

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204623Orig1s000**

**PHARMACOLOGY REVIEW(S)**

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

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: 204623

Supporting document/s: #1 (dated 5/4/12 in DARRTS)  
#20 (dated 1/28/13 in DARRTS)

Applicant's letter date: May 4, 2012

CDER stamp date: May 4, 2012

Product: PENNSAID® Topical Solution (2% w/w diclofenac sodium)

Indication: Topical treatment for [REDACTED] (b) (4)  
of osteoarthritis [REDACTED] (b) (4) of the knee(s)

Applicant: Mallinckrodt, Inc.

Review Division: Division of Anesthesia, Analgesia, and Addiction Products

Reviewer: Jay H. Chang, Ph.D.

Supervisor/Team Leader: Adam Wasserman, Ph.D.

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# 1 Executive Summary

## 1.1 Introduction

Mallinckrodt Inc. has submitted NDA 204623 for marketing approval of PENNSAID® (diclofenac sodium topical solution) 2% w/w (referred to hereafter as PENNSAID 2%) for twice daily (BID) administration as an alternative to the four times daily (QID) dosing of the previously approved product PENNSAID® (diclofenac sodium topical solution) 1.5% w/w (referred to hereafter as PENNSAID 1.5%) for the treatment (b) (4) of osteoarthritis of the knee. The NDA was submitted as a 505(b)(2) application referencing the Agency's previous finding of safety and effectiveness of Voltaren® (diclofenac sodium enteric-coated tablets) (NDA 19-201; Approved 7/28/99). The Applicant also has a Right of Reference letter to reference the diclofenac dermal carcinogenicity and dermal photocarcinogenicity data from NDA 21-005 for Solaraze (diclofenac sodium) Gel, 3% w/w.

Compared to the formulation of the marketed product PENNSAID 1.5%, the 2% formulation contains a (b) (4) diclofenac sodium and ethanol, excludes glycerin, incorporates hydroxypropyl cellulose, and maintains the same concentration of DMSO (45.5%). The maximum daily dose of PENNSAID 2% (e.g., 162 mg) is approximately the same as for PENNSAID 1.5% (e.g., 154 mg). Moreover, all inactive ingredients are at levels within those listed in the FDA Inactive Ingredient Guide for the topical route and therefore do not pose a safety risk.

## 1.2 Brief Discussion of Nonclinical Findings

As there is an extensive body of nonclinical pharmacology and pharmacokinetic literature on diclofenac, the Applicant conducted only a few new studies to support the PENNSAID 2% formulation. The Applicant has cross-referenced all of the nonclinical pharmacology and pharmacokinetic literature on diclofenac submitted to NDA 20-947 for PENNSAID 1.5%, which they own. Additionally, a series of new nonclinical pharmacokinetic studies were submitted that compared the absorption and distribution of diclofenac to the knees of swine after single and repeated administrations of PENNSAID 2% vs. the marketed PENNSAID 1.5% product. Both formulations showed rapid absorption of diclofenac through the skin with plasma levels detected within 1 hour after dermal application and increasing concentrations with repeated administrations. The highest levels of diclofenac were detected in the epidermis and dermis of the skin followed by synovial fluid with levels diminishing distal to the application site.

### ***Extractables and Leachables***

PENNSAID 2% will employ a different container closure system than the approved PENNSAID 1.5% product. The new system is the (b) (4) container, (b) (4) with a 1 mL metering pump. The safety of the container/closure system was assessed via extraction studies followed by a literature-based toxicological evaluation of the substances that were extracted to determine the safe level of exposure for this topical solution. Extraction with the PENNSAID 2% vehicle produced the compounds listed in the table below. Based on the concentrations identified through extraction, estimated maximum total daily exposures (TDEs) were

calculated. Note that these TDEs were all very low with levels ranging between (b) (4) to (b) (4) µg per day. With the exception of (b) (4) all were within the qualification threshold of 5 µg/day recommended by Product Quality Research Institute (PQRI) Leachables and Extractables Working Group, which has FDA representation. Compounds that were not identified after first pass analysis (NFPIs=no first pass identifications) were near or under the toxicologic threshold of concern of 1.5 µg/day for genotoxic or carcinogenic impurities. (b) (4) have been commonly used in pharmaceutical formulations and are included in the FDA Inactive Ingredient Guide with much higher listed potencies. Though there has been recent guidance from CDER to limit the use of certain (b) (4) in both marketed and investigational pharmaceutical products due to developmental and reproductive toxicity observed in nonclinical studies, the estimated TDE of (b) (4) µg/day is at least (b) (4)-fold lower than levels considered reasonably safe for (b) (4) by EPA<sup>1</sup>. Based on the above information, no further qualification of potential leachable compounds for the proposed container closure system is considered necessary by this Reviewer.

**Estimated Maximum Total Daily Exposure to identified Extractables**

Compound	Conc. (µg/g)	Component	Total Daily Exposure (µg/day) <sup>1</sup>	Safety Rationale
			(b) (4)	Below QT
				Listed in IIG & Below RfD
				Below QT
				Below QT
				Below QT

TDE = Estimated Concentration in Sample x Weight of Component x Daily Number of Doses (4)/ Total Number of Doses per Bottle (60)  
 NFPI = No First Pass Identification  
 QT=Qualification Threshold  
 IIG=FDA Inactive Ingredient Guide  
 RfD=Reference dose recommended by Environmental Protection Agency

Leachables testing on the (b) (4) container was incorporated in stability studies performed on the three registration lots under both long term (25°C/60%RH)

(b) (4)

and accelerated (40°C/75%RH) conditions. Only 6 month data were submitted with the NDA for both the long term and accelerated stability studies. It was noted by the CMC review team that although 12 months of stability data are typically required for filing of a new NDA, this application was submitted originally as an efficacy supplement and later changed to a new NDA after the filing meeting. Under accelerated conditions, several unknown leachables were detected above the Applicant's analytical evaluation threshold (AET), which represents a qualification threshold. Data from studies under accelerated conditions serve to predict longer shelf life stability and therefore if clean may support longer expiry than by the long term stability data alone. As such, the data submitted does not support the Applicant's proposed 24 month expiry. Rather, only 6 month expiry is supported by data from stability studies under 25°C long term conditions.

A teleconference was held with the Applicant on 1/24/13 in part to gain clarification on whether additional stability data was available. The Applicant stated that 18 month leachables data from the ongoing 25°C long term stability study was available and could be submitted as soon as possible. This data was submitted via email on 1/25/13 and subsequently via CMC amendment (supporting document #20) on 1/28/13. The new data showed that no unidentified compounds were identified above the AET from the (b) (4) container with any of the three registration lots at 18 months under 25°C long term conditions. Therefore, from the nonclinical perspective, this NDA may be approved with the Applicant's proposed expiry.

### 1.3 Recommendations

#### 1.3.1 Approvability

From the nonclinical perspective, this NDA may be approved.

#### 1.3.2 Additional Non Clinical Recommendations

N/A

#### 1.3.3 Labeling

The table below contains the draft labeling proposed by the Applicant, changes suggested by this Reviewer, and the rationale for this Reviewer's changes. Note that text to be omitted from the Applicant's proposed draft label is indicated by **~~bold strikethrough~~**. Text added by this Reviewer is indicated in **underlined bold**. Note that the language describing the nonclinical information in Sections 8 and 10 of the Applicant's proposed label are virtually identical to the respective sections of the PENNSAID 1.5% product label with just the product name PENNSAID changed to (b) (4). The actual nonclinical information in the Pregnancy section is from the Solaraze™ (diclofenac sodium) Gel label. The dermal carcinogenicity, photocarcinogenicity, and impairment of fertility information are also from the Solaraze™ (diclofenac sodium) Gel label. The oral carcinogenicity information is from the Voltaren® Gel (diclofenac sodium topical gel) label. The Applicant's proposed tradename (b) (4) was withdrawn during this review cycle and is noted in this Reviewer's suggested label as PENNSAID 2%. The proprietary name will likely be established after this review is finalized. For the finalized version of the label, please refer to the Action Letter.

Applicant's proposed labeling	Reviewer's suggested changes	Rationale for Reviewer's changes
<p><b>8.1 Pregnancy</b> Pregnancy Category C prior to 30 weeks gestation; Category D starting 30 weeks gestation.</p> <p><i>Teratogenic Effects:</i> There are no adequate and well-controlled studies of PENNSAID (b) (4) in pregnant women. PENNSAID (b) (4) should not be used by pregnant women as its safe use has not been adequately determined and starting at 30 weeks gestation, diclofenac and other NSAIDs should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur. Developmental studies in animals demonstrated that diclofenac sodium administration did not produce teratogenicity despite the induction of maternal toxicity and fetal toxicity in mice at doses up to 20 mg/kg/day (0.6-fold the maximum recommended human dose [MRHD] of (b) (4) mg/day based on body surface area comparison), and in rats and rabbits at doses up to 10 mg/kg/day (approximately 0.6-fold and 1.3-fold the MRHD, respectively). Published reproductive and developmental studies of dimethyl sulfoxide (DMSO, the solvent used in PENNSAID (b) (4)) are equivocal as to potential teratogenicity.</p> <p><i>Nonteratogenic Effects:</i> In rats, maternally toxic doses of diclofenac were associated with dystocia, prolonged gestation, reduced fetal weights and growth, and reduced fetal survival.</p> <p><b>8.2 Labor and Delivery</b> The effects of PENNSAID (b) (4) on labor and delivery in pregnant women are unknown. In rat studies maternal exposure to diclofenac, as with other NSAID drugs, known to inhibit prostaglandin synthesis, increased the incidence of dystocia,</p>	<p><b>8.1 Pregnancy</b> Pregnancy Category C prior to 30 weeks gestation; Category D starting 30 weeks gestation.</p> <p><i>Teratogenic Effects:</i> There are no adequate and well-controlled studies of PENNSAID 2% in pregnant women. PENNSAID 2% should not be used by pregnant women as its safe use has not been adequately determined and starting at 30 weeks gestation, diclofenac and other NSAIDs should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur. Developmental studies in animals demonstrated that diclofenac sodium administration did not produce teratogenicity despite the induction of maternal toxicity and fetal toxicity in mice at doses up to 20 mg/kg/day (0.6-fold the maximum recommended human dose [MRHD] of 162 mg/day based on body surface area comparison), and in rats and rabbits at doses up to 10 mg/kg/day (approximately 0.6-fold and 1.3-fold the MRHD, respectively). Published reproductive and developmental studies of dimethyl sulfoxide (DMSO, the solvent used in PENNSAID 2%) are equivocal as to potential teratogenicity.</p> <p><i>Nonteratogenic Effects:</i> In rats, maternally toxic doses of diclofenac were associated with dystocia, prolonged gestation, reduced fetal weights and growth, and reduced fetal survival.</p> <p><b>8.2 Labor and Delivery</b> The effects of PENNSAID 2% on labor and delivery in pregnant women are unknown. In rat studies maternal exposure to diclofenac, as with other NSAID drugs, known to inhibit prostaglandin synthesis, increased the incidence of dystocia, delayed parturition, and decreased</p>	<p>The maximum recommended human dose [MRHD] of (b) (4)</p>

<p>delayed parturition, and decreased offspring survival.</p> <p><b>8.3 Nursing Mothers</b> It is not known whether this drug is excreted in human milk; however, there is a case report in the literature indicating that diclofenac can be detected at low levels in breast milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from PENNSAID (b) (4), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.</p>	<p>offspring survival.</p> <p><b>8.3 Nursing Mothers</b> It is not known whether this drug is excreted in human milk; however, there is a case report in the literature indicating that diclofenac can be detected at low levels in breast milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from PENNSAID 2%, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.</p>	
<p><b>13. NONCLINICAL TOXICOLOGY</b> <b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b> Carcinogenicity studies in mice and rats administered diclofenac sodium as a dietary constituent for 2 years resulted in no significant increases in tumor incidence at doses up to 2 mg/kg/day corresponding to approximately (b) (4)- and (b) (4)-fold (mouse and rat, respectively) of the maximum recommended human topical dose of PENNSAID (b) (4) (based on apparent bioavailability and body surface area comparison).</p> <p>In a dermal carcinogenicity study conducted in albino mice, daily topical applications of diclofenac sodium for two years at concentrations up to 0.035% diclofenac sodium (a (b) (4)-fold lower diclofenac sodium concentration than present in PENNSAID (b) (4)) did not increase neoplasm incidence.</p> <p>In a photocarcinogenicity study conducted in hairless mice, topical application of diclofenac sodium at doses up to 0.035% diclofenac sodium (b) (4)-fold lower diclofenac sodium concentration than present in PENNSAID (b) (4) resulted in an earlier median time of onset of tumors.</p>	<p><b>13. NONCLINICAL TOXICOLOGY</b> <b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b> Carcinogenicity studies in mice and rats administered diclofenac sodium as a dietary constituent for 2 years resulted in no significant increases in tumor incidence at doses up to 2 mg/kg/day corresponding to approximately <u>0.85</u>- and <u>1.7</u>-fold (mouse and rat, respectively) of the maximum recommended human topical dose of PENNSAID 2% (based on apparent bioavailability and body surface area comparison).</p> <p>In a dermal carcinogenicity study conducted in albino mice, daily topical applications of diclofenac sodium for two years at concentrations up to 0.035% diclofenac sodium (a <u>57</u>-fold lower diclofenac sodium concentration than present in PENNSAID 2%) did not increase neoplasm incidence.</p> <p>In a photocarcinogenicity study conducted in hairless mice, topical application of diclofenac sodium at doses up to 0.035% diclofenac sodium (a <u>57</u>-fold lower diclofenac sodium concentration than present in PENNSAID 2%) resulted in an earlier median time of onset of tumors.</p>	<p>The margins have been changed to reflect the relative bioavailability (BA) of PENNSAID 2%, which was derived from topical and oral exposure data for PENNSAID 2% from a single clinical study. Note that the relative BA for PENNSAID 1.5% had been previously estimated based on topical exposure data for PENNSAID 1.5% and oral exposure data for Voltaren from separate studies, and therefore may not have been accurate.</p> <p>The margin was changed based on diclofenac sodium concentration of PENNSAID (b) (4). (b) (4)</p> <p>The margin was changed based on diclofenac sodium concentration of PENNSAID 2%. (b) (4)</p>

<p>Mutagenesis: Diclofenac was not mutagenic or clastogenic in a battery of genotoxicity tests that included the bacterial reverse mutation assay, in vitro mouse lymphoma point mutation assay, chromosomal aberration studies in Chinese hamster ovarian cells in vitro, and in vivo rat chromosomal aberration assay of bone marrow cells.</p> <p>Impairment of Fertility: Fertility studies have not been conducted with PENNSAID (b) (4) Diclofenac sodium administered to male and female rats at doses up to 4 mg/kg/day ( (b) (4) of the MRHD of PENNSAID (u) (4) based on apparent bioavailability and body surface area comparison) did not affect fertility. Studies conducted in rats found no effect of dermally applied DMSO on fertility, reproductive performance, or offspring performance.</p> <p><b>13.2 Animal Toxicology and/or Pharmacology</b>  <u>Ocular Effects:</u>                  No adverse effects were observed using indirect ophthalmoscopy after multiple-daily dermal application to rats for 26 weeks and minipigs for 52 weeks of DMSO at twice the concentration found in PENNSAID 1.5%. Published studies of dermal or oral administration of DMSO to rabbits, dogs and pigs described refractive changes of lens curvature and cortical fibers indicative of myopic changes and/or incidences of lens opacity or discoloration when evaluated using slit-lamp biomicroscopy examination, although no ocular abnormalities were observed in rhesus monkeys during daily oral or dermal treatment with DMSO for 9 to 18 months.</p>	<p>Mutagenesis: Diclofenac was not mutagenic or clastogenic in a battery of genotoxicity tests that included the bacterial reverse mutation assay, in vitro mouse lymphoma point mutation assay, chromosomal aberration studies in Chinese hamster ovarian cells in vitro, and in vivo rat chromosomal aberration assay of bone marrow cells.</p> <p>Impairment of Fertility: Fertility studies have not been conducted with PENNSAID 2%. Diclofenac sodium administered to male and female rats at doses up to 4 mg/kg/day (3.4-fold of the MRHD of PENNSAID 2% based on apparent bioavailability and body surface area comparison) did not affect fertility. Studies conducted in rats found no effect of dermally applied DMSO on fertility, reproductive performance, or offspring performance.</p> <p><b>13.2 Animal Toxicology and/or Pharmacology</b>  <u>Ocular Effects:</u>                  No adverse effects were observed using indirect ophthalmoscopy after multiple-daily dermal application to rats for 26 weeks and minipigs for 52 weeks of DMSO at twice the concentration found in PENNSAID 2%. Published studies of dermal or oral administration of DMSO to rabbits, dogs and pigs described refractive changes of lens curvature and cortical fibers indicative of myopic changes and/or incidences of lens opacity or discoloration when evaluated using slit-lamp biomicroscopy examination, although no ocular abnormalities were observed in rhesus monkeys during daily oral or dermal treatment with DMSO for 9 to 18 months.</p>	<p>The margin has been changed to reflect the relative bioavailability (BA) of PENNSAID 2%, which was derived from topical and oral exposure data for PENNSAID 2% from a single clinical study. Note that the relative BA for PENNSAID 1.5% had been previously estimated based on topical exposure data for PENNSAID 1.5% and oral exposure data for Voltaren from separate studies, and therefore may not have been accurate. of PENNSAID 2%</p>
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## 2 Drug Information

### 2.1 Drug

#### CAS Registry Number (Optional)

15307-79-6

#### Generic Name

Diclofenac sodium

#### Code Name

N/A

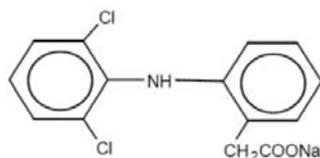
#### Chemical Name

2-[(2,6-dichlorophenyl)amino] benzeneacetic acid, monosodium salt

#### Molecular Formula/Molecular Weight

C<sub>14</sub>H<sub>10</sub>Cl<sub>2</sub>NNaO<sub>2</sub> / 318.14

#### Structure or Biochemical Description



#### Pharmacologic Class

Non Steroidal Anti-Inflammatory

### 2.2 Relevant INDs, NDAs, BLAs and DMFs

- IND 75,045 (PENNSAID® Diclofenac Sodium Topical Solution 2% w/w)
- IND 42,773 (PENNSAID® Diclofenac Sodium Topical Solution 1.5% w/w)
- NDA 20-947 (PENNSAID® Diclofenac Sodium Topical Solution 1.5% w/w)
- NDA 19-201 (Voltaren, Novartis, diclofenac sodium for oral administration)
- NDA 21-005 (Solaraze™, Bioglan Pharms Corp., 3% diclofenac gel for actinic keratoses)
- NDA 17-788 (RIMSO-50, Bioniche; 50% DMSO for interstitial cystitis, approved 1978)
- DMF (b) (4) (diclofenac sodium; Esteve Química)

### 2.3 Drug Formulation

The composition of PENNSAID (diclofenac sodium topical solution) 2% w/w is shown in the Applicant's table below. The active substance is diclofenac sodium, at a concentration of 2.0% w/w (20<sup>(b) (4)</sup> mg/mL). Dimethyl sulfoxide (DMSO) is included as a (b) (4).

**Composition of PENNSAID 2% Topical Solution Formulation**

Component	Function	Reference Standard	2.0% Solution	2.0% Solution	Max IID
			Quantity mg/g	Percent (%) w/w	
Diclofenac Sodium	Active Ingredient	USP	20	2.0%	N/A
Dimethyl Sulfoxide	(b) (4)	USP	455	45.5%	45.5%
Ethanol 95% (v/v)		USP	(b) (4)		
Purified Water		USP			
Propylene Glycol		USP			
Hydroxypropyl Cellulose		NF			

A comparison between the composition of PENNSAID 2% topical solution and the marketed PENNSAID 1.5% topical solution is shown in the Applicant's table below. Relative to the marketed formulation, the PENNSAID 2% topical solution contains a (b) (4) of the active ingredient diclofenac sodium and of the excipient ethanol, excludes glycerin, and incorporates (b) (4) hydroxypropyl cellulose.

**Composition of PENNSAID 1.5% and 2% Topical Solution Formulations**

Ingredient PENNSAI	D 1.5% Formulation Composition (w/w)	PENNSAID 2% Formulation Composition (w/w)
<b>Active Ingredient</b>		
Diclofenac sodium	1.5	2.0
<b>Inactive Ingredients</b>		
Dimethyl Sulfoxide	45.5	45.5
Ethanol 95% (v/v)	(b) (4)	
Propylene Glycol		
Hydroxypropyl Cellulose		
Purified Water		
Glycerin		
<b>Total</b>	<b>100%</b>	<b>100%</b>

**Container Closure System**

*Primary Packaging Components*

The PENNSAID 2% topical solution will employ the (b) (4) container with a 1 mL metering pump as the commercial multi-dose container closure system. Note, this is a change from the container closure system used for the marketed PENNSAID 1% topical solution. (b) (4)  
 (b) (4) The 1 mL (b) (4) metering pump with cap is snapped on the (b) (4) container to form (b) (4) delivery

system. Letters of authorization have been submitted for DMF (b) (4) and DMF (b) (4) for the bottle and pump, respectively. The target deliverable volume for this new configuration is 112 mL. The components for the (b) (4) container closure system are listed in the Applicant's Table below.

Component	Code <sup>a</sup>	Component	Material
White Oval Bottle	(b) (4)	(b) (4)	Polypropylene (b) (4)
			(b) (4)
Pump Dispenser			(b) (4) Polypropylene (b) (4)
	(b) (4)		

The safety of the container/closure system was assessed via an extraction study followed by a toxicological evaluation of the substances which are extracted to determine the safe level of exposure for this topical solution. Refer to the Special Toxicology Studies section of this review for an evaluation of the extraction study.

*Secondary Packaging Components*

The container closure system will be packaged in non-functional secondary paper carton containers. The proposed carton dimension is 2.375" x 1.8" x 7.0". The secondary packaging components are not required for product protection and are not expected to impact the safety or performance of the primary containers.

*Label and Printing Ink*

The label on the (b) (4) container will be printed with the same (b) (4) printing ink that is currently used for the marketed PENNSAID 1.5% product. Note that the product label at the time of NDA 20-947 approval employed a (b) (4) ink. Subsequently, a CBE-30 supplement (S-003) was submitted to NDA 20-947 on 11/8/10 proposing a change to a (b) (4) ink and it was approved on 7/15/11 (Refer to the NDA 20-947 Pharmacology Toxicology review dated 7/17/11).

**2.4 Comments on Novel Excipients**

There are no safety issues with the inactive ingredients contained in the PENNSAID 2% formulation. All are in the FDA Inactive Ingredient Guide within the listed maximum potencies for the topical route.

**2.5 Comments on Impurities/Degradants of Concern**

Drug Substance

The diclofenac sodium drug substance (DS) is manufactured by Esteve Química. A letter of Authorization to reference DMF (b) (4) for the DS was submitted with the NDA. The DS specifications are shown in the Applicant's table below. Esteve has set the qualification threshold for Impurity A at NMT (b) (4)%, which meets both the USP and Ph. Eur. Monograph requirements for diclofenac sodium. Though this level is above the ICH Q3A recommended qualification threshold for a DS of NMT 0.15% or 1.0 mg per day intake (whichever is lower) based on a maximum daily dose of 162 mg of diclofenac sodium, it is important to note that NDA 20-947 for Pennsaid 1.5% diclofenac sodium solution was approved with the USP monograph specifications for diclofenac sodium. Therefore, the impurity specifications are adequate for Pennsaid 2% diclofenac sodium solution. The specification of (b) (4) ppm for the residual solvent (b) (4) is within the qualification threshold of 5,000 ppm recommended in ICH Q3C document.

Specifications for Drug Substance supplied by Esteve Quimica

Test	Method	Specification
Description	USP/Ph. Eur.	(b) (4)
Identification A	USP/Ph. Eur.	(b) (4)
Identification B	USP	(b) (4)
Identification C	Ph. Eur.	(b) (4)
Identification D	USP	(b) (4)
Appearance of Solution	Ph. Eur.	(b) (4)
Color of Solution	USP	(b) (4)
Clarity of Solution	USP	(b) (4)
pH	USP	(b) (4)
Loss on Drying	USP/Ph. Eur.	(b) (4)
Heavy Metals	USP	(b) (4)
	Ph. Eur.	(b) (4)

		(Method C)
Assay	USP/Ph. Eur.	(b) (4)
Residual Solvents	USP <467>	
<b>Chromatographic Purity</b>		
Impurity A	USP	
Individual Impurity	USP	
Sum of the Impurities	USP	
<b>Related Substances</b>		
Impurity A	EP	
Individual Impurity	EP	
Sum of the Impurities	EP	

Drug Product

The drug product (DP) will be manufactured by Nuvo Manufacturing, a Division of Nuvo Research Inc. The acceptance limits for the DP are shown in the Applicant's table below. Note that the impurity specifications for identification and qualification thresholds for the DP are within those recommended by ICH Q3B Impurities in New Drug Products.

**Release and Stability Specifications and Acceptance Limits for PENNSAID 2% topical Solution**

TESTS		Acceptance Limits	
		Release	Stability
pH	pH (undiluted)	(b) (4)	(b) (4)
Specific Gravity			
Viscosity	Rotational Rheometry		
(b) (4)			
Ethanol (95% v/v) Assay	GC		
Dimethyl Sulfoxide Assay	GC		
Diclofenac Sodium Assay	HPLC		
Degradation Products: Impurity A Color Impurity Ind. Unknown Impurities Total Impurities	HPLC		
(b) (4)			
Deliverable Weight	Gravimetric		
Dispensing Weight per Actuation	Gravimetric		

The acceptance limits for each of the (b) (4) listed in the Applicant's table below are within the qualification thresholds recommended in the ICH Q3C document.

TESTS	Acceptance Limits	
	Release	Stability
(b) (4)	(b) (4)	Not Applicable

**2.6 Proposed Clinical Population and Dosing Regimen**

PENNSAID 2% Topical Solution is indicated as a topical treatment (b) (4) of osteoarthritis of the knee(s). Recommended dosing is 2 ml per dose (40. (b) (4) mg/dose) with a maximum of 2 doses per day per knee, which results in a total daily dose of 8 ml (b) (4)

**2.7 Regulatory Background (as related to the current submission)**

- 11/4/2009 – NDA 20-947 for Pennsaid 1.5% diclofenac topical solution approved for treatment of signs and symptoms of OA of the knee
- 9/25/2006 – Type B EOP2 meeting at FDA (Meeting Min dated 10/25/2006) to discuss development of Pennsaid 2% diclofenac topical gel
  - Sponsor's plan
    - Rely upon the Agency's finding of safety and effectiveness for Voltaren® tablets.
    - Rely upon the Agency's finding of safety and effectiveness for Solaraze® gel (3% diclofenac) if unable to obtain right to reference to Solaraze data for the dermal carci and dermal photocarci studies.
    - No plans for additional preclinical tox studies with 2% formulation
  - FDA response:
    - Conduct studies to characterize potential for dermal carci and dermal photocarci. If unable to obtain right of reference to Solaraze® data, a relative BA study should be completed in order to establish the relevance of the dermal carci data to Pennsaid 2% and accurately describe the exposure margins for label.
    - No additional nonclinical local tox studies required. (According to the Meeting Min – Though a clinical dermal safety study was initially required

with to-be marketed formulation, a Post-Meeting note indicated that the Division agreed this would not be required since clinical topical safety studies with 1.5% were provocative and performed under supra-therapeutic conditions, overall both products are similar, and mg dose of diclofenac and conc of DMSO are similar in both formulations.) Note, no tox studies were conducted to evaluate local tox of diclofenac for Pennsaid 1.5% formulation under original NDA 20-947.

- 5/2009 – Licensing rights transferred to Mallinckrodt Inc.
- 5/10/2010 – Mallinckrodt submitted IND 75,045
  - No new toxicology studies with 2% formulation included.
  - IND allowed to proceed 6/9/2010
- 5/4/2012 – Mallinckrodt submitted a prior approval supplement (S-009) under NDA 20-947 to market Pennsaid 2% with a different dosing regimen
  - The Agency decided to file the application but under a new NDA 204623
    - 505(b)(2) application relying on Agency's finding of efficacy and safety of Voltaren (diclofenac sodium enteric-coated tablets) (NDA 19-201)
    - Included a Letter authorizing Right of Reference to nonclinical information in NDA 21-005 for Solaraze™ (diclofenac sodium) Gel

### 3 Studies Submitted

#### 3.1 Studies Reviewed

Studies	Report Number	Location
<b>Pharmacokinetics</b>		
Pilot Study: Determination of Dose Application Methodologies and Assessment of the Distribution of 14C-Diclofenac Radioactivity in Minipigs Following Dermal Administration Using Quantitative Autoradiography	1531/11/045-E	eCTD 4.2.2.3
Pharmacokinetic study of PENNSAID solution compared to Solaraze Gel and two different doses of NRI-1004-06 Gel after multiple epicutaneous administration to German landrace pigs	1531/10/085-R03	eCTD 4.2.2.2
Determination of Diclofenac Concentrations in Plasma and the Biodistribution of 14C-Diclofenac in Selected Tissues Using Quantitative Autoradiography Following Repeated Dermal Administrations to Minipigs	1531/11/119-E	eCTD 4.2.2.3
Assessment of Localized Biodistribution of Diclofenac Sodium in Selected Tissues and Synovial Fluid Following Repeated Dermal Administrations to the Knees of Female Minipigs	1531/11/115-E	eCTD 4.2.2.3
Summary of F14/2 penetration studies		eCTD 4.2.2.2
<b>Special Toxicology Studies</b>		
Materials Extractables Characterization of a (b) (4) Pump Container Closure System	TTP-CQX-M0002.00	eCTD 3.2.P.2

#### 3.2 Studies Not Reviewed

N/A

### 3.3 Previous Reviews Referenced

- NDA 20-947 Nonclinical Review by Dr. Hamid Amouzadeh (dated 7/17/2002 in DARRTS)
- NDA 20-947 Nonclinical Review by Dr. L. Steve Leshin (dated 12/21/06 in DARRTS)
- NDA 20-947 Nonclinical Toxicology Review by Dr. L. Steve Leshin (dated 7/23/09 in DARRTS)
- NDA 20-947 Quality Review by Dr. Olen Stephens (dated 6/22/09 in DARRTS)

## 4 Pharmacology

### 4.1 Primary Pharmacology

No new nonclinical pharmacology studies were submitted with this NDA. The Applicant is cross-referencing nonclinical pharmacology literature for diclofenac that was submitted to NDA 20-947 for PENNSAID 1.5% Topical Solution. Rather than resubmit the literature, the Applicant has indicated the appropriate submission dates, volumes, and page numbers in the NDA 20-947 submission to locate this information (see table below).

Date of Submission	Volume Number / Item Number – Section - Page Number for Section Summary	Volume Number / Item Number – Section - Page Number for List of References
August 7, 2001*	Refer to October 5, 2001 for resubmission	
October 5, 2001**	Volume 6 - Page 12	Volume 6 – Page 33
June 28, 2006***	Item 5 – Section 5.5 – Page 40	Item 5 – Section 5.13 – Page 135
February 4, 2009***	Item 5 – Section 5.5 – Page 14	Item 5 – Section 5.13 – Page 49

\* Paper-based submission

\*\* Paper-based submission, and CD-ROM provided

\*\*\*Electronic Submission

Refer to the NDA 20-947 Pharmacology Toxicology Reviews by Dr. Hamid Amouzadeh dated 7/17/2002 and by Dr. L. Steve Leshin dated December 2006 for a discussion regarding the nonclinical pharmacology literature for diclofenac.

### 4.2 Secondary Pharmacology

N/A

### 4.3 Safety Pharmacology

N/A

## 5 Pharmacokinetics/ADME/Toxicokinetics

### 5.1 PK/ADME

The Applicant is cross-referencing NDA 20-947 for Pennsaid 1.5% solution, which they also own, to rely on the following nonclinical pharmacokinetic studies.

Study Name and Number	Date of Submission	Volume Number	Page Number
Study Number: UCSF study #95SU03: <i>In vitro</i> percutaneous absorption of [ <sup>14</sup> C]diclofenac sodium in human skin - date of report - December 17, 1996 - Sponsored by Dimethaid Research, Inc.	August 7, 2001	Refer to October 5, 2001 for resubmission	
	October 5, 2001	6	Page 166
Study Number: UCSF study # 96SU05: Bioavailability of [ <sup>14</sup> C]diclofenac <i>in vitro</i> in human skin - date of report - November 10, 1997 - Sponsored by Dimethaid Research, Inc.	August 7, 2001	Refer to October 5, 2001 for resubmission	
	October 5, 2001	6	Page 257

Additionally, Mallinckrodt is relying on the nonclinical pharmacokinetic literature submitted for marketing approval of NDA 20-947 for PENNSAID 1.5%. The references previously submitted to the NDA 20-947 were not resubmitted, but the cross-reference information (submission date, volume and page number) is indicated in the Applicant's table below.

Date of Submission	Item Number with Section or Volume Number and Page Number for Section Summary	Item Number with Section or Volume Number and Page Number for List of References
August 7, 2001*	Refer to October 5, 2001 for resubmission	
October 5, 2001**	Item 5 - Volume 6 - Page 30	Item 5 - Volume 6 - Page 140
June 28, 2006***	Item 5 - Section 5.11 - Page 117	Item 5 - Section 5.13 - Page 135

\*Paper-based submission

\*\*Paper-based submission, and CD-ROM provided

\*\*\*Electronic Submission

Refer to the NDA 20-947 Pharmacology Toxicology Reviews by Dr. Hamid Amouzadeh dated 7/17/2002 and by Dr. L. Steve Leshin dated December 2006 for a discussion regarding the nonclinical pharmacokinetic literature for diclofenac.

The following new pharmacokinetics studies were submitted with this NDA.

**Study title: Pilot Study: Determination of Dose Application Methodologies and Assessment of the Distribution of 14C-Diclofenac Radioactivity in Minipigs Following Dermal Administration Using Quantitative Autoradiography**

**Study No:** 1531/11/045-E

**Location:** eCTD 4.2.2.3

**Conducting laboratory and location:** (b) (4)

(b) (4)

**GLP compliance:** No  
**QA reports:** No

## Methods

- This study evaluated the distribution of diclofenac after dermal application of two different <sup>14</sup>C-diclofenac sodium formulations including PENNSAID 2% and PENNSAID 1.5% to knees of male Gottingen minipigs.
- One animal (Group 1) received a single dermal administration of PENNSAID 2% topical formulation applied to each knee at an average dose level of 308 µCi/knee. Blood was collected from the Group 1 animal at predose, 1, 2, 4, 6, 7, 8, 10, and 12 hours postdose.
- One animal (Group 2) received two dermal administrations, approximately 6 hours apart, of 1.5% PENNSAID topical formulation applied to each knee at a mean dose level of 173 µCi/knee/application (347 µCi/knee total). Blood was collected from the Group 2 animal at predose, 1, 2, 4, 6 (just prior to the second dose application), 7, 8, 10, and 12 hours postdose.
- Following animal euthanasia, knees with surrounding tissues from each hind limb were collected from Groups 1 and 2 at 12 hours after the initial dose.
- Blood and plasma were analyzed for radioactivity by using liquid scintillation counting.

## Study Design

Group	Number of Male Animals	Dose Route	Target Dose Level (mg/knee)	Target Dose Volume (mL/animal)	Samples Collected
1	1	Single Topical	10.3	0.5 <sup>a</sup>	Blood and Tissues for QA
2	1	BID Topical	7.62 <sup>b</sup>	0.5 <sup>a</sup>	Blood and Tissues for QA

BID Twice daily.

QA Quantitative autoradiography.

Note: For Group 1, the target radioactive dose for Formulation A (gel) was approximately 800 µCi/animal (400 µCi/knee).

For Group 2, the target radioactive dose for Formulation B (liquid) was approximately 800 µCi/animal (200 µCi/knee x 2).

a Target dose volume was approximately 0.5 mL per application per knee.

b Target dose of 7.62 mg/knee was applied BID for a total target dose of 15.2 mg/knee.

## Key findings:

- Radioactivity levels in plasma and blood were higher in the PENNSAID 1.5% (Group 2) treated animal with a maximum concentration of diclofenac about 9-fold higher in plasma and blood compared to the animal treated with PENNSAID 2% (Groups 1). Note that this was in part attributed to the higher administered dose for the Group 2 animal after BID administration.

**Table 2.6.4-1 Maximum Observed Concentrations of Radioactivity after Administration of [<sup>14</sup>C]Diclofenac in the PENNSAID 2% Topical Solution Vehicle or [<sup>14</sup>C]Diclofenac in the PENNSAID 1.5% Topical Solution Vehicle (Study 1531/11/045-E)**

Vehicle	Dose of [ <sup>14</sup> C]Diclofenac	Maximum Concentration (ng equivalents diclofenac/g)		Blood/Plasma Ratio Range for 1 – 12 h <sup>c</sup>
		Blood <sup>a</sup>	Plasma <sup>b</sup>	
PENNSAID 2% Topical Solution	8.93 mg (616 µCi)	10.9 at 10 h	19.2 at 10 h	0.534 – 0.592
PENNSAID 1.5% Topical Solution	13.82 mg (694 µCi)	96.7 at 8 h	186 at 8 h	0.521 – 0.635

<sup>a</sup> Source: Table 2 - 1531/11/045-E, Section 4.2.2.3

<sup>b</sup> Source: Table 3 - 1531/11/045-E, Section 4.2.2.3

<sup>c</sup> Source: Table 4 - 1531/11/045-E, Section 4.2.2.3

- At 12 hours post administration, substantial concentrations of radioactivity remained in the dosing area of the skin with little or no radioactivity in the subtended tissues of the knee.

**Study title: Pharmacokinetic study of PENNSAID solution compared to Solaraze Gel and two different doses of NRI-1004-06 Gel after multiple epicutaneous administration to German landrace pigs**

**Study No:** 1531/10/085-R03

**Location:** eCTD 4.2.2.2

**Conducting laboratory and location:** (b) (4)

**GLP compliance:** No

**QA reports:** No

### Methods

- This study evaluated the pharmacokinetics of diclofenac sodium after multiple topical administrations of PENNSAID 1.5%, Solaraze® (diclofenac sodium-3%) Gel, and two different volumes of PENNSAID 2% to 24 German landrace swine (n = 6/group)
- Test articles were applied by syringe onto the back area of the swine. Note for BID dosing, the doses were applied 10 hours apart; for QID dosing, the doses were applied 5 hours apart. Refer to study design below.

### Study Design

Group	Treatment	Volume or Weight per Dose	Dose of Diclofenac Sodium per Administration	Regimen
1	PENNSAID 1.5% solution	0.24 mL	3.9 mg (0.078 mg/cm <sup>2</sup> )	QID x 7 days + 1 dose on Day 8
2	Solaraze Gel, 3%	1 g	30 mg (0.6 mg/cm <sup>2</sup> )	BID x 7 days + 1 dose on Day 8
3	PENNSAID 2% solution	0.4 mL	8.1 mg (0.162 mg/cm <sup>2</sup> )	BID x 7 days + 1 dose on Day 8
4	PENNSAID 2% solution	1.49 mL	30 mg (0.6 mg/cm <sup>2</sup> )	BID x 7 days + 1 dose on Day 8

Notes: All treatments were applied to a 50 cm<sup>2</sup> area on the back. Doses in mg/cm<sup>2</sup> calculated by author of summary.

### Key findings:

- Diclofenac was absorbed after topical administration of all four formulations.
- The systemic exposure (AUC and  $C_{max}$ ) from the low dose PENNSAID 2% (8.1 mg diclofenac sodium) BID was similar to that for PENNSAID 1.5% (3.9 mg diclofenac sodium) QID, but was less than that for Solaraze Gel (30 mg diclofenac sodium) BID.
- The systemic exposure (AUC and  $C_{max}$ ) from the PENNSAID 2% (high dose) was higher than that of Solaraze Gel when administered at similar doses of diclofenac (30 mg BID).

### Summary of Pharmacokinetic Parameters for Diclofenac after Administration of PENNSAID 2%, PENNSAID 1.5%, and Solaraze Gel

Parameter	Mean ± Standard Deviation for Each Treatment			
	PENNSAID 2% Topical Solution (8.1 mg BID)	PENNSAID 2% Topical Solution (30 mg BID)	PENNSAID 1.5% Topical Solution (3.9 mg QID)	Solaraze Gel (30 mg BID)
$C_{max}$ (Day 7) (ng/mL)	9.39 ± 4.49 <sup>a,b</sup>	54.1 ± 29.2 <sup>d</sup>	11.7 ± 7.2 <sup>d</sup>	25.2 ± 12.0 <sup>d</sup>
$T_{max}$ (Day 7) (h)	11.3 ± 7.0 <sup>a,b</sup>	10.5 ± 8.8 <sup>d</sup>	11.8 ± 7.8 <sup>d</sup>	9.8 ± 8.0 <sup>d</sup>
AUC <sub>0-24</sub> (Day 7) (ng•h/mL)	155 ± 71.9 <sup>a,c</sup>	704 ± 270 <sup>d</sup>	106 ± 40.9 <sup>d</sup>	270 ± 140 <sup>d</sup>
$C_{trough}$ (Day 6) (ng/mL) <sup>e</sup>	4.35 ± 2.74	26.5 ± 12.6	2.32 ± 0.62	15.2 ± 11.3
$C_{trough}$ (Day 7) (ng/mL) <sup>e</sup>	4.68 ± 2.15	25.6 ± 15.1	2.57 ± 1.16	11.1 ± 7.75
$C_{trough}$ (Day 8) (ng/mL) <sup>e</sup>	6.59 ± 4.73	28.5 ± 14.9	3.93 ± 3.04	11.0 ± 6.54

<sup>a</sup> Values recalculated after exclusion of an outlier concentration (b) (4) Animal # 17 - Recalculation of AUC 0-24 inclusive of standard deviation - Date of Reanalysis 2010 03 17).

<sup>b</sup> Recalculation with exclusion of an outlier concentration done by author of summary based on Table 6 - 1531/10/085-R03.

<sup>c</sup> Source: Animal # 17 - Recalculation of AUC0-24 inclusive of standard deviation

<sup>d</sup> Source: Table 7 - 1531/10/085-R03

<sup>e</sup> Source: Table 8 - 1531/10/085-R03

### **Study title:** Determination of Diclofenac Concentrations in Plasma and the Biodistribution of <sup>14</sup>C-Diclofenac in Selected Tissues Using Quantitative Autoradiography Following Repeated Dermal Administrations to Minipigs

**Study No:** 1531-11-119-E

**Location:** eCTD 4.2.2.3

**Conducting laboratory and location:** (b) (4)

**GLP compliance:** No

**QA reports:** No

### Methods

- This study evaluated the distribution of drug-derived radioactivity in selected tissues and plasma concentrations of diclofenac following repeated dermal administrations of PENNSAID 2% or PENNSAID 1.5% containing <sup>14</sup>C-diclofenac sodium to knees of male Gottingen minipigs.
- Group 1 (N=4) minipigs were administered two daily dermal applications of PENNSAID 2%, approximately 12 hours apart, applied to the right knee for 7

consecutive days at a dose of 42.2  $\mu\text{Ci}$  per application. The final dose was a single dose on Day 8.

- Group 2 (N=4) minipigs received four daily dermal applications of PENNSAID 1.5% 6 hours apart, applied to the right knee for 7 consecutive days at a dose of 22.0  $\mu\text{Ci}$  per application. Two doses were administered on Day 8.
- Note the overall total dose of diclofenac administered for PENNSAID 2% (32.2 mg) was approximately 36% lower than that administered for PENNSAID 1.5% (50 mg).
- Blood was collected from all minipigs predose, and at 24, 48, 72, 96, 120, 144, and 168 hours after the initial dose, and at specified times after the last dose (Group 1) or after the second to last dose (Group 2).
- 2 minipigs/group/time point were euthanized at 12 and 48 hours after the last dose (Group 1) or after the second to last dose (Group 2). Following euthanasia, both the treated and untreated knees were collected for autoradiographic analysis, and a series of skin biopsies were acquired from each treated knee.
- Plasma and skin biopsies were analyzed for total radioactivity and plasma was analyzed for diclofenac.
- Samples of skin were collected from the residual application site of each minipig knee after sectioning for autoradiographic analysis.

## Study Design

Group	Number of Male Animals	Dose Route	Target Dose Level (mg/knee/dose)	Target Dose Concentration (mg/mL/dose)	Target Dose Volume (mL/dose)	Samples Collected
1	4	Topical <sup>a</sup>	2.3	21.4	0.11	Blood, Skin Biopsies, and Tissues for QA
2	4	Topical <sup>b</sup>	1.7	16.0	0.11	Blood, Skin Biopsies, and Tissues for QA

QA Quantitative autoradiography.

Notes: For Group 1, the target radioactive dose for Formulation A (gel) was approximately 100  $\mu\text{Ci}/\text{day}$ .

For Group 2, the target radioactive dose for Formulation B (solution) was approximately 100  $\mu\text{Ci}/\text{day}$ .

a Animals received two daily doses (0- and 12-hour) on study Days 1 through 7, followed by a single dose on Day 8.

b Animals received four daily doses (0-, 6-, 12-, and 18-hour) on study Days 1 through 7, followed by two daily doses on Day 8.

## Key findings:

- Following dermal applications of PENNSAID 2%, plasma concentrations were measurable at 4 to 12 hours post last dose in all Group 1 minipigs, but near or below the limit of quantitation from 24 to 120 hours post initial dose in 3 of 4 minipigs. In contrast, levels were measurable for all Group 2 PENNSAID 1.5%-treated animals at all timepoints. This may have been attributable in part due to the higher administered dose to Group 2 animals.
- Following repeated dermal applications of  $^{14}\text{C}$ -diclofenac sodium for 7 consecutive days, plasma concentrations of radioactivity were only slightly higher in the PENNSAID 1.5% treated animals compared to animals treated with PENNSAID 2%. However, the data suggested that most of the radioactivity found in the plasma may have resulted from the presence of metabolites rather than the parent compound.
- Skin biopsies showed that concentrations of radioactivity were highest at the dose site and generally decreased as distance from the dose site increased.

- Quantitative autoradiography analysis measured high concentrations of radioactivity in the epidermis and dermis of the skin following dermal applications of either PENNSAID 2% or PENNSAID 1.5%. All other evaluated tissues and blood generally contained radioactivity concentrations near or below the limit of quantitation.

### Concentrations of Diclofenac and Total Radioactivity after Repeated Administrations of PENNSAID 2% and PENNSAID 1.5% containing [<sup>14</sup>C]-diclofenac

Vehicle	Dose of [ <sup>14</sup> C]Diclofenac per Application	Concentration (ng/mL or ng-equivalents/g)		T <sub>max</sub> (h) (Day 7)
		C <sub>trough</sub> (pre-dose Day 7)	C <sub>max</sub> or C <sub>2</sub> (Day 7)	
PENNSAID 2% Topical Solution	2.1 mg	0.295 ± 0.590 <sup>a</sup>	5.38 ± 1.94 <sup>a</sup>	2 ± 0 <sup>a</sup>
	42.2 µCi	34.2 ± 23.0 <sup>b</sup>	40.1 ± 19.0 <sup>b</sup>	na
PENNSAID 1.5% Topical Solution	1.67 mg	3.32 ± 2.33 <sup>c</sup>	10.0 ± 8.7 <sup>c</sup>	2 ± 0 <sup>c</sup>
	22.0 µCi	51.1 ± 44.1 <sup>d</sup>	53.7 ± 47.6 <sup>d</sup>	na

na = not applicable since C<sub>max</sub> was not distinct.

<sup>a</sup> Source: Table 3 - 1531/11/119-E, Section 4.2.2.3

<sup>b</sup> Source: Table 5 - 1531/11/119-E, Section 4.2.2.3

<sup>c</sup> Source: Table 4 - 1531/11/119-E, Section 4.2.2.3

<sup>d</sup> Source: Table 6 - 1531/11/119-E, Section 4.2.2.3

### Study title: Assessment of Localized Biodistribution of Diclofenac Sodium in Selected Tissues and Synovial Fluid Following Repeated Dermal Administrations to the Knees of Female Minipigs

**Study No:** 1531/11/115-E:

**Location:** eCTD 4.2.2.3

**Conducting laboratory and location:**  (b) (4)

**GLP compliance:** No

**QA reports:** No

### Methods

- This study evaluated drug distribution in plasma, selected tissues, and synovial fluid in female Gottingen minipigs following repeated dermal applications of PENNSAID 2% or PENNSAID 1.5% for 6 consecutive days.
- Group 1 animals received PENNSAID 2% at 10 mg/dose for six consecutive days at BID dosing where doses were applied approximately 12 hours apart and then a single on the seventh day. The overall dose administered was 129 mg.
- Group 2 animals received PENNSAID 1.5% at 4.98 mg/dose for six consecutive days at QID dosing where the doses were approximately 6 hours apart, and then two doses on the seventh day. The overall dose administered was 133 mg.
- A control group of two female minipigs received no treatment.
- Blood was collected to evaluate diclofenac pharmacokinetics.
- Following euthanasia, selected tissues and synovial fluid were collected from treated and untreated minipig knees to evaluate diclofenac levels.

## Study Design

Group	Number of Female Animals	Dose Route	Target Diclofenac Dose Level (mg/dose)	Target Diclofenac Dose Concentration (mg/mL)	Target Dose Volume (mL/dose)	Samples Collected
1	27	Topical <sup>a,b</sup>	10	20.0	0.5	Blood and Tissues <sup>e</sup>
2	18	Topical <sup>c</sup>	4.98	16.05	0.31	Blood and Tissues <sup>e</sup>
3	2	NA <sup>d</sup>	NA	NA	NA	Control Blood and Tissues <sup>e</sup>

NA Not applicable.

- a Six animals/time point (sacrificed at 4, 12, and 24 hours postdose) received two daily doses (0- and 12-hour) of Formulation A (viscous solution) on Study Days 1 through 6, followed by a single dose on Day 7.
- b Six animals/time point (sacrificed at 36 hours postdose) and three animals/time point (sacrificed at 48 hours postdose) received two daily doses (0- and 12-hour) of Formulation A (viscous solution) on Study Days 1 through 6.
- c Six animals/time point (sacrificed at 2, 6, and 24 hours postdose) received four daily doses (0-, 6-, 12-, and 18-hour) of Formulation B (liquid formulation) on Study Days 1 through 6, followed by two doses (0- and 6-hour) on Day 7.
- d Animals were not dosed. Selected tissues and synovial fluid were collected to evaluate matrix effects for LC-MS/MS quantitation for Groups 1 and 2.
- e Selected tissues included skin, synovial fluid, underlying bone (patella, with bone marrow), underlying muscle, and underlying tendon.

### Key findings:

- PENNSAID 2% and PENNSAID 1.5% treatment showed showed rapid absorption of diclofenac through the skin with plasma levels detected within 1 hour after dermal application.
- Diclofenac plasma concentrations were higher after the final doses for both treatments compared to the initial doses.
- Diclofenac plasma concentrations tended to be higher with PENNSAID 2% treatment after initial doses but this was attributed to the higher individual doses with PENNSAID 2%. After multiple doses, concentrations were similar.

### Summary of Plasma Diclofenac Concentrations after Initial and Last Dose of PENNSAID 2% and PENNSAID 1.5%

	PENNSAID 2% Topical Solutions (10 mg BID)	PENNSAID 1.5% Topical Solution (4.98 mg QID)
<b>Time After Initial Dose</b>		
1 h	<sup>a</sup> 18.2 ± 21.2*	7.01 ± 4.21
3 h	18.9 ± 10.8***	8.62 ± 5.55
6 h	18.2 ± 7.98****	6.58 ± 2.99
12 h	19.3 ± 11.6***	10.8 ± 5.06
24 h	28.0 ± 11.4	21.5 ± 8.46
48 h	38.9 ± 13.8	34.7 ± 18.8
72 h	60.6 ± 23.3***	38.4 ± 22.6
96 h	54.8 ± 26.2	44.3 ± 16.0
120 h	62.2 ± 29.0	47.8 ± 20.8
144 h	74.1 ± 37.9	60.3 ± 24.9
<b>Time After Last Dose</b>		
0.5 h	65.3 ± 26.9	57.2 ± 19.8
1 h	79.0 ± 29.7*	56.5 ± 26.3
2 h	93.4 ± 27.7**	53.7 ± 19.7
3 h	99.2 ± 34.9****	50.2 ± 24.8
6 h	90.0 ± 43.0***	36.8 ± 17.0
12 h	69.0 ± 30.2****	18.5 ± 5.49
24 h	16.3 ± 5.57	15.3 ± 6.59

<sup>a</sup> Mean ± Standard Deviation of diclofenac concentration (ng/mL)

Asterisks denote significant difference (\*p < 0.05, \*\*p < 0.02, \*\*\*p < 0.01, and \*\*\*\*p < 0.001) compared to PENNSAID 1.5% Topical Solution by t-Test at each time point.

Source Table 1 - 1531/11/115-E, Section 4.2.2.3

- Substantial amounts of diclofenac were detected in the skin, synovial fluid, and other tissues after six days of dosing with either PENNSAID 2% or PENNSAID 1.5%. Interestingly, notable concentrations of diclofenac were also detected in the contralateral knees suggesting potential cross contamination of the applied dose to non-treated knees.
- Overall, similar tissue exposure was observed after BID applications of PENNSAID 2% and QID applications of PENNSAID 1.5% with the highest levels detected in skin followed by synovial fluid and then bone, muscle, and tendon.

### Summary of Tissue Diclofenac Concentrations after Last Dose of PENNSAID 2% and PENNSAID 1.5%

Sample from	PENNSAID 2% Topical Solution (10 mg BID)			PENNSAID 1.5% Topical Solution (4.98 mg QID)		
	Time After Last Dose			Time After Last Dose		
Treated HindLimb	4 Hours <sup>a</sup>	12 Hours <sup>b</sup>	24 Hours <sup>c</sup>	2 Hours	6 Hours	24 Hours
Skin (centered over patella)	*646000 ± 452000	542000 ± 403000	444000 ± 185000**	298000 ± 365000	194000 ± 4800	154000 ± 47000
Synovial fluid	41900 ± 55600	5340 ± 3740*	53400 ± 100000	18000 ± 22500	14700 ± 7030	228000 ± 321000
Underlying bone (patella)	1420 ± 1120	685 ± 541	189 ± 273	401 ± N.A.	166 ± 179	714 ± 742
Underlying muscle	879 ± 1100	1010 ± 509***	1290 ± 1840	220 ± 204	177 ± 218	739 ± 561
Underlying tendon	2230 ± 1460**	1160 ± 958	495 ± 478	54.9 ± 31.3	234 ± 301	530 ± 458
Sample from Non-Treated HindLimb						
Skin (centered over patella)	11900 ± 13400	10700 ± 9150	10400 ± 4740	13900 ± 10800	11600 ± 1020	9130 ± 4150
Synovial fluid	10600 ± 9440	21500 ± 36400	6800 ± 6880	10700 ± 8330	10500 ± 3480	10300 ± 8870
Underlying bone (patella)	1040 ± 588	200 ± 165	356 ± 322	N.A.	N.A.	287 ± 533
Underlying muscle	59.4 ± 35.5	104 ± 62.5	499 ± N.A.	55.7 ± 38.5	216 ± N.A.	57.1 ± 33.4
Underlying tendon	33.4 ± 8.58	101 ± 85.2	39.1 ± 52.0	53.2 ± 80.2	72.3 ± 106	33.8 ± 13.6

Not applicable

<sup>a</sup> Mean ± Standard Deviation of diclofenac concentration (ng/mL)

<sup>a</sup> Asterisks denote significant difference (\*p < 0.05, \*\*p < 0.02, \*\*\*p < 0.01) compared to PENNSAID 1.5% Topical Solution at 2 hours by t-Test.

<sup>b</sup> Asterisks denote significant difference (\*p < 0.05, \*\*\*p < 0.01) compared to PENNSAID 1.5% Topical Solution at 6 hours by t-Test.

<sup>c</sup> Asterisks denote significant difference (\*\*p < 0.02) compared to PENNSAID 1.5% Topical Solution at 24 hours by t-Test.

Source Table 2 - 1531/11/115-E, Section 4.2.2.3

**Study title: Summary of F14/2 penetration studies**

**Study No:** N/A  
**Location:** eCTD 4.2.2.2  
**Conducting laboratory and location:** (b) (4)  
**GLP compliance:** No  
**QA reports:** No

**Methods**

- In vitro Franz cell studies were conducted to test a variety of experimental diclofenac topical formulations
- Formulations contained either 1.5% or 2% diclofenac and varying amounts of carbopol, glycerol, ethanol, and hydroxypropyl cellulose.

**Key findings:**

- Penetration of diclofenac through skin was greater for 2% formulations compared to 1.5% after the application of equal or smaller volumes.
- Other characteristics such as viscosity, ethanol content and the absence of glycerin also enhanced penetration.

**5.2 Toxicokinetics**

N/A

**6 General Toxicology**

No new toxicology studies were required for this NDA.

**7 Genetic Toxicology**

No genetic toxicology studies were submitted with this NDA.

**8 Carcinogenicity**

No carcinogenicity studies were submitted with this NDA.

**9 Reproductive and Developmental Toxicology**

No reproductive and developmental toxicology studies were submitted with this NDA.

**10 Special Toxicology Studies**

**Study Title: Materials Extractables Characterization of a (b) (4) Pump Container Closure System (Protocol TTP-CQX-M0002.00)**

(Refer to the CMC Review for further details on the methodology and chemistry findings.)

**Study No: TTP-CQX-M0002.00**

**Location:** NDA 204623; eCTD 3.2.P.2 Pharmaceutical Development

**Conducting laboratory and location:** (b) (4)

**Date of study initiation:** January 22, 2010

**GLP compliance:** No

**QA reports:** No

Container Closure System

The PENNSAID 2% topical solution will employ the (b) (4) container with a 1 mL metering pump. (b) (4)

The 1 mL (b) (4) metering pump with cap is snapped on the (b) (4) container to form (b) (4) delivery system. The components and materials of this container closure system are shown in the Applicant's table below.

(b) (4) **Container Closure System Components**

Component	Code <sup>a</sup>	Component	Material
White Oval Bottle	(b) (4)	(b) (4)	Polypropylene (b) (4)
Pump Dispenser			
	(b) (4)		

Samples for Extraction

Only components in contact with the drug product were subjected to extraction procedures. (b) (4)

(b) (4). Components were separated into "Testing Groups" as shown in the Applicant's table below. Note, the dispensing pump tested in the extractables study was one designed to dispense (b) (4) mL product per actuation rather than the to-be-marketed pump, which dispenses 1 mL per actuation. However, since the components of both pumps are identical in size, material, and construction, the extractable studies are adequate to support the proposed container.

**Extraction Testing Groups**

Description	Material	Testing Group
Actuator	Polypropylene (PP) (b) (4)	1
(b) (4)	(b) (4)	2
		2
		2
		2
		3
		4
		5
		5

### Extraction Solvents

Samples were subjected to controlled extraction procedures using 3 extraction solvents of varying polarity that included water, methylene chloride, and a formulation mimic. Note that the formulation mimic consisted of the Pennsaid 2% topical solution product formulation without the active ingredient diclofenac sodium and therefore was the most relevant of the solvents for identifying potential leachables from the container system. For tests utilizing water or methylene chloride, semi-volatile, non-volatile, and polar extractables were extracted by boiling the components under reflux for 24 hours. For tests utilizing the formulation mimic, a 24 hour 70°C maceration extraction was performed in addition to the reflux extraction. For each solvent and extraction technique, blanks were analyzed concurrently with the component extracts.

### Analytical Methods

The characterization methods used in this study are shown in the table below. The extracts were profiled using GC-MS and HPLC-UV-MS after appropriate concentration and/or solvent exchange. For metals testing, individual components were extracted in 1% nitric acid for 24 hours at ambient temperature followed by analysis using ICP-MS.

Compound Class	Analytical Technique	Analytical Test Method
Semi-volatile Compounds	Gas Chromatography-Mass Spectrometry (GC-MS)	PDR-ATM-CPS-0040
Non-Volatile and Polar Compounds	High Performance Liquid Chromatography-Mass Spectrometry (HPLC-MS)	PDR-ATM-CPS-0041
Metals and Inorganic Elements	Inductively Coupled Plasma-Mass Spectrometry (ICP-MS)	PDR-ATM-MAG-0012

### AET Selection/Rationale

The Applicant utilized an identification reporting threshold for extractables that was based on a final Analytical Evaluation Threshold (AET) set according to a Toxicological Threshold of Concern (TTC) level of 1.5 µg total daily intake (TDI) for materials in

continuous direct contact with the drug product. The AET was calculated to be (b) (4)  $\mu\text{g}/\text{device}$  using the following equation:



*Reviewer's note:* The AET is described in a document by the Product Quality Research Institute (PQRI) Leachables and Extractables Working Group, which has FDA representation, as an approach to establish safety thresholds for extractables and leachables recommended for orally, inhaled, and nasal drug products<sup>2</sup>. This document indicates that a Safety Concern Threshold (SCT) of 0.15  $\mu\text{g}/\text{day}$  represents a level where a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and noncarcinogenic toxic effects. Additionally, the document recommends that a Qualification Threshold of 5  $\mu\text{g}/\text{day}$  represent a level where a given leachable is not considered for safety qualification unless the leachable presents structure–activity relationship (SAR) concerns. Although the Applicant's SCT of 1.5  $\mu\text{g}/\text{day}$  is higher than recommended by the PQRI working group, it has been CDER policy to allow exposure levels of up to 1.5  $\mu\text{g}/\text{day}$  without further qualification for genotoxic or carcinogenic impurity for marketing applications<sup>3</sup>.

The AET was adjusted according to Test Group component weights to achieve a final AET in  $\mu\text{g}/\text{g}$  using the following equation:



Final AETs calculated for each Test Group are shown in the Applicant's table below.

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<sup>2</sup> Refer to Safety Thresholds And Best Practices For Extractables And Leachables In Orally Inhaled And Nasal Drug Products (September 8, 2006) which can be found at [http://www.pqri.org/pdfs/LE\\_Recommendations\\_to\\_FDA\\_09-29-06.pdf](http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf)

<sup>3</sup> Draft Guidance for Industry on Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (December 2008)

**Final AETs used to Determine Theoretical Reporting Thresholds**

Testing Group	Components	Number of Components Tested	AET (µg/g)
1	(b) (4)		
2			
3			
4			
5			

All reportable peaks were assigned first pass identifications based on the following parameters according to the PQRI document on Safety Thresholds and Best Practices for Extractables in Orally Inhaled and Nasal Drug Products.

**Identification Code and Property Used for Identifications**

- A Mass spectrometric fragmentation behavior
- B Confirmation of molecular weight
- C Confirmation of elemental composition
- D Mass spectrum matches automated library or literature spectrum
- E Mass spectrum and chromatographic retention index match authentic specimen

Identification Codes From: [http://www.pqri.org/pdfs/LE\\_Recommendations\\_to\\_FDA\\_09-29-06.pdf](http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf), Table 2, Page 118

Peaks observed in the aqueous extracts in the GC-MS and HPLC-UV-MS profiles of the components above the reporting thresholds (e.g., final AETs) were quantified using a respective external reference standard. Peaks that showed fragmentation patterns that were similar to or were consistent with other observed species but could not be attributed to a specific compound were assigned as "Related" species. Peaks that could not be identified by reference library matching or otherwise manually interpreted were tentatively assigned to a related class of compounds. Peaks that did not produce acceptable library matches or could not be manually interpreted were assigned as No First Pass Identification (NFPI).

**Results**

The Applicant noted that semi-quantitation was not appropriate for the methylene chloride extraction as it was only used to facilitate identification of extractables. Therefore, concentrations for compounds identified via the methylene chloride extraction were not provided. Though water formulation extractables were identified and quantified if above the component AET, only first pass identification of formulation solution extractables are shown below since the evaluation with this solvent was the most representative of probable leachables that could arise from the drug product.

**Test Group 1 Extraction: Actuator**

**First Pass Identifications and Semi-Quantitative Estimates of Extractable Compounds GC-MS Analysis of Actuator, Testing Group 1, Formulation Solution Extract**

Reported Average RT (min)	RRT	First Pass Identification	CAS Number	Identification Code	Concentration (µg/g)
[REDACTED]	[REDACTED]	[REDACTED]	(b) (4)	A,D	(b) (4)
			A,D		
			A,D		
			NA		
			A,D		

NFPI=No First Pass Identification was assigned when peaks did not produce acceptable library matches or could not be manually interpreted

Note, there were no first pass identifications of extractable compounds from the LC-MS analysis of Testing Group 1 components that were above the AET Level from the formulation solution extracts

Test Group 2 Extraction: [REDACTED] (b) (4)

There were no first pass identifications of extractable compounds from the GC-MS or LC-MS analyses of Testing Group 2 components that were above the AET Level from the formulation solution extracts.

Test Group 3 Extraction: [REDACTED] (b) (4)

There were no first pass identifications of extractable compounds from the GC-MS or LC-MS analyses of Testing Group 3 components that were above the AET Level from the formulation solution extracts.

Test Group 4 Extraction: [REDACTED] (b) (4)

There were no peaks except blank related that were detected in all extracts by GC-MS and LC-MS analyses.

Test Group 5 Extraction: [REDACTED] (b) (4)

**First Pass Identifications and Semi-Quantitative Estimates of Extractable Compounds GC-MS Analysis of [REDACTED] (b) (4), Testing Group 5, Formulation Solution Extract**

Reported Average RT (min)	RRT	First Pass Identification	CAS Number	Identification Code	Concentration (µg/g)
[REDACTED]	[REDACTED]	[REDACTED]	(b) (4)	A	(b) (4)
			NA		
			NA		

**First Pass Identifications and Semi-Quantitative Estimates of Extractable Compounds LC-MS Analysis of (b) (4), Testing Group 5, Formulation Solution Extract**

Reported Average RT (min)	RRT	First Pass Identification	CAS Number	Identification Code	Concentration (µg/g)
(b) (4)		(b) (4)	NA	A	(b) (4)

The summary table below shows all extractable compounds identified through first pass that were above the AET Level from the formulation solution extracts.

**Summary – First Pass Identifications of Extractables from Formulation Solution**

First Pass Identification	Method	Approx Retent time (min)	Relative Retent time (min)	CAS	Concentration (µg/g)
(b) (4)	GC-MS	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	GC-MS	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	GC-MS	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	GC-MS	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	GC-MS	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	GC-MS	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	GC-MS	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	GC-MS	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	LC-MS	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Total daily exposures (TDEs) for potential leachables were calculated by this reviewer (as shown in the table below) based on a worst case scenario in which 100% of the formulation mimic extracted compounds leach into the drug product and evenly distribute throughout the bottle with subsequent exposure to patients through daily administration. Calculations were based on the following equation:

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

**Estimated Maximum Total Daily Exposure to identified Extractables**

Compound	Conc. (µg/g)	Component	Total Daily Exposure (µg/day) <sup>1</sup>	Safety Rationale
[Redacted]	[Redacted]	[Redacted]	(b) (4)	Below QT
				Listed in IIG & Below RfD
				Below QT

**TDE =** [Redacted] (b) (4)

**Ave Weight of Actuator =** [Redacted]  
**Ave Weight of Pouch and Pouch Adapter** [Redacted] (b) (4)  
**NFPI = No First Pass Identification**  
**QT=Qualification Threshold**  
**IIG=FDA Inactive Ingredient Guide**  
**RfD=Reference dose recommended by Environmental Protection Agency**

TDEs for formulation solution extractables were all very low with levels ranging between [Redacted] (b) (4) µg per day. Based on the safety rationale discussed below, no further qualification is necessary for any of the identified formulation solution extracted compounds.

**NFPI:** All three of the compounds that were assigned a No First Pass Identification (NFPI) had approximate TDEs of 1.5 µg/day, which is the qualification threshold for any impurities including genotoxic and carcinogenic compounds as recommended by the Draft CDER Guidance for Industry on Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (December 2008). Therefore, no further identification or qualification is necessary.

[Redacted] (b) (4) is listed in the FDA Inactive Ingredient Guide (IIG) with a maximum potency of [Redacted] (b) (4) mg for the oral route. With a TDE of [Redacted] (b) (4) µg/day, it is well below the qualification threshold of 5 µg/day recommended by the Product Quality Research Institute (PQRI) Leachables and Extractables Working Group, which has FDA representation. Additionally, the [Redacted] (b) (4) [Redacted] was associated with a TDE of [Redacted] (b) (4) µg/day, which

is below the qualification threshold for genotoxic and carcinogenic impurities. Therefore, no additional safety data are necessary for these potential leachable as they pose minimal safety risk.

(b) (4) (b) (4) is listed in the FDA IIG with maximum potencies of (b) (4) mg and (b) (4) % for the oral and topical routes, respectively. With a TDE of (b) (4) µg/day, the (b) (4) is near the qualification threshold for genotoxic and carcinogenic impurities and falls well within the qualification threshold of 5 µg/day recommended by the Product Quality Research Institute (PQRI) Leachables and Extractables Working Group. The (b) (4) had a TDE of (b) (4) µg/day, which is below the threshold for genotoxic and carcinogenic impurities. Therefore, neither compound poses a safety risk.

(b) (4) Numerous (b) (4) including (b) (4) are listed in the FDA IIG with maximum potencies of (b) (4) mg, (b) (4) mg, (b) (4) mg, and (b) (4) mg, respectively, all for the oral route. (b) (4) have been widely used in pharmaceutical formulations primarily as a (b) (4) oral drug products (b) (4). They have been studied extensively in animals and though most have no appreciable toxicity, certain (b) (4) have been shown to be developmental and reproductive toxicants in laboratory animals. (b) (4)

The document focused on the nonclinical toxicity data existing for (b) (4) in particular. The developmental and reproductive findings associated with exposure to (b) (4) included decreased sperm counts, reduced fertility in both female and male animals, skeletal abnormalities and malformations. Based on the available nonclinical data, the EPA recommended an oral Reference Dose (RfD) for (b) (4) mg/kg/day where the RfD is an estimate of a daily oral exposure to a human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Exposure to (b) (4) showed similar adverse effects on the male reproductive system and skeletal and cardiovascular malformations, neural tube defects, developmental delays, and intrauterine death of the offspring when administered to females during gestation. The EPA recommended an RfD for (b) (4) mg/kg/day. (b) (4) were identified in the formulation solution extraction with a maximum TDE of (b) (4) µg/day, which is approximately (b) (4) and (b) (4) -fold below the EPA-recommended RfDs for (b) (4) and (b) (4) respectively. Taken together, this potential leachable poses very little safety risk from daily use of the PENNSAID 2% topical solution.

(b) (4) This compound is also known as (b) (4). With a TDE of (b) (4) µg/day, this potential leachable is near the qualification threshold for genotoxic and carcinogenic impurities and well within the threshold recommended by the PQRI. According to the Hazardous Substances Data Bank (HSDB), (b) (4) was not determined to be a mutagen when tested at concentrations up to (b) (4) µg/mL in the absence of (b) (4) and up to (b) (4) µg/mL in the presence of (b) (4) (based on unreviewed data from (b) (4)).

Taken together, this potential leachable poses very little safety risk from daily use of the PENNSAID 2% Topical Solution.

Leachables Data Summary

Leachables testing on the (b) (4) container is currently being conducted during stability studies on three registration lots (Lot No.: C1101PR, S11113, and S11114). Only a single target leachable compound of interest, (b) (4), was chosen to be monitored based on being identified at levels greater than the calculated AET in the extraction studies. This Reviewer notes that (b) (4) was not identified from extractions with the formulation solution so it is of minimal concern. Only 6 month data from both long-term (e.g., 25°C/60%RH) and accelerated (e.g., 40°C/75%RH) stability studies were provided with the NDA. The Applicant noted that (b) (4) was not detected through 6 months under either condition. Importantly, several unknown leachables were detected above an AET of (b) (4) µg/mL under accelerated conditions. Note, the proposed AET of (b) (4) µg/mL for unknown compounds is based on a qualification threshold of (b) (4) µg/day (e.g., AET = (b) (4) µg/day divided by (b) (4) mL total daily dose volume), which was allowed for NDA 20-947 (Refer to FDA communication included in NDA submission Section 3.2.P.2 p 543 or 574; NDA 20-947 Pharmacology Toxicology review dated 7/23/09; NDA 20-947 CMC review dated 6/22/09). The Applicant stated “although several unknown leachable compounds were observed in the 40°C accelerated (b) (4) data, it is unknown whether this is truly predictive of the long-term condition. Therefore, the 25°C long term leachables program will be continued until 24 months.” The highest concentration observed for an unknown compound was (b) (4) µg/mL, which translates to an estimated maximum total daily exposure of (b) (4) µg/day. This exceeds the qualification threshold for genotoxic or carcinogenic impurities. Without identification, it is impossible to assess the safety risk. Therefore, the leachables data from the 6 month accelerated stability study does not support a longer expiry than that supported by the data from the 6 month long term stability study.

(b) (4) **Leachables after 6 months storage at 25°C/60%RH**

Table 3.2.P.8.3-5. (b) (4) leachables after 6-month storage at 25°C/60%RH.

Stability Lot			C1101PR	S11113	S11114	Proposed Acceptable Limits (Potential Known) (ug/mL) <sup>2</sup>
Nuvo Lot			11-0002-120B	11-0004-120A	11-0005-120A	
Compound	Source	RRT	Results (ug/mL)	Results (ug/mL)	Results (ug/mL)	
(b) (4)			ND	ND	ND	(b) (4)
(b) (4)			ND	<LOQ	ND	(b) (4)
(b) (4)			ND	ND	ND	(b) (4)
(b) (4)			ND	0.85	0.81	(b) (4)



40°C 6 month data. With a designated analytical evaluation threshold of  $\mu\text{g/mL}$  (as described in Section 3.2.P.2.4, NDA 204623, Sequence 0000) several unknown leachables also dropped below the threshold. <sup>(b) (4)</sup>

The following tables show the corrected 40°C 6 month data presented alongside the new 18 month 25°C long term stability data from the three registration lots. No compounds including unknown leachables were observed above the AET at 18 months under 25°C long term conditions. Moreover, once the data were corrected only two unknown leachables were observed above the AET at 6 months from the accelerated 40°C stability studies, and these same compounds (e.g., identical peaks) were under the AET at 18 months under 25°C conditions. Therefore, the new data supports the Applicant's proposed expiry of 24 months.



(b) (4) **Leachable Data for Lot S11113 (Nuvo Lot 11-0004-120A)**  
**UPDATED**

Stability Lot: S11113	Interval:	18 Month	6 Month			
Nuvo Lot: 11-0004-120A	Condition:	25°C/ 60%	40°C/ 75%			
	Date Tested:	19-Nov-2012	02-Dec-2011			
Compound	Source	RRT	Results (µg/mL)	RRT	Results (µg/mL)	Proposed Acceptable Limits (Potential Known) (µg/mL) <sup>2</sup>
		(b) (4)	ND	(b) (4)	(b) (4)	(b) (4)
			< LOQ <sup>4</sup>		ND	
			ND		ND	
						Proposed AET (Unknowns) (b) (4)
Unknown peak		ND	ND	(b) (4)		Long-term condition: ND Accelerated condition: < AET
Unknown peak		(b) (4)		(b) (4)		Long-term condition: < AET Accelerated condition: < AET
Unknown peak		ND	ND			Long-term condition: ND Accelerated condition: < AET
Unknown peak		ND	ND			Long-term condition: ND Accelerated condition: < AET
Unknown peak		ND	ND			Long-term condition: ND Accelerated condition: < AET
Unknown peak		ND	ND			Long-term condition: ND Accelerated condition: < AET
Unknown peak		ND	ND			Long-term condition: ND Accelerated condition: < AET
Unknown peak		(b) (4)		(b) (4)		Long-term condition: < AET Accelerated condition: < AET
Unknown peak		ND	ND			Long-term condition: < AET Accelerated condition: < AET
Unknown peak		(b) (4)		(b) (4)		Long-term condition: < AET Accelerated condition: < AET
Unknown peak		ND	ND			Long-term condition: ND Accelerated condition: < AET
Unknown peak		(b) (4)		(b) (4)		Long-term condition: < AET Accelerated condition: < AET
Unknown peak		ND	ND			Long-term condition: ND Accelerated condition: < AET

(b) (4)



## **11 Integrated Summary and Safety Evaluation**

Refer to the Executive Summary

## **12 Appendix/Attachments**

N/A

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JAY H CHANG  
01/28/2013

ADAM M WASSERMAN  
01/28/2013

I concur with Dr. Chang that the NDA may be approved from the nonclinical perspective.