CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-067

CHEMISTRY REVIEW(S)

NDA 22-067
Review #1

Flo-Pred
(prednisolone acetate oral suspension)

Taro Pharmaceuticals U.S.A., Inc.

Brian Rogers
Pre-Marketing Assessment and Manufacturing Science
Division III
Office of New Drug Quality Assessment

Division of Anesthesia, Analgesia and Rheumatology Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-067

2. REVIEW #1

3. REVIEW DATE: July 12, 2007

4. REVIEWER: Brian Rogers

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	August 11, 2006
Amendment (BL)	October 2, 2006
Amendment (BL)	November 22, 2006
Amendment (BL)	March 12, 2007
Amendment (AC)	May 23, 2007
Amendment (BC)	May 30, 2007
Amendment (BL)	June 26, 2007
Amendment (BC)	July 11, 2007

7. NAME AND ADDRESS OF APPLICANT:

Name: Taro Pharmaceuticals U.S.A., Inc.

Address: 3 Skyline Drive, Hawthorne, NY 10532

Representative: N/A

Chemistry Review Data Sheet

Telephone: 914-345-9001

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Flo-Pred
b) Non-Proprietary Name (USAN): prednisolone acetate oral suspension
c) Code Name/# S40216
d) Chem. Type/Submission Priority:

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

A40-364 Prednisolone Syrup (KV)
A40-423 Prednisolone Syrup (KV)
A80-354 Prednisolone Tablets (Watson)

10. PHARMACOLOGICAL CATEGORY: Corticosteroid

11. DOSAGE FORM: Oral Suspension (non-spill)

12. STRENGTH/POTENCY: 5.6 mg and 16.7 mg prednisolone acetate per 5 mL formulation

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

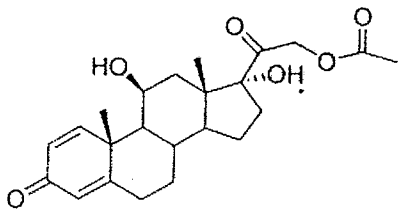
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemistry Review Data Sheet



(11ß)-11,17,21-Trihydroxypregna-1,4-diene-3,20-dione, 21-Acetate
Prednisolone 21-Acetate
$C_{23}H_{30}O_6$
MW = 402.49
CAS # [52-21-1]

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
			Prednisolone manufacture	1	Adequate	12/28/06	
			Prednisolone manufacture	1	Inadequate (see Comments)	7/11/07	Site has been withdrawn from the application - DMF status is irrelevant
				3	Adequate	9/24/04 by C-H Kim	Reviewed for 141.18074
				*	N/A		
				3	Adequate	6/29/05 by C-H Kim	N21-734
				3	Adequate	7/25/05 by C-H Kim	N21-734
				3	Adequate	9/16/04 by C-H Kim	N21-734
				3	Adequate	9/23/04 by C-H Kim	N21-734
				3	Adequate	7/19/05 by C-H Kim	N21-734
				3	Adequate	8/12/99 by J. Vidra	N21-734
				3	Adequate	2/12/03 by Rodriguez	N21-734
				3	Adequate	1/7/04 by M. Cooper	[redacted]
				3	Adequate		N21-734
				3	Adequate	5/18/04 by Pun	N21-604

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application

5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
N21-604	Taro	ElixSure ibuprofen oral suspension	AP	1/7/2004	Same excipients as current application
N21-734	Taro	ElixSure - 24 HR Antihistamine Oral Suspension	AP	10/4/2005	Same excipients and container/closure as current application

b(4)

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
NDA	N21-604	Taro	Children's ElixSure ibuprofen oral suspension
NDA	N21-734	Taro	Children's ElixSure - 24 HR Antihistamine

b(4)

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				N/A
EES	cGMP compliance	07/18/2007	Completed	Acceptable Recommendation
Pharm/Tox				N/A
Biopharm			Completed (Sally Choe)	Approvable (5/23/07)
LNC			Received comments from DMETS (Felicia Duffy) and DDMAC (Michelle Safarik)	Comments passed on to Applicant. Flo-Pred approved by DMETS and DDMACas proprietary name.
Methods Validation			Deferred	May not meet any of the seven criteria for requesting method validation.
ODS/DMETs				N/A
EA				N/A (Categorical exclusion granted)
Microbiology				N/A (Does not support microbial growth)

The Chemistry Review for NDA 22-067

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
We have received an overall ACCEPTABLE recommendation on proposed manufacturing and testing sites from the Office of Compliance; therefore, this application is recommended for approval from a CMC standpoint pending resolution of the remaining labeling comments.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
None at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

The drug substance is prednisolone acetate, USP micronized, manufactured from prednisolone. Prednisolone is purchased from [redacted] b(4)

Prednisolone (for which prednisolone acetate is a pro-drug in this application) and its forms (i.e. acetate, sodium phosphate) are well established molecules. Prednisolone is a glucocorticoid. Glucocorticoids are adrenocortical steroids, which are readily absorbed from the gastrointestinal tract. The active ingredient in Taro's formulation is the 21-acetate ester of prednisolone that has been previously used in ophthalmic and injectable products. The drug substance is hydrolyzed *in vivo* to provide prednisolone as the active moiety.

Drug Product

Prednisolone Acetate [redacted] Oral Suspension will be marketed in two strengths 5.6 mg/5 mL and 16.7 mg/5 mL prednisolone acetate, filled into [redacted] bottles [redacted] b(4) **The lined-out presentations have been withdrawn from the application in the 5/23/07 amendment.** A spoon of 5-mL nominal volume will be provided with the bottled formulation. In the 6/26/07 amendment, the applicant has proposed adding an additional 2.5-mL spoon into the packaging to provide this volume of formulation instead of filling the 5-mL spoon half-way.

The [redacted] bottles are amber [redacted] oval bottles with [redacted] dispensing plug and a lined [redacted] child resistant cap. The immediate container and a dosing spoon are placed in a carton. b(4)

[redacted]: **The lined-out presentations have been withdrawn from the application in the 5/23/07 amendment.** All container closure components have been previously reviewed and approved in NDA 21-734 for Loratadine NonSpil Oral Suspension, which bears formulation resemblance with this drug product. b(4)

Excipients are butylparaben, carbomer 934P, disodium edetate, glycerin, masking agent, poloxamer 188, propylene glycol, purified water, sodium hydroxide, sobitol crystalline, sucralose liquid concentrate, and cherry flavor. All excipients except disodium edentate and cherry flavor have been previously reviewed and approved in NDA 21-734 for Loratadine NonSpil Oral Suspension.

The in-process pH target for the final formulae is established to be 5.0 and the range to be 4.8 to 5.2 based on screen stability data. [redacted] b(4)

Six months accelerated and long-term stability data were provided with the original application. A stability update was requested in the 4/9/07 IR letter. The applicant provided 12 months of L-T stability data in the stability update.

A [redacted] expiry is requested. This expiry is not supported by statistical analysis of the stability data. The variability in the pH measurement justifies an 18-month expiry. This recommendation will be sent to the applicant.

The applicant should delete all instances [redacted] labeling. b(4)

B. Description of How the Drug Product is Intended to be Used

The drug product will be administered orally in a 5-mL spoon. The high viscosity of the formulation is intended to prevent spillage.

C. Basis for Approvability or Not-Approval Recommendation

CMC deficiencies were sent to the applicant in the 4/9/07 IR letter. The major issues were a lack of information about the manufacture and stability of prednisolone obtained from [redacted], the lack of information on the stability of the drug substance manufactured from prednisolone obtained from the aforementioned supplier, inadequate controls on the drug substance, and inadequate labeling of deliverable formulation. b(4)

These deficiencies were resolved by, in the first case, withdrawal of the proposed supplier from the application; and in the second case, performing a patient in-use study and determining the deliverable formulation with the results reflected in the labeling.

There are no significant quality and manufacturing issues that need to be resolved. The comments listed on page # 140 do not affect the approvability of the NDA. They should be included in the action letter.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Brian Rogers/7/25/07
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

55 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry-1

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

/s/

Brian Rogers
7/26/2007 08:40:03 AM
CHEMIST

Ravi Harapanhalli
7/26/2007 12:37:26 PM
CHEMIST
AP recommendation pending resolution of minor labeling issues.

Initial Quality Assessment
Branch V
Pre-Marketing Assessment and Manufacturing Science Division III
Office of New Drug Quality Assessment
Division of Anesthesia, Analgesia and Rheumatology Products

OND Division:	Anesthesia, Analgesia and Rheumatology Products
NDA:	22-067
Applicant:	Taro Pharmaceuticals USA
Stamp date:	August 14, 2006
PDUFA Date:	June 14, 2007
Trademark:	Prednisolone
Established Name:	Prednisolone Acetate Oral Suspension
Dosage Form:	Oral solution (non-spill)
Route of Administration:	Oral
Indication:	Endocrine disorder, rheumatic disorder, [redacted] dermatologic disease, allergic states, ophthalmic disease, respiratory disease, hematologic disorder, neoplastic disease, [redacted] gastrointestinal diseases, [redacted]

b(4)

[redacted]

Pharmaceutical Assessment Lead: Ali Al-Hakim, Ph.D.

	YES	NO
ONDQA Fileability:	√	___
Comments for 74-Day Letter:	√	___

Summary, Critical Issues and Comments

A. Summary

This is a 505(b) (2) New Drug Application (NDA) seeking approval to market a prescription drug product, Prednisolone Oral Suspension, 5 mg/5 mL and 15 mg/5 mL.

Prednisolone and its forms (i.e. acetate and sodium phosphate) are adrenocortical steroids. The active ingredient acetate form of prednisolone has been used in ophthalmic and injectable products. However, Prednisolone Acetate is formulated into special delivery system called NonSpil™ which is spill resistant syrup and provides better masking properties (improved taste properties over bitter taste approved products) and, therefore, it has significant benefits in the administration over liquid medication. The special delivery system was designed to resist spilling from a spoon, increasing the ease and reliability of dosing with a liquid medication.

The formulation is dispersion rather than dissolving of the suspension; the suspension appears to have less oxidative degradation and hydrolysis compared to solution.

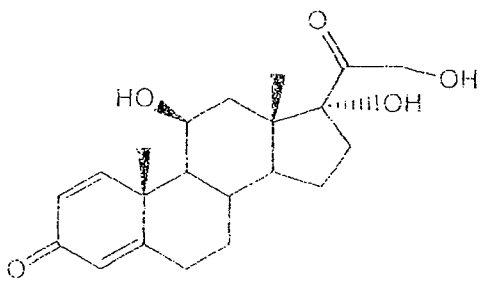
B. Review, Comments and Recommendations

Drug Substance Manufacturing Process

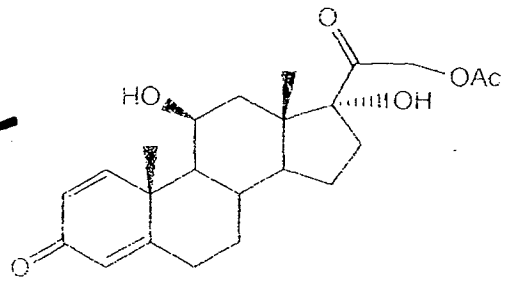
Taro Pharmaceutical Industries, Ltd. is the drug substance manufacturer (prednisolone acetate) and it has manufactured the NDA batches (batch analysis was provided for 3 lots). The starting material, prednisolone, for these batches was supplied by [redacted] b(4)
. [redacted]. However, the applicant is proposing to use prednisolone starting material supplied by [redacted]. The NDA contains batch analysis for prednisolone lot manufactured with starting material obtained form b(4)
the [redacted] site.

Synthesis/manufacturing process of Prednisolone acetate

[redacted] b(4)



[redacted] b(4)



Prednisolone

Prednisolone Acetate

Chemical name:	(11β)-11,17,21-Trihydroxypregma-1,4-diene-3,20-dione,21-Acetate
Molecular formula:	$C_{23}H_{30}O_6$
Molecular Weight:	402.49
Solubility:	Soluble in toluene and sparingly soluble in alcohol. Insoluble in water b(4)

[redacted]

The NDA contains all information regarding structural elucidation and characterization of Prednisolone acetate. This information needs to be reviewed with emphasis on acetylation position especially there are two additional OH groups in prednisolone moiety that may be susceptible to acetylation during the above reaction process.

The NDA contains information about the manufacturing process of prednisolone starting material b(4)
supplied by [redacted]

Drug Substance issue(s)

The main issues for the drug substance are the starting material, prednisolone, and the [redacted] final drug substance, prednisolone acetate. Therefore, it essential that DMF for the starting material, prednisolone be evaluated and reviewed with respect to its adequacy (the material was produced by two different suppliers [redacted] Regarding the synthesis/manufacturing process, the focus should be on issues and parameters used for the controls of intermediates in the synthetic process, [redacted] process and the scientific rational for having [redacted] and if such limit has any impact on the drug product dissolution profile. Additionally, the following sections of the drug substance should be reviewed and evaluated accordingly: b(4)

- Comparison of the drug substances batches produced using starting material obtained from two different sites.
- Evaluation of the drug substances proposed specifications including analytical methods, stability, and validation. Test data obtained from batch analysis and stability may provide information regarding the validity of the proposed acceptance criteria.
- Reviewing and subsequent assessment of the impurity profile (characterization and identification) and potential related impurities.
- Evaluation of the supporting stability test data for prednisolone acetate (holding time)

Drug product

Synopsis of the drug product manufacturing process

Prednisolone Acetate drug product is formulated into special delivery system called NonSpil™ which is spill resistant syrup and provides improved taste properties over bitter taste approved products and, therefore, it has significant benefits in the administration over liquid medication. The special delivery system was designed to resist spilling from a spoon, increasing the ease and reliability of dosing with a liquid medication.

The following is a brief summary of the manufacturing process, however, detailed description of the each step is provided in the NDA.

[redacted] b(4)

Components and composition of the drug product and the function of the excipients are provided in the following table.

Strength (Label claim):	0.097% (w/w) equivalent to 5 mg/5 mL		*0.293% (w/w) equivalent to 15 mg/5 mL		
Component and Quality Standard	Quantity per unit[1] (mg/5 ml)	%	Quantity per unit[1] (mg/5 ml)	%	Function of each component
Purified water, USP*					
EDTA Disodium, USP					
Carbomer 934P					
Sorbitol crystalline, NF					
Glycerin, USP					
Sucralose liquid concentrate[1]					
Masking agent					
Cherry flavor					
Butylparaben, NF					
Sodium hydroxide, NF					
Poloxamer 188, NF					
Propylene glycol, USP					
Prednisolone Acetate, USP[8]					
Total Weight / Volume	--	100	--	100	

b(4)

Flow diagram of the manufacturing process is provided below

b(4)

*Critical process steps

The above flow diagram showed the manufacturing steps and related critical processes which need to be reviewed and evaluated with respect to the essential parameters [redacted] of prednisolone acetate during the manufacturing process. The reviewer may need to focus on the process controls used in step 1 ; [redacted] and its impact on the viscosity of drug product. b(4)

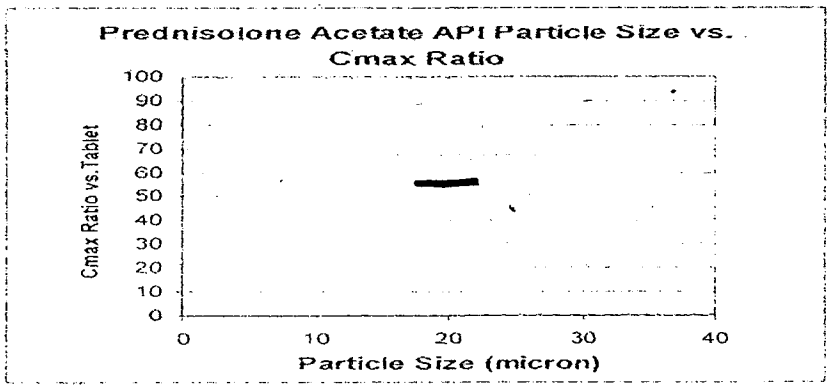
The filling process (filling the bottles) is not included in the above manufacturing section of the drug product. This is an important part of the manufacturing process and the applicant needs to provide the information.

The NDA reported that the manufacturing process was evolved over various stages and passed through various modifications which led to the production of the final formulation. Therefore, the reviewer may review the development of the manufacturing process with emphasis on the following steps:

- Development of the initial phases and related manufacturing processes and equipment used in exhibit batch [redacted] process and the proposed commercial batch [redacted] process (e.g., equipment, conditions, mixing and [redacted] conditions, etc). b(4)
- The impact of using different particle size (small and large) on the dissolution profiles
- Batches of prednisolone manufactured supplied by two different suppliers and different [redacted] equipment.
- Development work performed in order to obtains the desired bioavailability for the suspension
- The changes/variations used in the development studies regarding particle size, excipients concentration, pH , and preservatives
- Microbiological attributes and the use of the antimicrobial preservatives
- Adequacy of the homogeneity testing with respect to the non-spill properties

The non-spill (Non-Sipl®) feature of the formulation is one of the most important properties of the drug product. This property differentiates this product from the previously approved application (i.e. prednisolone oral solution). For example, evaluation and subsequent assessment of the critical parameters such as particle size distribution with respect to Cmax ratio relationship (see figure below) should be performed.

Figure 2. Prednisolone Acetate Particle Size vs. C_{max} Ratio in 15 mg/5 mL Exhibit Batches.



Particle Size	Cmax Ratio
[redacted]	49.8
	85.89

b(4)

In evaluating this type of dosage form, the reviewer may need to concentrate on evaluating critical attributes related to particle size, viscosity and on the dissolution profile of the final drug product, nature and amount of preservatives used in the proposed formulation, physical/chemical properties of drug substance obtained form the corresponding API, and affect of pH on viscosity.

[redacted] process of the drug substance is a critical factor in establishing test limits for viscosity and dissolution methods. This process needs to be assessed and evaluated with respect to proposed limits generated during the pharmaceutical development studies. Other related parameters which need to be evaluated include temperature fluctuation which may decrease or increase the viscosity of the drug product, dissolution profile of the drug product with respect to viscosity, particle size distribution, rheological profile (its impact on the two strengths (5mg and 15mg) and pH. b(4)

Other related drug product issues which need to be reviewed may include:

- The effects of the [redacted] process on the critical parameters of the formulation, e.g., non-spill nature of the drug, viscosity range, pH, etc. The relationships between pH and viscosity should be evaluated with respect to the final non-spill formulation parameters.
- Process controls and key steps during the manufacturing process ([redacted] mixing, sequence of reactions and addition of excipients, equipment, containers, etc. Brief examination of the Master Production Records may be useful to track the above information
- Process controls that performed during manufacturing of the drug process include pH adjustment, Viscosity test, Blend uniformity and homogeneity. These critical steps need to be evaluated and assessed with respect to the overall quality of the drug product and overall impact of these intermediates controls to produce consistent drug product. Justification and scientific rationale for the using the proposed limits for the above tests need to be also evaluated.
- Gelling properties, sources and quality of excipients regarding safety, qualifications levels, justification, specifications and analytical testing.

Some of the critical analytical methods, and related acceptance criteria for this type of dosage form need to be reviewed and evaluated thoroughly especially homogeneity, viscosity and dissolution. The reviewer may need to concentrate on evaluating critical methods for this type of dosage form which includes:

- Homogeneity test (particulates, lumps, agglomerates, phase separation, particle size
- Viscosity test (justification for the proposed acceptance criteria of [redacted]
- Dissolution (evaluating the proposed acceptance criteria of NLT [redacted] dissolves in 30 minutes)

- Related impurities (justifications for acceptance criteria based on long term available stability data). The reviewer may need to investigate purity profile of the drug product during stability program and the possibility that the impurities profile changes (i.e. formation of new impurities or increase of the initial impurities). b(4)

Stability

Stability data for the 3 NDA batches packaged in the proposed commercial container/closure system performed at long term and accelerated conditions should be evaluated in relationship to the proposed expiry dating and stability commitments. In addition, the proposed holding time [redacted] for the bulk, prednisolone oral suspension, should be justified based on the available data.

Labeling

Labeling information of the primary, secondary and label insert should be assessed with respect to CMC related information. The information was not available and during the filing meeting, the PM indicted that the sponsor will be asked to provide the missing information. b(4)

Container/closure system

The container/closure system including the spoon should be evaluated wit respect to compatibility of the suspension with the physical properties of drug product on the (viscosity, non-spilling when pouring of the drug, and homogeneity of the suspension). Other components of the system which need to be evaluated include [redacted]

C. Critical issues for review and recommendation

During reviewing and evaluation of the quality of the CMC information provided in this NDA, the primary reviewer may consider performing the assessment with emphasis on the following topics and any other related issues that may have a potential impact on the quality of the drug substance and the drug product.

Drug Substance

- Review and evaluate the DMF for the starting material, prednisolone, with respect to its adequacy. The material was produced by two different suppliers [redacted] however, DMF for the [redacted] site was not provided. b(4)
- Parameters used for the controls of intermediates of the synthetic process which lead to the production of the final drug substance
- [redacted] process and the scientific rational for having [redacted] and if such limit has any impact on the drug product dissolution profile.
- Comparison of the drug substances batches produced by using starting material obtained from two different sites.
- Evaluation of the drug substances proposed specifications including analytical methods, stability, and validation. Test data obtained from batch analysis and stability may provide information regarding the validity of the proposed acceptance criteria.
- Reviewing and subsequent assessment of the impurity profile (characterization and identification) and potential related impurities (justification for specifications limits) and if these limits were based on ICH-Q3A (impurities in drug substances), Q3C (residual solvents and ICH-Q6A (Specifications-test procedures and acceptance criteria).
- Evaluation of the supporting stability test data regarding the proposed holding time for prednisolone acetate [redacted] b(4)

Drug Product

The manufacturing steps and related critical process (see flow diagram) need to be reviewed and evaluated with respect to the following essential parameters:

1. [redacted] of prednisolone acetate during the manufacturing process b(4)
2. Process controls used in step 1 [redacted] and its impact on the viscosity of drug product
3. The filling process (filling the bottles) is not included in the above manufacturing section of the drug product. The applicant needs to provide the information.

The NDA reported that the manufacturing process was evolved over various stages and passed through various modifications which led to the production of the final formulation. Therefore, the reviewer may review the development of the manufacturing process with emphasis on the following steps:

- Development of the initial phases and related manufacturing processes and equipment used in exhibit batch [redacted] process and the proposed commercial batch [redacted] process (e.g., equipment, conditions, mixing and [redacted]
- The impact of using different particle size (small and large) on the dissolution profiles b(4)
- Batches of prednisolone manufactured supplied by two different suppliers and different [redacted] equipment.
- Development work performed in order to obtains the desired bioavailability for the suspension
- The changes/variations used in the development studies regarding particle size, excipients concentration, pH , and preservatives
- Microbiological attributes and the use of the antimicrobial preservatives
- Adequacy of the homogeneity testing with respect to the non-spill properties
- Impact of the particle size on the viscosity and on the dissolution profile of the final drug product. dissolution profile
- The amount and the nature of preservatives used in the proposed formulation
- The sources of starting materials and the physical/chemical properties obtained form the corresponding API b(4)
- The affect of pH (addition of NaOH) on the viscosity
- [redacted] process of the drug substance as a critical factor in establishing test limits for viscosity and dissolution methods.
- Temperature fluctuation which may decrease or increase the viscosity of the drug product. This issue may be also addressed with relation to the stability studies and the proposed storage conditions
- Evaluation of the dissolution profile of the drug product with respect to, viscosity, particle size distribution, rheological profile (its impact on the two strengths (5mg and 15mg), and pH.
- Manufacturing process development and the effects of the [redacted] process on the critical parameters of the formulation, e.g., non-spill nature of the drug, viscosity b(4)

range, pH, etc. The relationships between pH and viscosity should be evaluated with respect to the final non-spill formulation parameters.

- Process controls and key steps during the manufacturing process / [redacted] mixing, sequence of reactions and addition of excipients, equipment, containers, etc. Brief examination of the Master Production Records may be useful to track the above information b(4)
- Other process controls that performed during manufacturing of the drug process include pH adjustment, viscosity test, blend uniformity and homogeneity. These critical steps need to be evaluated and assessed with respect to the overall quality of the drug product and overall impact of these intermediates controls to produce consistent drug product. Justification and scientific rationale for the using the proposed limits for the above tests need to be also evaluated.
- Gelling properties, sources and quality of excipients regarding safety, qualifications levels, justification, specifications and analytical testing.

Some of the essential analytical methods, and related acceptance criteria for this type of dosage form need to be reviewed and evaluated thoroughly especially homogeneity, viscosity and dissolution. The reviewer may need to concentrate on evaluating critical methods for this type of dosage form which includes:

- Homogeneity test (particulates, lumps, agglomerates, phase separation, particle size
- Viscosity test (justification for the proposed acceptance criteria of [redacted]
- Dissolution (evaluating the proposed acceptance criteria of NLT [redacted] dissolves in 30 minutes) b(4)
- Related impurities (justifications for acceptance criteria based on long term available stability data). The reviewer may need to investigate purity profile of the drug product during stability program and the possibility that the impurities profile changes (i.e. formation of new impurities or increase of the initial impurities).

Stability

Stability data for the 3 NDA batches packaged in the proposed commercial container/closure system performed at long term and accelerated conditions should be evaluated in relationship to the proposed expiry dating and stability commitments. In addition, the proposed holding time [redacted] for the bulk, prednisolone oral suspension, should be justified based on the available data. b(4)

Labeling

Labeling information of the primary, secondary and label insert should be assessed with respect to CMC related information. The information was not available and during the filing meeting, the PM indicted that the sponsor will be asked to provide the missing information.

D. **Comments for 74-day Letter:**

- Statement regarding that the manufacturing, testing and packaging sites are ready for inspection
- CMC information with respect to description of the filling process of the drug product suspension into the bottles should be provided
- Labeling and packaging insert should be provided

E. **Recommendation for fileability:** The NDA is recommended to be filed because there is a considerable amount of CMC information and data which are suitable for

evaluation and assessment based on the FDA and related ICH guidelines for submitting CMC information for New Drug Application.

- **Recommendation for Team Review:** It is recommended that NDA be reviewed by two reviewers due to the nature of the drug substance and the manufacturing process and formulation of the drug product.
- **Consults**

The reviewer, in conjunction with project manager, should initiate the following consults/requests as early as possible (see fileability template below).

Ali Al-Hakim, Ph.D. 10/02/2006
Pharmaceutical Assessment Lead Date

Ravi Harapanhalli, Ph.D. 10/02/2006
Branch Chief Date

Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?		√	Include the request for the 74 day letter
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			
11	Have draft container labels been provided?		√	
12	Has the draft package insert been provided?		√	This was requested in the filing meeting
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?		√	Oral Suspension
16	Have all consults been identified and initiated?	√ √ N/A N/A	 √ √ N/A	Pharm/Tox Biopharm Statistics OCP/CDRH/CBER LNC DMETS/ODS Microbiology

Have all DMF References been identified? Yes (√) No ( )

DMF Number	Holder	Description	LOA Included	Status
		Predinsolone	√	
			√	
			√	
			√	
			√	
			√	
			√	
			√	
			√	
			√	
			√	
			√	
			√	
			√	

b(4)

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

/s/

Ali Al-Hakim
10/2/2006 12:53:35 PM
CHEMIST

Ravi Harapanhalli
10/3/2006 06:20:46 PM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 22067/000	Action Goal:	
Stamp:	14-AUG-2006	District Goal:	16-JUL-2007
Regulatory Due:	14-SEP-2007	Brand Name:	PREDNISOLONE ACETATE
Applicant:	TARO PHARMS (US)	Estab. Name:	ORAL SUSPENSION
	3 SKYLINE DR	Generic Name:	PREDNISOLONEACETATE ORAL
	HAWTHORNE, NY 10532		SUSPENSION
Priority:	3S	Dosage Form:	(FOR ORAL SUSPENSION)
Org Code:	170	Strength:	5MG/5ML AND 15MG/5ML

Application Comment:

Contacts:	P. JANI	301-796-1232	, Project Manager
	B. ROGERS	301-796-1742	, Review Chemist
	R. HARAPANHALLI	301-796-1676	, Team Leader

Overall Recommendation: ACCEPTABLE on 18-JUL-2007by S. ADAMS (HFD-322)301-827-9051

ACCEPTABLE on 29-MAR-2007by S. FERGUSON(HFD-322)301-827-9009

Establishment: CFN [redacted] FEI [redacted]

[redacted]

b(4)

DMF No: [redacted] [redacted]

Profile: [redacted] OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	27-SEP-2006				ALHAKIMA
C RECOMMENDATION	27-SEP-2006			ACCEPTABLE BASED ON PROFILE	DAMBROGIO

Establishment: CFN FEI

[redacted] b(4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CTL OAI Status: NONE

Lab. Comment:

[redacted] b(4)

APPEARS THIS WAY ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	27-SEP-2006				ALHAKIMA
SUBMITTED TO DO	28-SEP-2006	GMP			ADAMSS
ASSIGNED INSPECTION T	11-OCT-2006	GMP			ADAMSS
DO RECOMMENDATION	14-FEB-2007			ACCEPTABLE	ADAMSS
				BASED ON FILE REVIEW	
BASED ON REVIEW OF [redacted] REPORT.					
OC RECOMMENDATION	14-FEB-2007			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	

b(4)

Best Possible Copy

lishment: CFN FEI [redacted]

[redacted]

b(4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CTL OAI Status: NONE

Estab. Comment:

[redacted]

b(4)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	27-SEP-2006				ALHAKIMA
SUBMITTED TO DO	28-SEP-2006	GMP			ADAMSS

ASSIGNED INSPECTION T MFADDEN

INSPECTION SCHEDULED [redacted] MFADDEN

INSPECTION PERFORMED b(4) MFADDEN

NO FD 483 ISSUED TO THE FIRM. TWO VERBAL RECOMMENDATIONS MADE REGARDING LABORATORY PROCEDURES AND REVIEW. MANAGEMENT WAS RECEPTIVE TO THE RECOMMENDATIONS AND PROMISED TO MAKE APPROPRIATE CHANGES.

INSPECTION PERFORMED [redacted] b(4) MARIE.FADDE

See full EIR

DO RECOMMENDATION 29-MAR-2007 ACCEPTABLE MFADDEN

INSPECTION

[redacted] CONDUCTED A PRE-APPROVAL AND CURRENT GOOD MANUFACTURING PRACTICE (CGMP) INSPECTION ON [redacted] THIS INSPECTION FOCUSED ON THE PACKAGING TESTING CONDUCTED FOR THE NDA APPLICANT, TARO PHARMACEUTICALS. THE CURRENT INSPECTION DID NOT RESULT IN THE ISSUANCE OF A FD 483. VERBAL SUGGESTIONS WERE MADE DURING THE INSPECTION TO WHICH MANAGEMENT WAS RECEPTIVE. b(4)

PROPRIATE CHANGES WERE PROMISED

OC RECOMMENDATION 29-MAR-2007 ACCEPTABLE FERGUSONS

DISTRICT RECOMMENDATION

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Establishment: CFN [redacted] FEI [redacted]

[redacted] b(4)

DMF No: 1432 AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN OAI Status: NONE

Estab. Comment:

[redacted] b(4)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	07-JUN-2007				ROGERSB
OC RECOMMENDATION	07-JUN-2007			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: CFN [redacted] FEI [redacted]

[redacted] b(4)

DMF No: AADA:

Responsibilities: FINISHED DRUG OTHER TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: [redacted] b(4)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	27-SEP-2006				ALHAKIMA
SUBMITTED TO DO	28-SEP-2006	GMP			ADAMSS
DO RECOMMENDATION	11-OCT-2006			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	11-OCT-2006			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: CFN 9610271 FEI 3002808385

TARO PHARMACEUTICAL INDUSTRIES LTD

26110 FCIS026

HAIFA BAY, 26110, , IS

DMF No: AADA:

APPEARS THIS WAY ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE OTHER TESTER

Profile: CSN OAI Status: NONE

Estab. Comment: THIS SITE MANUFCATURRES THE DRUG SUBTANCE WHICH IS PREDNISOLONE ACETATE AND ALSO PERFOMES ANALYTICAL TESTING ON THE FINISHED DRUG PRODUTS. (on 28-SEP-2006 by A. AL HAKIM () 301-796-1323)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	27-SEP-2006				ALHAKIMA
SUBMITTED TO DO	28-SEP-2006	10D			ADAMSS
DO RECOMMENDATION	11-OCT-2006			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	11-OCT-2006			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: CFN 9614240 FEI 3002808384
TARO PHARMACEUTICALS INC
130 EAST DRIVE
BRAMPTON, ONTARIO, CA

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER

Profile: [illegible] OAI Status: [illegible]

Estab. Comment: [illegible] SEP-2006 by A. AL HAKIM [illegible]

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator

SUBMITTED TO OC	27-SEP-2006				ALHAKIMA
OC RECOMMENDATION	28-SEP-2006			ACCEPTABLE BASED ON PROFILE	ADAMSS

Profile: [redacted] OAI Status: NONE

Estab. Comment: THIS SITE PERFORMS (on 28-SEP-2006 by A. AL HAKIM () 301-796-1323)
THIS SITE PERFORMS DRUG SUBSTANCE RELEASE TESTING, FINISHED DOSAGE FORM MANUFACTURING, PACKAGING, LABELING, TESTING, STORAGE, AND DISTRIBUTION
(on 20-FEB-2007 by B. ROGERS () 301-796-1742)

b(4)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	27-SEP-2006				ALHAKIMA
OC RECOMMENDATION	28-SEP-2006			ACCEPTABLE BASED ON PROFILE	ADAMSS
)BMITTED TO OC	20-FEB-2007				ROGERS
SUBMITTED TO DO	20-FEB-2007	GMP			ADAMSS
DO RECOMMENDATION	20-FEB-2007			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

OC RECOMMENDATION	20-FEB-2007	ACCEPTABLE	DAMBROGIOJ
		DISTRICT RECOMMENDATION	

APPEARS THIS WAY ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Best Possible Copy

Application:	NDA 22067/000	Action Goal:	
Stamp:	14-AUG-2006	District Goal:	15-APR-2007
Regulatory Due:	14-JUN-2007	Brand Name:	PREDNISOLONE ACETATE
Applicant:	TARO PHARMS (US)	Estab. Name:	ORAL SUSPENSION
	3 SKYLINE DR	Generic Name:	PREDNISOLONEACETATE ORAL
	HAWTHORNE, NY 10532		SUSPENSION
Priority:		Dosage Form:	(FOR ORAL SUSPENSION)
Org Code:	170	Strength:	5MG/5ML AND 15MG/5ML

Application Comment:

F ontacts:	P. JANI	301-796-1232	, Project Manager
	A. AL HAKIM	301-796-1323	, Review Chemist
	R. HARAPANHALLI	301-796-1676	, Team Leader

Overall Recommendation: ACCEPTABLE on 29-MAR-2007by S. FERGUSON(HFD-322)301-827-9009

Establishment: CFN [redacted] FEI [redacted]

[redacted]

b(4)

DMF No: AADA:

Responsible Test: FINISHED DOSAGE OTHER TESTER

[illegible]: DTI: DAI Status: NONE

[illegible] Type Type Beg. Date Formula # Range Test #

SUBMITTED TO OC	27-SEP-2006			ALHAKIMA
OC RECOMMENDATION	27-SEP-2006	ACCEPTABLE BASED ON PROFILE		DAMBROGIOJ

Establishment: CFN FEI

[redacted] b(4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CTL OAI Status: NONE

Estab. Comment:

[redacted] b(4)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator

APPEARS THIS WAY ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

SUBMITTED TO OC	27-SEP-2006			ALHAKIMA
SUBMITTED TO DO	28-SEP-2006	GMP		ADAMSS
ASSIGNED INSPECTION T	11-OCT-2006	GMP		ADAMSS
DO RECOMMENDATION	14-FEB-2007		ACCEPTABLE	ADAMSS
			BASED ON FILE REVIEW	
BASED ON REVIEW OF [redacted] REPORT.				
OC RECOMMENDATION	14-FEB-2007		ACCEPTABLE	ADAMSS
			DISTRICT RECOMMENDATION	

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lishment: CFN FEI

[redacted] b(4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CTL OAI Status: NONE

Estab. Comment:

[redacted] b(4)

Name	Date	Type	Insp. Date	Decision & Reason	Name
SUBMITTED TO OC	27-SEP-2006				ALHAKIMA
SUBMITTED TO DO	28-SEP-2006	GMP			ADAMSS

ASSIGNED INSPECTION T MFADDEN

INSPECTION SCHEDULED [redacted] MFADDEN b(4)

INSPECTION PERFORMED MFADDEN

NO FD 483 ISSUED TO THE FIRM. TWO VERBAL RECOMMENDATIONS MADE REGARDING LABORATORY PROCEDURES AND REVIEW. MANAGEMENT WAS RECEPTIVE TO THE RECOMMENDATIONS AND PROMISED TO MAKE APPROPRIATE CHANGES.

DO RECOMMENDATION 29-MAR-2007 ACCEPTABLE MFADDEN

INSPECTION

[redacted] CONDUCTED A PRE-APPROVAL AND CURRENT GOOD MANUFACTURING PRACTICE (CGMP) INSPECTION ON [redacted] THIS INSPECTION FOCUSED ON THE PACKAGING TESTING CONDUCTED FOR THE NDA APPLICANT, TARO PHARMACEUTICALS. THE CURRENT INSPECTION DID NOT RESULT IN THE ISSUANCE OF A FD 483. VERBAL SUGGESTIONS WERE MADE DURING THE INSPECTION TO WHICH MANAGEMENT WAS RECEPTIVE. b(4)

APPROPRIATE CHANGES WERE PROMISED

OC RECOMMENDATION 29-MAR-2007 ACCEPTABLE FERGUSONS

DISTRICT RECOMMENDATION

Establishment: CFN [redacted] FEI [redacted] b(4)

APPEARS THIS WAY ON ORIGINAL

Estab. Comment: THIS SITE MANUFCATURRES THE DRUG SUBTANCE WHICH IS PREDNISOLONE ACETATE AND ALSO PERFOMES ANALYTICAL TESTING ON THE FINISHED DRUG PRODUTS. (on 28-SEP-2006 by A. AL HAKIM () 301-796-1323)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	27-SEP-2006				ALHAKIMA
SUBMITTED TO DO	28-SEP-2006	10D			ADAMSS
DO RECOMMENDATION	11-OCT-2006			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	11-OCT-2006			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: CFN 9614240 FEI 3002808384

TARO PHARMACEUTICALS INC

130 EAST DRIVE

BRAMPTON, ONTARIO, CA

DMF No: AADA:

APPEARS THIS WAY ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER

Profile: CTL OAI Status: NONE

Estab. Comment: AS INDICATED, THIS SITES INVLOVES IN RELEASE TESTING OF THE DRUG SUBSTANCE AND LABEL AND PCKAGING TESTING OF THE DRUG PRODUCT. (on 28-SEP-2006 by A. AL HAKIM () 301-796-1323)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	27-SEP-2006				ALHAKIMA
OC RECOMMENDATION	28-SEP-2006			ACCEPTABLE BASED ON PROFILE	ADAMSS

---

le: [redacted] OAI Status: NONE

Estab. Comment: THIS SITE PERFORMS (on 28-SEP-2006 by A. AL HAKIM () 301-796-1323)
THIS SITE PERFORMS DRUG SUBSTANCE RELEASE TESTING, FINISHED DOSAGE FORM MANUFACTURING, PACKAGING, LABELING, TESTING, STORAGE, AND DISTRIBUTION (on 20-FEB-2007 by B. ROGERS () 301-796-1742)

b(4

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	27-SEP-2006				ALHAKIMA
OC RECOMMENDATION	28-SEP-2006			ACCEPTABLE BASED ON PROFILE	ADAMSS
SUBMITTED TO OC	20-FEB-2007				ROGERSB
SUBMITTED TO DO	20-FEB-2007	GMP			ADAMSS
DO RECOMMENDATION	20-FEB-2007			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	20-FEB-2007			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROSIOJ