatibility Testing of Housing, Top, E- TRANS™ (acute) [redacted] code number [redacted], ALZA Study No. TR-99- 1561-056, February 2000

H 1[redacted] USP 23: Biological testing of Housing, Bottom [redacted], red, E-TRANS™ (acute), code number [redacted] ALZA Study No. TR-97-1561-009, April 1998.

H 19 [redacted] USP 23: Biological testing of Housing, Bottom [redacted], E-TRANS™ (acute), code number [redacted], ALZA Study No. TR-97-1561-010, April 1998

H 20 USP XXII: Biological testing of [redacted] ALZA Study No. TR-94-1561-020, December 1996.

H 21 [redacted] 3: Biological testing of [redacted] [redacted] ALZA Study No. TR-96-1561-044, May 1998.

H 22 [redacted] USP 23: Biological testing of film, [redacted] PIB adhesive, code no. [redacted] ALZA Study No. TR-96-1561 -01 1, January 1997.

H 23 [redacted] LISP XXII: Biological testing of [redacted], ALZA Study No. TR-93-2420-068, December 1994.

H 24 [redacted] USP XXII: Biological testing of Lower Housing, acute system, code [redacted] ALZA Study No. TR-93-8888-059, April 1994.

H25 [redacted] LISP 23: Biological testing of Lower Housing, acute system, code number [redacted], ALZA Study No. TR-95-1561-031, December 1996.

H 26 In vitro biological testing of [redacted] Lot No. T790, Part No [redacted] LISP Elution and MTT Assay. ALZA Study No. TR-98-1561-023, January 1999.

Q 1 [redacted] studies on intramuscular injections of McN-JR-4263 in rabbits. McNeil Laboratories, Inc., Toxicological Research Report No. 18 (630725).

[redacted] Colorimetric assay for cytotoxicity of fentanyl. ALZA Final Report TR-86- 1772-023 [redacted], September 1986

Q 3 [redacted] A comparison of the acute intravenous toxicity of the narcotic analgesic fentanyl (R4263) and its potential impurity [redacted] in male mice. B. The toxicity of [redacted] Janssen Research Foundation, November 1993; Toxicological Research Report, Experiment No. 3108.

Q 4 [redacted] A comparison of the acute intravenous toxicity of the narcotic analgesic fentanyl (R4263) and its potential impurity [redacted] in male rats. B. The toxicity of [redacted] Janssen Research Foundation, November 1993; Toxicological Research Report, Experiment No. 3106.

L 1 Kurilenko VM, et al. Synthesis and analgesic of piperidine and decahydroquinoline derivatives. Pharmaceutical Chemical Journal 10: 1193-6 (1976).

L 2 Bianchi C, Franceschini J. Experimental observations on Haffner's method for testing analgesic drugs. British Journal of Pharmacology 9: 280-4 (1954).

L 3 Jennett S. Assessment of respiratory effects of analgesic drugs. British Journal of Anaesthesia 40: 746-56 (1968).

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I concur