CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-067

MEDICAL REVIEW(S)

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Rheumatology Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Deputy Division Director Review and Basis for Approval

Date:	January 14, 2008
Drug:	Flo-Pred (Prednisolone acetate oral suspension) 5 mg/5ml 15mg/5ml
NDA Number	22-067
Type of Submission:	505 (b)(2)
Sponsor:	Taro Pharmaceuticals
Indication:	Multiple indications

Taro Pharmaceuticals submitted a 505(b)(2) application for an oral suspension formulation of prednisolone acetate in August, 2006. The applicant was seeking marketing approval for two strengths: 5 mg/5ml and 15 mg/5 ml. In support of their application, the applicant submitted the results from three clinical pharmacokinetic studies conducted in healthy volunteers to establish the bioequivalence to two reference products, prednisolone syrup, and prednisolone tablets. The studies performed compared the pharmacokinetics of the 15 mg/5 ml suspension to the syrup and the tablet formulations under fed and fasted conditions, and the 5 mg/5 ml suspension to the tablet formulation under fasted conditions.

Although the NDA contained adequate clinical pharmacology data to support an approval, the supplement received an Approvable action on September 14, 2007, due to inability to reach an agreement with the applicant on the packaging labels. The letter indicated the following deficiency:

> Before this application may be approved, however, you must submit revised draft labeling identical to the enclosed labeling and revise your carton and container labels as indicated below:

1. The proposed tradename Flo-Pred [redacted] is misleading. Delete the promotional phrases [redacted] and [redacted] from the proposed trade name. b(4)
2. The two dosing spoons should be attached to minimize loss of a spoon and the colors should be accurately reflected on the labels.
3. Revise the Attention statement on all the panels to read "The product is packaged with one purple (2.5 mL) and one blue (5 mL) spoons for accurate dosing. Use the appropriate spoon(s) based on your prescription. Can also be used with an [redacted] syringe."

The applicant submitted a complete response to the approvable letter on November 21, 2007. The label proposed by the applicant was discussed with the applicant through telephone conversations, and e-mail communications, and an agreement on the label has been reached.

The applicant has requested a waiver of the requirement to conduct pediatric studies with their formulation, as mandated under the Pediatric Research Equity Act (PREA) of 2003, based on data that indicate that the pharmacokinetics of orally administered prednisolone are similar in adults and pediatric patients (rate and extent of absorption, as well as the distribution, metabolism and elimination). The applicant asserted that since the safety and efficacy of the new formulation was supported by the comparative bioavailability to the referenced products in adults, further studies in pediatric patients are unnecessary.

In my memo of September 14, 2007, I recommended that a waiver not be granted in the event of approval because the applicant's rationale would not necessarily apply to all the indications for which prednisolone is approved. However, during a meeting of the Pediatric Review Committee (PeRC) held on January 11, 2008, it was determined that in the case of corticosteroids, the requirements for efficacy studies in the pediatric indications were either waived or fulfilled; in the case of the rheumatological indications, the determination was they have been fulfilled. Further, after additional internal discussions in the Division, it was determined that even if the requirement for efficacy studies had not been fulfilled, they could, in fact be waived, because the clinical pharmacology information on the new formulation was sufficient due to the extensive clinical experience with corticosteroids in juvenile rheumatoid arthritis, and the fact that the actual therapeutic dose is titrated based on the clinical response. Therefore, for multiple reasons, additional efficacy studies are not necessary.

Recommended Action:
Approval.

Rigoberto Roca, M.D.
Deputy Division Director
Division of Anesthesia, Analgesia, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Rigoberto Roca
1/14/2008 05:37:56 PM
MEDICAL OFFICER

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Rheumatology Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Deputy Division Director Review and Basis for Approvable Action

Date:	September 14, 2007
Drug:	Flo-Pred (prednisolone acetate oral suspension) 5 mg/5ml 15mg/5ml
NDA Number	22-067
Type of Submission:	505 (b)(2)
Sponsor:	Taro Pharmaceuticals
Indication:	Multiple indications

Taro Pharmaceuticals has submitted a 505(b)(2) application for an oral suspension formulation of prednisolone acetate; they are seeking marketing approval for two strengths: 5 mg/5ml and 15 mg/5 ml. In support of their application, the applicant has submitted the results from three clinical pharmacokinetic studies conducted in healthy volunteers to establish the bioequivalence to two reference products, prednisolone syrup and prednisolone tablets. The studies performed compared the pharmacokinetics of the 15 mg/5 ml suspension to the syrup and the tablet formulations under fed and fasted conditions, and the 5 mg/5 ml suspension to the tablet formulation under fasted conditions. The table below summarizes the three studies conducted.

Study	Conditions	Study Groups			Subjects
		Flo-Pred	Syrup	Tablet	
PEN-P5-319	Fasted	15 mg/5ml	15 mg/5ml	5 mg x 3	12 males 12 females
PEN-P5-320	Fed	15 mg/5ml	15 mg/5ml	5 mg x 3	12 males 12 females
PEN-P5-321	Fasted	5 mg/5ml	5 mg/5ml	5 mg	12 males 12 females

KV Pharmaceutical is the holder for the two ANDAs for the syrup [5 mg/5ml (ANDA 40-423), and 15 mg/5ml (ANDA 40-364)] and Watson Laboratories is the holder for the ANDA for the tablet (5 mg tablet, ANDA 80-354).

The clinical reviewer for this application was James Witter, M.D., with Jeffrey Siegel, M.D., as the secondary reviewer; the clinical pharmacology reviewer was Sally Choe, Ph.D., and Suresh Doddapaneni, Ph.D., was the secondary clinical pharmacology reviewer. The pharmacology/toxicology review was performed by Jerry Cott, Ph.D., with Adam Wasserman, Ph.D., as the secondary reviewer. The chemistry, manufacturing and controls evaluation was performed by Brian Rogers, Ph.D., with Ali Al-Hakim, Ph.D., and Ravi Harapanhalli, Ph.D., performing the secondary reviews.

Consultations were obtained from the Division of Drug Marketing, Advertising, and Communications (DDMAC); the Division of Scientific Investigations (DSI); the Study Endpoints and Labeling Development (SEALD) Team; the Pediatric and Maternal Health Team; and the Office of Surveillance and Epidemiology (Division of Surveillance, Research, and Communication Support, Division of Medical Errors and Technical Support, and Division of Drug Risk Evaluation).

This memorandum will briefly review the effectiveness and safety data summarized in the primary and secondary clinical reviews, as well as any relevant information found in the reviews by the other disciplines, and document my recommendations for action on this NDA.

Efficacy:
There were no clinical trials performed to evaluate the efficacy of the new formulation. The conclusion regarding the safety and efficacy of the new formulation is predicated on the demonstration of bioequivalence to the approved, referenced formulations of prednisolone.

Safety:
The bioequivalence studies were reviewed in detail by Dr. Witter to determine if there were any unexpected safety concerns. The number and type of adverse events reported did not reveal any unique safety concerns for the new formulation.

In addition, the applicant performed videoflouroscopy evaluations in 6 healthy adults and in 7 patients with amyotrophic lateral sclerosis to determine whether the new formulation would be predisposed to aspiration. Neither study demonstrated aspiration or retention of the new formulation in the esophagus.

Clinical Pharmacology and Biopharmaceutics:
The conclusion of the clinical pharmacology reviewers was that the Flo-Pred suspensions are bioequivalent to the same strength syrup and tablets under fed and under fasted conditions. This was based on the finding that the 90% confidence interval of the relative geometric mean of the Flo-Pred formulation was within the pre-specified range of 80 –

125%, with respect to the reference drugs. The data are summarized in the table below, adapted from Dr. Witter's review.

Parameter	Study PEN-P5-319 (fasted)				
	Flo-Pred 15 mg/ 5 ml	Syrup 15 mg/ 5 ml	Tablet 5 mg x 3	Ratio (%) Flo-Pred vs Syrup [90% CI]	Ratio (%) Flo-Pred vs Tablet [90% CI]
C_{max}* (ng/ml)	298.20	345.00	308.72	86.44 [82.76-90.27]	96.59 [92.49-100.88]
AUC $_{(0-t)}$* (ng/ml)	1770.09	1700.64	1760.79	104.08 [100.82-107.45]	100.53 [97.38-103.78]
AUC $_{(0-\infty)}$* (ng/ml)	1818.71	1745.80	1813.57	104.18 [100.96-107.49]	100.28 [97.19-103.47]
	Study PEN-P5-320 (fed)				
	Flo-Pred 15 mg/ 5 ml	Syrup 15 mg/ 5 ml	Tablet 5 mg x 3	Ratio (%) Flo-Pred vs Syrup [90% CI]	Ratio (%) Flo-Pred vs Tablet [90% CI]
C_{max}* (ng/ml)	235.72	252.09	269.92	93.51 [90.13-97.01]	87.33 [84.23-90.54]
AUC $_{(0-t)}$* (ng/ml)	1956.86	1818.90	1756.10	107.58 [103.45-111.89]	111.43 [107.22-115.81]
AUC $_{(0-\infty)}$* (ng/ml)	2023.74	1865.25	1804.51	108.50 [104.27-112.90]	112.15 [107.85-116.62]
	Study PEN-P5-321 (fasted)				
	Flo-Pred 5 mg/ 5 ml	Syrup 5 mg/ 5 ml	Tablet 5 mg	Ratio (%) Flo-Pred vs Syrup [90% CI]	Ratio (%) Flo-Pred vs Tablet [90% CI]
C_{max}* (ng/ml)	157.85	175.70	172.23	89.84 [86.25-93.58]	91.65 [87.99-95.47]
AUC $_{(0-t)}$* (ng/ml)	798.39	768.83	793.73	103.84 [101.27-106.48]	100.59 [98.09-103.14]
AUC $_{(0-\infty)}$* (ng/ml)	828.90	802.53	827.99	103.29 [100.84-105.80]	100.11 [97.93-102.54]

*Expressed as geometric LS means

Non-clinical Pharmacology and Toxicology:

Although non-clinical studies were not performed by the applicant, the review team used the literature information submitted by the applicant, as well as others obtained by the review team, to update the label with available non-clinical toxicology findings. Additionally, the pregnancy and nursing mothers section of the label will be updated.

Chemistry, Manufacturing, and Controls:
There were several requests for additional information sent to the applicant during the course of the review, and all issues have been resolved to the review team's satisfaction. There are no outstanding issues from a CMC perspective.

Of particular interest for this formulation are the distinct qualities of the drug product which allow its physical properties. It can not be easily classified as a suspension, solution or a syrup. It exists in a gel-like state in the bottle with reasonably high viscosity, but when exposed to a small amount of pressure or shearing forces, the viscosity changes and it becomes more like a liquid. As it settles in the spoon, it rapidly reverses to its more viscous state, resisting spilling, while still sliding off the spoon without difficulty.

The company also notes that the formulation is unable to maintain its gel-like structure in the presence of additional water, or upon exposure to dilute salt solutions. These properties will cause it to liquefy when it encounters the environment in the mouth, a process which is also aided by the shearing forces that the formulation will be subjected to from the tongue, cheeks, and teeth.

Although Dr. Witter's review refers to the formulation as the incorporation of prednisolone acetate into a patented "delivery system," it is probably more accurate to describe the formulation as having unique physicochemical characteristics rather than being a new drug delivery system. That type of characterization usually describes a situation where a drug is formulated with a specific delivery system, e.g., an orally disintegrating tablet, a dispersible tablet, or an iontophoretic device.

Data integrity:
The Division of Scientific Investigation (DSI) performed a routine audit of the clinical and analytical portions of Study PEN-P5-319. Although there were several items noted in the Form 483 for the analytical site, the findings were deemed to not be significant enough to impact the study outcome. No Form 483 was issued for the clinical site.

Discussion:
The applicant has submitted data from three pharmacokinetic studies that demonstrated that their suspension is bioequivalent to the referenced drugs. No new safety concerns were identified with respect to the new formulation.

This submission was required to have a label submitted in the new Physician Labeling Rule (PLR) format. With consultations obtained from the SEALD team, Pediatric and Maternal Health team, and other review divisions, substantial revisions were done to the text of the label in order for it to conform to current standards.

With respect to requirements to do pediatric studies as mandated under the Pediatric Research Equity Act (PREA) of 2003, the applicant has requested a waiver based on data that indicate that the pharmacokinetics of orally administered prednisolone are similar in

adults and pediatric patients (rate and extent of absorption, as well as the distribution, metabolism and elimination). The applicant asserts that since the safety and efficacy of the new formulation is supported by the comparative bioavailability to the referenced products in adults, further studies in pediatric patients are unnecessary.

The premise that a pharmacokinetic bridge is sufficient to assume comparable efficacy and safety of the new formulation in the pediatric patient population is predicated on the demonstration that the pathophysiological process being treated is comparable between the adult and pediatric populations. This is not necessarily the case for all of the indications for which prednisolone is approved, e.g., efficacy studies are usually required in pediatric patients with juvenile rheumatoid arthritis. Therefore, the applicant's request for a waiver can not be granted at this time.

During the course of the labeling discussions, it became apparent that the applicant would not be amenable to labeling that [redacted] specifically, the wording [redacted] The review team and DDMAC felt that the incorporation of the words [redacted] in the labeling would be inappropriate because it is misleading, [redacted] b(4)

This issue was further discussed with the applicant today in a telecon. The applicant understands our concerns and has agreed to explore other labeling options post-action.

Recommended Action:
Approvable; pending agreement on labeling.

Rigoberto Roca, M.D.
Deputy Division Director
Division of Anesthesia, Analgesia, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Rigoberto Roca
9/14/2007 06:37:39 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Memorandum

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and
Rheumatology Products/ODE 2
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: October 4, 2006

From: James Witter, M.D., Ph.D., Medical Reviewer, DAARP, ODE II

Through: Jeffrey Siegel, M.D. Team Leader, DAARP, ODE II

To: Bob Rappaport, M. D., Division Director, DAARP, ODE II:

Topic: Clinical Review of PK studies:

NDA 22-067; 505(b)(2)
Product: prednisolone oral suspension: 5 mg/5 mL and 15 mg/5mL
Sponsor: Taro Pharmaceuticals U.S.A., Inc.

Table of Contents **Page**

I. Background

Taro Pharmaceuticals U.S.A. is seeking approval via a 505(b)(2) NDA to market Prednisolone [redacted] Oral Suspension, 5 mg/5 mL and 15 mg/5 mL. To support this application, the sponsor has conducted three adult human bioequivalence (BE) studies in fasted and fed healthy subjects to compare the rate and extent of absorption of their formulation to that of prednisolone syrup (KV Pharmaceuticals [redacted] and prednisolone tablets (Watson Laboratories). As discussed below, both concentrations of prednisolone [redacted] suspension are bioequivalent under fasting and fed (15 mg/5ml) and fasting (5 mg/5ml) conditions to their respective comparators based upon C_{max}, AUC_T and AUC_∞; the reader is referred to the biopharmaceutics review (Dr. Doddapaneni) for further details. b(4) b(4)

Prednisolone containing products have been available in various dosage forms (tablets, oral syrups/solutions, ophthalmic suspensions and injectables) for over 50 years (NDA 9987; June 21, 1955, Delta Cortef Tablets). The sponsor has taken prednisolone acetate (currently in use for ophthalmic and injectables) and incorporated it into a patented delivery system (NonSpil™) which has been designed to resist spilling from a spoon facilitating ease and reliability of dosing. The chemical nature of acetate bonding with prednisolone with this formulation is reported to remove the bitterness noted with currently available syrups and solutions; this improved taste is felt to enhance acceptability and compliance within the pediatric population. An additional benefit in this regard is that the spill-resistant formulation does not need shaking prior to dosing.

The sponsor has similar formulations in pediatric strengths including Loratidine NonSpil Suspension (Children's Elixsure®-24 hour Antihistamine; NDA 21,734), ElixSure® Fever/Pain (Acetaminophen 160 mg/5mL), ElixSure® Cough (Dextromethorphan hydrobromide 7.5 mg/5 mL), ElixSure® Congestion (Pseudoephedrine Hydrochloride) and ElixSure® IB™ Fever/Pain (ibuprofen 100 mg/5mL).

No pediatric BE studies for prednisolone NonSpil were included in this NDA. As noted by the sponsor, a comparative BE study in healthy children was waived by the Division of Pulmonary and Allergy Drug Products for loratadine. Review of the loratadine approval notes that there was a partial waiver for BE studies for ages 0-2 years since the condition does not exist in this age group but also reflected the fact that other loratidine formulations had previously been approved for RX and OTC use down to two years of age.

II. Bioequivalence Studies (PEN-P5-319, 320, 321)

A. Study Characteristics

Conduct of studies:
There were three bioequivalence studies PEN-P5-319, PEN-P5-320 and PEN-P5-321 submitted to support this 505(b)(2) application. All were three-way crossover design studies conducted at a single center [redacted] with a single dose of prednisolone [redacted] (5 or 15 mg/mL) or comparators (5 or 15 mg/5mL syrup-KV Pharmaceutics; 5 mg tablets-Watson Laboratories) as described in Table 1. b(4)

Table 1

Study	Study Design	Tested Product Dose	Subjects
PEN-P5-319	Fasting	Prednisolone 15 mg	24 healthy males and females
PEN-P5-320	Fed	Prednisolone 15 mg	24 healthy males and females
PEN-P5-321	Fasting	Prednisolone 5 mg	24 healthy males and females

Subjects were non-or ex-smokers, at least 18 years of age with a BMI between 19 and 30 kg/m^2. Subjects were determined to be in good health by medical history, physical exam with vital signs, laboratory evaluations (hematology, biochemistry, urinalysis) and were negative for HIV, hepatitis B and C. Subjects were also negative at screening for alcohol and drug abuse (done randomly) as well as having negative pregnancy tests (at screening and post-study).

A single dose of study medication (fasted for 10 hours previously or fed standardized high-fat, high calorie meal 30 minutes prior) was given with 240 mL of water, followed by PK blood sampling for the next 24 hours after which time subjects were allowed to leave the clinic. Concomitant medications were not given during this time, but if they were taken they were recorded. Adverse events (AE) were collected during the time at the study center (approximately 24 hours) while the clinical laboratories (CBC, chemistry including liver, renal, endocrine and urinalysis) were assessed at screening (pre-study sample) and again at the completion of the study (post-study sample). All information was recorded on the Case Report Forms. Vital signs were monitored only when judged necessary by the physician in charge. No ECGs or physical exams were recorded during these studies. There was a minimum of 7 days allowed for washout before the next dosing; subjects were dosed on day 1, 8 and 15.

Disposition of subjects:
Table 2 lists the disposition of subjects who participated in these three BE studies. As can be seen, most completed all three dosing regimens. There was one patient (#001) in PEN-P5-320 who completed 2 of 3 regimens but withdrew her consent for personal reasons before the final dosing period. There was also one patient in study PEN-321 (#010) who was not included in the final analyses; she also dropped out for personal reasons after receiving only one (NonSpil) of the three regimens. None of the AEs

experienced by subjects in these three BE studies resulted in their withdrawal from the trial.

Table 2: Disposition of Subjects-NDA 22-067

Subjects	Study		
	PEN-P5-319	PEN-P5-320	PEN-P5-321
Enrolled	24	24	24
Completed	24	23	23
Experienced AE (#pts/total # events)	11/26	13/48	10/26
Consent withdrawn	0	1	1
Withdrew due to AE	0	0	0

Demographic and Baseline Characteristics

Table 3 summarizes some baseline demographic characteristics for the subjects who participated in the three pharmacokinetic studies for prednisolone NonSpil suspension. As can be seen, subjects were generally older in study 321 while most subjects in all trials were Caucasian with an approximate equal mix of males and females. The mean height of subjects in all three trials was around 167 cm with a mean weight of approximately 70 kg and a BMI of 25.

Table 3: Demographic and Baseline Characteristics of Subjects in NDA 22-067

Demographic Parameter	Study		
	PEN-P5-319	PEN-P5-320	PEN-P5-321[a]
Age (years)			
Mean ± SD	37 ± 14	43 ± 13	49 ± 14
Range	20-74	22-63	27-71
Groups			
-18-39	15 (63%)	11 (46%)	6 (26%)
-40-64	8 (33%)	13 (54%)	13 (57%)
-65-75	1 (4%)	0	4 (7%)
Gender			
-male	11	12	11
-female	13	12	12
Race			
-Black	2 (8%)	1 (4%)	1 (4%)
-Caucasian	22 (92%)	23 (96%)	21 (91%)
-Hispanic	0	0	0
-Other	0	0	1 (4%)
Height-mean cm (SD)	166.5 (8.5)	167.8 (8.3)	166.2 (9.6)
Weight-mean kg (SD)	69.2 (11.0)	73.5 (10.3)	71.6 (9.7)
BMI- kg m^2 (SD)	24 (3)	25 (3)	25 (2)

[a] Does not include subject #010 who withdrew consent before the second dosing period.

C. Safety

There were two types of safety information provided in this NDA. One involved those adverse events experienced during the conduct of the three BE studies with the NonSpil vs. reference comparators. The other was from a review of the literature. Each of these sources will be discussed separately.

Incidence of Adverse Events in Individual BE Studies:

Safety measurements in the BE studies included evaluations of adverse events (AE) and clinical safety parameters. For all these studies, the period of observation for AEs included from the initial dosing until completion of the lab PK blood sample (basically 24 hours). During this period, all AEs spontaneously reported by volunteers, observed by the Clinical Investigator or elicited by general questioning were documented in the CRF and included in the study report. The terminology used to classify AEs employed the PT (Preferred term) level of MedDRA (version 8.1).

Table 5 presents all the adverse events that occurred in study 319. There were 9 subjects (38%) who experienced 10 AEs with prednisolone NonSpil, 6 subjects (25%) with 7 AEs for prednisolone syrup, and 7 (29%) with 9 AEs for prednisolone tablets for a total of 26 events. Overall, 19 of the 26 events (73%) were considered possibly related to the drug. However, only 11 unique subjects experienced AEs during the study; several experienced more than one event and the laboratory AEs (see below) are counted more than once. All subjects completed the study. The AEs ranged from mild to moderate.

One of these events (bilirubin increased) occurred in the same individual (#021) who had elevations both before and after all three single doses. The only laboratory observations of interest were the increase of lymphocytes and the decrease of neutrophils as usually these patterns are reversed with prednisolone use; this may reflect the short-term nature of this study. Of note, all of the AEs listed under "Investigations" have the same incidence rates in all three treatment arms because such laboratory investigations were only done at the beginning of the dosing period (screening) and at the end of the final (of three) dosing (post-study). Therefore, these AEs represent the same person, not up to three different subjects as is the case with the other AEs. This same caveat applies to all BE studies in this NDA.

These AEs, associated with single doses of the three drugs and frequent blood sampling, are not unexpected types of AEs in such a trial. There were no significant increases of AEs with the NonSpil as compared to other prednisolone formulations. There were no serious adverse events (SAE) or deaths in study 319.

Table 5: Adverse Events in Study PEN-P5-319 of NDA 22-067

MedDRA Classification SOC / Adverse Event	Reported Incidence by Treatment Groups					
	Fasted Bioequivalence Study Study No. PEN-P5-319					
	NonSpil		Syrup		Tablet	
	Number of subjects reporting adverse events	% of subjects exposed	Number of subjects reporting adverse events	% of subjects exposed	Number of subjects reporting adverse events	% of subjects exposed
Gastrointestinal Disorders						
Dyspepsia	1	4	1	4	1	4
General Disorders and Administration Site Conditions						
Fatigue	1	4	0	0	0	0
Hot flush	0	0	1	4	0	0
Injury, Poisoning and Procedural Complications						
Venipuncture site pain	1	4	0	0	1	4
Venipuncture site swelling	1	4	0	0	0	0
Investigations						
Blood bilirubin increased	1	4	1	4	1	4
Lymphocyte count increased	2	8	2	8	2	8
Neutrophil count decreased	1	4	1	4	1	4
Metabolism and Nutrition Disorders						
Increased appetite	0	0	0	0	1	4
Musculoskeletal and Connective Tissue Disorders						
Arthralgia	0	0	0	0	1	4
Nervous System Disorders						
Headache	1	4	0	0	0	0
Somnolence	0	0	1	4	0	0
Respiratory, Thoracic and Mediastinal Tissue Disorders						
Pharyngolaryngeal Pain	0	0	0	0	1	4
Skin and Subcutaneous Disorders						
Blister	1	4	0	0	0	0
Number Exposed	24		24		24	

Table 6 presents all the adverse events that occurred in study 320. There were 9 subjects (38%) who experienced 20 AEs with prednisolone NonSpil, 6 subjects (25%) had 9 AEs with prednisolone syrup, and 10 subjects (42%) had 19 AEs with prednisolone tablets for a total of 48 events. Overall, 26 of the 48 events (54%) were considered possibly related to the drug. However, only 13 unique subjects experienced AEs during the study; several experienced more than one event and the laboratory AEs (see discussion above for study 319) are counted more than once. All subjects except one (see below) completed the study.

The AEs ranged from mild to severe (one episode of nausea, headache and diarrhea). Four AEs (arthralgia, headache, nausea and vomiting) required the use of concomitant medications. Headache was the most frequent event but this occurred more often with the prednisolone tablets than the NonSpil formulation. These AEs, associated with single doses of the three drugs and frequent blood sampling, are not unexpected types of AEs in such a trial. As depressed production of lymphocytes is known to occur with prednisolone use, an observation of interest was the increase of lymphocytes noted in one subject (even though other subjects had values higher than normal) which did return to normal on repeat testing,; this may reflect the short-term nature of this study.

Subject #001 completed 2 periods of 3 since she withdrew consent for personal reasons. Her period 3 results were, therefore, excluded from analysis; she had received the NonSpil and prednisolone tablets.

There were no serious adverse events (SAE) or deaths in study 320.

Table 6: Adverse Events in Study PEN-P5-319 of NDA 22-067

MedDRA Classification SOC / Adverse Event	Reported Incidence by Treatment Groups					
	Fed Bioequivalence Study Study No. PEN-P5-320					
	NonSpil		Syrup		Tablet	
	Number of subjects reporting adverse events	% of subjects exposed	Number of subjects reporting adverse events	% of subjects exposed	Number of subjects reporting adverse events	% of subjects exposed
Eye Disorders						
Ocular hyperaemia	1	4	0	0	1	4
Gastrointestinal Disorders						
Abdominal distension	0	0	0	0	1	4
Abdominal pain	0	0	0	0	1	4
Abdominal pain upper	0	0	0	0	1	4
Diarrhoea	0	0	0	0	1	4

Dry mouth	1	4	0	0	0	0
Dyspepsia	1	4	1	4	0	0
Flatulence	1	4	0	0	0	0
Lip dry	1	4	1	4	0	0
Nausea	2	8	1	4	1	4
Vomiting	1	4	0	0	1	4
General Disorders and Administration Site Conditions						
Fatigue	1	4	0	0	1	4
Hot flush	1	4	1	4	0	0
Venipuncture site pain	0	0	1	4	0	0
Vessel puncture site bruise	1	4	0	0	0	0
Investigations						
Lymphocyte count increased	1	4	1	4	1	4
Musculoskeletal and Connective Tissue Disorders						
Arthralgia	0	0	0	0	1	4
Nervous System Disorders						
Dizziness	1	4	1	4	0	0
Headache	3	13	1	4	6	25
Somnolence	1	4	1	4	1	4
Tremor	1	4	0	0	0	0
Reproductive System and Breast Disorders						
Metrorrhagia	1	4	0	0	0	0
Respiratory, Thoracic and Mediastinal Tissue Disorders						
Nasal congestion	0	0	0	0	1	4
Rhinorrhoea	0	0	0	0	1	4
Skin and Subcutaneous Tissue Disorders						
Fixed eruption	1	4	0	0	0	0
Number of subjects exposed	**24**		**23**		**24**	

Table 7 presents all the adverse events that occurred in study 321. There were 6 subjects (25%) who experienced AEs with prednisolone NonSpil, 5 subjects (22%) with prednisolone syrup, and 7 (30%) with prednisolone tablets for a total of 26 events. Overall, 15 of these 26 events (58%) were considered possibly related to the drug. However, only 10 unique subjects experienced AEs during the study; several experienced more than one event and the laboratory AEs (see discussion above for study 319) are counted more than once. All subjects except one (see below) completed the study.

The AEs ranged from mild to moderate. Headache required the use of concomitant medications in 2 subjects. These AEs, associated with single doses of the three drugs and frequent blood sampling, are not unexpected types of AEs in such a trial. One subject (003) had a post-study potassium elevation of 5.6 which returned to normal (4.8) on repeat testing.

Subject #010 completed only 1 of 3 dosing periods (NonSpil) since she withdrew consent for personal reasons.

There were no serious adverse events (SAE) or deaths in study 321.

Table 7: Adverse Events in Study PEN-P5-319 of NDA 22-067

MedDRA classification SOC / Adverse Event	Reported Incidence by Treatment Groups					
	Fasted Bioequivalence Study Study No. PEN-P5-321					
	Test		Reference-1		Reference-2	
	Number of subjects reporting adverse event	% of subjects exposed	Number of subjects reporting adverse event	% of subjects exposed	Number of subjects reporting adverse event	% of subjects exposed
Eye Disorders						
Ocular hyperaemia	0	0	0	0	1	4
Gastrointestinal Disorders						
Lip dry	0	0	0	0	1	4
Nausea	1	4	0	0	0	0
General Disorders and Administration Site Conditions						
Catheter site pain	1	4	0	0	0	0
Catheter site reaction	1	4	0	0	0	0
Shivering	1	4	0	0	0	0
Investigations						
Blood potassium increased	1	4	1	4	1	4
Neutrophil count	2	8	2	9	2	9

decreased						
Musculoskeletal and Connective Tissue Disorders						
Arthralgia	0	0	0	0	1	4
Nervous System Disorders						
Dizziness	0	0	1	4	0	0
Headache	1	4	1	4	1	4
Hypoaesthesia	0	0	1	4	0	0
Somnolence	0	0	0	0	1	4
Number of subjects exposed	**24**		**23**		**23**	

Review of the literature:
The sponsor conducted a Medline search for randomized clinical trials that were published over the last 10 years comparing prednisolone to a placebo control. Only those trials that reportedly contained detailed adverse event data (tabular or textual) were included in this summary. From this search, ten studies were identified; four in the pediatric population (Csonka *et al*, 2003; Goebel *et al*, 2000; Ruohola *et al*, 1999; van Woensel *et al*, 1997) and six in adults patients (Buchbinder *et al*, 2004; Dunlop *et al*, 2003; Gerlag *et al*, 2004; Kirwan *et al*, 2004; Munck *et al*, 2003; Wassenberg *et al*, 2005).

In the pediatric trials, the mean age of the patients was under 2 years and the duration of therapy was under 1 week. Three of these pediatric studies used a dose of 2 mg/kg/day while the other used 1 mg/kg/day. In the six adult trials, the age range was 40-60 years, duration of therapy ranged from 2 weeks to 2 years and the doses ranged from 5-60 mg daily.

Table 8 presents the top 10 adverse events mentioned in these literature trials. Owing to the lack of rigorous and detailed event reporting in published trials, and the large variability inherent in comparing studies of this nature, it is not possible to draw any meaningful conclusions from this data that differs in any important way from adverse events already noted in the label of prednisolone and related steroid products.

Table 8: Incidence of Adverse Events reported by Sponsor-Medline search

Adverse Event	Pediatric		Adult	
	Placebo (n = 195)	Prednisolone (n = 187)	Placebo (n = 182)	Prednisolone (n = 189)
Vomiting-Nausea	2%	5%	5%	5%
Diarrhea	4%	3%	-	-
Restlessness	1%	2%	-	-
Rash-Exanthema	0	1%	4%	5%
Jittery	0	1%	-	-

Headache	-	-	**2%**	**9%**
Gastric Distress	-	-	**4%**	**8%**
Insomnia	-	-	**1%**	**6%**
Weight gain	-	-	**2%**	**6%**
Abdominal pain	-	-	**2%**	**5%**
Mood swings	-	-	**2%**	**4%**
Aggravated RA	-	-	**6%**	**3%**
Hypertension	-		**2%**	**3%**

D. Conclusions regarding efficacy and safety of prednisolone

Since there were no clinical trials in this NDA, there can be no comment regarding the efficacy of prednisolone [redacted] or any of the other formulations tested. The efficacy "link" in this NDA is via the 505(b)(2) route and the use of BE studies. However, the long history of usage of prednisolone and other glucocorticoids along with their pivotal role in many aspects of medicine speak to their efficacy and real world effectiveness. b(4)

Regarding safety, for the drug substance itself, once again the 505(b)(2) route helps to establish the relative safety of prednisolone and other types of steroids as discussed below. However, particular to this formulation are the ingredients that give it the characteristics of resisting spilling like a traditional suspension or syrup.

Since in at least one prior NDA submission there had been concerns about whether the NonSpil formulation may somehow predispose to aspiration, the sponsor briefly summarized in this NDA a study conducted with their ibuprofen 100 mg/5mL NonSpil suspension in which 6 healthy adults swallowed 30mL of this suspension made radiopaque with 10% barium sulfate. Employing videofluoroscopy, there was no evidence for aspiration or retention in the esophageal mucosa. Also described was a companion study involving 7 patients with amyotrophic lateral sclerosis (ALS) with mild-to-moderate difficulty in swallowing due to neurologic impairment. Although these patients did have evidence of aspiration (cough or wet phonation) with 20 ml of less of water, none had similar problems with a similar amount of pureed food or the NonSpil formulation.

To further support the safety of this formulation, the sponsor notes that there were an estimated [redacted] NonSpil OTC units sold during the time period of September 1, 2003 to April 30, 2004. During this time period, there were 123 complaints received of which 62 related to taste or texture while there were no apparently related to difficulty with swallowing NonSpil products. b(4)

Therefore, there do not appear to be any unique safety concerns to the NonSpil formulation itself nor any meaningful differences in the safety of the NonSpil formulation compared to the two reference products. However, due to the single-dose nature of these studies, it is not possible to draw robust conclusions regarding longer-term usage; such a conclusion is derived from the nature of the NDA submission as a 505(b)(2) application

as discussed below. Although limited in scope, the literature review provided by the sponsor does not suggest any unique safety concerns with prednisolone not already included in the label. Due to the long history of clinical use of prednisolone and the wide variety of dose forms and routes of administration, a search of the AERS database was not conducted for this NDA review as it would be difficult, if not impossible, to draw any meaningful conclusions from such a search.

Similarly, the link to efficacy of the NonSpil formulation to the efficacy of prednisolone in general has been established by the demonstration of bioequivalence in the three BE studies submitted in this NDA.

III. 505(b)(2) discussion:

By filing a 505(b)(2) NDA application, the sponsor relies on the Agency's previous findings of safety and efficacy of prednisolone; the sponsor has not obtained right of reference for these studies but has submitted three unique BE studies to establish bioequivalence to two reference products, prednisolone syrup (KV Pharmaceuticals [redacted] and prednisolone tablets (Watson Laboratories). b(4)

Glucocorticoids were first introduced into clinical medicine in 1948 (i.e. cortisone); this work was rewarded with a Nobel Prize in 1950. During the 1950's and 60's, new glucocorticoids were synthesized that attempted to have less mineralocorticorticoid activity and more anti-inflammatory (i.e. glucocorticoid) activity. Examples include the drug involved with this NDA (i.e. prednisolone) along with prednisone (both introduced in 1955), methylprednisolone (1957) and later fluorinated glucocorticoids such as dexamethsone and betamethasone. The relative anti-inflammatory potency, degree of mineralocorticorticoid and biologic half-life of these differing formulations vary substantially. In addition, there are now a wide-variety of routes of administration (i.e. oral, rectal, topical, inhaled, parenteral) of glucocorticoids; the NonSpil as the most recent oral variation in this regard for prednisolone.

These drugs, of which prednisolone is an example, are among the most important drugs used in routine clinical practice due to their anti-inflammatory and immunosuppressive effects. Although early results with early use of corticosteroids in diseases such as rheumatoid arthritis were dramatic, it was subsequently realized that long-term supraphysiologic therapy with these drugs could produce devastating side effects. This early realization that the benefits of prednisolone and related corticosteroids need to be balanced against a consideration of risk continues to be the situation today in all facets of medicine where these drugs are employed.

There continue to be efforts to produce safer glucocorticoids by employing innovative designs such as nitrosteroids (i.e. NO-prednisolone) or glucocorticoid-receptor ligands (i.e. selective-receptor agonists-SEGRAs) or by utilizing different delivery systems such as liposomes. Emerging research in this area suggests that the effects of glucocorticoids can be divided into genomic (interaction with cytosolic receptors and ultimately the genome) or non-genomic effects. The genomic effects, which may be most important, can be divided into transrepression (inhibits synthesis of regulatory proteins) and

transactivation (induces synthesis of regulatory proteins). Emerging evidence suggests that many adverse events are predominantly caused by transactivation while anti-inflammatory effects are mediated mostly by transrepression. Therefore, future efforts to develop drugs in this area likely will try to dissociate these two differing mechanisms of glucocorticoids.

IV Conclusions:

The efficacy and relative safety of prednisolone for both short- and long-term use has been established by prior approvals and decades of use of these critically important drugs. The current submission serves as a bioequivalence bridge between the new formulation and the widely-accepted clinical usage. This conclusion regarding the efficacy and safety of prednisolone is also supported by the long list of indications and associated adverse events in previously-approved FDA labeling.

The labeling included in this submission and attached below reflects the new format for labels as originally proposed Dec. 22, 2000 (65 FR 81082) and subsequently finalized in the Federal Register on Jan. 24, 2006 (vol. 71, No. 15, Docket # 2000N-1269). As of June 30, 2006, all labeling needs to comply with this revised format, commonly known as the Physician Labeling Rule.

V Recommendations:

Prednisolone [redacted] should be approved with revisions to the proposed labeling. b(4)

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NDA 2-067 clinical review

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