DETERMINATION OF SERUM FENTANYL LEVELS AFTER USING REFERENCE AND GENERIC TRANSDERMAL FENTANYL PATCHES WITH AND WITHOUT STANDARDIZED HEAT APPLICATION IN HEALTHY HUMAN VOLUNTEERS

Short title: The Effect of Heat on Fentanyl Release from Fentanyl Patches in Healthy Adults

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STATEMENT OF COMPLIANCE

This study will be conducted in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice E6 (ICH-GCP) and the applicable Food and Drug Administration and other Department of Health and Human Services regulatory requirements.

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

PROTOCOL SUMMARY

Title:	Determination of Serum Fentanyl Levels after using Reference and Generic Transdermal Fentanyl Patches with and without Standardized Heat Application in Healthy Human Volunteers
Population:	Healthy adults age 18 – 45 years
Number of Sites:	Single site: University of Maryland School of Medicine
Study Duration:	Approximately 18 weeks including the screening period
Subject Participation Duration:	Approximately 12 weeks including the screening period
Description of Study Product:	Fentanyl (Duragesic®, matrix type, Janssen Pharmaceutics; Mylan (fentanyl) matrix type, Mylan Pharmaceuticals and Apotex (fentanyl) matrix type, Apotex Corp.) transdermal patches, and naltrexone hydrochloride tablet and naloxone hydrochloride injections
Objective:	To determine serum fentanyl levels after using reference (Duragesic®) and generic fentanyl (Mylan and Apotex) transdermal patches with and without standardized heat application in healthy adult volunteers
Description of Study Design:	The study will be an open-label, study with six procedure days (n=10 healthy subjects completing all 6 procedure days) with at least two weeks between each procedure day and the subsequent one. Each of the 10 subjects will be enrolled to complete all six procedure days. For each of the fentanyl products (n=3) there will be two procedure days, and on all procedure days the patches will be applied for 19 hours. The study will contain six procedure days: • Procedure Day 1: The heating pad will be set to induce a skin temperature of 42.0 ± 2°C and applied for 1 hour, 11 hours after application of the Apotex (fentanyl) transdermal patch (25 µg/h). • Procedure Day 2: The heating pad will be set to induce a

skin temperature of 42.0 ± 2°C and applied for 1 hour, 18 hours after application of the Apotex (fentanyl) transdermal patch (25 µg/h).

- Procedure Day 3: The heating pad will be set to induce a skin temperature of 42.0 ± 2°C and applied for 1 hour, 11 hours after application of the Duragesic® transdermal patch (25 µg/h).
- Procedure Day 4: The heating pad will be set to induce a skin temperature of 42.0 ± 2°C and applied for 1 hour, 18 hours after application of the Duragesic® transdermal patch (25 µg/h).
- Procedure Day 5: The heating pad will be set to induce a skin temperature of 42.0 ± 2°C and applied for 1 hour, 11 hours after application of the Mylan (fentanyl) transdermal patch (25 µg/h).
- Procedure Day 6: The heating pad will be set to induce a skin temperature of 42.0 ± 2°C and applied for 1 hour, 18 hours after application of the Mylan (fentanyl) transdermal patch (25 µg/h).

1 KEY ROLES

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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

There are numerous transdermal drug delivery systems (TDDS) that are currently available in the United States, the first of which was approved by the Food and Drug Administration (FDA) in 1979 [1]. TDDS are very attractive, convenient and easy to use systems and are available in various forms including patches (matrix or reservoir), sprays, gels, and ointments. Drug release from these TDDS varies significantly and is dependent on a number of factors including system design, physicochemical properties of the drug, excipients, occlusion, sweat, skin condition, skin type and temperature. Investigating the influence of these factors on drug release from reference and generic products that are often available in different forms is important to ensure that generic products are not less safe than the reference product. In this proposal we will focus on investigating the influence of heat on drug release from reference and generic products that are available in matrix systems. Systemic absorption of drugs is dependent on cutaneous blood flow. Application of, or exposure to heat, allows gradual increase in cutaneous blood flow and an increase in the absorption rate. Indeed, exposure to heat has been demonstrated to increase drug release from TDDS, which led to increased serum concentrations of numerous drugs (e.g., fentanyl and nicotine) and raised a number of safety concerns [2-8]. As a result, almost all TDDS that are currently available have warnings against heat exposure. The issue is, if a reference product has a warning against applying heat, the generic product will have the same warning regardless of the dissimilarity that may exist between them (i.e., differences in inactive ingredients or type of TDDS), and it is possible that release rate and absorption rate of the same drug differs from different TDDS in response to heat.

2.2 Rationale

The objective of this proposal is to conduct in vivo studies to compare the influence of heat on fentanyl drug release from FDA approved TDDS products (reference e.g. Duragesic®, versus generic products e.g. Apotex and Mylan transdermal patches) that have different inactive ingredients. While there is data in the literature for heat effect on different active pharmaceutical ingredients (API's), specifically reference listed drugs (RLD), from exposure to heating blankets, sauna, hot showers, exercising, there is no head to head comparisons for heat effect on RLD versus generic drugs. This study will help support policy development for characterization of heat effects for future generic applications. Furthermore, if in-vitro in-vivo correlation (IVIVC) can be established, then in vitro studies can be used for generic applications in the future, which would mitigate

exposure of human beings to out of label studies. This approach will help ensure that patients would not be subjected to additional risks if they use a generic TDDS rather than its respective reference product.

Fentanyl was selected for this study because it is a drug with significant and well characterized heat effect studies in the literature, and for which an antidote exists. Fentanyl has the most variability available in terms of generic transdermal systems with different formulations that are approved and already on the market. This study will provide data that could potentially help us determine if one formulation/adhesive is more prone to heat effect/changes in delivery compared to another. Furthermore by demonstrating IVIVC then in vitro studies can be conducted on generic fentanyl transdermal patches in the future without the need to subject human volunteers to additional testing. To mitigate the potential risk of a higher absorption of fentanyl through the skin, the lowest strength patch is being used in this study (25 µg/hr).

Duragesic® versus Apotex (fentanyl) and Mylan (fentanyl) transdermal patches

	Duragesic®	**Apotex (fentanyl) patch**	**Mylan (fentanyl) patch**
Inactive ingredients	Alcohol, ethylene vinyl acetate-copolymer membrane and hydroxyethyl cellulose, polyester film backing, silicone adhesive	Isopropyl myristate, octyldodecanol, polybutene and polyisobutene adhesive	Dimethicone NF, polyolefin film backing, silicon adhesive
TDDS type	Matrix	Matrix	Matrix
Manufacturer	Janssen	Apotex	Mylan

3 OBJECTIVES

3.1 Study Objectives

Rate of drug release and kinetics of drug absorption could vary from patches with different dosage form designs. The influence of heat on reference vs. generic products that are formulated differently impose a critical safety issue for users of generic TDDS. As such, the main objective of this project is to determine serum fentanyl levels after using reference (Duragesic®, matrix type patch, Janssen Pharmaceutics) and generic fentanyl (Apotex and Mylan) transdermal patches with and without standardized heat application in healthy adult volunteers.

3.2 Study Outcome Measures

The main outcome measure of the study is the measurement of maximum serum concentration (Cmax); time of maximum serum concentration (Tmax) of fentanyl and area under the curve (AUC) attained with and without heating in each of the three fentanyl patches (reference and generic).

4 STUDY DESIGN

This is an open-label, non-placebo controlled pharmacokinetic (PK) assessment study. The study will consist of six-procedure days (10 subjects) with at least two weeks between procedure days. The half-life of fentanyl is approximately 24 hours. Hence, 7 days (i.e. 5 half-lives) will be sufficient for >95% of fentanyl to be eliminated from the body. Each of the 10 subjects will be enrolled to complete all six procedure days (Procedure Days 1 to 6). The study is open label and not blinded, because PK assessment is not subject to participant and/or observer bias. After each procedure session (procedure day) is completed, the available safety data will be reviewed by an Independent Safety Monitor (ISM) to determine whether or not to proceed to the next procedure day.

The six procedures days are as follows:

Procedure Day 1: An **Apotex** (fentanyl) patch will be applied without heat for 11 hours, then a theratherm® heating pad will be applied over it (see details in Manual of Procedures) and set to induce a skin temperature of 42.0 ± 2°C for 1 hour then removed, and the patch will be kept on for another 7 hours (patch will be applied for a total of 19 hours), then it will be removed. Each subject will receive a naltrexone hydrochloride 50 mg oral tablet 12 ± 1 hour and shortly prior to patch application and then every 12 ± 1 hour for 8 additional doses, then one dose every 24 ± 2 hours for two more doses. A total of twelve 50 mg oral doses of naltrexone will be administered.

Procedure Day 2: An **Apotex** (fentanyl) patch will be applied without heat for 18 hours, then a theratherm® heating pad will be applied over it and set to induce a skin temperature of 42.0 ± 2°C for 1 hour, then the patch and the heating pad will both be removed (patch will be applied for a total of 19 hours). Each subject will receive a naltrexone hydrochloride 50 mg oral tablet 12 ± 1 hour and shortly prior to patch application and then every 12 ± 1 hour for 8 additional doses, then one dose every 24 ± 2 hours for two more doses. A total of twelve 50 mg oral doses of naltrexone will be administered.

Procedure Day 3: A **Duragesic®** patch will be applied without heat for 11 hours, then a theratherm® heating pad will be applied over it and set to induce a skin temperature of 42.0 ± 2°C for 1 hour then removed, and the patch will be kept on for another 7 hours (patch will be applied for a total of 19 hours), then it will be removed. Each subject will receive a naltrexone hydrochloride 50 mg oral tablet 12 ± 1 hour and shortly prior to patch application and then every 12 ± 1 hour for 8 additional doses, then one dose every 24 ± 2 hours for two more doses. A total of twelve 50 mg oral doses of naltrexone will be administered.

Procedure Day 4: A **Duragesic®** patch will be applied without heat for 18 hours, then a theratherm® heating pad will be applied over it and set to induce a skin temperature of 42.0 ± 2°C for 1 hour, then the patch and the heating pad will both be removed (patch will be applied

for a total of 19 hours Each subject will receive a naltrexone hydrochloride 50 mg oral tablet 12 ± 1 hour and shortly prior to patch application and then every 12 ± 1 hour for 8 additional doses, then one dose every 24 ± 2 hours for two more doses. A total of twelve 50 mg oral doses of naltrexone will be administered.

Procedure Day 5: A **Mylan** (fentanyl) patch will be applied without heat for 11 hours, then a theratherm® heating pad will be applied over it and set to induce a skin temperature of 42.0 ± 2°C for 1 hour then removed, and the patch will be kept on for another 7 hours (patch will be applied for a total of 19 hours), then it will be removed. Each subject will receive a naltrexone hydrochloride 50 mg oral tablet 12 ± 1 hour and shortly prior to patch application and then every 12 ± 1 hour for 8 additional doses, then one dose every 24 ± 2 hours for two more doses. A total of twelve 50 mg oral doses of naltrexone will be administered.

Procedure Day 6: A **Mylan** (fentanyl) patch will be applied without heat for 18 hours, then a theratherm® heating pad will be applied over it and set to induce a skin temperature of 42.0 ± 2°C for 1 hour, then the patch and the heating pad will both be removed (patch will be applied for a total of 19 hours). Each subject will receive a naltrexone hydrochloride 50 mg oral tablet 12 ± 1 hour and shortly prior to patch application and then every 12 ± 1 hour for 8 additional doses, then one dose every 24 ± 2 hours for two more doses. A total of twelve 50 mg oral doses of naltrexone will be administered.

5 STUDY ENROLLMENT AND WITHDRAWAL

Only adult subjects who meet the inclusion/exclusion criteria will be eligible for enrollment into this study. Ten subjects will be recruited, and five alternates who could replace subjects who drop out from the study for any unforeseen reason. The study population selected for this study includes healthy adult men and women ages 18 to 45, inclusive. The selection criteria are designed to exclude persons who might have medical conditions that could pose a safety risk and persons whose medical conditions might interfere with the objectives and results of the study.

Subjects may be recruited from the databases at the Center for Vaccine Development (CVD), by referral from another healthcare professional, and by advertisements local to the study center. Potential subjects who are interested in the study will be informed of the study and if they wish to participate, will receive additional study information, including an informed consent form. Each of the 10 subjects enrolled will be expected to complete the 6 procedure day sessions.

5.1 Subject Inclusion Criteria

Subjects are eligible for this study if they fulfill the inclusion criteria specified below:

1. Men or non-pregnant women of any ethnic background between the age of 18 and 45 years old.
2. Subjects must be non-smokers (must have refrained from the use of nicotine-containing substances, including tobacco products (e.g., cigarettes, cigars, chewing tobacco, gum, patch or electronic cigarettes) over the previous 2 months and are not currently using tobacco products.
3. Provide written informed consent before initiation of any study procedures.
4. Available for follow-up for the planned duration of the study.
5. Able to communicate well with the investigators.
6. Able to adhere to the study protocol schedule.
7. Subjects who are within their ideal body weight (BMI>17 and ≤ 28).
8. Demonstrate comprehension of the protocol procedures and knowledge of study by passing (>70% correct responses) a written examination containing 20 multiple choice and true false questions covering all aspects of the study including the purpose, procedures, risks and benefits.
9. Subjects deemed to be healthy as judged by the Medically Accountable Investigator (MAI) and determined by medical history, physical examination, and medication history.

10. Negative urine drug screening test.
11. Have a normal blood pressure (systolic: 90-140 mmHg; diastolic: 50-90 mmHg) and heart rate (55-100 bpm).
12. Have normal screening laboratories for WBC, Hgb, platelets, sodium, potassium, chloride, bicarbonate, BUN, creatinine, ALT, AST and total bilirubin.
13. Have normal screening laboratories for urine protein and urine glucose.
14. Female subjects must be of non-childbearing potential (as defined as surgically sterile [i.e. history of hysterectomy or tubal ligation] or postmenopausal for more than 1 year), or if of childbearing potential must be non-pregnant at the time of enrollment and on the morning of each procedure, and must agree to use hormonal or barrier birth control such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence, or a vasectomized partner.
15. Agrees not to participate in another clinical study during the study period.
16. Agrees not to donate blood to a blood bank throughout participation in the study and for at least 3 months after last procedure day.
17. Have a normal ECG.

5.2 Subject Exclusion Criteria

Subjects will be excluded for any of the following conditions/reasons:

1. Women who are pregnant, lactating breast feeding or have a positive serum pregnancy test at enrollment or on the morning of any procedure day.
2. Smokers (current use or use over the previous 2 months of nicotine-containing substances, including tobacco products (e.g., cigarettes, cigars, chewing tobacco, gum, patch or electronic cigarettes).
3. Participation in any ongoing investigational drug trial or clinical drug trial.
4. Abnormal Vital signs, defined as:
    - Hypertension (systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg) at rest on 2 separate days)
    - Heart rate <55 at rest on 2 separate days
    - Respiratory rate >20
5. Temperature > 38.0°C (100.4°F) or symptoms of an acute self-limited illness such as an upper respiratory infection or gastroenteritis within 7 days of application of the transdermal fentanyl patch.
6. History of chronic obstructive pulmonary disease.
7. Active positive Hepatitis B, C, and HIV serologies.

8. Positive urine drug screening test.
9. Use of any prescription medication during the period 0 to 30 days or over-the counter medication (vitamin, herbal supplements and birth control medications not included) during the period 0 to 3 days before entry to the study.
10. Donation or loss of greater than one pint of blood within 60 days of entry to the study.
11. Any prior serious adverse reaction or hypersensitivity to fentanyl, naltrexone or naloxone or any of the inactive ingredients in the patch (alcohol, ethylene vinyl acetate-copolymer membrane and hydroxyethyl cellulose, polyester, silicone adhesive, isopropyl myristate, octyldodecanol, polybutene, polyisobutene, dimethicone NF, or polyolefin).
12. Have a diagnosis of schizophrenia or other major psychiatric diagnosis or mental illness (e.g. major depression).
13. Received an experimental agent (vaccine, drug, biologic, device, blood product or medication) within 1 month before enrollment in this study or expects to receive an experimental agent during the study.
14. Any condition that would, in the opinion of the Medically Accountable Investigator (MAI), place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol.
15. Inability to communicate or co-operate with the investigators.
16. History of consumption of alcohol within 24 hours prior to dose administration.
17. Within 72 hours prior to dosing, use of antihistamines or use of topical drugs at patch site.
18. Subject has an obvious difference in skin color between arms or the presence of a skin condition, open sore, scar tissue, tattoo, or coloration that would interfere with placement of test articles, skin assessment, or reactions to drug.
19. Use of monoamine oxidase inhibitors 21 days prior to study.
20. Failure to pass opioid dependence challenge test on each procedure day before application of the fentanyl patch. Each subject will be injected subcutaneously with naloxone HCl (0.8 mg injection) and will be observed for 45 minutes for signs and symptoms of opioid withdrawal.

6 STUDY PRODUCT

6.1 Study Product Description

6.1.1 Apotex (fentanyl) patch 25 µg/hour

Apotex (fentanyl) is a prescription transdermal patch that contains fentanyl which is a federally controlled substance (CII). Apotex (fentanyl) patches deliver fentanyl at a rate of 25 µg/hour and are only for patients with chronic (around the clock) pain that is moderate to severe and expected to last for weeks or longer.

6.1.2 Mylan (fentanyl) patch 25 µg/hour

Mylan (fentanyl) is a prescription transdermal patch that contains fentanyl which is a federally controlled substance (CII). Mylan (fentanyl) patches deliver fentanyl at a rate of 25 µg/hour and are only for patients with chronic (around the clock) pain that is moderate to severe and expected to last for weeks or longer.

6.1.3 Duragesic® (fentanyl) patch 25 µg/hour

Duragesic® is a prescription patch that contains fentanyl which is a federally controlled substance (CII). Duragesic® patches deliver fentanyl at a rate of 25 µg/hour and are only for patients with chronic (around the clock) pain that is moderate to severe and expected to last for weeks or longer.

6.1.4 Naltrexone hydrochloride tablets, USP 50 mg

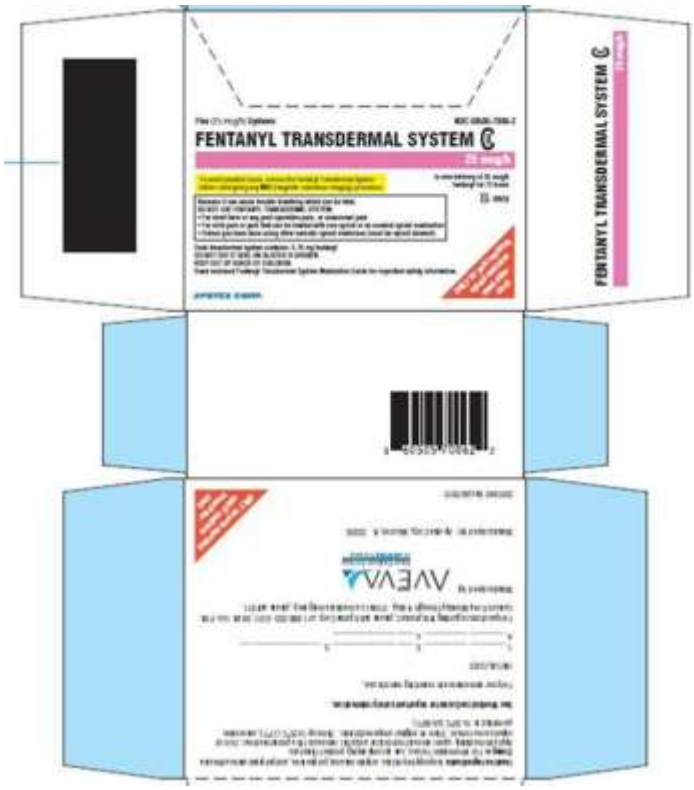
Naltrexone hydrochloride is an opioid antagonist which attenuates or reversibly blocks the effects of opioids. It is available as a prescription medication and is used to treat opioid addiction.

6.2 Formulation, Packaging, and Labeling

6.2.1 Apotex (fentanyl) patch 25 µg/h

Active ingredient (in each patch): Fentanyl, 25 µg delivered per hour. In addition to the active ingredient (fentanyl), the following inactive ingredients are present in the patch: polyester film (backing layer), isopropyl myristate, octyldodecanol, polybutene and

polyisobutene (adhesive matrix), and polyester protective release liner. This product should be stored below 25°C (77°F).

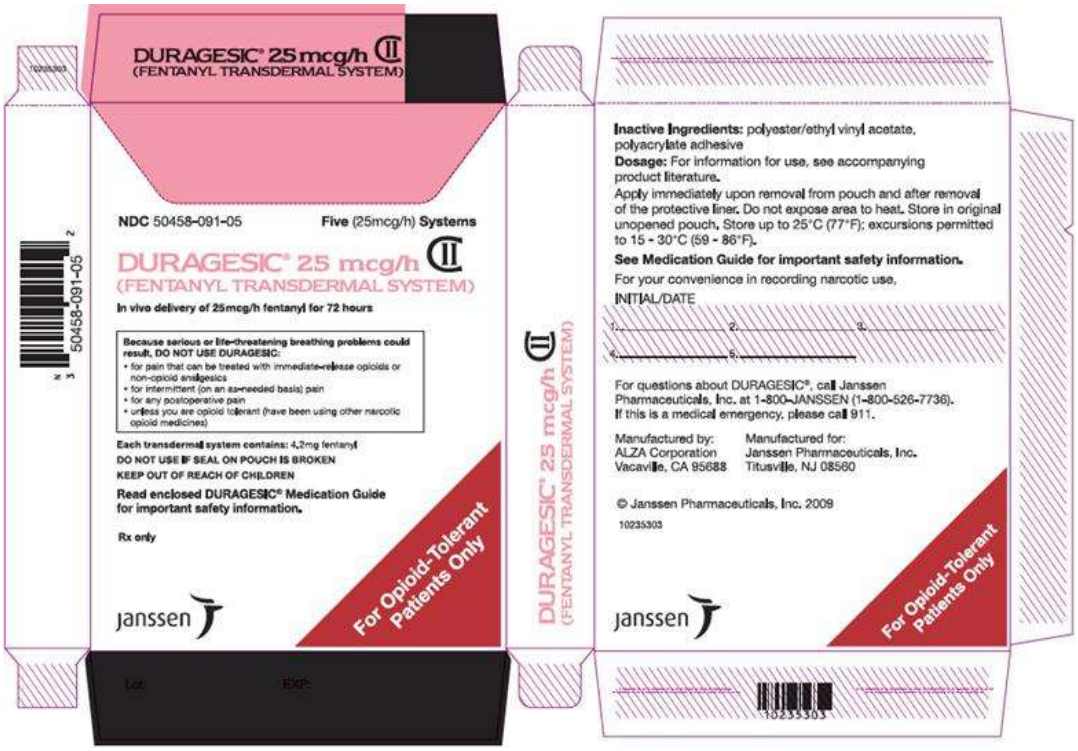


6.2.2 Mylan (fentanyl) patch 25 µg/h

Active ingredient (in each patch): Fentanyl, 25 µg delivered per hour. In addition to the active ingredient (fentanyl), the following inactive ingredients are present in the patch: Dimethicone NF and silicon adhesive and polyolefin film backing. This is a matrix type patch, manufactured by Mylan Pharmaceuticals Inc. This product should be stored below 25°C (77°F).

6.2.3 Duragesic® (fentanyl) patch 25 µg/h

Active ingredient (in each patch): Fentanyl, 25 µg delivered per hour. In addition to the active ingredient (fentanyl), the following inactive ingredients are present in the patch: alcohol, ethylene vinyl acetate-copolymer membrane and hydroxyethyl cellulose, polyester film backing, silicone adhesive. This is a matrix type patch, manufactured by ALZA and distributed by Janssen pharmaceutics. This product should be stored below 25°C (77°F).



6.2.4 Naltrexone hydrochloride tablets, USP 50 mg

Active ingredient (in each tablet): Naltrexone hydrochloride, USP 50 mg. In addition to the active ingredient (naltrexone hydrochloride), the following inactive ingredients are present in the patch: crospovidone, hypromelloses, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycols, polysorbate 80, silicon dioxide, titanium dioxide, ferric oxide yellow and ferric oxide red. This is an oral tablet, manufactured by Covidien Ltd. and distributed by Mallinckrodt Pharmaceuticals. This product will be stored at room temperature, 20 to 25°C (68 to 77°F).

6.2.5 Naloxone hydrochloride injection, USP 0.4 mg/ml

Active ingredient (in each injection): Naloxone hydrochloride, USP 0.4 mg/ml single dose ampoule for intravenous, intramuscular or subcutaneous use. This product will be stored at room temperature, 20 to 25°C (68 to 77°F).

7 PHARMACOKINETICS AND STATISTICAL CONSIDERATIONS

7.1 Study Hypotheses

Due to differences in inactive ingredients between reference and generic fentanyl transdermal patches the release rate of fentanyl may differ from these patches upon exposure to heat. As a result, in this study the influence of standardized heat application (two heat periods) on the pharmacokinetics (PK) parameters of fentanyl will be studied after using Duragesic® (reference), Apotex (fentanyl) (generic), and Mylan (fentanyl) (generic) transdermal patches.

The primary analysis will be to determine whether heat differentially impacts fentanyl serum concentrations among Duragesic® (reference), Apotex (fentanyl), and Mylan (fentanyl) transdermal patches. We will test the null hypothesis (H_0) that the coefficient for the patch-by-heat interaction equals zero, adjusting for time.

7.2 Pharmacokinetics (PK) Analyses

Fentanyl concentrations will be measured in serum samples collected from each subject from the opposite arm to which the fentanyl system will be applied. Blood samples (approximately 5 mL) will be collected during each procedure day, 15 min before patch application and then at 1:00, 10:00, 10:55, 11:05, 11:15, 11:25, 11:35, 11:45, 12:00, 13:00, 14:00, 16:00, 17:00, 17:55, 18:05, 18:15, 18:25, 18:35, 18:45, 19:00 20:00, 21:00 and 22:00 hr post-patch application. The fentanyl PK parameters to be estimated using non-compartmental analysis (NCA) after each system application are: maximum serum concentration (Cmax) at different time intervals; 0-11, 0-19, 0-22, 11-12, 12-18, 18-19 and 19-22 hr; apparent elimination rate constant (k); apparent half-life (t1/2), calculated as 0.693/k; AUC of the serum concentration–time at different time intervals; 0-11, 0-19, 0-22, 11-12, 12-18, 18-19 and 19-22 hr determined by the linear trapezoidal method; and AUC value extrapolated to infinity (AUCinf), calculated as the sum of AUC_{22} and the area extrapolated to infinity: AUCinf = AUC_{22} + C_{22}/k where C_{22} would be the last quantifiable concentration. All NCA analyses will be conducted using Phoenix® WinNonlin® 6.3 (Pharsight, a Certara Company, CA).

7.3 Final Analysis Plan

The main objective of this study is to investigate the influence of heat application on the PK parameters of fentanyl after using reference and generic patch products. The primary PK parameters to be compared are 1) Cmax, before and after heat application and 2) AUC before and after heat application consistent with similar PK studies [4, 5, 7, 8, 16-22]. Analysis of variance (ANOVA) followed by post-hoc Bonferroni test will be used for comparing the differences in the means of the PK parameters and significant differences will be declared at $p<0.05$. The statistical comparisons will be conducted as follow:

Three pair-wise comparisons between the patches (Apotex v Mylan; Apotex v Duragesic®; and Mylan v Duragesic®) will be performed using the results of a three-way repeated-measures ANOVA. The model will include time, type of patch (e.g., Apotex or Mylan), application of heat (yes or no), and interaction between patch and application of heat. The time term comprises multiple indicator variables for maximum model flexibility to perform the comparison at different time points specified above. We will test the null hypothesis that the coefficient for the patch-by-heat interaction equals zero, adjusting for time.

If fentanyl concentrations are found to be non-normally distributed, then we will examine Box-Cox transformations (e.g., log, square-root, etc.) that can achieve normality. If no transformation can achieve normality, then we will use permutation tests to compute empirical p-values, and we will use the bootstrap to compute standard errors and confidence intervals that account for within-person correlation.

A secondary analysis will assess the effects of heat and time on fentanyl within a patch. Specifically, the ANOVA will also include interaction terms of time with patch and heat, and a three-way interaction between time, heat, and patch. Inclusion of the three-way term allows the effects of heat on fentanyl to differ by patch. Testing the time-by-heat interaction, separately for each patch, using the same procedure outlined above produces estimates of intra-procedure effects.