CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-114

PHARMACOLOGY REVIEW(S)

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:	**22-114**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**11/21/2006**
PRODUCT:	**Zingo™ - Sterile Lidocaine Hydrochloride Monohydrate (LHM) by dermal administration using a PowderJect® dispenser**
INTENDED CLINICAL POPULATION:	**pediatric venipuncture or cannulation patients**
SPONSOR:	**Anesiva, Inc.**
DOCUMENTS REVIEWED:	**electronic submission modules 2.4, 2.6, & 4**
REVIEW DIVISION:	**Division of Anesthesia, Analgesia and Rheumatology Products**
PHARM/TOX REVIEWER:	**Gary P. Bond, Ph.D., DABT**
PHARM/TOX SUPERVISOR:	**Adam M. Wasserman, Ph.D.**
DIVISION DIRECTOR:	**Bob Rappaport, M.D.**
PROJECT MANAGER:	**Geri Smith**

Date of review submission to Division File System (DFS): 30-Jul-07

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

NDA approval is recommended.

B. Recommendation for nonclinical studies

None.

C. Recommendations on labeling

Two animal:human dose ratio calculation errors were noted in adapting the Synera™ Label for the proposed lidocaine drug product (suggested changes below):

See entire labeling sections with recommendations at end of the review.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Proposed:

Teratogenic Effects

(b) (4)

Nonteratogenic Effects

Lidocaine, containing 1:100,000 epinephrine, at a dose of 6 mg/kg ((b) (4) fold the SDA) …

Suggested:

Teratogenic Effects

Pregnancy Category B. Lidocaine was not teratogenic in rats given subcutaneous doses up to 60 mg/kg [360 mg/m^2 or 1200-fold the single dermal administration (SDA) of 0.5 mg lidocaine in a 60 kg individual (0.3 mg/m^2)] or in rabbits up to 15 mg/kg (180 mg/m^2 or 600-fold the SDA). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Zingo™ should be used during pregnancy only if clearly needed.

Nonteratogenic Effects

Lidocaine, containing 1:100,000 epinephrine, at a dose of 6 mg/kg (36 mg/m^2 or 120-fold the SDA)…

13 NONCLINICAL TOXICOLOGY (ANIMAL TOXICOLOGY AND/OR PHARMACOLOGY)

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Proposed:

Impairment of Fertility:

(b) (4)

Suggested:

Impairment of Fertility:

Lidocaine did not affect fertility in female rats when given via continuous subcutaneous infusion via osmotic minipumps up to doses of 250 mg/kg/day [1500 mg/m^2 or 5000-fold the SDA (single dermal administration) of 0.5 mg lidocaine in a 60 kg individual (0.3 mg/m^2)]. Although lidocaine treatment of male rats increased the copulatory interval and led to a dose-related decreased homogenization resistant sperm head count, daily sperm production, and spermatogenic efficiency, the treatment did not affect overall fertility in male rats when given subcutaneous doses up to 60 mg/kg (360 mg/m^2 or 1200-fold the single dermal administration [SDA]).

II. Summary of nonclinical findings

The active pharmaceutical ingredient (API), lidocaine, is a local anesthetic which is also an antiarrhythmic. Briefly, local anesthetics are divided into three types on the basis of the bond (ester, amide, or neither) between their aromatic and amino groups. Local anesthetics were first used in 1884; in that year Dr. Karl Koller announced the use of cocaine to anesthetize the eye. Novocaine (procaine hydrochloride) was introduced by Dr. Heinrich Braun in 1905. Novocaine is a comparatively weak anesthetic agent with a slow onset and short duration of action and is not used very often today. Local anesthetics such as cocaine and Novocaine, which are amino esters, are metabolized by plasma esterases, accounting for their short duration of action. Lidocaine, discovered in 1943 by

Swedish chemists Nils Lofgven and Bengt Lundquist, is an potent, amide local anesthetic with a fast onset and longer duration of action, due to lack of plasma esterase metabolism. Lidocaine was approval by the FDA in 1948.

The proposed drug product, Sterile LHM Product, is a single-use, disposable, needle-free injection system capable of delivering 0.5 mg of powdered lidocaine hydrochloride monohydrate (LHM) through the stratum corneum into the epidermis in a relatively small (10-12 mm diameter) area of skin to provide rapid, local anesthesia to reduce or eliminate the pain associated with venipuncture or cannulation procedures. For the active pharmaceutical ingredient (API), lidocaine, and LHM, the sponsor submitted a 505(b)(2) application with the reference drugs being LIDODERM® (NDA 20-612 - a lidocaine 5% topical patch for relief of pain associated with post-herpetic neuralgia) and Synera™ (NDA 21-623 - a lidocaine:tetracaine 70 mg:70 mg topical patch for use on intact skin to provide local dermal analgesia for superficial venous access and superficial dermatological procedures). NDA 20-612 was approved March 19, 1999 and NDA 21-623 was approved June 23, 2005.

Nonclinical considerations include: 1) systemic safety of the active drug product LHM in children and adults, 2) a repeat dose dermal toxicology study to support both local and systemic safety of the proposed drug product and satisfy registration requirements for a single use drug product, 3) local tolerance testing (extent of dermal damage and dermal responses including phototoxicity) following typical and excessive device use and 4) identification and evaluation of potential risks associated with the helium propellant, non-drug particulates, and contaminants that potentially could be entrained in the device's propellant gas stream (helium), and 5) adequacy of 505(b)(2)-reference listed drugs to support the proposed label. In addition, the Center for Devices and Radiological Health (CDRH) will review ISO 10993 mandated testing of the device components relative to safety considerations associated with health care providers and patients coming in contact with device components and/or contaminants introduced during device manufacture (not covered in this review).

A. Brief overview of nonclinical findings

Support for approval of Sterile LHM Product is derived from regulatory support from the reference drugs, nonclinical studies demonstrating absence of systemic exposure, lack of significant skin penetration of non-drug particulates, adequate local tolerance and absence of dermal toxicity, and lack of phototoxicity.

1) The low potential for systemic toxicity with use of Sterile LHM Product is supported by comparing plasma exposure produced (< 5 ng/mL) with known human toxic effect levels. Systemic concentrations of lidocaine associated with therapeutic cardiovascular effects range from 1500-5500 ng/mL and toxic effects are seen at concentrations >5,000 ng/mL (Benowitz, 1978; Roden 2006). Concentrations associated with systemic effects in infants and children are not well defined; however, in newborns the threshold for production of bradycardia is reported to be 2500 ng/mL and neonatal depression is likely at

concentrations exceeding 3000 ng/mL (Dodson 1976). Concentrations resulting from treatment with the Sterile LHM Product are well below these toxic levels. In addition, systemic safety is also supported by the observation that absorbed lidocaine for the proposed Sterile LHM Product is less than or equal to that reported for the approved reference drugs (see table). Note that amount of lidocaine in the product, stated as 0.41 mg, is equivalent to 0.5 mg for the LHM Product minus the salt and water content.

Comparison of Products

Product	Lidocaine in Product	Lidocaine Delivered to Patient	Plasma Levels Following Treatment
Sterile LHM Product	0.41 mg	0.28–0.32 mg	<5 ng/mL[a]
Synera™	70 mg	1.7 mg	<5 ng/mL[a] 63 ng/mL[b]
LIDODERM® (3 patches)	2100 mg	64 mg	130 ng/mL

[a] Following one application in adults.

[b] Following one application in children (4 months to 12 years).

2) Safety for the route of application of the proposed drug product has been demonstrated nonclinically for the proposed conditions of use in local tolerance studies assessing for dermal irritation and phototoxicity. More than typical use of the proposed drug product was assessed as multi-dosing was modeled in several studies in the minipig, which is considered a good model for assessing dermal tolerance in humans. The three multi-dose local tolerance studies performed included four administrations to separate sites per day on six days over a 28 day period; two administrations to the same site at various intervals over a 24 hour period; and twelve administrations to a single site over 1 hour. All dosing was well tolerated with no clinical signs of discomfort and minimal, reversible dermal responses with the most severe effects occurring with use of PowderJect® devices with specifications in excess of the proposed drug product. The relative safety of the proposed drug product was also supported by a "worst-case" scenario in which a relatively severe dermal response was intentionally produced. Microscopic examination determined that effects were limited to the stratum corneum, epidermis, and papillary dermis, well distanced from the significant arterioles and venules that approach the dermis from the subcutaneous layer. Additionally, nonclinical evaluation of antiseptic pre-swabbing of the site of injection with alcohol or Betadine provided no indication that this common clinical practice will have an impact on the dermal response to the drug product. The drug product was also shown not to be phototoxic in hairless mice.

3) In support of this NDA, consistent with ICH guidelines for a single or acute use dermally administered drug, the sponsor conducted a 14-day repeat-dose dermal toxicology study. This study in minipigs was submitted to characterize the potential for the drug product to cause systemic toxicity and a local tissue reaction following multiple, repeated applications. The study used

1, 2, or 3 actuations of the to be marketed drug product to the same site for 14 days followed by the same actuations pattern to new skin sites for 14 days. This treatment regimen, which exceeded the proposed human daily exposure of 1-2 actuations, did not produce any evidence of systemic toxicity, local tissue irritation, or histopathological evidence of damage to the site of application compared to the untreated site.

4) Helium in the device canister and non-drug particulates are not considered to present any health hazards relative to local and systemic exposure from the proposed drug product under specified conditions of use. The safety of propellant and non-drug particulate exposure was demonstrated in a number of nonclinical studies that included actuating devices into various collection media (e.g., glass containers) and tissues that included pig and human skin from cadavers. The list of non-drug particulates that potentially could be generated by actuation of the device, and could therefore be concern for exposure included: (b) (4) Additionally, in a comparative risk assessment, the potential for foreign body/solid state carcinogenesis was assessed for the particles that penetrated the skin compared to that for actual solid state carcinogens. Of these, (b) (4) have been measured in emissions from devices and found to be low for PowderJect® ND5 series devices with comparable specifications to the proposed drug product (PowderJect® ND5.3A). (b) (4) were below the lower limit of quantification. The presence of a small amount of (b) (4) was identified in the stratum corneum and some adjacent epidermal layers, but not in dermal tissue, when the device was actuated against human cadaver skin. As levels were none to minimal with no dermal penetration and expected clearance with the normal sloughing of the skin, there is unlikely to be an exposure concern. (b) (4) particles could not be generated during actuation of any devices and are, therefore, unlikely to be an exposure concern. In summary, virtually all non-drug particulates evaluated in deposition studies were confined to the epidermal layers and therefore are not expected to be absorbed and will be removed by epidermal sloughing. When an occasional particle was observed in the dermis, it was with devices which had higher specifications compared to the proposed drug product (e.g., greater canister pressure), which would not be expected with the device as currently constructed.

5) No distribution, metabolism, excretion, single dose toxicity, genotoxicity, carcinogenicity, reproductive and development toxicity studies were required with lidocaine based on the extensive history of clinical use of lidocaine and

general knowledge of lidocaine with nearly 60 years of approved use, extremely small dose of LHM in the Sterile LHM Product (0.5 mg), the lack of detectable systemic exposure to lidocaine following treatment with the Sterile LHM Product, and on the Agency's findings of safety of higher doses of lidocaine applied topically to intact skin in approved lidocaine patches Synera™ and LIDODERM®.

B. Pharmacologic activity (based on NDA 21-623)

Lidocaine is a sodium (Na^+) channel blocker used as a local anesthetic and antiarrhythmic. Local anesthetics block nerve impulses by blocking the pore of voltage-gated Na^+ channels and thereby decreasing or preventing the large transient increase in the permeability of excitable membranes to Na+ that normally is produced by a slight depolarization of the membrane. Blockade of neuronal conduction prevents the action potential of sensory neurons and therefore blocks the transmission of pain signals to the CNS. Lidocaine blockade demonstrates both frequency and voltage-dependency. It blocks both open and inactivated Na+ channels. The frequency dependence of this blockade makes smaller unmyelinated nerve fibers more sensitive to blockade than larger heavily myelinated fibers. Therefore, Type C fibers (dorsal root and sympathetic nerves) and Type B (preganglionic autonomic nerves) are blocked at lower concentrations than heavily myelinated Type A (alpha, beta, gamma and delta) fibers. Of the type A fibers, pain and temperature sensitive neurons (delta) are more susceptible to local anesthetics than muscle spindles (gamma) and touch and pressure sensitive neurons (beta), which are, in turn, more sensitive than proprioception and motor neurons (alpha). This sensitivity also correlates with the diameter of the nerve fiber, with smaller fibers being more sensitive to the local anesthetic action. Local anesthetics can also bind to other membrane proteins such as K+ channels. However, blockade of conduction is not accompanied by any large or consistent change in resting membrane potential due to block of K+ channels since the interaction of local anesthetics with K+ channels requires higher drug concentrations. [NDA 21-623]

C. Nonclinical safety issues relevant to clinical use

Based upon the information available to date, there do not appear to be any specific safety issues related to the use of this active pharmaceutical ingredient that have not already been previously described for the class of compounds. There do not appear to be any apparent risks with use of the PowderJect® device as systemic lidocaine was not detectable and local tolerability has been adequately demonstrated in repeated use nonclinical studies over multiple days. There also does not appear to be any apparent risks from the helium propellant or non-drug particulates contained in the helium stream as long as the drug product is used according to the label. Local anesthetics, particularly the ester-linked anesthetics, may cause allergic reactions which can be life-threatening. However, amide-type anesthetics such as lidocaine are believed to pose less risk for this reaction.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

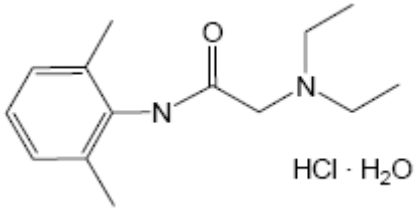
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-114
Review number: 1
Sequence number/date/type of submission: 000/November 21, 2006/original
000/March 2, 2007/BP
000/April 13, 2007/BL
000/June, 22, 2007/BZ
000/July 24, 2007/BZ
Information to sponsor: Yes ( ) No (x)
Sponsor and/or agent: Anesiva, 650 Gateway Boulevard, South San Francisco CA 94080
Manufacturer for drug substance:
Unfinished drug substance: (b) (4)
Finished drug substance: (b) (4)
LHM Filled Cassette: (b) (4)

Reviewer name: Gary P. Bond, Ph.D., DABT
Division name: Division of Anesthesia, Analgesia and Rheumatology Products
Review completion date: July 30, 2007

Drug:
Trade name: (b) (4)
Generic name: Lidocaine hydrochloride monohydrate
Code name: ALGRX-3268 (prior development code name)**;** dermal PowderJect® lidocaine HCl
Chemical name: 2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide monohydrochloride, monohydrate
CAS registry number: 6108-05-0
Molecular formula/molecular weight: $C_{14}H_{23}ClN_2O \cdot H_2O$/288.8 Daltons

Structure:



Relevant INDs/NDAs/DMFs: IND 54740 (ALGRX 3268), NDA 20-612 (LIDODERM®), NDA 21-623 (Synera™); (b) (4) for LHM powder

Reference approved drugs are dermally applied Lidoderm® (lidocaine) and Synera™ (lidocaine and tetracaine); both are topical patches. The 0.41 mg lidocaine for the Sterile LHM Product is the 0.5 mg minus the hydrochloride and water.

Comparison of Products

Product	Lidocaine in Product	Lidocaine Delivered to Patient	Plasma Levels Following Treatment
Sterile LHM Product	0.41 mg	0.28–0.32 mg	<5 ng/mL[a]
Synera™	70 mg	1.7 mg	<5 ng/mL[a] 63 ng/mL[b]
LIDODERM® (3 patches)	2100 mg	64 mg	130 ng/mL

[a] Following one application in adults.
[b] Following one application in children (4 months to 12 years).

Application History: IND 54,740 was originally submitted to the FDA by Chiroscience Limited on 10 December 1997. PowderJect Technologies, Ltd. assumed sponsorship of the IND on 9 March 2001. On 21 March 2002, AlgoRx Pharmaceuticals, Inc. acquired PowderJect Technologies, Ltd. On 15 December 2005, AlgoRx Pharmaceuticals, Inc. and Corgentech, Inc. merged to become the newly combined company called Corgentech, Inc. In 2006, Corgentech, Inc. changed its name to Anesiva, Inc.

Drug class: local anesthetic

Intended clinical population: For use on intact skin to provide local analgesia prior to venipuncture and intravenous cannulation in pediatric patients (aged 3-18 years).

Clinical formulation:

The Sterile LHM Product is a single-use, disposable, needle-free injection system capable of delivering 0.5 mg of powdered lidocaine hydrochloride monohydrate (LHM) drug particles through the stratum corneum into the epidermis of the skin to provide rapid, local analgesia. The system contains 0.5 mg LHM Sized Powder and uses pressurized helium to accelerate drug particles to velocities sufficient to penetrate into the epidermis.

For the drug substance, at a maximum daily dose of 0.5 mg, all impurities are below qualification thresholds, even for any potential structural alerts at a level of (b) (4) total daily intake (TDI) as the largest potential impurity dose is (b) (4) TDI.

Quantitative Composition of LHM Filled Cassette

Components	Amount	Total Weight/ (b) (4)	Function	Reference to Standard
LHM Sized Powder	0.500 mg		Active drug substance	USP*

* Derived from lidocaine hydrochloride, USP.

LHM Sized Powder (Drug Substance) Proposed Commercial Specifications

(b) (4)

For the drug product, the levels of the impurities in the Sterile LHM Product are all well below the qualification threshold of 1.0% (5 µg TDI) for drug products, as outlined in the ICH Impurities in New Drug Products guideline (Q3B), with most of the impurity levels below the (b) (4) reporting threshold.

Proposed Commercial Analytical Test Methods and Specifications for Sterile LHM Product (Part Number 37-0001)

(b) (4)

The container closure system for drug product cassette is as follows:

Container Closure System for LHM Filled Cassette (Drug Product)

Component	Packaging Type	Vendor
(b) (4) Cassette Body—Female	Primary	The Tech Group
(b) (4) Cassette Body—Male	Primary	The Tech Group
(b) (4) Film, 10 µm	Primary	(b) (4)

During drug product development, multiple configurations of the drug product cassettes and device (ND1, ND2, ND5, ND5.2, ND5.3, and ND5.3A) were used to deliver a range of LHM doses (0–3 mg) at a variety of pressures (20–60 bar) in the nonclinical studies.

The finalized Sterile LHM Product is defined as the ND5.3A configuration, which is comprised of six main components: an (b) (4) helium gas-filled, pressurized (21 bar) microcylinder with a proprietary tip, an internal housing, an in-line (b) (4) filter, 0.5 mg of powdered LHM particles of specific size (40 µm) that are held in a two-piece (b) (4) cassette with 10 micron (b) (4) film ((b) (4) a (b) (4) nozzle, and a silencer. The drug is administered using a helium gas stream at 21 bar pressure. The table lists the development history of the drug device used in clinical studies. Nonclinical review emphasis will be focused on the commercial configuration.

(b) (4)

The ultimate drug product device is as follows:

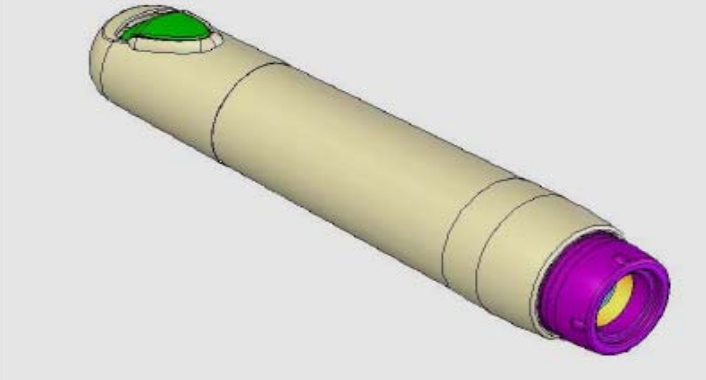
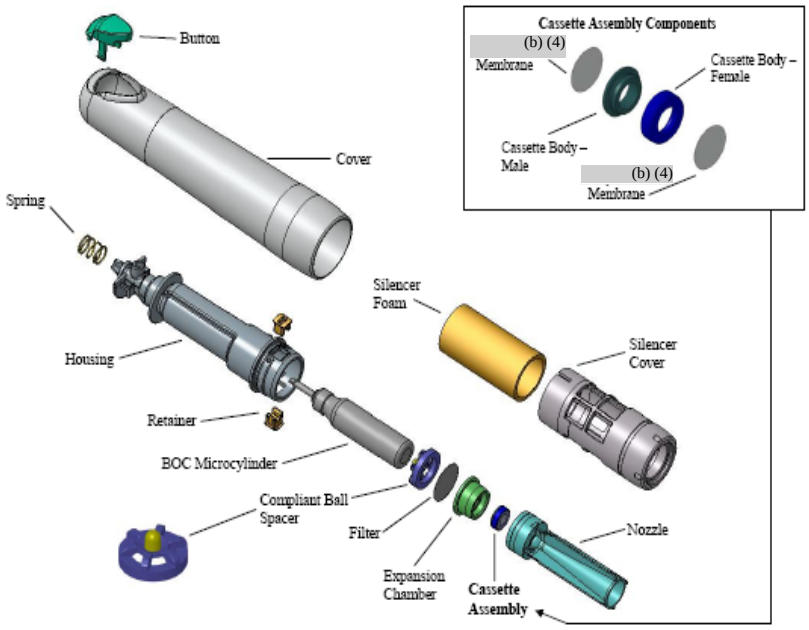


Figure 1: Sterile LHM Product and Components



Note: The Pharmacology/Toxicology review will only include studies dealing with the administered drug and directly associated device components (helium propellant, spacer, (b) (4) filter, cassette assembly components, and nozzle).

Route of administration: topical

Disclaimer: Tabular and graphical information are not constructed by the reviewer unless cited otherwise. Sponsor's submission text may have been used with none to minor modifications after text and supporting data have been corroborated by the reviewer.

Data reliance : For this 505(b)(2) application, except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-114 are owned by Anesiva or are data for which Anesiva has obtained a written right of reference. Any information or data necessary for approval of NDA 22-114 that Anesiva does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Anesiva does not own or from FDA reviews or summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 22-114.

Studies reviewed within this submission:

PHARMACOKINETICS/TOXICOKINETICS

Lidocaine:

ALGRX-3268: A pharmacokinetic evaluation in Gottingen minipigs (b) (4), August 2006.

TOXICOLOGY

Repeat-dose toxicity:

Sterile LHM Product: A two-week dermal toxicity study in Gottingen Minipigs® (b) (4), February 2007.

Local Tolerance:

Assessment of acute and sub-chronic dermal tolerance to the dermal PowderJect® lidocaine HCl (ND5.3) in conscious pigs (b) (4) - GLP), May 2002.

Local dermal tolerance to lidocaine administered by various configuration-combinations of ALGRX 3268 (PowderJect® Dermal Lidocaine Devices) (b) (4) - GLP), March 2004.

Local dermal tolerance to duplicate dose of lidocaine administered by PowderJect® devices (b) (4) - GLP), December 2002.

Local dermal tolerance to multiple doses of lidocaine administered by PowderJect® devices ((b) (4) - GLP), December 2002.

Histopathological measurement of a Draize erythema grade 4 response (PowderJect® Technologies Ltd., PJT PC TM 146 – non-GLP), March 2003.

Betadine and Lidocaine HCl: Between Local Skin Antisepsis with Betadine and Transdermal Delivery of Local Anesthetic by PowderJect® to Conscious Rabbit ((b) (4) - GLP), July 1997.

Topical Primary Irritancy and Phototoxicity Test of ALGRX 3268 in hairless mice when topically administered using the PowderJect® System (b) (4) - GLP), June 2006.

Special toxicology studies: (skin penetration of lidocaine and non-drug particulates)

Quantitative HPLC analysis of lidocaine from excised pig skin following the delivery of powdered lidocaine hydrochloride via Dermal PowderJect® ((b) (4) - non-GLP), June 1999.

Non Drug Particulate of ND 5.3 devices ((b) (4) - non-GLP).

(b) (4) fragmentation from BOC microcylinder (PowderJect Pharmaceuticals PLC, PJT NR 018 - non-GLP), September 2000.

(b) (4) mass results from PJT PR-055 (PowderJect Pharmaceuticals PLC, LID 0014 DD RT - non-GLP), March 2000.

Mass assay of (b) (4) membrane fragmentation by UV/Vis Spectroscopy (PowderJect Technologies Inc., DEV1998.012, non-GLP), May 1998.

(b) (4) fragment analysis – size/count and particle morphology (PowderJect Technologies Inc., DEV.1998.013, non-GLP), December 1998.

Analytical Test Report: Nonvolatile Organic Compounds by Methylene Chloride Extraction and GC-MS Analysis - Evaluation of (b) (4) ((b) (4) Particulates from Actuated Devices (b) (4) - non-GLP), September 2006.

Analysis of (b) (4) Fragmentation for Dermal PowderJect (PowderJect Pharmaceuticals PLC, BO PC01 98 - non-GLP), October 2001.

(b) (4) fragmentation study, ND5: Extent and skin penetration (PowderJect Technologies Inc., DV1999.015 - non-GLP), November 1999.

Contract Histology: Investigative study to determine the distribution of (b) (4) and other fragments generated during the activation of PowderJect devices in human cadaver skin ((b) (4) - ISO 10993 compliant), October 2004.

Contract Histology: Investigative study to determine the distribution and penetration of (b) (4) and other fragments generated during the activation of PowderJect devices in human cadaver skin (b) (4) - ISO 10993 compliant) July 2005.

Contract Histology: Validation study to determine suitable histological techniques in the assessment of various fragment types generated during the actuation of PowderJect® devices in human and porcine cadaver skin (b) (4) - ISO 10993 compliant), June 2006.

Contract Histology: Investigative study to assess penetrative depth of various fragments generated during the activation of PowderJect devices in human cadaver skin (b) (4) - ISO 10993 compliant), October 2004.

Risk Assessments:

Considerations of induced helium penetration and embolism (AlgoRx Pharmaceuticals, Inc.), April 2003.

Risk Assessment for the PowderJect ND5 Device – A Review of Issues Related to [redacted], November 2002.

Risk Assessment for the PowderJect ND5 Device – A Review of Issues Related to [redacted], August 1999.

Norris RJ. A Review of [redacted] Membrane Fragmentation: Foreign Body Carcinogenesis and the Potential for [redacted] Fragments to Produce this Effect in Man (PowderJect Pharmaceuticals PLC), July 1998.

Literature References:

Bauer J et al. A Strikingly Constant Ratio Exists Between Langerhans Cells and Other Epidermal Cells in Human Skin. A Stereologic Study Using the Optical Disector Method and the Confocal Laser Scanning Microscope. J Invest Dermat 313-318

Benowitz NJ and Meister W. Clinical Pharmacokinetics of Lignocaine. Clinical Pharmacokinetics 3:177-201, 1978.

Dodson WE. Neonatal Drug Intoxication: Local Anesthetics. Pediatric Clinics of North America, 23(3):399-411, 1976.

Catterall WA and Mackie K. Chapter 14: Local Anesthetics. In: Goodman & Gilman's - The Pharmacological Basis of Therapeutics, 11th edition, McGraw-Hill, pp. 369-386, 2006.

Epstein WL and Maibach HI. Cell Renewal in Human Epidermis. Arch Dermat 92:462-468, October 1965.

Kendall MAF, Wrighton Smith PJ, and Bellhouse. Transdermal Ballistic Delivery of Micro-Particles: Investigation into Skin Penetration. Published in the Proceedings of the 22nd Annual EMBS International Conference, pp. 1621-1624, July 23-28, 2000. (in July 24, 2007 submission)

Nicoll PA and Cortese TA Jr. The Physiology of the Skin, 1972.

Roden DM, Chapter 34: Antiarrhythmic Drugs. In: Goodman & Gilman's - The Pharmacological Basis of Therapeutics, 11th edition, McGraw-Hill, pp. 899-932, 2006.

Topham SJ and Dempster AC. A Comparison between the Skin of Humans and Other Mammalian Species (PJT RN 163), February 2000.

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Studies not reviewed within this submission:

Literature-references:

2005, Synera™ (Lidocaine 70 mg and tetracaine 70 mg) Topical Patch - label.

Bergstresser, 1977, Epidermal 'Turnover Time' - A New Examination

Cassidy, 1996, Serum Lidocaine Concentrations After Subcutaneous Administration in Patients Undergoing Cardiac Catheterization in a Pediatric Institution.

Dezwart, 2004, Role of Biokinetics in Risk Assessment of Drugs and Chemicals in Children.

Ellenhorn, 1997, Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning.

Emla, 2005, Department of Health & Human Services – NDA 19-941/S017 label.

Endo, 2006, Lidoderm (Lidocaine Patch 5%) – NDA 20-612/S-008 label.

Fluhr, 2000, Direct Comparison of Skin Physiology in children and Adults with Bioengineering Methods.

DV.1998.028 Foster, 1998, Acute Systemic Toxicity Study in the Mouse.

DV.1998.025 Foster, 1998, Cytotoxicity Study Using the ISO Elution Method.

DV.1998.026 Foster, 1998, Cytotoxicity Study Using the ISO Elution Method.

DV1998.023 Foster, 1998, ISO Acute Intracutaneous Reactivity Study in the Rabbit.

DV1998.024 Foster, 1998, ISO Acute Intracutaneous Reactivity Study in the Rabbit.

Gammaitoni, 2002, Pharmacokinetics and Tolerability of Lidocaine Patch 5% with Extended Dosing.

Garner, 2004, Bacterial Reverse Mutation Test (FST0001).

Garner, 2005, Bacterial Reverse Mutation Test (FST0002).

1 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Pharm/Tox-1

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Lidocaine binds reversibly to a specific site within the pore of voltage-gated sodium channels found in nerve axons as well as other tissues and blocks ion movement through this pore. When applied locally to nerve tissue in appropriate concentrations, lidocaine reversibly blocks the action potentials responsible for nerve conduction. The effects of clinically relevant concentrations are reversible with recovery of nerve function and no evidence of damage to nerve fibers or cells (Catterall 2006). Lidocaine blocks both open and inactivated cardiac sodium channels and is used at much higher doses (1.5-5 µg/mL) as an antiarrhythmic drug (Roden 2006). Recovery from block is very rapid (Roden 2006).

2.6.2.2 Primary pharmacodynamics - no studies were conducted for the proposed drug product as for old, well-understood drugs with significant clinical experience these studies are not required (see referenced drugs for lidocaine)

2.6.2.3 Secondary pharmacodynamics - no studies were conducted for the proposed drug product as for old, well-understood drugs with significant clinical experience these studies are not required (see referenced drugs for lidocaine)

2.6.2.4 Safety pharmacology - no studies were conducted for the proposed drug product as for old, well-understood drugs with significant clinical experience these studies are not required (see referenced drugs for lidocaine).

2.6.2.5 Pharmacodynamic drug interactions - no studies were conducted for the proposed drug product as for old, well-understood drugs with significant clinical experience these studies are not required (see referenced drugs for lidocaine)

2.6.3 PHARMACOLOGY TABULATED SUMMARY – N/A

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Upon actuation of the Sterile LHM Product, lidocaine hydrochloride monohydrate (LHM) plus non-drug particulates become entrained in the helium gas flow. The dermal absorption of lidocaine is discussed below. The dermal penetration of non-drug particulates are reviewed in the Special Toxicology section of section 2.6.6 Toxicology. Risk assessments for non-drug particulates and helium will be incorporated into the Overall Conclusions and Recommendations of this document.

Pharmacokinetic (PK) data show that the systemic exposure to lidocaine is below detection at the lower limit of quantitation detection (LLOQ = 5 ng/mL) following a

single actuation of the Sterile LHM Product in adult and juvenile minipigs, consistent with the lack of detection in adult humans. Plasma levels were also below the LLOQ in adult minipigs and were less than 6.5 ng/mL following three treatments in rapid succession in juvenile pigs indicating a low level of systemic exposure to lidocaine using the proposed drug product.

2.6.4.2 Methods of Analysis - detection methods will be described as appropriate in the review of studies.

2.6.4.3 Absorption (Dermal Penetration)

Lidocaine - The PK of lidocaine was evaluated following 1 and 3 actuations of Sterile LHM Product using a PowderJect® ND5.3A device to the dorsal pinna of adult (17-19 kg) and juvenile (3.7-6.5 kg) Gottingen minipigs (study 1204-009). Pig skin is generally accepted as the best animal model for human skin and the pinna was chosen as the site of administration in the PK study because the thickness of the epidermis of the pig pinna most closely approximates the thickness of human epidermis at the most likely injection sites (back of hand, antecubital fossa) (Topham 2000). Lidocaine was not detected in plasma following a single administration of Sterile LHM Product (N5.3A) to adult and juvenile animals or following three administrations to adult animals [lower limit of quantification (LLOQ) = 5 ng/mL]. Plasma concentrations of lidocaine were just above the LLOQ (5.2-6.1 ng/mL) at a single time point in three of four juvenile animals that received three administrations of Sterile LHM Product (two animals at 5 minutes and one at 20 minutes after the third dose), which returned to levels below the LLOQ at the following time points of 20 and 60 minutes, respectively. These results are consistent with clinical PK findings (study 3268-1-101-001), in which no lidocaine was detected in plasma from adult patients, and indicate extremely low levels of systemic exposure following treatment with the Sterile LHM Product.

2.6.4.4 Distribution - no studies were conducted for the proposed drug product as for old, well-understood drugs with significant clinical experience these studies are not required (see referenced drugs for lidocaine)

2.6.4.5 Metabolism - no studies were conducted for the proposed drug product as for old, well-understood drugs with significant clinical experience these studies are not required (see referenced drugs for lidocaine)

2.6.4.6 Excretion- no studies were conducted for the proposed drug product as for old, well-understood drugs with significant clinical experience these studies are not required (see referenced drugs for lidocaine)

2.6.4.7 Pharmacokinetic drug interactions - no studies were conducted for the proposed drug product as for old, well-understood drugs with significant clinical experience these studies are not required (see referenced drugs for lidocaine)

2.6.4.8 Other Pharmacokinetic Studies - none

2.6.4.9 Discussion and Conclusions - The general pharmacokinetic characteristics of lidocaine are well understood due to the long clinical use and research history with this local anesthetic. Nonclinical and clinical pharmacokinetic (PK) data obtained with the proposed drug product both support low systemic exposure to lidocaine [below the detection level (5 ng/mL)] following a single actuation of the Sterile LHM Product in adult and juvenile minipigs (1204-009) and in human adults (3268-1-101-001). Plasma levels were also below the lower limit of quantitation (LLOQ) in adult minipigs and were less than 6.5 ng/mL following three treatments in rapid succession in juvenile pigs (5.5-6.6 kg; approximately half the size of the smallest child in the target population).

2.6.4.10 Tables and figures to include comparative TK summary - none

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Study Type	Study Number/ GLP Status	Study Title	Device	Species	LHM Dose and size	Route	Key Finding or Conclusion
Absorption lidocaine	(b) (4) NO. 1204-009 GLP	ALGRX-3268: A pharmacokinetic evaluation in Gottingen minipigs	ND5.3A, 21 bar pressure	Minipig (adult and juvenile)	0.5 mg x 1 and 0.5 mg x 3; 38 µm	Topical (pinna)	No detectable lidocaine above the LLOQ (4.69 ng/ml) at any time point following 1 or 3 administrations to adults and following 1 administration to juveniles. Lidocaine concentrations just above the LLOQ (5.1–6.1 ng/mL) in 3 of 4 animals at a single timepoint, 5 or 20 m post-dose after 3 administrations to juveniles.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

Three male and three female Gottingen Minipigs® received two treatment regimens consisting of one, two, or three successive actuations of the proposed PowderJect® ND5.3A device containing Sterile LHM Product, a single alcohol wipe (wipe control), or no treatment to the skin for 14 consecutive days (days 1-14 and days 13-26 at different sites). Treatment caused no erythema, edema, or histologically confirmed skin damage (only local tissue site evaluated). No systemic effects related to clinical symptoms, EKG, hematology, clinical chemistry, gross pathology or other effects of treatment were observed to have occurred. The NOAEL for local dermal toxicity was three successive actuations per day for 14 days of the PowderJect® ND5.3A device containing Sterile LHM Product.

Local Tolerance:

Erythema and edema of treated skin sites were evaluated in the studies using the following Draize scoring method (Draize, J.H., Woodard, G., and Calvery, H.O. (1944).

Methods for the Study of Irritation and Toxicity of Substances Applied Topically to the Skin and Mucous Membranes, J. Pharmacol. Exp. Ther., 82:377-390).

Erythema and eschar formation	Grade
No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries to depth)	4

Oedema formation	Grade
No oedema formation	0
Very slight oedema (barely perceptible)	1
Slight oedema (edges of area well defined by definite raising)	2
Moderate oedema (edges raised approximately 1mm)	3
Severe oedema (raised by more than 1mm and extending beyond the area of exposure)	4

During the course of development, PowderJect® devices with varying specifications were tested leading to the proposed commercial device configuration (see table). The commercialized drug product has the following typical specifications: 0.5 mg lidocaine with 40 µm particle size, 10 µm (b) (4) film thickness, and 21 bar microcylinder pressure.

The purpose of study 1683/33 was to assess the acute and sub-chronic dermal tolerance using a PowderJect® ND5.3 device over a period of 28 days. The PowderJect® ND5.3 device is comparable to the proposed drug product with 0.5 mg lidocaine of a particle size of 40 µm, 10 µm (b) (4) film, and a canister pressure of 20 bar. Eight female pigs were treated with single actuations of the device on four separate sites on the flank per day on days 0, 14, 21, 25, 27, & 28 and then observed for erythema and edema. On day 28, all animals received a gross necropsy and skin sites were excised and fixed. Skin sites were observed for erythema and edema using the Draize method. No effects on clinical signs, body weight, food consumption or gross necropsy were observed after total daily dosing with 2 mg of lidocaine on six days of 28 (actual emitted dose was 68% or 1.4 mg). Very slight dermal irritation (grade 1 erythema) was observed with blind scoring Findings were observed within 30-60 minutes following the first days of administration, peaked between 1-3 days (~ 50% of dosing sites), and were generally reversible within 4 days after dose administration and no later than 10-14 days after dosing. Erythema tended to be more prevalent at dosing sites that were more ventrally located than at sites closer to the spine. A similar though not as clear a trend was observed for sites that were closer to the tail than those closer to the head. No edema was observed. Fixed, excised skin was not evaluated due to lack of macroscopic findings. In summary, very slight, reversible erythema was observed with no general systemic toxicity at 1.4 mg lidocaine per day administered 6 times over 28 days.

The purpose of study 2203/008 was to determine local dermal tolerance using preliminary PowderJect® ND5.3 devices, in this case an ALGRX 3628 device, in various

combinations of cassette membrane thickness and device power. The devices with 0.5, 1, 2, or 3 mg lidocaine with l0 µm thick (b) (4) film and 20 and 40 bar pressure (eight devices) or with 0, 1, 2, or 3 mg lidocaine with 20 µm thick (b) (4) film at 40 bar pressure (four devices) were used to treat six female pigs with single actuations of each device on three separate sites on the flank at 0, 4, & 24 hours prior to necropsy. For the 4- and 24-hours treatments sites, dosing site assessment for erythema and edema were conducted using the Draize method) pre-dosing and post-dosing at 0, 0.5, 1, 2, 4, 8, & 24 hours as applicable. One thousand total sites were scored. All animals received a gross necropsy and skin sites were excised and fixed. Total lidocaine dosing was 57 mg over a 24 hour period (actual emitted dose was 70% or 40 mg). No effects of treatment were noted for clinical symptoms, body weight, and gross necropsy other than for treatment sites. In general, the onset, severity, and frequency of occurrence of erythema and edema increased with increasing amounts of lidocaine, increasing canister pressure, and increasing (b) (4) film thickness in an additive manner with the change in canister pressure having the most profound effect. Grade 3 erythema was observed in two pigs (7 of 1000 observations). All other pigs exhibited grade 2 erythema (119 observations) or grade 0 or 1 erythema (874 observations). Erythema incidence and severity peaked between one and four hours post-dose and, while reversal of effects was ongoing by 24 hours, it had not fully resolved. Compared to erythema, edema was less severe and with a lower incidence (9, 40, 851 observations at grade 2, 1, & 0, respectively). The incidence of edema peaked between 2-4 hours post-dose with only occasional observations at longer time-periods. Microscopic findings at treated sites showed various results consistent with minor epidermal damage and little significant dermal damage with the highest severity being minimal for all groups. Findings consisted of cellular crust (a consolidated surface mass of keratin and cellular debris, within or above the keratinized epidermal layer) for the 0-40-20 (lidocaine-pressure-(b) (4) thickness) control, and minor epidermal injury (eosinophilia, sometimes with vasodilation of superficial dermal blood vessels and intra-epidermal vesicles), and occasional superficial perivascular dermatitis (with extravasation of inflammatory cells, mainly neutrophils, predominantly at four hours post-dose) with little or no significant dermal damage for treated sites. These findings were most evident at four hours post-dose and, in general, more pronounced for devices configured at 40 bar, and more pronounced with increasing amounts of lidocaine and (b) (4) film thickness. At 24 hours post-dose, reversal of treatment effects was demonstrated as the predominant finding was limited to cellular crust, the incidence and/or severity of which was slightly higher than for the control for devices that had highest lidocaine payload, bar pressure and (b) (4) film thickness (2-40-20, 3-40-l0, and 3-40-20). At specifications for the proposed drug product, mean Draize scores ranged from 0.33-0.83 for erythema and 0-0.08 for edema with minimal, reversible microscopic effects observed using a PowderJect® ND5.3 device at 0.5 mg lidocaine, 20 bar canister pressure, and 10 µm (b) (4) film.

The purpose of study 2203/004 was to determine local dermal tolerance after two actuations on the same skin site using preliminary PowderJect® ND5.3 devices at increased device pressure compared to the proposed drug product. These devices with 0.5 mg lidocaine at 35 µm particle size with l0 µm thick (b) (4) film and 40 bar

pressure instead of the 20 bar in the proposed drug product were used to treat seven female pigs with duplicate actuations of each device on two separate sites on each flank with differing time periods between the first and second dose (5, 10, 20, 30, & 60 minutes, and 24 hours) prior to necropsy. Control sites received a single actuation at each site. There were 7 separate dosing days over a 10 day period with 0.5 (single dose control) & 1 mg lidocaine for each of the 4 test sites for control and other groups, respectively (actual emitted dose was 73% or 0.36 or 0.73, mg lidocaine, respectively). Skin sites were observed visually for erythema and edema using the Draize method pre-dose, and at 0.5, 1, 2, 4, & 8 hours post-dosing and at l, 3, & 7 days post-dosing. There were no post-mortem microscopic assessments of the local site. No effects on clinical symptoms or body weight were observed. Very slight dermal irritation (measured as ≤ grade 1 erythema and edema) was observed. The highest mean Draize scores were 0.97 for erythema at 8 hours using the 30 minute interval dosing and 0.25 for edema at 4 hours using the 20 minute dosing. Draize irritation values were 0 by 1 day after dosing. Generally, findings were observed within 30-60 minutes and peaked at 4-8 hours and were reversed within 24 hours after dose administration. Maximum responses tended to occur in treatment groups receiving duplicate doses from 10 to 60 minutes apart. Responses tended to be more prevalent at injection sites that were more ventrally located than at sites closer to the spine. Minimal and reversible erythema and edema were observed after 2 doses at twice the canister pressure to be used in the proposed drug product.

The purpose of study 2203/005 was to determine local dermal tolerance using preliminary PowderJect® ND5.3 devices after twelve actuations in one hour (excessive use) on the same skin site at increased device pressure compared to the proposed rug product. These devices with 0.5 mg lidocaine at 35 µm particle size with l0 µm thick (b) (4) film and 40 bar pressure (20 bar for proposed drug product) were used to treat six female pigs with multiple actuations of each device on two separate sites/day on each flank with 12 actuations approximately 5 minutes apart on day 0, 5, 8, 9 (24 & 12 hours before necropsy), and day 10 (30-45 minutes before necropsy). Daily dosing was with 6 mg lidocaine/day over 10 days (actual emitted dose was 80% or 4.8 mg). Skin sites were observed visually for erythema and edema using the Draize method pre-dosing and post-dosing at 30 & 60 minutes, 2, 4, & 8 hours, and 1, 3, & 7 days as applicable. All animals received a gross necropsy and skin sites were excised, fixed, and evaluated. No effects of treatment were noted for clinical symptoms, body weight, and gross necropsy other than for treatment sites. Well defined (grade 2) to severe (grade 4) erythema was observed at 100% of the sites (24 of 24) to 8% (2 of 24) sites, respectively. Peak response was noted between 0.5 hours and 1 day after dosing and the average response was 2.5 at 8 hours. The response had resolved significantly by day 3. Anterior sites tended to have higher erythema scores than middle and posterior sites. Edema occurred at 80% of the sites and scores were primarily very slight-slight (grade 1-2) with a peak response at 0.5-8 hours and resolution by day 3, with 5 of 24 sites exhibiting no edema. Peak response was noted between 0.5 hours and 1 day after dosing and the average response was 0.8 at between 0.5 and 8 hours. Histopathology findings at injection sites were reported as consistent with minor epidermal injury and repair without significant dermal damage. The sequence of findings consisted of epidermal eosinophilia, vasodilation of the

superficial dermal blood vessels and minimal superficial perivascular dermatitis. At l2 hours, there was evidence of minor epidermal necrosis accompanied by an increased inflammatory reaction consisting of superficial perivascular dermatitis, intraepidermal vesicular dermatitis, and an individual case of minimal folliculitis. The peak inflammatory response was noted at l2 and 24 hours post-treatment. At 24 hours post-treatment, inflammation was accompanied by acanthosis (thickening of epidermal spinosum layer) and an increase in cellular crust formation. Two days post treatment, the inflammatory reaction declined, and acanthosis and crust formation increased. By day 5, post-dose, acanthosis and crust formation had reduced, and by 10 days post-treatment, all findings had resolved to background levels. There was no evidence of ulceration of the epidermis or significant dermal injury at any time point. There was no evidence of repair by fibrosis or scarring.

The purpose of study PJT-PC-TM-146 was to assess the histopathology of sections acquired from skin punches of Draize 4 dermal porcine responses that were associated with surface bleeding, considered representative of administration of an overpowered preliminary PowderJect® device to human skin. Porcine skin sections from a previous developmental study were evaluated for histopathology under increased magnification for sections that exhibited grade 4 dermal responses as an attempt to explain comparable clinical observations. Such a nonclinical response was associated with surface bleeding, after dosing with PowderJect® ND1 with 1 mg of protein (particle size 53-75 µm), and 60 bar canister pressure. Frank bleeding in a single patient in a clinical trial using a PowderJect® ND5 device with 40 bar canister pressure and lidocaine particle sizes of 38-53 µm (study ICR 031091). Despite the aggressive device configuration and relatively severe appearance of the dermal response in the porcine skin, physical damage was limited to the stratum corneum, epidermis, and papillary dermis and was well distanced from the significant arterioles and venules that approach the dermis from the subcutaneous layer. The damage consisted of splits in the stratum corneum at the site of particle entry, destruction of underlying epidermal cells (diameter of zone of damage ~50 µm, corresponding to particle size), extravasation of red blood cells from particle penetration into the papillary dermis, the presence of inflammatory (PMN) infiltrate down to depths of l50-300 µm but not beyond the papillary dermis, and red blood cells on the outside of the stratum corneum consistent with surface bleeding. There was no evidence of full thickness damage to the skin so direct access of gas or particulates to the systemic circulation following treatment is considered extremely improbable. These worst case dermal responses occurred at 60 bar canister pressure in pigs and at 40 bar in a single patient, and is considered unlikely to occur at 20 bar canister pressure for the proposed drug product.

The purpose of study 755-003 was to investigate the possible interaction of local skin antisepsis with Betadine and local anesthetic delivery using the PowderJect® device. Preliminary PowderJect® ND1 devices with single actuations of 0, 3, & 6 mg lidocaine or 2 actuations of 3 mg lidocaine at 60 bar pressure were administered to the backs of 6 conscious rabbits in order to assess if pre-dosing treatment with alcohol or the local skin antiseptic, Betadine, affected the dermal response to the PowderJect®-delivered doses. Device specifications were excessive and may not reflect response for the proposed drug

product at 0.5 mg lidocaine and 20 bar canister pressure. The 2 actuations of 3 mg were only with alcohol wipe pre-treatment and negative control. Test sites were evaluated for erythema and edema post-dosing using the Draize method at 10 minutes and 1, 6, 24, & 72 hours after treatment. Treatment sites were excised and fixed. Daily dosing totaled 33 mg lidocaine (estimated emitted dose was 70% based on other studies or 23 mg). No effects on body weight were observed. Pre-treatment with nothing, alcohol wipes, and Betadine had no differing effect on erythema, edema, or histological findings following single actuation of devices with 3 mg and 6 mg lidocaine. Mean erythema scores at 10 minutes through 24 hours were 2.8, 2.2, & 1.8, respectively, for the 3 mg lidocaine/60 bar pressure treatment with reduction of scores by 72 hours for a device with specifications at 6-fold the proposed dose and 3-fold the proposed canister pressure to be used in the proposed drug product. Mean edema scores were uniformly low (none or barely detectable) with reduction of score during the observation period. Physical damage and hemorrhage of dermal capillaries at appeared to start to resolve by the 72 hour and 24 hour assessments for the 3 mg and 6 mg doses, respectively. Histopathology findings consisted of minimal to slight acanthosis, minimal to slight chronic inflammatory cell infiltrates, and minimal focal dermal hemorrhage. Dermal findings for sites where 2 x 3 mg doses were administered tended to be greater than findings at sites where a single 6 mg dose was administered. Sites administered 0 mg lidocaine had either no or minimal findings. Pretreatment with Betadine and alcohol wipes did not appear to significantly alter erythema, edema or histological changes associated LHM delivery using ND1 devices. The severity of the damage is not considered relevant to the proposed drug product which will operate at 0.5 mg lidocaine and 20 bar canister pressure.

The purpose of study ACZ00009 was to select doses based on skin irritation and then further evaluate this irritation and the phototoxic potential of ALGRX 3268 (now Sterile LHM product) when administered topically using the PowderJect® 5.3A device. Using the proposed PowderJect® ND5.3A devices with 0.5 mg lidocaine with 30-46 µm particle size, 10 µm (b) (4) film, and 20-21 bar canister pressure, 3 female hairless mice were dosed 0, 1, or 3 times in a single day to assess dermal irritancy. To assess phototoxicity, six (6) additional mice received 0 or 1 actuation with the device or methoxypsoralen positive control topically and then exposed to simulated sunlight radiation for 30 minutes at 15, 15, & 60 minutes post-dosing, respectively. Another group received a single actuation without radiation. Test sites were evaluated for erythema and edema post-dosing using the Draize method at 1, 2, & 3 days after treatment. Daily dosing was with 0.5 mg (phototoxicity study) or 2 mg (dermal irritancy study) lidocaine (actual emitted dose was 68% or 0.34 and 1.36 mg, respectively). In the primary irritancy study phase, a single administration of the device elicited mild to moderate skin reactions while three administrations of the device elicited mild, moderate and marked cutaneous reactions. The severity of the reactions with three administrations of the device would mask detection of phototoxicity, and therefore this dose regimen was not used in the phototoxicity phase of the study. A single administration of the device, followed by a single exposure to simulated sunlight did not elicit skin reactions attributable to phototoxicity. Skin reactions that occurred in mice administered the device with and without simulated sunlight exposure were equivalent. Negative and positive controls performed as expected. Skin reactions that occurred in mice were attributed to a primary

irritant response to the device and there was no evidence of a light-induced enhancement of the primary irritancy (phototoxicity). The sponsor considered the increased severity of the dermal irritation in the hairless mice compared to other nonclinical testing using the PowderJect® ND5.3A device, the proposed drug product, to be specific to the hairless mice and not relevant to any potential for human dermal irritation with the drug product.

Special toxicology studies:

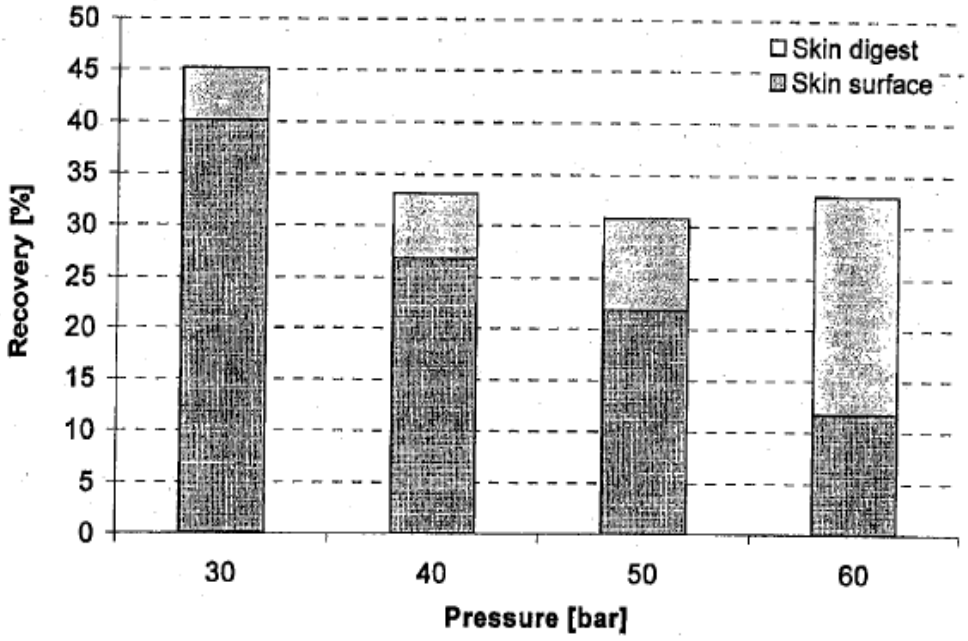
Dermal Penetration of Lidocaine

The skin penetration of lidocaine was measured in the process of developing a HPLC method for lidocaine after extraction from (a) complete skin digests, (b) polypropylene adhesive tape strips of stratum corneum, and/or (c) cotton buds used to wash and wipe the skin surface (study (b) (4)). At decreasing device pressure, the majority of lidocaine (%) was administered only to the skin surface (stratum corneum and surface of epidermis), thereby suggesting little chance for other than superficial skin damage from lidocaine in the proposed drug product (see tables and chart).

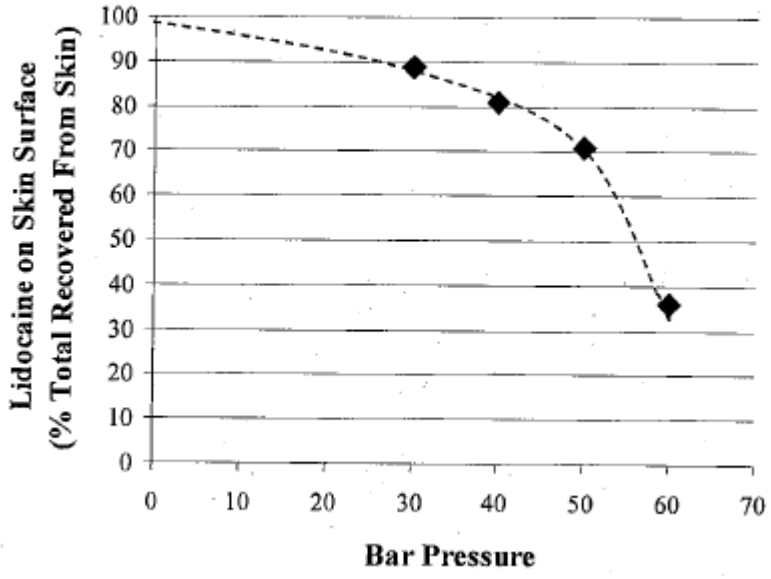
Effect of gas driver pressure (30 -60 bar) on distribution of lidocaine in skin.

Pressure	Skin surface*	Skin digest
30 bar	40.09 ± 16.53	5.05 ± 2.31
40 bar	26.86 ± 17.68	6.26 ± 3.75
50 bar	21.84 ± 9.09	8.98 ± 3.67
60 bar	11.77 ± 10.20	21.21 ± 12.06

* Results representing mean ± standard deviation (n=10)



Lidocaine Recovery on Skin Surface



Characterization and Dermal Penetration of Non-drug Particulates (Introduction)

Characterization of Non-drug Particulate after Emission by PowderJect® Devices (see below) and Non-drug Particle Analysis and Skin Penetration after Emission by PowderJect® Devices (see below) were addressed because of the possibility for non-drug particulate-induced protracted dermal irritation (see local tolerance), systemic toxicity,

foreign object carcinogenicity (solid state carcinogenicity), and phototoxicity (see local tolerance). Characterization of non-drug particles from PowderJect® devices actuated into collection vessels were evaluated in a series of non-GLP studies. Dermal penetration of human cadaver skin by non-drug particles from PowderJect® devices purposely overloaded with potential non-drug particulates or PowderJect® devices of varying specifications, including the proposed drug product, were evaluated in a series of non-GLP or ISO compliant studies, respectively.

The potential non-drug particulates include:

(b) (4)

It is anticipated that few non-drug particles are of sufficient size (>25 µm) to penetrate to the skin. This statement is based on:

1) batch analysis for release testing of four lots of the Sterile LHM Product manufactured in 2006 (21 bar pressure, 10 µm (b) (4) film, and 0.5 mg LHM) using standard testing (USP <788>) showed that devices generated, on average, 165 to 224 particles > 10 µm and 15 to 40 particles > 25 µm. The non-drug particulate data for the Sterile LHM Device show that greater than 90% of the particles found are less than 25 µm.
2) ability of particles to penetrate into the skin is a function of their size, density and velocity (Kendall, 2000). The LHM device entrains particles in a high velocity gas flow in order to accelerate them to velocities suitable for skin penetration. The velocity achieved by a particle in a given gas flow is a function of the particle shape, size and density. Therefore, the ability of a particle delivered by a LHM Device to penetrate into the skin is a function of the particle shape, size and density. The ability of particles to penetrate the skin will tend to decrease with decreasing particle size. Particles with a diameter greater than 25 microns are therefore considered more likely to penetrate the skin than particles with a diameter lower than 25 microns.

Characterization of Non-drug Particles after Emission by PowderJect® Devices

Early in development of PowderJect® ND1 devices, it was observed that the number of (b) (4) particles was reduced by substituting trilaminar (TL) cassettes for 7-piece cassettes in the device. Devices were actuated into collection vessels and (b) (4) was

analyzed using light obscuration and Coulter counting for particle size and number and by UV/Vis spectroscopy for composition. Devices containing empty TL cassettes produced approximately 10-fold less (b) (4) than devices containing empty 7-piece cassettes (5.7 µg/actuation compared to 54 µg/actuation). Addition of a 3 mg, 38-53 µm mannitol charge to the TL cassettes increased (b) (4) 2-fold at the same (60 bar) pressure but had no impact at 40 bar pressure. (b) (4) mass emitted from ND1 devices with TL cassettes (empty and loaded) ranged from 4 to 15 µg/actuation. Particle size distribution indicated that 50-68% of the particles were >10 µm size, but, on average, fewer than two particles per device were >25 µm in size. Particle morphology consisted of flakes or strands with thickness thinner than 20 µm film. There were no spheres present. Although the relative distribution of particles was comparable using Coulter counting, the total number of particles counted per device by this method was considerably fewer than by the light obscuration method (18.7 versus 94.4 per device). It was reported that the morphology and size distribution of (b) (4) particles is such that the probability of these particles penetrating skin is extremely low. (studies DEV.1998.012 & DEV, 1998.013)

Particle sizes were characterized for PowderJect® ND5.3 devices with 10 µm (b) (4) film, 20 bar helium pressure, and 0, 0.25, and 0.5 mg LHM (mean 35 µm particle size). Devices were actuated into a particle collection apparatus and analyzed by a light obscuration method. Two devices were actuated in Trial 1 and ten devices were actuated in Trial 2. In Trial 1, the average number of particulates ≥10 µm was 119, 217, & 105 for 0, 0.25 and 0.5 mg LHM devices, respectively, and the average number of particles ≥25 µm was 0, 14, & 7 respectively. In Trial 2, the average number of particulates for these devices that were ≥10 µm was 244, 314, & 202 respectively, and that were ≥25 µm were 20, 19, & 14, respectively. No more than 20 of the non-drug particles that were emitted from ND5.3 devices (per device) were reported to be of sufficient size (≥25 µm) to penetrate more than superficial layers (stratum corneum) of skin. ((b) (4) memorandum)

The amount of (b) (4) ((b) (4) fragmenting from the British Oxygen Company (BOC) microcylinder was measured using a PowderJect® ND5 device with 40 bar pressure actuated into collection vessels. Light obscuration was used for particle sizing and counting and ICP-MS was used to determine composition. Without the in-line filter in place there was an average of 28 µg (b) (4) per 10 actuations (2.8 µg (b) (4) per actuation). With the in-line filter in place, as will be the case in the proposed drug product, (b) (4) mass was reduced to 0.28 µg per 10 shots (0.028 µg per shot), which approaches background levels in blank samples. As the BOC cleaning process improved, (b) (4) was detected at an average of 1.2 µg per shot without filter and 0.034 µg/shot with the in-line filter. It was reported that the level of (b) (4) that already exists in the human body is roughly 900 ppb by weight. Thus, a person weighing 70 kg would contain over 63 µg of (b) (4) in their body. What exits the Dermal PowderJect® System represents less than one nine-hundredth of this value. However, what exists in the human body will not take the form of solid particles. In addition, minimal epidermal penetration is expected as particle sizes ≥25 µm needed for epidermal penetration and measured particles were: 14-240 particles (8.4-14% of total) at ≥10 µm, 0 to 9 particles (0.00 to 0.48% of total) at ≥25 µm, and only a single particle ≥50 µm. (study PJT NR 018)

The amount of [redacted] fragmenting from the British Oxygen Company (BOC) microcylinder was measured using PowderJect® ND5.2 devices that were actuated into collection vessels (50 actuations pooled for devices with 20 bar BOC microcylinders with and without an in-line filter and 25 actuations pooled for devices with 25 bar BOC microcylinders with an in-line filter). ICP-MS was used to determine composition. The average [redacted] emitted per actuation of the devices was 0.047 µg (for devices at 20 bar with an in-line filter), 0.147 µg (for devices at 20 bar without an in-line filter), and 0.070 µg (for devices at 25 bar with an in-line filter), which are consistent with data reported previously. The average amounts of [redacted] emissions, (calculated from iron content) per actuation were 0.014, 0.014, and 0.029 µg. Increasing the pressure, increases particulate emission, removal of the filter increases [redacted] emission. The filter itself does not contribute to the amount of [redacted] particulates entrained in the helium gas flow. (study LID 0014 DD RT)

The amount of [redacted] and monomer styrene emitted in to a collection vessel from twenty PowderJect® ND5.3A devices containing Sterile Lidocaine Hydrochloride Monohydrate (LHM) Product was measured. Collected and analyzed by GC-MS as a single sample, the amount of [redacted] were below the level of detection (160 ppm). Therefore, the level of [redacted] emitted during actuation of the Sterile LHM Product is negligible. (study WO 600352B)

Non-drug Particle Analysis and Skin Penetration after Emission by PowderJect® Devices

The objective of study 2203/001 was to determine the appropriate histological procedures to be used for the examination of fired particles in skin tissue in subsequent *in vitro* and *in vivo* studies and the intradermal distribution and penetration of particles generated during the firing of various PowderJect® ND5.3 devices. The dermal penetration of fragments from PowderJect® ND5.3 was reported as part of the development and validation of histological techniques. Devices with in-line, [redacted] filters, and pressurized at 30 bar with 10 µm [redacted] film were loaded with 0.5 mg [redacted] fragments upstream of the filter or pressurized at 40 bar and loaded with 0.5 mg [redacted] (70 µm particle size) upstream of the filter, 0.05 mg [redacted] (70 µm particle size) downstream of the filter (only for comparison purposes to upstream of filter values), or containing a BOC [redacted] upstream of the filter were actuated in triplicate on full thickness porcine skin (fresh; mid-dorsal flank), human skin (fresh; dissected from amputated upper leg; used for [redacted] device only), and human skin (frozen and thawed from cadaver upper and lower backs; four separate donors but only one donor used per device). Adjacent areas were used for controls. Sites were fixed, stained, and examined by light microscopy for particle numbers (described as very few, few, several, or numerous without further clarification/quantification of terms), for depth of particle penetration, and for particle morphology. Particles were either on the surface and within stratum corneum, within strata granulosal and spinosal layers of epidermis, within collagenous dermal tissue, or within the dermis. Non-drug particles could be distinguished from one another based on their size, shape, and color. The distribution of [redacted] particles in fresh and frozen human skin was similar. Particles were detected in all

human and porcine skin specimens. The majority of (b) (4) particles did either not penetrate or were confined to the stratum corneum of the epidermis. A few (b) (4) particles were visible in strata granulosal and spinosal layers of the epidermis and a few were visible within collagenous dermal tissue. A single isolated particle was present in the dermis. (b) (4) particles penetrated porcine skin more poorly, with only very few particles detected in the strata granulosal and spinosal layers and no particles detected in collagenous dermal tissue or in the dermis. (b) (4) particles loaded downstream of the filter (not representative of the proposed drug product) were present in all human skin specimens and two of three porcine specimens. In human tissue, several particles were present on the skin surface, within the stratum corneum, and within strata granulosal and spinosal layers, a few were detected in the collagenous dermal tissue, and none were present in the dermal layer. Porcine skin had fewer particles present on the surface and in the stratum corneum, strata granulosal and spinosal layers, and none in the collagenous dermal tissue or dermal layer. (b) (4) particles emitted from devices in which they were loaded upstream of the filter were detected in two of three human specimens and in none of the porcine specimens. Their distribution in human skin was described as occasional on the surface and in the stratum corneum, strata granulosal and spinosal layers, and none in the collagenous dermal tissue or dermal layer. (b) (4) particles were detected in three of three human skin specimens but in none of the three porcine specimens. When detected, they were described as only being occasionally noted on the surface and in stratum corneum, strata granulosal and spinosal layer, and when observed, they were aggregated in clusters and occasionally present between the keratinous layers encircling hair shafts. No (b) (4) particles were detected in collagenous dermal tissue or in dermal layers of human skin. Control samples from all three types of skin specimens had 2-3 birefringent particles that did not penetrate the skin as they were not contiguous with the skin tissue. Relative to particle load, very few particles penetrated skin. (b) (4) and (b) (4) upstream of the filter penetrate human skin poorly (with only occasional particles in the strata granulosal and spinosal layers), compared to particles downstream of the filter, as would be expected. Maximum penetration of (b) (4) loaded downstream of the filter is into collagenous dermal tissue. Maximum penetration of (b) (4) (with exception of a single particle) is collagenous dermal tissue. Penetration of non-drug particulates into porcine skin relative to human skin is poor. Penetration into fresh and freeze thawed human skin appears comparable.

The amount of non-drug particulate released into collection vessels with varying the thickness of (b) (4) ((b) (4) film and the penetration into human cadaver skin by (b) (4) was evaluated by HPLC and UV detection using PowderJect® ND5 devices with 30 bar canister pressure and 10 or 20 µm (b) (4) film thickness. Two-piece cassettes using 20 µm (b) (4) film generated almost no (b) (4) debris. The cassettes with 10 µm (b) (4) film had a higher incidence of generated debris as quantifiable amounts ranged from 0.9-27.7 µg with an average of 11.2 µg. For the skin penetration part of the study, the devices with 20 µm (b) (4) film had no detectable particles. For the devices with 10 µm film, two skin samples of ten had a detectable amount of debris. Mean exposure levels were as follows: 35-53 ng (b) (4) actuation for 20 µm (b) (4) film with 30 bar pressure and 1.2-1.3 µg (b) (4) actuation for 10 µm (b) (4) film with 30 bar pressure. (b) (4) emission was variable and only detected for three out of 100 ND5 devices with 20 µm (b) (4) film and 25 out of 100 ND5 devices with 10 µm

film. No measurable (b) (4) was recovered from skin following 10 actuations of either device. (study DV1999.015)

Using early stage development PowderJect® devices, (b) (4) ((b) (4) penetration was determined in human cadaver skin after overnight extraction in solvent and compared to total (b) (4) emitted into collection vessels by HPLC and UV detection. PowderJect® ND1 devices were used (60 bar pressure; 20 µm (b) (4) film) with 7-piece empty cassettes, trilaminar (TL) empty cassettes and TL cassettes containing 3 mg (25-55µm) Lidocaine Hydrochloride Monohydrate (LHM). To determine skin penetration of (b) (4) ten actuations of the device were made to the same spot and repeated at five different locations on the skin. The recovery of (b) (4) from single actuations with TL cassettes (empty and filled) identified only 5 of 10 and 4 of 10, respectively, containing enough (b) (4) to be quantifiable (LLOQ = 2 µg), and the amounts in these samples ranged from 4-91 µg. (b) (4) in skin samples was measurable at 3 of 5 sites for empty 7-piece cassettes ((b) (4) = 4.8-14.5 µg/10 actuations), at 2 of 5 sites when for empty TL cassettes ((b) (4) = 2-3.2 µg/10 actuations), and at 1 of 5 sites with TL cassettes filled with 3 mg of LHM were used ((b) (4) = 2 µg/10 actuations). The levels of (b) (4) in skin, when detectable, were low (2-14.5 µg/10 actuations) relative to levels emitted. Evaluation of the values of (b) (4) recovered from the skins samples treated with 10 actuations indicate that, on average <0.2 µg of (b) (4) are delivered to the skin per actuation. This amount represents a small percentage of the total amount of (b) (4) generated upon actuation. (study BO PC01 98)

With the purpose of determining the intradermal distribution and penetration of (b) (4) ((b) (4) and other particles generated during the firing of various PowderJect® devices and to assess the extent of tissue damage, penetration of particles into full thickness human cadaver skin using PowderJect® ND5.3 devices containing 0 mg of Lidocaine Hydrochloride Monohydrate (LHM) at 40 bar pressure, 0.5 mg of LHM at 20 or 40 bar pressure, and 3.0 mg of LHM at 40 bar pressure was determined. Devices were actuated in triplicate skin obtained from three different donors using skin from back or abdomen (n = 9 actuations per configuration). Visible particles from fixed and stained sections were counted and assigned to depths of penetration. In addition, a qualitative microscopic histopathological assessment of each section was made. All of the particles seen were black, irregular in shape, and, for the most part, present in the center of sections. No particles were birefringent, therefore were not (b) (4) Distribution of particles through the tissue was similar for each device type, with 55-69% of total particles in the outer epidermis near the stratum corneum, 29-43% in the stratum corneum, and 1.3-3% in other, deeper layers of the epidermis. With only one exception (a single particle discharged from the device containing 3.0 mg LHM at 40 bar (0.2% of total particles counted), no particles penetrated the dermis. Actuation of these devices resulted in occasional penetration of particles through the stratum corneum to other layers of the epidermis (<1 particle per actuation), and extremely rare dermal penetration (a single particle out of 36 actuations; found following use of a device at the highest dose, 3.0 mg and pressure, 40 bar). The absence of birefringent particles indicates no skin penetration by (b) (4) though the particles could not be further identified. Tissue damage in the form of small holes in the epidermis was dose related. Tissue damage in the form of small holes in the dermis was rare. (study 2203/006)

With the purpose of determining the intradermal distribution of (b) (4) ((b) (4) and other fragments generated during the firing of PowderJect® devices, penetration of particles into full thickness human cadaver skin was determined in another study using PowderJect® ND5.3 devices containing 0.5 mg of Lidocaine Hydrochloride Monohydrate (LHM) of 35-40 µm nominal diameter at 20 bar pressure. This device is comparable to the proposed drug product. Actuations were in triplicate on full thickness frozen/thawed cadaver skins obtained from the central back of one donor, the antecubital fossa of another donor, and the back of the hand of another of these geriatric donors. Adjacent areas, which received no actuation of the device, were used as controls. Samples were fixed and stained and evaluated microscopically for particle counts. Penetration depth levels of 1-4 were used where level 1 had no penetration (particles not contiguous with the epidermis) and level 4 was dermis penetration. Particles transcending two or more depth levels were assigned to the deepest level, dermis penetration. Scoring for the number of particles was semi-quantitative with descriptors of none, occasional (1-5), few (6-10), several (11-20) and many (> 20) particles. Nine of 28 slides, 9 of 28 slides, and 13 of 28 slides from the back of the hand, antecubital fossa and back, respectively, had occasional (1-5) particles not contiguous with the surface of the skin, and 2 of 15 slides from the antecubital fossa had a few particles (6-10) at this depth. Nine of 28 slides, 4 of 15 slides and 8 of 16 slides from these respective sites had occasional particles in the stratum corneum and 3 of 15 slides from the antecubital fossa also had a few particles (6-10) at this depth. One of 28 slides from the back of hand, 1 of 15 slides from the antecubital fossa, and 2 of 16 slides from the back had occasional (1-5) particles within the other layers of the epidermis No particles were observed within the dermis following actuation of the ND5.3 device. Non-drug particle penetration in human cadaver skin following ND5.3 device actuation was comparable at all anatomical sites evaluated. Particle numbers decrease with increasing depth of penetration. Tissue damage was limited to splits and holes in the epidermis for dosing conditions similar to that for the proposed drug p product. (study 2203/009)

The purpose of study 2203/007-D66149 was to determine the penetrative depth of various fragments in human cadaver skin, generated during the firing of PowderJect® 5.3 devices that contained different possible contaminants of the devices under more extreme specifications than the proposed drug product (e.g., 40 bar pressure). Penetration of particles into full thickness human cadaver skin was determined using PowderJect® ND5.3 devices at 40 bar pressure containing either (b) (4) ((b) (4) loaded upstream of the filter (0.5 mg, 20-200 µm particle size), 0.5 mg (b) (4) ((b) (4) loaded upstream of the filter (20-300 µm particle size), 0.05 mg (b) (4) loaded downstream of the filter (20-300 µm particle size), silicone composite ball loaded upstream of the filter, or (b) (4) ((b) (4) 0.05 mg, 20-150 µm particle size). Devices were actuated in triplicate on each of three full thickness cadaver skins (from backs of three different donors; n = 9 actuations per type of loaded device). This device configuration is not relevant to the final device design and is included here only for completeness of reporting. Actuation sites were fixed, stained, and evaluated using a quantitative microscopic measurement of penetrative depth of the individual particles that utilized a calibrated image analysis system for each section of tissue. For each different particle

load, a total of 180 sections were evaluated (20 per device actuation). Only particles that were contiguous with the stratum corneum or penetrated deeper than the skin surface were counted. Over 4000 particles were counted in sections evaluated from devices loaded with (b) (4) particles. Of these, only 6.7% penetrated the skin, with an average depth of penetration of 28 µm and a maximum depth of 95 µm (from raw data; report indicates maximum depth of 82 microns). Three particles from the nine actuations (<1 per actuation) were at depths >70 microns. Most of the particles were birefringent, but approximately 3.2% were black in appearance, some of which penetrated the stratum corneum to deeper layers of the skin. A total of 515 particles were counted in sections evaluated from devices loaded with 0.05 mg aluminum downstream of the filter (not relevant to proposed drug product and only included for comparative purposes as these values should be relatively higher than those for aluminum upstream of the filter). All particles were black, irregular in shape, and variable in size. Of these, 13% penetrated the epidermis and dermis, with an average depth of 53 µm and maximum depth of 142 µm. Only 15 particles (<2/device) penetrated to a depth >70 µm. A total of 348 particles were counted from devices loaded with 0.5 mg aluminum upstream of the filter (this configuration is relevant to the final device design). Again, the vast majority (all but 3.7%) was contiguous with the skin surface. Of the 12 particles that did penetrate the skin, the average depth was 71 µm, the maximum depth was 172 µm, and only six particles (<1/device) were counted at a depth >70 µm. A total of 515 particles were counted from devices containing (b) (4) 3.3% of which penetrated the skin but only to a maximum depth 31 µm (mean depth of 11 µm). Only 33 silicone particles were counted, and none of these penetrated the skin. There was no tissue damage with firing devices loaded with silicone composite balls. Actuation of devices loaded with (b) (4) (b) (4) (downstream and upstream of filters), or (b) (4) was associated with tissue damage recorded as splits, indentations and holes which were mostly limited to the epidermis, with occasional areas affecting the dermis to a maximum depth of 125, 160, 100, and 31 µm, respectively. Very few of non-drug particles emitted from particle loaded devices penetrated human cadaver skin. Silicone particles do not penetrate skin at all, (b) (4) particles rarely penetrate to depths >20 µm, and <1 (b) (4) particle per device and <1 (b) (4) particles per device (when loaded upstream of filter) penetrated to depths >70 µm, which, depending upon epidermal thickness, could potentially put it them in the dermis. Note that canister pressure was 40 bar; double that in the proposed drug product.

No studies have been performed to investigate how long non-drug particles resulting from device actuation persist in skin. Under normal use, none to few particles penetrate the dermis. It is therefore expected that any particles that do penetrate the skin would be shed at the same rate as skin turnover. Skin turnover will be discussed in the Toxicology section 2.6.6.9 (Conclusions and Recommendations) at the end of this section.

Special toxicology studies: phototoxicity

- see previous local tolerance section for irritation/phototoxicity study (study ACZ00009)

2.6.6.2 Single-dose toxicity - no studies were conducted for the proposed drug product as for old, well-understood drugs with significant clinical experience these studies are not required (see referenced drugs for lidocaine)

2.6.6.3 Repeat-dose toxicity

Study title: Sterile LHM Product: A Two-Week Dermal Toxicity Study in Gottingen Minipigs®

Key study findings:

- One, two, or three successive actuations of the proposed drug product, a PowderJect® 5.3A device containing Sterile LHM Product (0.5 mg/actuation), onto the same skin site of Gottingen Minipigs® for 14 consecutive days caused no erythema, edema, or histologically confirmed skin damage (only local tissue was evaluated histologically)
- No systemic effects or other effects of treatment were observed
- The NOAEL for local dermal toxicity was three actuations per day and for systemic toxicity was 3 mg lidocaine/day by dermal administration for 14 days for the PowderJect® device containing Sterile LHM Product

Study no.: 1074-004
Volume #, and page #: electronic submission for NDA 21-114 (March 2, 2007; N-000-BP); 295 pages
Conducting laboratory and location: (b) (4)
Date of study initiation: November 1, 2006 (report date February 26, 2007)
GLP compliance: yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: Sterile LHM Product, lot no. ANSV000000004, % purity not reported (drug product supplied in 0.5 mg pouches by sponsor)

Methods

Doses: 0.5, 1.0, 1.5 mg of Sterile LHM Product by 1, 2, or 3 actuations, respectively, of the PowderJect® 5.3A (needle-free dispenser) to each animal as listed in the table; naive control and alcohol wipe control (all sites except naive control wiped with alcohol prior to dosing). Total daily dermal dose of 3.0 mg lidocaine. See table for dosing schedule.

STUDY DESIGN

GROUP	CONCENTRATION (mg)	DAYS DOSED	NUMBER OF ACTUATIONS	SITE	NUMBER OF ANIMALS M/F
1	0.5	1-14	1	1	3/3
	1.0	1-14	2	2	
	1.5	1-14	3	3	
	0.5	13-26	1	4	
	1.0	13-26	2	5	
	1.5	13-26	3	6	
	0 (alcohol control)	--[a]	0	7	
	0 (naïve control)	--	0	8	

[a] Site 7 will be wiped with an alcohol wipe in the same manner as the treated groups.

Species/strain: experimentally naive Gottingen Minipigs®
Number/sex/group (main study): 3/sex with 1 test group
Route, formulation, volume, and infusion rate: dermally using the proposed drug product
Satellite groups used for toxicokinetics or recovery: none
Age: 5 months old
Weight: 9.85 to 12.75 kg (males) and 12.40 to 12.90 kg (females)
Sampling times:
Unique study design or methodology (if any):
- proposed drug product was used in these tests
- each animal used for both dermal application periods
- 1-3 actuations of the dispenser using different sites for days 1 to 14 and 13 to 26 (see table above)

Observations and times:
Mortality, morbidity, injury, and availability of food and water: 2x daily
Clinical signs: weekly
Dermal Irritation: The test sites were evaluated for dermal irritation at 1, 4, and 24 hours post the initial and last dose (Days 1 and 14 for sites 1 to 3 and 7 to 8 and Days 13 and 26 for sites 4 to 6 and 7 to 8) and daily on non-dosing days using the Draize scale for scoring skin irritation.

Erythema and Eschar Formation	
Score	Observation
0	No erythema
1	Very slight erythema (barely perceptible)
2	Well defined erythema
3	Moderate to severe erythema
4	Severe erythema (beet redness) to slight eschar formation (injuries in depth)
Maximum possible score = 4	

Edema Formation	
Score	Observation
0	No edema
1	Very slight edema (barely perceptible)
2	Slight edema (edges of area well defined by definite raising)
3	Moderate edema (raised approximately 1 millimeter)
4	Severe edema (raised more than 1 millimeter and extending beyond area of exposure)
Maximum possible score = 4	

Draize, J.H., Woodard, G., and Calvery, H.O. (1944). Methods for the Study of Irritation and Toxicity of Substances Applied Topically to the Skin and Mucous Membranes, J. Pharmacol. Exp. Ther., 82:377-390.

Body weights: upon arrival and on Days -1, 7, 14, 21, and 28 during the study
Food consumption: none
Ophthalmoscopy: pretest and prior to termination
EKG: pretest and prior to termination. Standard ECGs (6 Lead) were recorded at 50 mm/sec. Using Lead II (or another appropriate lead) recorded at 50 mm/sec, the RR, PR, and QT intervals, and QRS duration were measured and heart rate was determined. Corrected QT (QTc) interval was calculated using a procedure based on Fridericia.
Hematology: pretest and prior to termination (fasted with water access)
- leukocyte count (total and differential), erythrocyte count, hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration (calculated), absolute and percent reticulocytes, platelet count, prothrombin time, activated partial thromboplastin time

Clinical chemistry: pretest and prior to termination (fasted with water access)
- alkaline phosphatase, total bilirubin (with direct bilirubin if total bilirubin exceeds 1 mg/dL), aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, sorbitol dehydrogenase, urea nitrogen, creatinine, total

protein, albumin, globulin and A/G (albumin/globulin) ratio (calculated), glucose, total cholesterol, electrolytes (sodium, potassium, chloride), calcium, phosphorus

Urinalysis: none

Gross pathology: at termination, animals were examined carefully for external abnormalities including masses. The skin was reflected from a ventral midline incision and any abnormalities were identified and correlated with antemortem findings. The abdominal, thoracic, and cranial cavities were examined for abnormalities and the organs removed, examined, and, where required, placed in fixative. All designated tissues were fixed in neutral buffered formalin, except for the eye (including the optic nerve) and testes, which were fixed using a modified Davidson's fixative7. Formalin was infused into the lung via the trachea.

Organ weights: adrenal gland, brain (cerebrum, midbrain, cerebellum, medulla/pons), epididymis, heart, kidney, liver, lung, ovary, pituitary, mandibular salivary gland, spleen, testis, thymus, thyroid gland

- paired organs weighed together

Histopathology: Adequate Battery: yes (x), no ( )—explain

Peer review: yes ( ), no (x)

- full battery of tissues collected and preserved, but only dermal application site (treated and untreated) and gross lesions were evaluated (none noted)

Results

Mortality: none

Clinical signs: nothing remarkable

Dermal Irritation: No erythema or edema was noted during the dosing interval at any test site, whether 1 to 3 actuations of the dispenser.

Body weights: nothing remarkable

Ophthalmoscopy: nothing remarkable

EKG: nothing remarkable

Hematology: nothing remarkable

Clinical chemistry: nothing remarkable

Gross pathology: nothing remarkable

Organ weights: nothing remarkable

Histopathology: nothing remarkable (only treated and control dermal tissue evaluated)

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2.6.6.4 Genetic toxicology - no studies were conducted for the proposed drug product as for old, well-understood drugs with significant clinical experience these studies are not required (see referenced drugs for lidocaine)

2.6.6.5 Carcinogenicity - no studies were conducted and are not necessary for the proposed drug product as there is no detectable systemic exposure for the single use drug product and, for old, well-understood drugs with significant clinical experience these studies are not required (see referenced drugs for lidocaine)

2.6.6.6 Reproductive and developmental toxicology - no studies were conducted and are not necessary for the proposed drug product as there is no detectable systemic exposure for the single use drug product and, for old, well-understood drugs with significant clinical experience these studies are not required (see referenced drugs for lidocaine)

2.6.6.7 Local tolerance (see written summaries in section 2.6.6.1 and summary tables in section 2.6.7)

2.6.6.8 Special toxicology studies (also see written summaries in section 2.6.6.1 and summary tables in section 2.6.7)

Study title: Contract Histology: Validation study to determine suitable histological techniques in the assessment of various fragment types generated during the activation of PowderJect® devices in human and porcine cadaver skin.

Key study findings:

- The objective of this study was to determine the appropriate histological procedures to be used for the examination of fired particles in skin tissue in subsequent in-vitro and in-vivo studies and the intradermal distribution and penetration of particles generated during the firing of various PowderJect® ND5.3 devices with 10 µm (b) (4) film and containing the following contaminants:
    1. 30 bar pressure, 0.5 mg (b) (4) fragments upstream of the filter,
    2. 40 bar pressure, loaded with 0.05 mg aluminum powder downstream of the filter, 70µm particle size
    3. 40 bar pressure, loaded with 0.5 mg aluminum powder upstream of the filter
    4. 40 bar pressure, loaded with a composite silicone ball upstream of the filter
- Particles could be identified in processed tissue thereby validating histological processing techniques to study the effect of PowderJect® devices on site of application.
- At 30-40 bar canister pressure, greater than the 20 bar to be used in the proposed drug product, few particles penetrated the epidermis with no penetration of the dermis being observed.

➢ Results indicate relative safety of the devices towards the integrity of the skin.

Study no.: 2203/001
Volume # and page #: Module 4 – 13 pages
Conducting laboratory and location: (b) (4)

Date of study initiation: August 2002
GLP compliance: No (in spirit of GLP), ISO 10993, Part 6 compliant.
QA report: yes ( ) no (x)
Drug, lot #, and % purity: see methods

Methods:

PowderJect® ND5.3 devices with 10 µm (b) (4) film manufactured to the following specifications were supplied by the sponsor:

1. pressurized to 30 bar, loaded with 0.5 mg (b) (4) fragments upstream of the filter, with a l0 µm membrane (lot no. 0263SW11).
2. pressurized to 40 bar, loaded with 0.05 mg aluminum powder downstream of the filter, 70µm particle size, with a 10µm membrane (lot no. RES0127).
3. pressurized to 40 bar, loaded with 0.5 mg aluminum powder upstream of the filter, with a 10 µm membrane (lot no. RES0128).
4. pressurized to 40 bar, loaded with a (b) (4) ball upstream of the filter, with a 10 µm membrane (lot no. RES0153).

The devices were stored at ambient temperature from receipt to use.

Four types of skin tissue were used for the application of the (b) (4) containing devices:

Human (fresh)
Porcine (fresh) - adult and juvenile
Human (frozen)

Three types of skin tissue were used for the application of the upstream aluminum, downstream aluminum and silicone-containing devices:

Porcine (fresh) - adult and juvenile
Human (frozen)

Skin tissues were upper back (1 female and 2 males) and mid-dorsal flank (juvenile and adult porcine. The human (fresh) and porcine (fresh) samples were treated on the same day as surgery/necropsy. The human (frozen) tissue was all owed to thaw to room temperature for approximately 2 hours before treatment.

Three replicate fired samples and one unfired control were prepared from each skin type. The tissues were fixed in 10% neutral buffered formalin for a minimum of 3 days, dehydrated in ethanol, cleared in toluene and infiltrated with paraffin wax (melting point 56°C) prior to forming paraffin blocks. Horizontally-orientated sections of 5µm nominal thickness were cut from all blocks at nominal 50 µm intervals, staring at the exposure of stratum corneum on the block face and continuing until substantial dermal tissue was

present. All sections were stained with hematoxylin and eosin and examined by light microscopy.

Results: (see summary table on depth of particles for all four test groups at end of this section)

1. Microscopic appearance and location of (b) (4) fragments:

(b) (4) particles were visible in all treated samples. The particles were irregular in shape and variable in size. The largest particles were approximately 10-20x larger than the smallest visible particles. Particles were unstained with H&E but exhibited a bright white birefringence when viewed with plane polarized light.

Human (frozen)
Numerous particles were visible in the upper tissue section levels that comprised a high proportion of epidermis to dermis. The majority of these particles were either not apparently contiguous with adjacent tissue or confined to the stratum corneum of the epidermis. A few particles were visible in strata granulosal and spinosal layers of the epidermis. A few particles were visible within collagenous dermal tissue. The deeper tissue sections consisted predominantly of dermal tissue. These contained either no particles or an isolated particle in the dermis. One section level of the untreated control sample showed 2-3 birefringent particles not contiguous with adjacent tissue. All other sections of the untreated control sample showed no particles.

Human (fresh)
The location of particles in this tissue type was similar to the location in human (frozen). One section level of the untreated control sample showed a single birefringent particle not contiguous with adjacent tissue. All other sections of the untreated control sample showed no particles.

Porcine (fresh) - adult and juvenile
A few to several particles were visible in upper tissue section levels. Nearly all particles were either not apparently contiguous with adjacent tissue, within the noncellular debris on the surface of the skin, or confined to the stratum corneum of the epidermis. A very few larger particles were impacted into the deeper layers of the epidermis of adult porcine skin, just breaching the stratum germinativum. The deeper tissue sections consisted predominantly of dermal tissue. These contained no particles. One section level of the untreated adult control sample showed 2-3 birefringent particles not contiguous with adjacent tissue. All other sections of the untreated control samples (adult and juvenile) showed no particles.

2. Microscopic appearance & location of aluminum particles loaded downstream of the filter:

Aluminum particles were visible in all human treated samples. Particles appeared black under light microscopy. The particles were irregular in shape and variable in size, the majority being approximately l0-50 μm long along their longest axis.

Several particles were visible in the upper tissue section levels that comprised a high proportion of epidermis to dermis. The majority of these particles were confined to the corneal and spinosal layers of the epidermis. A few particles were visible within collagenous dermal tissue. Some score lines were present on the tissue section in association with dermally positioned particles. The deeper tissue sections consisted predominantly of dermal tissue. No particles were visible in the deeper dermal areas. Aluminum particles were visible in 2/3 adult porcine samples and 3/3 juvenile porcine samples. Particles were less frequent than in the human samples and largely confined to the epidermis. An occasional particle breaching the stratum germinativum was visible in the juvenile pro cine samples.

No particles were visible in the untreated control samples.

3. Microscopic appearance & location of aluminum particles loaded upstream of the filter:

Aluminum particles were visible in 2/3 human treated samples and 2/3 juvenile porcine samples. The particles had a similar irregular appearance to particles in devices downstream of the filter but were generally smaller and occurred less frequently.

An occasional particle was visible in the upper tissue section levels. These particles were confined to the corneal and spinosal layers of the epidermis. No particles were visible within collagenous dermal tissue. No particles were visible in the adult porcine samples.

No particles were visible in the untreated control samples.

4. Microscopic appearance & location of composite silicone particles loaded upstream of the filter:

Small particles were visible in all human treated samples. Particles were colored red/purple to blue under light microscopy. The particles were uniformly circular in shape and less than 5 μm diameter.

The particles were aggregated in clusters and were occasionally present between the keratinous layers encircling hair shafts. No particles were visible in dermal tissue.

No particles were visible in the adult and juvenile porcine samples.

Similar particles were visible encircling occasional hair shafts along one edge of the untreated human control sample.

Depth of Particles

Particle Load	Skin type	Injection Sites With Particles	Depth Scores of Particle Counts			
			Surface + Stratum Corneum	Within the Stratum Corneum and Spinosal Layers of Epidermis	Within Collagenous Dermal Tissue	Within Dermis
(b) (4) (0.5 mg)	human	3/3	numerous	few	few	None to 1
	porcine	3/3	Few--several	very few	none	none
(b) (4) (0.05 mg) Downstream of Filter	human	3/3	several	several	few	none
	porcine	2/3	present (few)	present (few)	none	none
(b) (4) (0.5 mg) Upstream of Filter	human	2/3	occasional	occasional	none	none
	porcine	0/3	none	none	none	none
(b) (4) composite	human	3/3	occasional	occasional	none	none
	porcine	0/3	none	none	none	none

Conclusions:

(b) (4) containing devices

This validation study showed that (b) (4) fragments fired from dermal PowderJect® devices prepared as specified can be retained in human and porcine skin during conventional histology processing/microtomy procedures, and subsequently examined. The slide preparations from all three different tissue types used in this study are suitable for the quantitative evaluation of (b) (4) particles fired from Dermal PowderJect® devices.

In all tissue types, most particles were present either not touching surrounding tissue (on the surface without skin penetration) or only breaching the stratum corneum. The relatively fewer particles seen in the porcine samples compared to the human (fresh) and human (frozen) samples may be due to the increased 'toughness' of porcine skin. There was a marked reduction in the number of particles visible in the deeper (predominantly dermal) sections in both human tissue types (fresh and frozen) and no intra-dermal particles visible in the porcine skin samples. No significant differences were observed between juvenile and adult porcine treated skin samples.

Aluminum (both types) and silicone-containing devices

Aluminum and composite silicone particles fired from Dermal PowderJect® devices prepared to the above specification, can also be retained in human frozen/thawed skin during conventional histology processing/microtomy procedures, and subsequently examined.

The absence of upstream aluminum and silicone particles from the porcine skin samples may be indicative of the more resilient nature of porcine skin compared to human frozen skin. No significant differences were observed between juvenile and adult porcine treated skin samples.

The overall smaller sizes and lower frequency of the aluminum particles in human frozen skin fired from upstream of the filter, compared to those fired from downstream of the filter may be indicative of the filter membrane's ability to retain larger aluminum particles.

In both tissue types, most aluminum particles were present either surrounded by stratum corneum, or embedded in the deeper layers of the epidermis. The relatively fewer particles seen in the porcine samples compared to the human samples may be due to the increased 'toughness' of porcine skin.

The clusters of small particles within hair shaft keratinous layers of the human samples were assumed to originate from the composite silicone ball. The absence of these particles from the more open areas of epidermal tissue may be due to a tissue washing effect during fixation and/or processing. The particles did not indent tissue keratin and therefore were unlikely to be held in place during histology procedures.

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Study title: Histology: Investigative study to determine the distribution of (b) (4) and other fragments generated during the activation of PowderJect® devices in human cadaver skin

Key study findings:

- The objective of this study was to determine the intradermal distribution and penetration of particles generated during the firing of various PowderJect® ND5.3 devices with a 10 µm (b) (4) film.
    1. 0.5 mg lidocaine at 40 bar pressure
    2. 0.5 mg lidocaine at 20 bar pressure
    3. 3.0 mg lidocaine at 40 bar pressure
    4. 0.0 mg lidocaine at 40 bar pressure
    5. control – no treatment
- All of the particles seen were black and irregular in shape; they were mostly present in the center of the sections. These particles were assumed to be aluminum and (b) (4) which would appear birefringent.
- Distribution of particles through the tissue was similar for each device type. No particles or tissue damage were seen on any sections of control tissue.
- The most particles were seen from devices containing only the delivery gas with most of these present adjacent to or within the stratum corneum.
- Tissue damage, in the form of holes in the epidermis and occasionally the dermis was varied across the device types though the degree of damage appeared to be directly

consistent with the amount of lidocaine. Most damage was seen in the devices containing 3.0 mg lidocaine at 40 bar. No holes were seen in the sections from devices that did not contain lidocaine.

- The proposed drug product contains 0.5 mg lidocaine at 20 bar and based on these findings should have no more than minimal potential for skin damage as 3% of the particles were in the epidermis and 0% in the dermis.

Study no.: 2203/006
Volume # and page #: Module 4, 27 pages
Conducting laboratory and location: (b) (4)

Date of study initiation: March 6, 2003 (report date October 2004)
GLP compliance: No (in spirit of GLP). ISO 10993, Part 6 compliant.
QA report: yes (x) no ( )
Drug, lot #, and % purity: devices provided by sponsor and described below.

Methods

Doses: PowderJect® ND5.3 devices with 10 µm (b) (4) film containing different types of contaminant fragments were tested:

1. 0.5 mg lidocaine at 40 bar pressure
2. 0.5 mg lidocaine at 20 bar pressure
3. 3.0 mg lidocaine at 40 bar pressure
4. 0.0 mg lidocaine at 40 bar pressure
5. control – no treatment

Evaluation: Full thickness human cadaver skin (frozen and thawed) obtained at autopsy was used. Dosing was to three replicate samples from 3 donors. Following dosing, the samples were fixed in 10% neutral buffered formalin and processed into paraffin wax blocks. Horizontally oriented sections of nominal 5 µm thickness were prepared form each block at nominal 50 µm intervals. Sections were stained with H&E and evaluated under a microscope.

Evaluation was based on the size and number of particles, their distribution and the potential effect upon tissue morphology by the impact of the pressurized delivery gas. The amount of tissue damage was recorded using the following criteria:

few = 1-3 holes per field
several = 4-6 holes per field
numerous = >7 holes/field

Results:

All particles were black, irregular in shape and varied in size. Most particles and tissue damage were located in the central region of each section.

The amount of tissue damage was recorded using the following criteria:

few = 1-3 holes/splits per field
several = 4-6 holes/splits per field
numerous = >7 holes/splits per field.

The amount of tissue damage was as follows for each group:

1. 0.5 mg lidocaine at 40 bar - The particles were mostly present either close to the epidermis (69%) or within the stratum corneum (29%). 2% of particles were within the other layers of the epidermis and none in the dermis. Tissue damage, in the form of a few small holes, was seen in the epidermis of 14 out of 49 slides (in two out of three specimens).

2. 0.5 mg lidocaine at 20 bar (comparable to proposed drug product) - The particles were mostly present either close to the epidermis (68%) or within the stratum corneum (29%). 3% of the particles were within the other layers of the epidermis and none were seen in the dermis. Tissue damage was seen in all specimens, with varying frequency. Few small holes were seen in 19 out of 55 sections, with 'several' being seen in 2 out of 55 sections. One slide for specimen 4 had a small hole in the dermis.

3. 3.0 mg lidocaine at 40 bar - The particles were mostly present either close to the epidermis (55%) or within the stratum corneum (43%). 1.4% of the particles were within the other layers of the epidermis and one particle (0.2%) was located in the dermis.

Tissue damage was seen in all the specimens with varying frequencies. 'Few' small holes were seen in 18 sections, 'several' in 12 sections and 'numerous' in 16 out of 72 sections. There were also a few holes seen in the dermis of two slides and a single hole seen in the dermis on one slide. A single hole in the epidermis was seen on one section.

4. 0.0 mg lidocaine at 40 bar - The particles were mostly present either close to the epidermis (66%) or within the stratum corneum (33%). 1.3% of the particles were within the other layers of the epidermis and none seen in the dermis. Tissue damage, in the form of splits in the epidermis was seen in 15 out of 24 slides for one specimen. This damage was characteristic of freeze-thaw artifact.

5. Controls - No particles or tissue damage were seen on any section of control tissue.

Tabular distribution of the results for each group follows in a summary and individual tables:

(b) (4)

[redacted]

TABLES

0.5 mg Lidocaine/40 bar

	Depth Score Totals				
Specimen N°	1	2	3	4	N° of Sections
1	30	25	0	0	23
2	74	21	2	0	14
3	27	9	2	0	12
Totals	131 (69%)	55 (29%)	4 (2%)	0	49

Specimen 1 - Few holes in epidermis x 10 slides
Specimen 2 - Few holes in epidermis x 4 slides

0.5 mg Lidocaine/20 bar

	Depth Score Totals				
Specimen N°	1	2	3	4	N° of Sections
4	6	1	1	0	24
5	13	9	0	0	15
6	83	33	3	0	16
Totals	102 (68%)	43 (29%)	4 (3%)	0	55

Specimen 4 - Few holes in epidermis x 10 slides, several holes in epidermis x 1 slide, hole in dermis x 1 slide.
Specimen 5 - Few holes in epidermis x 3slides.
Specimen 6 - Few holes in epidermis x 6 slides, several holes in epidermis x 1 slide.

3.0 mg Lidocaine/40 bar

	Depth Score Totals				
Specimen N°	1	2	3	4	N° of Sections
7	76	105	2	1	24
8	75	36	1	0	24
9	132	79	4	0	24
Totals	283 (55%)	220 (43%)	7 (1.4%)	1 (0.2%)	72

Specimen 7 - Few holes in epidermis x 7slides, several holes in epidermis x 4 slides, numerous holes in epidermis x 6 slides, few holes in dermis x 2 slides.
Specimen 8 - Few holes in epidermis x 8 slides, several holes in epidermis x 5 slides, numerous holes in epidermis x 3 slides, hole in epidermis x 1 slide, hole in dermis x 1 slide.
Specimen 9 - Few holes in epidermis x 3 slides, several holes in epidermis x 3 slides, numerous holes in epidermis x 7 slides.

0.0 mg Lidocaine/40 bar

	Depth Score Totals				
Specimen N°	1	2	3	4	N° of Sections
10	51	45	1	0	24
11	148	70	5	0	24
12	161	63	1	0	24
Totals	360 (66%)	178 (33%)	7 (1.3%)	0	72

Specimen 11 - Few splits in epidermis x 15 slides.

Controls

	Depth Score Totals				
Specimen N°	1	2	3	4	N° of Sections
13	0	0	0	0	8
14	0	0	0	0	8
15	0	0	0	0	8
Totals	0	0	0	0	24

Conclusions:

There were no particles seen on any control tissue samples.

On all other samples, a number of particles were present on the slides. These particles were varied in size, and all black in appearance. No particles were seen which were characteristic of (b) (4) fragments (birefringent under polarized light).

The most particles were seen from devices containing only the delivery gas. Most particles were either adjacent to or in the stratum corneum, with only 1.3% penetrating further into the epidermis.

The particles seen from the 3.0 mg lidocaine at 40 bar pressure devices were less in number than the unloaded, no drug devices, but a similar percentage of particles penetrated into the epidermis and one particle (0.2%) was present in the dermis.

The devices containing 0.5 mg lidocaine at 40 and 20 bar pressure gave similar numbers (and percentages) of particles detected. Slightly more tissue damage was seen in the 20 bar than in the 40 bar devices as, while both treatments resulted in a few small holes, the 20 bar group also had 2 sections that exhibited several holes and 1 section exhibited small holes in the dermis.

The distribution of particles was similar across all the device types.

Tissue damage, in the form of holes in the epidermis/dermis is varied across the device types. With use of the 0.5 mg lidocaine, 40 bar device, there was very little damage seen (a few holes on 14 slides). Most tissue damage was seen in the devices containing 3.0 mg lidocaine at 40 bar (50 slides had differing degrees of damage – 16 of these with numerous holes). This appeared to be consistent with the increased amount of lidocaine being administered through the skin.

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Study title: Contract Histology: Investigative study to assess penetrative depth of various fragments generated during the activation of PowderJect® devices in human cadaver skin

Key study findings:

- The objective of this study was to determine the penetrative depth of various fragments in human cadaver skin, generated during the firing of PowderJect® devices. Specification of the devises were ND5.3 at 40 bar with 10 µm (b) (4) film, containing the following contaminants:
    1. (b) (4)
    2. 0.05 mg (b) (4) loaded downstream of the filter
    3. 0.5 mg (b) (4) loaded upstream of the filter
    4. (b) (4) loaded upstream of the filter
    5. (b) (4) (b) (4)
- Devices containing (b) (4) expelled more particles than other devices. Those particles that penetrated the skin did not, in general travel through the epidermis. Most of the particles had not penetrated the skin and remained contiguous with the stratum corneum.
- The devices loaded with aluminum downstream of the filler generated slightly more particles than those with aluminum upstream of the filter. A smaller percentage of

particles penetrated the skin from devices with aluminum upstream, compared to those with aluminum downstream, but on average, these traveled further into the skin.
- The devices loaded with [redacted] expelled only a small number of particles, and only a small percentage of these penetrated the skin and traveled through the stratum corneum.
- Silicone loaded devices generated few particles, none of which penetrated the skin.

➢ While there was some degree of epidermal damage associated with the firing of devices loaded with the contaminants (except silicone) with these ND5.3 devices at 40 bar, which was not seen on the control samples, minimal damage is expected at 20 bar.

Study no.: 2203/007
Volume # and page #: module 4, 127 pages
Conducting laboratory and location: [redacted]
Date of study initiation: March 2003 (report date October 2004)
GLP compliance: No (in spirit of GLP). ISO 10993, Part 6 compliant.
QA report: yes (x) no ( )
Drug, lot #, and % purity: see methods

Methods

PowderJect® ND5.3 devices at 40 bar pressure and 10µm [redacted] film containing five different types of contaminant fragments were supplied and identified by the sponsor:

1. [redacted]
2. 0.05 mg [redacted] loaded downstream of the filter
3. 0.5 mg [redacted] loaded upstream of the filter
4. [redacted] loaded upstream of the filter
5. [redacted]

Full thickness human cadaver skin (frozen and thawed) was used for the test firing of devices. The tissue was obtained at autopsy. Tissue from three different donors was used. Each PowderJect® device was applied centrally within an area of marked felt-pen dots, by holding firmly against the epidermal surface of the skin and simultaneously depressing the firing button. A single shot was heard to indicate the device had fired. The test firing of devices was carried out on three replicate samples per donor. Following this, the samples were fixed in 10% neutral buffered formalin. Two adjacent central sections were taken from each firing site and processed into paraffin wax blocks. Twenty vertically orientated sections of nominal 5 µm thickness were prepared from each block at 50 µm intervals. Blocks were cut with the epidermis perpendicular to the blade, to ensure particles were not displaced vertically through the tissue. Sections were stained with hematoxylin and eosin.

Controls
A single unfired sample from each donor was similarly prepared for comparison.

Slide Evaluation
A quantitative microscopic measurement of penetrative depth of individual particles was performed using a calibrated image analysis system for each section of tissue.
The measurement of the depth of each particle was taken from the outer edge of the stratum corneum to the approximate centre of the particle. A qualitative assessment was also made considering the effect of particles on the tissue morphology. Representative photomicrographs were prepared for inclusion into, the study report.

Comparator Photographs
Comparator photographs were included of samples prepared for study 2203/001.
These photographs represent each of the device types for the study fired into DPX mounting media on a glass slide. This was then covered with a coverslip to provide a permanent preparation.

Results:

Summaries of the particle counts and measurements are presented in Tables for each particulate with a chart of penetration depth at end of this section.

Controls
Occasional small black particles (9 in 60 sections) were seen on control sections, these were all contiguous with the stratum corneum, but had not penetrated into the deeper layers of the epidermis. No areas of damage were apparent on these control sections.

(b) (4)

Numerous particles were seen on all sections (many were present in addition to those counted which were not contiguous with the stratum corneum) on the skin surface on the surface without skin penetration (see table 1).

Specimen Number	Number of non-penetrated particles	Number of penetrated particles	Number of sections
1	1226	128	60
2	1434	42	60
3	1127	102	60

Table 1

Most particles seen were irregular in shape and variable in size. These particles demonstrated bright birefringence when viewed using plane polarized light. Over the three specimens, 122 (3.2%) particles were black in appearance, most of these were contiguous with the stratum corneum, but some had penetrated into the epidermis and dermis.

The majority of particles (93.3%) were only present on the skin surface lying contiguous with the stratum corneum. Particles that had penetrated the epidermis (6.7%) traveled an average (mean) of 28 µm with a maximum depth of 82 µm.

Across the sections, there were occasional areas of damage apparent. These were recorded as indents, splits or holes, and appeared to be due to the firing of the device (as there were none of these recorded on control samples). Most of these areas of damage had little or no evidence of particles present and ranged up to approximately 125 µm deep. Occasionally areas of damage were associated with multiple small particles. Most of this damage was limited to the epidermis with occasional dermal damage.

0.05 mg (b) (4) downstream of filter

The particles present on the slides were all black, irregular in shape and varied in size. There were no additional particles to those measured (see table 2).

Specimen Number	Number of non-penetrated particles	Number of penetrated particles	Number of sections
4	165	32	60
5	175	16	60
6	110	20	60

Table 2

The majority of particles (87%) were only present on the skin surface, lying contiguous with the stratum corneum. Particles that had penetrated the epidermis (13%) traveled an average (mean) depth of 49 µm, with a maximum depth of 142 µm.

Across the sections, areas of damage were seen (average 20 per specimen). These were recorded as splits, indents or holes and appeared to be due to the firing of the device (as none seen in controls). These areas of damage had no particles associated with them. Most of the damage was limited to the epidermis with occasional areas affecting the dermis to a maximum depth of approximately l60 µm.

0.5 mg (b) (4) upstream of filter

The particles present on the slides were black, irregular in shape and varied in size. There were no additional particles to those measured (see table 3).

Specimen Number	Number of non-penetrated particles	Number of penetrated particles	Number of sections
7	86	1	60
8	111	10	60
9	139	2	60

Table 3

The majority of the particles (96.3%) were present on the skin surface, lying contiguous with the stratum corneum. The 3.7% of particles that had penetrated the skin traveled an average (mean) of 67 µm, with a maximum depth of 172 µm.

There were a few areas of damage to the skin (average 3 per specimen) which were recorded as splits, indents or holes. All of these areas of damage had no particle associated with them; most of the damage was limited to the epidermis, with occasional areas affecting the dermis to a total depth of approximately 100 µm.

(b) (4)

The few particles present on the slides were black and irregular in shape and relatively small compared to the sizes seen for aluminum. The particles were all contiguous with the stratum corneum, with no penetration of the skin (see table 4).

Specimen Number	Number of non-penetrated particles	Number of penetrated particles	Number of sections
10	5	0	60
11	14	0	60
12	14	0	60

Table 4

There were no areas of damage recorded for these specimens.

(b) (4) ((b) (4)

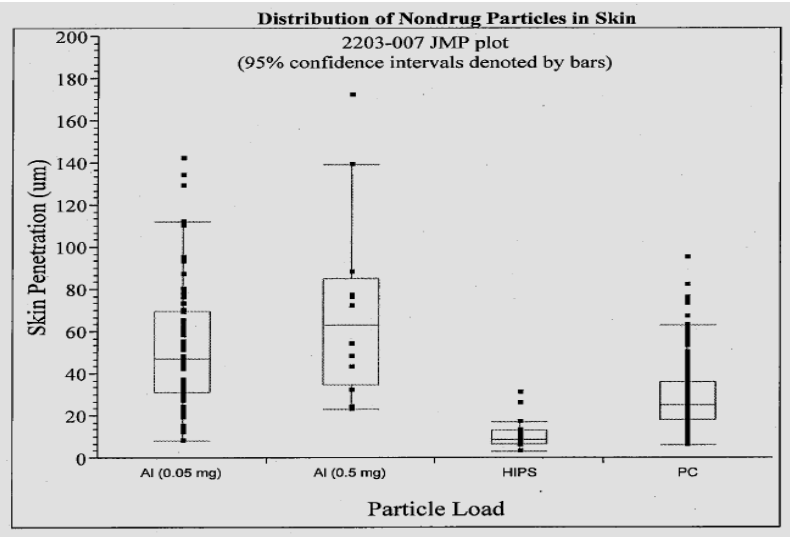
The particles present on the slides were black and irregular in shape, and relatively small compared the sizes seen for aluminum. There were two particles that were measured in the dermis and annotated as such, which were not counted in the summary data. On re-examination, there was no evidence of epidermal or dermal damage associated with these particles (see table 5).

Specimen Number	Number of non-penetrated particles	Number of penetrated particles	Number of sections
13	109	13	60
14	154	3	60
15	235	1	60

Table 5

The majority of particles (96.7%) were present on the skin surface lying contiguous with the stratum corneum. The 3.3% that had penetrated the skin traveled an average (mean) of 9 µm, with a maximum depth of 31 µm.

There were areas of damage present on the sections (average 18 per specimen); these were recorded as splits, indents or holes. There were no particles present associated with these areas. The deepest area was approximately 190 µm deep. Most of the damage was to the epidermis, but occasionally the dermis was affected.



Conclusions:

The (b) (4) loaded devices resulted in many more particles being expelled and remaining with the tissue through histological processing than any of the other devices. Many of these particles were on the skin surface not contiguous with the skin and therefore not counted. Even so, these devices had the highest number of particles counted.

The devices with (b) (4) downstream of the filter generated a similar number of particles than those with the (b) (4) upstream. Although particles were of similar sizes, a smaller number penetrated from the devices with (b) (4) upstream, but on average, these traveled further.

The (b) (4) upstream and (b) (4) devices gave a similar percentage of particles being measured. The (b) (4) particles had a greater range of size and on average penetrated further.

The silicone devices generated only a small number of particles, none of which penetrated the skin.

All of the device types, except (b) (4), appeared to cause damage to the skin, which was not associated with a particle remaining present. These areas were possibly caused by particles hitting the skin on firing the device, and bouncing off prior to histological processing.

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Study title: Histology: Investigative study to determine the distribution and penetration of (b) (4) and other fragments generated during the activation of PowderJect® devices in human cadaver skin.

Key study findings:

- The objective of this study was to determine the intradermal distribution of (b) (4) and other fragment types generated during firing of a PowderJect® device very similar, to the to be marketed product with 35-40 μm diameter particles of 0.5 mg lidocaine at 20 bar pressure.
- Occasional small black particles were seen in control samples adjacent to, but not contiguous with the epidermis. No tissue damage was seen on controls.
- Most of the particles seen on fired skin tissue samples were small and black with medium and large black particles also seen. Small and medium birefringent ((b) (4) particles were also seen across the specimens.
- All of the fired skin tissue specimens (except one) had evidence of tissue damage caused by the lidocaine content of the devices. This was seen as splits and holes in the epidermis.

- One specimen has indented splits in the epidermis that appear to be caused by larger particles.
- ➢ As the proposed drug product contains similar specifications, no more that potential epidermal damage is expected.

Study no.: 2203/009
Volume # and page #: Module 4, 26 pages
Conducting laboratory and location: (b) (4)

Date of study initiation: (report date July 2005)
GLP compliance: No (in spirit of GLP). ISO 10993, Part 6 compliant.
QA report: yes (x) no ( )
Drug, lot #, and % purity: batch no. C0110L001; 35-40 µm diameter particles of 0.5 mg lidocaine at 2-0 bar pressure (consistent with to be marketed product)

Methods

Doses: single actuation of above device
Tissue Samples:
Tissue samples used on this study were:
Skin sites: Central Back, Antecubital Fossa, Back of Hand
Donor type:
90 years old: 2 Caucasian female donors
71 years old: 1 Caucasian male donor
Tissue was obtained at post-mortem and retained frozen until thawed immediately prior to use.

The PowderJect® device was applied onto the skin surface centrally within an area of four marked feltpen dots that described a square approximately 15mm x 15mm. The device was held firmly against the epidermal surface and the firing button depressed. A single shot was heard to indicate the device had fired. The firing of devices was carried out on three replicates per site.

Tissue samples were fixed in 10% neutral buffered formalin for a minimum of 2 days and processed to paraffin wax blocks. Horizontally orientated sections of nominal 5 µm thickness were prepared from each block at nominal 50µm intervals. Sectioning began when approximately 50% of block surface area comprised cellular material and continued until substantial dermal tissue was present. Sections were stained with hematoxylin and eosin.

Controls
A single unfired control from each skin site was similarly prepared for comparison.

Slide Evaluation
A microscopic assessment of the particles visible in each section was made to include a semi-quantitative evaluation of their penetrative depth. Microscopy included observation under plane polarized light. Particle types were identified by their

characteristic appearances as observed in [redacted] (b) (4), where possible. A qualitative assessment of tissue morphology was also made.

The following scheme was used for recording number of particles per section and depth of penetration:

Semi-quantitative assessment
- N – None
- O – Occasional (1-5)
- F – Few (6-10)
- S – Several (11-20)
- M – Many (>20)

Depth level
- 1 Particles not contiguous with epidermis
- 2 Particles within stratum corneum of epidermis
- 3 Particles within other epidermal layers
- 4 Particles within dermis

Particles transcending two or more depth levels were assigned to the deepest level.

Results:

Controls
Occasional small black particles were seen across the control samples. These were all at depth level 1 and were not contiguous with the epidermis. There were no areas of tissue damage on any of the control samples.

Fired Samples
Particles were seen across all fired specimens. These were mostly small black particles with some medium black particles and one specimen with large particles. Some small and medium birefringent particles were also present across the fired specimens.

Most of the particles present were at depth level 1 with occasional particles present at depth level 2, and a few particles present at depth level 2. Occasional particles were present at depth level 3. No particles were seen at depth level 4.

Damage was seen across all fired specimens except one. These were mostly in the forms of splits or holes within the epidermis. Some indents (with spi1ts) were present in the epidermis of one specimen.

No significant differences were found between anatomic sites and/or between donors.

A summary of the results is presented in the following summary and individual tables:

Depth of Penetration

Anatomical Site	Depth Score Estimated Totals from Three Actuations				Number of Sections
	Toughing Surface	Within Stratum Corneum	Within Epidermis	Within Dermis	
Back of hand	9 × (1-5) = 27	9 × (1-5) = 27	1 × (1-5) = 3	0	28
Antecubital fossa	9 × (1-5) + 2 × (6-10) = 43	4 × (1-5) + 3 × (6-10) = 36	1 × (1-5) = 3	0	15
Back of body	13 × (1-5) = 39	8 × (1-5) = 24	2 × (1-5) = 6	0	16

TABLES

Specimens 1-3: Back of Hand (28 slides)

Depth 1	Occasional (9)
Depth 2	Occasional (9)
Depth 3	Occasional (1)
Depth 4	None

Particles small irregular, black and birefringent.
Splits in epidermis of 8 slides (specimens 1 and 3 only)

Specimens 5-7: Antecubital Fossa (15 slides)

Depth 1	Occasional (9), Few (2)
Depth 2	Occasional (4), Few (3)
Depth 3	Occasional (1)
Depth 4	None

Particles small (and medium in specimen 7) irregular, black and birefringer
Splits in epidermis of 10 slides (many in 2 slides)
Holes in epidermis of 2 slides
Indented splits in 2 slides

Specimens 9-11: Back (16 slides)

Depth 1	Occasional (13)
Depth 2	Occasional (8)
Depth 3	Occasional (2)
Depth 4	None

Particles small (medium and large in specimen 9), irregular, black and birefringent particles.
Splits in epidermis of 15 slides
Holes in epidermis of 15 slides.

Specimens 4, 8, 12: Controls (23 slides)

Depth 1	Occasional (7)
Depth 2	None
Depth 3	None
Depth 4	None

Particles small black and irregular.

Conclusions:

Control samples had only occasional small black particles that were not contiguous with the epidermis, and had no tissue damage.

Fired skin tissue samples had particles at all levels of epidermis, but none in the dermis. Particles were mainly small and black with some medium and large black particles. There were also small and medium birefringent particles present which correlate to (b) (4) particles described in (b) (4).

Damage across specimens reported as holes and splits in the epidermis correlates with similar damage seen in (b) (4) which was attributed to the lidocaine content of the devices.

Indented splits appeared to be due to larger particles causing damage to the epidermis but being removed during histological procedures.

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2.6.6.9 Discussion and Conclusions

Nonclinical support for absence of systemic absorption and safety of proposed lidocaine dosing:

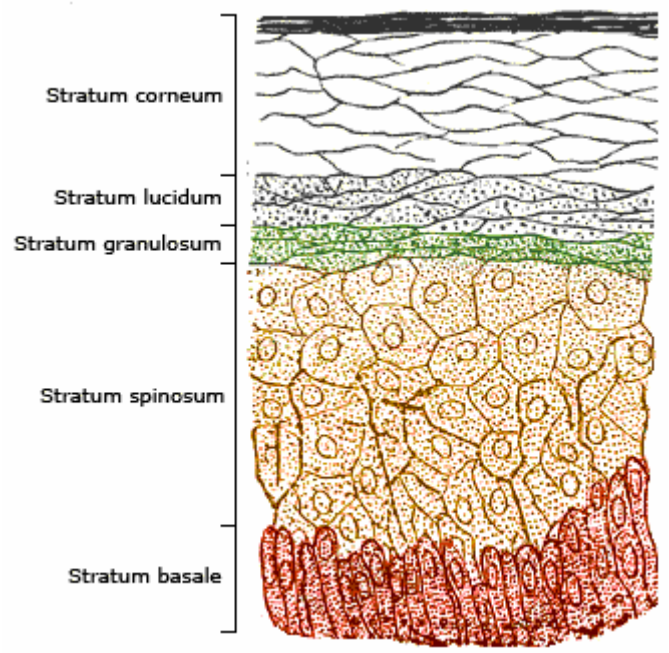
Pharmacokinetic data in humans and minipigs and repeat dose toxicity and local tolerance data in pigs and rabbits support the systemic safety of the dosing with the proposed drug product.

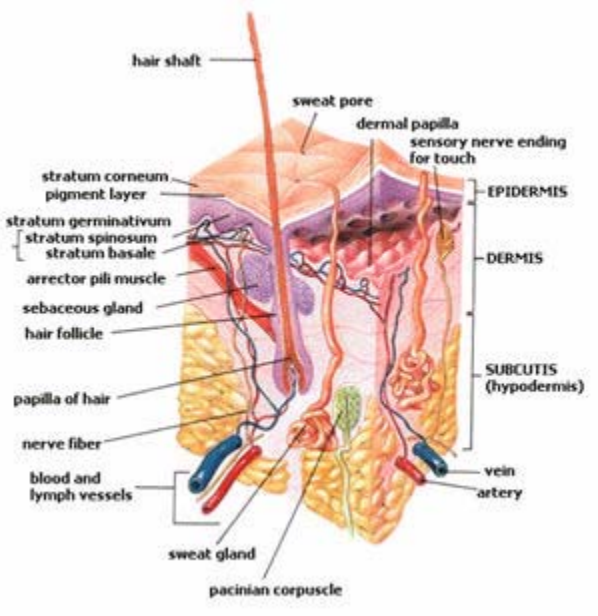
Nonclinical and clinical pharmacokinetic (PK) data both support low systemic exposure to lidocaine. Following a single actuation of the Sterile LHM Product in adult and juvenile minipigs (study 1204-009) and in human adults (study 3268-1-101-001) blood levels were below the lower limit of quantitation (LLOQ) of 5 ng/mL. Three treatments in rapid succession in juvenile pigs (5.5-6.6 kg; approximately half the size of the smallest child in the target population) also support anticipated none to low systemic exposure in humans as blood levels were also below the LLOQ. Systemic concentrations of lidocaine associated with therapeutic cardiovascular effects range from 1500-5500 ng/mL and toxic effects are seen at concentrations >5,000 ng/mL (Benowitz, 1978; Roden 2006). Concentrations associated with systemic effects in infants and children are not well defined; however, in newborns the threshold for production of bradycardia is reported to be 2500 ng/mL and neonatal depression is likely at concentrations exceeding 3000 ng/mL (Dodson 1976). Therefore, nonclinical and clinical observations that all systemic levels of lidocaine following single or triple treatment in minipigs and a single treatment in humans are below or near the LLOQ of 5 ng/mL and well below the levels required for systemic therapeutic (1.5-5 µg/mL) or toxic (2.5-5 µg/mL) effects in newborns and adults supports the safety of the proposed drug product for children (>3 years old) and adults.

An additional indicator of the systemic safety of the proposed dosing comes from the repeat dose and local tolerance studies where lidocaine exposure was in clear excess of the anticipated administered daily dose of 0.5 to 1 mg lidocaine for a single or two actuations of the device, respectively. For single dose studies, maximum lidocaine doses delivered at canister pressure of 20 to 60 bar were as high as 33 mg (study 755-003 - rabbits) and 40 mg (study 2203/008 - pigs) per day, based on emitted dose of 70% of the nominal lidocaine amount of 0.5 mg per actuation. On this basis, the single day systemic safety margin with human administration of 0.5 mg lidocaine is 66-80X. For repeated dosing of lidocaine at 20-40 bar canister pressure in pigs, 2 mg/day for 14 days (study 1074-004), 8 mg/day on 6 of 28 days (study 1683/33), and 29 mg/day on 6 days out of 10 (study were administered, assuming 70% of the nominal dose of 0.5 mg was actually emitted upon actuation of the device On this basis, repeated dose safety margins are 4-59X for systemic toxicity or 2-30 for 2 doses with the drug product on a single day. No changes in clinical symptoms, body weights, or gross necropsy were observed in studies where these observations were conducted. For local tolerance, 1, 2, or 3 actuations per day for 14 days caused no skin effects, identifying adequate safety for the proposed drug product as doses were administered to the same site for 14 days without any local effects. Therefore, both single- and repeat-dose studies using PowderJect® devices support the local and systemic safety of the proposed drug product when used as intended.

Skin structure and clearance of non-drug particulates:

The epidermal layers of the skin and the full skin are pictured, illustrating epidermal penetration and how shallow the penetration of particles actually are relative to the full skin thickness (modified from Grey's Anatomy as contained on Wikipedia) The stratum basale is also known as the stratum germinativum.





Epidermal thickness in humans ranges from approximately 40 to 100 µm for areas other than the fingers where it ranges from approximately 140 to 370 µm in thickness (PJT RN 163).

Penetration and clearance of non-drug particulates from the skin are based on skin turnover rates. Whereas the data on replacement times for the stratum corneum are well known and generally accepted to be approximately 14 days (Nicoll 1972), the data on the replacement times for the nucleated epidermis are more difficult to interpret. Reported replacement time vary from 14 days to 50 days (Epstein 1965, Bauer 2001). More specific to the current situation, gold particles have been used in PowderJect® Systems to carry DNA fragments for delivery. The gold particles are produced for optimal skin penetration and a system designed for vaccine delivery. For the administered dose using a PowderJect® device, of the 15% of the gold particles that could reach the epidermal-dermal junction, the gold was cleared to below the limit of detection in 15 days largely by normal skin sloughing (Norris 1998). The rapid turnover of the gold particles that penetrated into the epidermis together with even the longest estimates of the complete turnover of the viable epidermis and stratum corneum and sloughing of skin suggest that the rare non-drug particles that penetrate into the deep epidermis would be eliminated rapidly. On this basis, non-drug particulates are expected to be removed from the skin as soon as 2 weeks and no more than 5 weeks after treatment without penetration to the vascular dermis and without subsequent systemic absorption.

Characterization and skin penetration of non-drug particulates: \

Non-drug particulates are not considered to present a health hazard risk to the skin based on small particle size (most <25 µm) and essentially no penetration of the dermis with limited damage to the epidermis even under exaggerated conditions.

In studies that evaluated particulate count and size by collecting particles generated into collecting vessels (not into skin) using PowderJect® ND1 devices, 8.7 and 14.8 µg of [redacted] ([redacted] actuation were measured at 40 and 60 bar canister pressure and a 20 µm [redacted] film, respectively, when using 3 mg of mannitol as the drug charge (DEV1998.12 & .13). Using PowderJect® ND5.2 devices with an in-line filter, as will be for the proposed drug product, up to 0.047 and 0.034 µg/actuation of [redacted] ([redacted] was collected at 20 and 40 bar pressure, respectively, with particle size being 8-14% ≥ 10µm, 0-0.48% ≥ 25 µm, and 0-0.2% ≥ 50 µm (PJT NR 018, LD0014 DD RT). [redacted] particles were present at 0.014 µg/actuation at 20 bar pressure (LD0014 DD RT). Using a PowderJect® ND5.3 the number of particles ≥ 10µm were 244, 314, & 202 and ≥ 25µm were 20, 19, & 14 at 0, 0.25, & 0.5 mg lidocaine drug charge using the proposed drug product specifications for the device ([redacted] memorandum). Under similar conditions, the amount of [redacted] were below the lower level of quantitation (LLOQ). All this data indicates low amounts of potential exposure to relevant particle size particles for skin penetration of ≥ 25 µm with anticipated rapid clearance.

PowderJect® ND5.3 devices at 30 or 40 bar pressure were loaded with [redacted], but no lidocaine, and actuated onto human or porcine cadaver skin. Most [redacted] and [redacted] particles were located on the surface or in the stratum corneum with a few particles in the epithelium and no particles in the dermis. [redacted] particles from the pressure canister were occasionally found in the epidermis (2203/001). Under similar study conditions at 40 bar pressure, of the 4000 particles counted, that penetrated the skin (i.e., not on surface), 6.7% of the [redacted] particles penetrated to an average depth of 28 µm with a maximum depth of 95 µm. Less than 1 particle/actuation was >70 µm in diameter. Of the 348 [redacted] particles that penetrated from upstream of the in-line filter, 3.7% penetrated an average of 71 µm with a maximum depth of 172 µm. Less than 1 particle/actuation was >70 µm in diameter. For [redacted]), 3.3% penetrated an average of 11 µm with a maximum depth of 31 µm. [redacted] did not penetrate the skin (2203/007). There was very little skin penetration and skin damage under these exaggerated conditions, supporting the relative safety of the proposed drug product.

Penetration of human cadaver skin using standard PowderJect® devices also indicated little penetration in to the epidermis. For an ND1 device at 60 bar pressure with 3 mg lidocaine and 20 µm [redacted] ([redacted] film, <0.2 µg of [redacted] penetrated the skin per actuation of the device (BO PCO198). Using PowderJect® ND5 device with no lidocaine, 10 or 20 µm [redacted] film, and 30 bar pressure, increased [redacted] was emitted per actuation at 10 versus 20 µm [redacted] film (1.2-1.3 µg/actuation versus 35-53 nanograms/actuation, respectively). No definite skin penetration was observed (DV.1999.015). Using PowderJect® ND5.3 devices with specifications comparable to the proposed drug product specifications, 29% of particles were in the stratum corneum, 68% of the particles were in the epithelium near the stratum corneum, 3% of the particles were in the deeper epithelium, and no particles were in the dermis. Penetrating particles were not [redacted] (2203/006). In another study, few particles were in the stratum corneum and

epidermis with no particles in the dermis. Again, (b) (4) particles did not penetrate the skin (2203/009). Limited penetration to other than the epidermis or more superficial stratum corneum with rapid elimination in renewing skin suggests relative safety of the proposed drug product.

Risk assessments for potential systemic effects: Helium in the device canister and non-drug particulates are not considered to present any health hazard based on use of the proposed drug product under specified conditions of use (i.e., single actuation per intact skin site) for potential for local and systemic toxicity. The list of non-drug particulates that potentially could be generated by actuation of the device, and could therefore be concern for exposure included (b) (4) from the drug cassette, (b) (4) from the nozzle, (b) (4) from the composite ball used to temporarily seal the helium filled (b) (4) from the microcylinder tip that is broken upon device actuation, and (b) (4) from the filter that is employed to minimize the risk of non-drug particles being expelled from devices upon actuation. In addition, foreign body carcinogenesis is a concern for the particles that have penetrated the skin. Of these, (b) (4) and (b) (4) have been measured in emissions from devices and found to be low for PowderJect® ND5 devices under comparable specifications to the proposed drug product (DV1999.015, LID 0014 DD RT, and LID 0014 DD RT, respectively). (b) (4) and monomer styrene were below the lower limit of quantification (2203/007). The presence of (b) (4) was identified in the stratum corneum and some adjacent epidermal layers of cadaver tissue, but not quantified (2203/001). (b) (4) particles could not be generated during actuation of any devices and are, therefore, unlikely to be an exposure concern.

Dermal penetration of helium - The potential for dermal penetration of skin by helium and the potential for embolism formation were addressed using risk assessment (Considerations of induced helium penetration and embolism. AlgoRx Pharmaceuticals, Inc., April 2003). The volume of helium that potentially would diffuse to the capillary bed of intact skin was calculated to be <1 µL. In damaged skin with exposed capillaries, that volume would increase to potentially 0.12 mL under a worst-case scenario, and could potentially pose a risk of embolism. This scenario is extremely unlikely because the Sterile LHM Product is only intended for use on intact skin and, even under conditions of misuse (study 2203-005 – 12 actuations in 1 hour in pigs); tissue damage is limited to reversible microscopic epidermal injury. The conditions that would have to exist for the worst-case scenario for helium embolism (extensive tissue trauma and hemorrhage at the site of injection) have not been observed even following use of far more aggressive devices (pressures up to 60 bar delivering 3 mg of LHM; 2203/004). To address the question of what histological findings would correspond to severe dermal findings (Draize scores of 4) and surface bleeding, pig skin injection sites obtained from a study using prototype devices with a protein as the drug charge were examined microscopically (PJT PC TM 146). Despite the relatively severe appearance of the dermal response, physical damage was limited to the stratum corneum, epidermis, and papillary dermis, and was well distanced from significant arterioles and venules. Even under conditions designed to simulate product abuse (12 closely spaced actuations of the device to the

same site); there was no indication of sufficient tissue disruption to cause vascular damage. Taken together, these studies indicate that direct access of gas or particulates to the systemic circulation following treatment is extremely improbable. Thus, the risk of helium embolism was considered insignificant.

(b) (4) - A risk assessment, related to exposure to (b) (4) Bisphenol A (BPA), and trichloroethylene (TCE) from use of PowderJect® ND5 devices was performed by (b) (4) in August 1999 (EH20054). The drug cassette consists of (b) (4) film heat-sealed onto two (b) (4) washers. During the actuation process these (b) (4) films burst, and some particulate fragments of (b) (4) film material, along with lidocaine, become entrained in the gas flow and emitted from the device. Although (b) (4) is not considered to have toxicological properties, there was a concern that BPA, the monomer from which (b) (4) is constructed, may have endocrine-disrupting properties. The US EPA reference dose (RFD) for BPA (dose not associated with health risks) is a dietary exposure of 50µg/kg-d. Trichloroethylene (TCE), which can leach from (b) (4) particulates, may be carcinogenic at large doses. The U.S. EPA drinking water standard for TCE is 5 µg/L or 143 µg/kg-d at 2L of water/day. Exposure to BPA and TCE via devices is estimated to be far less than required for any effects, especially with limited penetration of skin by (b) (4) particles.

(b) (4) - For ND5 devices with in-line (b) (4) filters, the mean amount of (b) (4) ejected upon device actuation is 0.034 µg/shot (range 0.013-0.076 µg/shot) or a maximum of 1 ng/kg-day for a 70 kg human. The U.S. EPA federal drinking water standard for (b) (4) is 50-200 µg/L or 1.4-5.7 µg/kg-day at 2L/day. Maximum levels of (b) (4) for the proposed drug product are at least 1,400-fold less than the allowable ingestion level. Exposure to (b) (4) via devices is estimated to be far less than required for any effects, especially with limited penetration of skin by non-drug particles with no dermis penetration and rapid clearance from the skin layer. In addition, it was reported that the level of (b) (4) that already exists in the human body is roughly 900 ppb by weight. Thus, a person weighing 70 kg would contain over 63 µg of (b) (4) in their body (0.9 µg/kg or 900 ng/kg compared to the 1 ng/kg dose of (b) (4) per actuation). What exits the Dermal PowderJect® System represents one ninehundreth of the normal body burden for (b) (4) However, what exists in the human body will not take the form of solid particles PJT NR 018. A risk assessment conducted by (b) (4) in November 2002 also supports the lack of safety concern for (b) (4) (8602343).

(b) (4) – These non-drug particulates are not considered a safety issue as levels were below the lower limit of quantitation (LLOQ) with only superficial skin surface penetration (maximum depth of 31 µm) with anticipated rapid clearance.

(b) (4) – While the use of a (b) (4) ball during manufacture of BOC helium filled microcylinders is not considered to present a risk to human safety (PJT DD TM Draft) by the sponsor, as there was no skin penetration under exaggerated conditions of cadaver skin exposure (2203/001), human safety is not considered at risk from (b) (4).

(b) (4) - Attempts failed to generate relevan (b) (4) particles from molded drug cassette components even after dipping in liquid nitrogen and milling, which yielded particulates >1 mm, too large to pass out of the device through the in-line filter. Given the difficulty in generating (b) (4) particles, it is extremely unlikely that (b) (4) particles will be generated during the operation of devices.

(b) (4) – Skin penetration of (b) (4) was measured at 0.014 µg/actuation. Potential health effects are of minimal concern as few particles reached the epidermis with the proposed drug product (2203/009) and rapid clearance is expected.

Foreign Body Carcinogenesis - In addition, as there was a concern that dermal penetration by (b) (4) (and other) non-drug particulates potentially could cause foreign body carcinogenesis, a risk assessment was conducted (Norris 1998). Foreign body carcinogenicity in rodents is associated with large solid implants (not particulates) and is not predictive of carcinogenicity in man. The formation of a thick connective tissue enveloping the implant precedes tumor formation in rodents, and this rarely occurs with implants in non-susceptible species. There is no epidemiological link between implants and incidence of cancers in humans. Predicted depth of penetration for (b) (4) particles from devices in human skin puts very few particles in the dermis (minimizing risk) with rapid clearance of other particles and little risk of cancer developing.

Local tolerance: The safety of the proposed drug product has been demonstrated nonclinically for the proposed conditions of use. The local tolerance of single and multiple actuations for a single day and multiple days of PowderJect® devices ranging in composition from the same/similar to the proposed drug product to greater amounts of lidocaine (up to 6 mg), (b) (4) film size (40 µm), and/or canister pressure (40 bar) conditions were evaluated. Using devices of greater composition specifications than the proposed drug product simulate multiple dosing and misuse of the drug product.

Patterns of multi-dosing were modeled in several studies in the pig, which is considered a good model for assessing dermal tolerance in humans. The three multi-dose local tolerance studies performed included four administrations to independent sites daily for six days over a 28 day period (1683/33), two administrations to the same site at various intervals over a 24 hour period (2203/004), and 12 administrations to a single site over 1 hour (2203/005). The results adequately address multi-dose local tolerance at single and multiple sites as all dosing was well tolerated with no clinical signs of discomfort and minimal, reversible dermal responses.

To further investigate the nature of potential damage in a "worst-case" scenario (PJT-PC-TM-146), biopsies from sites with Draize scores of 4 and surface bleeding (taken from an early development study using the ND1 device delivering 1 mg of a protein versus a lidocaine payload using 60 bar of pressure) were evaluated. Despite the aggressive device configuration and relatively severe appearance of the dermal response, physical damage, consisting of splits in the stratum corneum at the site of particle entry, destruction of underlying epidermal cells, extravasation of red blood cells from particle penetration into the papillary dermis, and the presence of inflammatory (PMN) infiltrate

down to depths of 150-300 microns but not beyond the papillary dermis, were limited to the stratum corneum, epidermis, and papillary dermis, well distanced from the significant arterioles and venules that approach the dermis from the subcutaneous layer.

A study in rabbits in which dermal exposure was preceded by antiseptic pre-swabbing of the site of injection with alcohol or Betadine provided no indication that this common clinical practice will have an impact on the dermal response to the drug product (755-003). The dermal response was comparable with or without antiseptic pre-swabbing of the injection site prior to dosing with the drug product.

Phototoxicity was addressed because non-drug particles that absorb in the UV range are, or potentially could be, emitted from the PowderJect® device. A phototoxicity study (ACZ00009) in hairless mice demonstrated no significant difference in dermal findings on animals administered the device alone, and those administered the device, followed by UV exposure, suggesting that there are no concerns regarding possible phototoxicity regarding drug product use.

2.6.6.10 Tables and Figures

2.6.7 TOXICOLOGY TABULATED SUMMARY

LOCAL TOLERANCE STUDIES TABLES

Overview of Local Tolerance Studies

Study Type	Study Number/ GLP Status	Study Title	Device	Species	LHM Dose & Particle Size	Route	Key Finding or Conclusion
Local Tolerance	1683/33 GLP	Assessment of acute and sub-chronic dermal tolerance to the dermal PowderJect® lidocaine HCl (ND5.3) in conscious pigs	ND5.3 (20 bar, 10 µm (b)(4) film)	Pig	0.5 mg; 40 µm	Topical	No signs of animal distress or discomfort. No edema. Minimum, transitory erythema in <50% of sites (Draize scores ≤1; Mean ΔAbs using (b) (4) (b) (4) 111% of pre-dose values) peaking 1–3 d post-dose; subsiding by 7 d post-dose.
Local Tolerance	2203/008 GLP	Local dermal tolerance to Lidocaine administered by various configuration-combinations of ALGRX 3268 (Powderject® Dermal Lidocaine Devices)	Varied	Pig	Varied	Topical	No signs of animal distress or discomfort. All treatments produced only mild skin reactions. Higher payloads, higher device power, greater thickness o (b) (4) film had most significant dermal response. Histological findings indicate minor epidermal injury with little or no significant dermal damage immediately post-dose, peak inflammatory response 4 h post-dose, and well advanced healing by 24 h post-dose.
Local Tolerance	2203/004 GLP	Local dermal tolerance to duplicate dose of Lidocaine administered by PowderJect® devices	ND 5.3 (40 bar, 10 µm (b)(4) film)	Pig	0.5 mg; 35 µm	Topical	No signs of animal distress or discomfort. No edema. Increase in erythema, ΔAbs and ΔTEWL when 2nd administered ≤60 minutes after 1st dose, with maximum effect of 2nd dose on dermal findings when dose separation = 20 min. No effect of 2nd dose on dermal findings when dose separation = 24 h Maximum effects were all mild.

Overview of Local Tolerance Studies *(cont'd)*

Study Type	Study Number/ GLP Status	Study Title	Device	Species	LHM Dose & Particle Size	Route	Key Finding or Conclusion
Local Tolerance	2203/005 GLP	Local dermal tolerance to multiple doses of Lidocaine administered by PowderJect® devices	ND 5.3 (40 bar, 10 µm (b)film)	Pig	0. 5 mg; 35 µm	Topical	No signs of animal distress or discomfort. Infrequent, very mild edema; mild to moderate erythema. Initially, minor epidermal injury followed by superficial dermal and epidermal inflammatory response leading to repair by epidermal regeneration. Resolution within 10 d post-treatment.
Local Tolerance	PJT PC TM 146 GLP	Histopathological measurement of a Draize erythema Grade 4 response	ND1	Pig	1 mg protein-based product; 53-75 µm	Topical	Histopathology on sites with Draize scores of 4 (severe erythema to slight eschar formation and surface bleeding) show damage limited to stratum corneum, epidermis and papillary dermis (and well distanced from the SC layer). Damage consists of extravasation of RBC into the papillary dermis; inflammatory infiltrates up to 150–300 µm but not beyond the papillary dermis; RBC on surface (frank bleeding) from damaged capillary bed; splits in stratum corneum with destruction of epidermal cells directly below (diameter of zone of damage ~50 µm corresponds to particle size.
Local Tolerance	755/003 GLP	Betadine and Lidocaine HCl: Between Local Skin Antisepsis with Betadine and Transdermal Delivery of Local Anesthetic by PowderJect to Conscious Rabbit	ND1; 60 bar	NZW rabbits	0, 3, 6, and 2x3 mg; pretreatment none, alcohol or betadine	Topical	Pretreatment with betadine and alcohol wipes did not appear to significantly alter erythema, edema or histological changes associated with LHM delivery using ND1 devices.

Overview of Local Tolerance Studies *(cont'd)*

Study Type	Study Number/ GLP Status	Study Title	Device	Species	LHM Dose & Particle Size	Route	Key Finding or Conclusion
Photo-toxicity	ACZ00009 GLP	Topical Primary Irritancy and Phototoxicity Test of ALGRX 3268 in hairless mice when topically administered using the PowderJect® System	ND5.3A	Crl:SKH1-hr hairless mice (female)	0, 0.5, and 3 × 0.5 (primary irritancy test only)	Topical	Three administrations not well tolerated in primary irritancy test, likely due to the thickness of mouse skin vs human or pig skin. Single administration had mild to moderate skin reactions. No evidence of light-induced enhancement of primary irritancy.

Special Toxicology Studies Tables

Study Type	Study Number/ GLP Status	Study Title	Device	Species	LHM Dose and size	Route	Key Finding or Conclusion
Absorption lidocaine	(b) (4) HPLC Analysis of Lidocaine Non-GLP	Quantitative HPLC analysis of lidocaine from excised pig skin following the delivery of powdered lidocaine hydrochloride via Dermal PowderJect®	ND1; Trilaminated and 7-piece drug cassettes; (30–60 bar pressure)	Pig	3.0 mg; 38–53 µm	Topical	Lidocaine-skin extraction procedures and HPLC quantitation methods were developed and validated. Skin stripping method proved variable, but wash and wipe procedures were fairly reproducible. Maximum total recovery was 52% of payload. Using wipe method, data indicate the % of drug on the skin surface increases with decreasing pressure. At 60 Bar, 36% of the recovered dose was on the skin surface; at 30 bar, 89% of the recovered dose was on the surface.
Absorption (nondrug particulates)	Memorandum (b) (4) Non-GLP	Nondrug Particulate of ND 5.3 devices	ND5.3 (20 bar, 10 µm (b)film) ( )	Not applicable	0, 0.25 and 0. 5 mg; 35 µm	Not applicable	No. of nondrug particles with >25 µm diameter per device actuation is <20 (all configurations)
Absorption (nondrug particulates)	PJT NR 018 Non-GLP	(b) (4) fragmentation from BOC microcylinder	ND5, 40 bar pressure, w/without in-line filter plus BOC cylinders alone	Not applicable	0 mg	Not applicable	With in-line filter and disposable microcylinders, Al emissions averaged 0.028 µg/actuation and stainless steel (Fe, Cr, and Ni) emissions were below detectable levels.

Study Type	Study Number/ GLP Status	Study Title	Device	Species	LHM Dose and size	Route	Key Finding or Conclusion
Absorption lidocaine	(b) (4) HPLC Analysis of Lidocaine Non-GLP	Quantitative HPLC analysis of lidocaine from excised pig skin following the delivery of powdered lidocaine hydrochloride via Dermal PowderJect®	ND1; Trilaminated and 7-piece drug cassettes; (30–60 bar pressure)	Pig	3.0 mg; 38–53 µm	Topical	Lidocaine-skin extraction procedures and HPLC quantitation methods were developed and validated. Skin stripping method proved variable, but wash and wipe procedures were fairly reproducible. Maximum total recovery was 52% of payload. Using wipe method, data indicate the % of drug on the skin surface increases with decreasing pressure. At 60 Bar, 36% of the recovered dose was on the skin surface; at 30 bar, 89% of the recovered dose was on the surface.
Absorption lidocaine	(b) (4) No. 1204-009 GLP	ALGRX-3268: A pharmacokinetic evaluation in Gottingen minipigs	ND5.3A, 21 bar pressure	Minipig (adult and juvenile)	0.5 mg x 1 and 0.5 mg x 3; 38 µm	Topical (pinna)	No detectable lidocaine above the LLOQ (4.69 ng/ml) at any time point following 1 or 3 administrations to adults and following 1 administration to juveniles. Lidocaine concentrations just above the LLOQ (5.1–6.1 ng/mL) in 3 of 4 animals at a single timepoint, 5 or 20 m post-dose after 3 administrations to juveniles.
Risk Assessment, helium gas	Not applicable	Considerations of induced helium penetration and embolism	ND5.3	Not applicable	Not applicable	Topical	Under conditions of use, <1 µL helium would penetrate skin. Risk of helium gas causing embolism considered highly unlikely.
Absorption (nondrug particulates)	Memorandum (b) (4) Non-GLP	Nondrug Particulate of ND 5.3 devices	ND5.3 (20 bar, 10 µm (b) film)	Not applicable	0, 0.25 and 0. 5 mg; 35 µm	Not applicable	No. of nondrug particles with >25 µm diameter per device actuation is <20 (all configurations)
Absorption (nondrug particulates)	PJT NR 018 Non-GLP	(b) (4) fragmentation from BOC microcylinder	ND5, 40 bar pressure, w/without in-line filter plus BOC cylinders alone	Not applicable	0 mg	Not applicable	With in-line filter and disposable microcylinders, Al emissions averaged 0.028 µg/actuation and stainless steel (Fe, Cr, and Ni) emissions were below detectable levels.

Study Type	Study Number/ GLP Status	Study Title	Device	Species	LHM Dose and size	Route	Key Finding or Conclusion
Absorption (nondrug particulates)	LID 0014 DD RT Non-GLP	(b) (4) results from PJT PR-055	ND5.2 (20 and 25 bar pressure, w/without in-line filter	Not applicable	0 mg	Not applicable	With in-line filter, 20 bar pressure, mass of (b) (4) actuation. Increasing pressure to 25 bar increased (b) (4) to 0.07 µg/actuation. Removing filter increased (b) o (b) (4) actuation. ( ) Mass of (b) (4) (w/without filter at 20 bar pressure) = 0.014 µg /actuation.
Absorption (nondrug particulates)	DEV1998.012 Non-GLP	Mass assay of (b) (4) membrane fragmentation by UV/Vis Spectroscopy	ND1 (7 piece and TL cassettes, 20 µm (b) film, 40 and 60 bar pressure)	Not applicable	0, and 3.0 mg mannitol (38–53 µm and 25–38 µm)	Not applicable	(b) mass from TL cassettes is 4–15 µg/actuation. Amount is 10-fold LESS than from 7-piece cassettes.
Absorption (nondrug particulates)	DEV.1998.013 Non-GLP	(b) (4) fragment analysis – size/count and particle morphology	ND1 (7 piece and TL cassettes, 20 µm (b) film, 60 bar pressure)	Not applicable	0, and 3.0 mg mannitol (38–53 µm)	Not applicable	95% of (b) particles (all but 1–2 /actuation) from TL cassettes were <20µm and all appeared as flakes or strands. Size and morphology inconsistent with skin penetration.
Absorption (nondrug particulates)	WO 600352B Non-GLP	(b) (4) from Actuated Devices	ND5.3A	Not applicable	0.5 mg	Not applicable	The amount of (b) emitted from 20 devices was below the detection limit standard of 160 ppm or <8000 ng/actuation.
Absorption (nondrug particulates)	BO PC01 98 Non-GLP	Analysis of (b) (4) fragmentation for dermal PowderJect	ND1 (7 piece and TL cassettes, 20 µm (b) film, 60 bar)	Human cadaver skin	3 mg (25–55 µm)	Topical	Method for extracting (b) from skin developed. Amount of (b) emitted from devices variable (none to 91 µg) for ND1 with TL cassettes), with only a small % (<0.2 µg/device) penetrating the skin.
Absorption (nondrug particulates)	DV1999.015 Non-GLP	(b) (4) fragmentation study, ND5: Extent and skin penetration	ND5 (TL cassettes, 10 and 20 µm (b) film, 30 bar)	Human cadaver skin	0 mg	Topical	(b) (4)

Study Type	Study Number/ GLP Status	Study Title	Device	Species	LHM Dose and size	Route	Key Finding or Conclusion
Absorption (nondrug particulates)	2203/006-D6149 ISO 10993 compliant	Contract Histology: Investigative study to determine the distribution of (b) (4) and other fragments generated during the activation of PowderJect devices in human cadaver skin	ND5.3 with 0, 0.5, or 3.0 mg LHM at 40 bar or 0.5 mg at 20 bar pressure	Full thickness Human Cadaver skin	0, 0.5, or 3.0 mg; size not specified	Topical	Penetration of nondrug particles into skin is poor. <1 particle/device penetrated the epidermis and only a single particle (out of 36 actuations) penetrated the dermis. Tissue damage (small holes in epidermis) noted for all devices with lidocaine, and frequency dose dependent. Dermal damage rarely noted.
Absorption (nondrug particulates)	2203/009-D6149 ISO 10993 compliant	Contract Histology: Investigative study to determine the distribution and penetration of (b) (4) and other fragments generated during the activation of PowderJect devices in human cadaver skin	ND5.3 (20 bar)	Full thickness Human cadaver skin (upper back, back of hand and antecubital fossa)	0.5 mg; 35-40 µm	Topical	Nondrug particulate penetration was comparable at all anatomical sites. Most particles were on the surface or in the stratum corneum, with occasional particles in deeper layers of the epidermis. No particles were detected in the dermis. Tissue damage limited to splits (all sites) and holes (2 of 3 sites) in the epidermis.

Study Type	Study Number/ GLP Status	Study Title	Device	Species	LHM Dose and size	Route	Key Finding or Conclusion
Absorption (nondrug particulates)	2203/001 ISO 10993 compliant	Contract Histology: Validation study to determine suitable histological techniques in the assessment of various fragment types generated during the actuation of PowderJect® devices in human and porcine cadaver skin	ND5.3, 30 bar, loaded with 0.5 mg (b) upstream of the filter and ND5.3, 40 bar, loaded with 0.05 mg (b) (70 µm) downstream of filter; 0.5 mg (b) upstream of filter; silicone composite ball upstream of filter	Full thickness Porcine skin (fresh); human skin (fresh from amputee leg); Human cadaver skin (Freeze/ thawed)	Not applicable	Topical	Porcine skin less penetrable than human skin. Penetration in fresh and frozen human skin comparable. Maximum depth of penetration in human skin was dermis [single (b) particle]; collagenous dermal tissue (b) loaded downstream of filter]; strata granulosal and spinosal layers (b) (4) upstream of filter).
Absorption (nondrug particulates)	2203/007-D6149 ISO 10993 compliant	Contract Histology: Investigative study to assess penetrative depth of various fragments generated during the activation of PowderJect devices in human cadaver skin	ND5.3 containing one of the following 5 different types of contaminant fragments: (b) (4)	Human cadaver skin	Not applicable	Topical	(b) (4) particles do not penetrate skin. (b) (4) particles rarely penetrate to depths >20 µm. (b) (4) particles from loads upstream and downstream of filter rarely (<1, <1 and <2 particles/device, respectively) penetrate >70 µm.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Support for approval of Sterile LHM Product is derived from regulatory support from the reference drugs, nonclinical studies demonstrating absence of systemic exposure, lack of significant skin penetration of non-drug particulates, adequate local tolerance and absence of dermal toxicity, and lack of phototoxicity.

Regulatory-based support for NDA 22-114: The proposed drug product is supported by prior Agency findings of safety and efficacy for the approved reference drugs Synera™ and LIDODERM®. No distribution, metabolism, excretion, single dose toxicity,

genotoxicity, carcinogenicity, reproductive and developmental toxicity studies were performed with lidocaine based on the extremely small dose of LHM in the Sterile LHM Product (0.5 mg), the extremely limited bioavailability of and systemic exposure to lidocaine following treatment with the Sterile LHM Product, and on the Agency's findings of safety of higher doses of lidocaine applied topically to intact skin based on the approval of the lidocaine patches, Synera™ and LIDODERM®. Anesiva references the FDA's findings of safety of lidocaine applied topically to intact skin based on the approval of Synera™ (lidocaine 70 mg and tetracaine 70 mg) topical patch indicated for use on intact skin to provide local dermal analgesia for superficial venous access and superficial dermatological procedures (NDA 21-623) and on the approval of LIDODERM® (5% lidocaine) topical patch for relief of pain associated with post-herpetic neuralgia (NDA 20-612) under section 505(b)(2) of the Food, Drug, and Cosmetic Act.

Nonclinical support for absence of systemic absorption and indication of safety of proposed lidocaine dosing: Pharmacokinetic data in humans and minipigs and repeat dose toxicity and local tolerance data in pigs, minipigs, and rabbits support the systemic safety of the dosing with the proposed drug product. This data includes a 14-day repeated dose GLP study conducted in minipigs to support the NDA registration. Potential systemic exposure is ≤ that for approved reference drugs LIDODERM® and Synera™, well below the levels required for systemic therapeutic (1.5-5 µg/mL) or toxic (2.5-5 µg/mL) effects in newborns and adults, which supports the safety of the proposed drug product for children (>3 years old) and adults. Safety margins of 4-60 for a single device actuation are considered adequate based on the nonclinical studies conducted as part of this submission.

Characterization and skin penetration of non-drug particulates: Non-drug particulates are not considered to present a health hazard risk to the skin based on small particle size (most <25 µm) and essentially no penetration of the dermis with limited damage to the epidermis even under exaggerated conditions. Non-drug particulates are expected to be removed from the skin as soon as 2 weeks and no more than 5 weeks after treatment without penetration to the vascular dermis and without subsequent systemic absorption.

Risk assessments for potential systemic effects of helium propellant and non-drug particulates: Helium in the device canister and non-drug particulates are not considered to present any health hazard for local and systemic toxicity based on use of the proposed drug product under specified conditions of use (i.e., single actuation per intact skin site). The list of non-drug particulates that potentially could be generated by actuation of the device, and could therefore be safety concern for exposure, but are not, included [redacted] and [redacted]) from the drug cassette, [redacted] from the nozzle, [redacted] from the composite ball used to temporarily seal the helium filled [redacted] from the [redacted] tip that is broken upon device actuation, and [redacted] from the filter that is employed to minimize the risk of non-drug particles being expelled from devices upon actuation. In addition, foreign body carcinogenesis was determined not to be a concern for the particles that have penetrated the skin.

Local tolerance and phototoxicity: The safety of the proposed drug product has been demonstrated nonclinically for the proposed conditions of use. The local tolerance of single and multiple actuations for a single day and multiple days of PowderJect® devices ranging in composition from the same/similar to the proposed drug product to greater amounts of lidocaine (up to 6 mg), (b) (4) film size (40 µm), and/or canister pressure (40 bar) conditions were evaluated. Using devices of greater composition specifications than the proposed drug product simulate multiple dosing and misuse of the drug product adequately address single- and multi-dose local tolerance at single and multiple sites as all dosing was well tolerated with no clinical signs of discomfort and minimal, reversible dermal responses. The proposed drug product was not phototoxic in hairless mice.

Conclusions: Safety issues have been adequately addressed through reference to NDAs 21-623 (Synera™) and 20-612 (LIDODERM®) and the proposed drug product-specific nonclinical studies as submitted in this NDA for any potential dermal and systemic toxicity. The results of the nonclinical studies show the proposed drug product to be well tolerated and lack dermal toxicity and detectable systemic exposure to lidocaine.

Unresolved toxicology issues: none

Recommendations: Approve submission based on nonclinical assessment.

Suggested labeling:

Proposed label with suggested changes indicated:

8 Use in Specific Populations

8.1 Pregnancy

Teratogenic Effects

(b) (4)

Nonteratogenic Effects

Lidocaine, containing 1:100,000 epinephrine, at a dose of 6 mg/kg (36 mg/m^2 or 120 (b) (4)-fold the SDA) injected into the masseter muscle of the jaw or into the gum of the lower jaw of Long-Evans hooded pregnant rats on gestation day 11 led to developmental delays in neonatal behavior among offspring. Developmental delays were observed for negative geotaxis, static righting reflex, visual discrimination response, sensitivity and response to thermal and electrical shock stimuli, and water maze acquisition. The developmental delays of the neonatal animals were transient with responses becoming comparable to untreated animals later in life. The clinical relevance of the animal data is

uncertain. No adequate and well–controlled studies have been conducted in pregnant women. Because animal studies are not always predictive of human response, Zingo™ should be used during pregnancy only if the potential benefit justifies risk to the fetus.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of lidocaine.

Mutagenesis

No mutagenic potential of lidocaine was demonstrated in the in vitro Ames Bacterial Reverse Mutation Assay, the in vitro chromosome aberration assay using Chinese hamster ovary cells, and the in vivo mouse micronucleus assay.

Impairment of Fertility

Lidocaine did not affect fertility in female rats when given via continuous subcutaneous infusion via osmotic minipumps up to doses of 250 mg/kg/day [1500 mg/m^2 or 5000-fold the SDA (b) (4) of 0.5 mg lidocaine in a 60 kg individual (0.3 mg/m^2)]. Although lidocaine treatment of male rats increased the copulatory interval and led to a dose-related decreased homogenization resistant sperm head count, daily sperm production, and spermatogenic efficiency, the treatment did not affect overall fertility in male rats when given subcutaneous doses up to 60 mg/kg (360 mg/m^2 or 1200 (b) (4) fold the SDA). (b) (4)

Signatures (optional):

Reviewer Signature Gary P. Bond, Ph.D., DABT

Supervisor Signature Adam M. Wasserman, Ph.D. Concurrence Yes X No ___

APPENDIX/ATTACHMENTS - none

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Gary Bond
7/30/2007 10:54:41 PM
PHARMACOLOGIST

Adam Wasserman
7/30/2007 11:11:37 PM
PHARMACOLOGIST
I concur with the nonclinical evaluation of Dr. Gary Bond and agree that the application may be approved. Labeling recommendations described in Dr. Bond's review have are preliminary and will be negotiated with the Sponsor.

PHARMACOLOGY/TOXICOLOGY NDA FILEABILITY CHECKLIST
Division of Anesthesia, Analgesia, and Rheumatology Products

NDA Number: 22-114 **Applicant: Anesiva, Inc.** **Stamp Date: 11/21/2006**
Drug Name: Zingo (formerly AGLRX 3268)

IS THE PHARM/TOX SECTION OF THE APPLICATION FILEABLE? Yes [X] No [ ]

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameters	Yes	No	Comment
1	On its face, is the Pharmacology/Toxicology section of the NDA organized in a manner to allow substantive review to begin?	X		
2	Is the Pharmacology/Toxicology section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X		Inadequate but useable table of contents as studies listed by report number and not title.
3	On its face, is the Pharmacology/Toxicology section of the NDA legible so that substantive review can begin?	X		Readable electronic copies provided.
4	Are **final reports** of ALL required* and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility*, juvenile studies, ocular toxicity studies*, acute adult studies*, chronic adult studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)? Have electronic files of the carcinogenicity studies been submitted for statistical review?		X	Repeated-dose minipig study to be completed and submitted early in review cycle in accordance with preNDA meeting agreement. All other required studies submitted in this NDA. No carcinogenicity studies required
5	If the formulation to be marketed is different from that used in the toxicology studies, has the sponsor made an appropriate effort to either repeat the studies with the to be marketed product or to explain why such repetition should not be required?		X	Formulation to be tested in pending toxicology study to be same as marketed product per proposed protocol
6	Are the proposed labeling sections relative to pharmacology appropriate (including human dose multiples expressed in mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	X		Some risk assessment-based eliminated text from labels compared to proposed reference product labels (e.g., impurity 2,6-xylidine carcinogenicity), which can be resolved in review.
7	For a 505(b)(2) submission, has the sponsor identified a referenced product?	X		LIDODERM® and Synera™ are the reference products (NDA 20-612 & 21-623, respectively).
8	For a 505(b)(2) submission, has the sponsor submitted patent certification information to support the information referenced in the proposed drug product labeling?	X		Sponsor lists 4 of 5 LIDODERM® patents and no Synera™ patents regarding proposed label, which is almost exclusively Synera™ label text.
9	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions?		X	Required special study (repeated-dose minipig study) to be submitted early in review cycle, which was agreed upon by Division in preNDA meeting.
10	Based upon a cursory review, do the excipients appear to have been adequately qualified?	X		Numerous studies for nondrug particulate effects submitted.
11	Has the applicant submitted any studies or data to address any impurity or extractable issues (if any)?	X		ISO 10993 studies for extractables included. No reported impurity issues, structural alert review needed by CMC.
12	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale	X		Proposed marketed product used/to be used in pivotal nonclinical studies.

	to justify the alternative route?			
13	Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		Statements contained in individual study reports.
14	Has the sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?	X		Not directly stated, but can be inferred from protocols.
15	From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not.	X		
16	If the NDA is fileable, are there any filing review issues that need to be conveyed to Sponsor? If so, specify:	X		Filing review issues for the 74-day letter: pivotal 2-week repeated dose study not yet submitted.

Note: Primary **r**eviewer Gary P. Bond, Ph.D.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Gary Bond
1/11/2007 07:45:45 AM
PHARMACOLOGIST

Adam Wasserman
1/11/2007 08:55:47 AM
PHARMACOLOGIST
It is noted that exclusivity for the RLD Lidoderm expires March 19, 2006 but that exclusivity for the RLD Synera runs through June 23, 2008.