

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202020Orig1s000

CHEMISTRY REVIEW(S)

NDA 202-020

Rayos (Prednisone, Delayed Release) Tablet

Horizon Pharma, Inc.

Xiaobin Shen, Ph.D.

for

**Division of Pulmonary, Allergy and Rheumatology Drug
Products**

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Chemistry Review Data Sheet

1. NDA 202-020
2. REVIEW #: 1 Amendment 2
3. REVIEW DATE: 25-Jul-2012
4. REVIEWER: Xiaobin Shen, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	26-Sep-2011
Amendment 0004	08-Dec-2011
Amendment 0005	12-Dec-2011
Amendment 0006	29-Dec-2011
Amendment 0007	20-Jan-2012
Amendment 0009	31-Jan-2012
Amendment 0010	02-Feb-2012
Amendment 0011	21-Mar-2012
Amendment 0013	13-Apr-2012
Amendment 0015	09-May-2012

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment 0017	25-Jun-2012

Only Amendments containing CMC information are listed.

7. NAME & ADDRESS OF APPLICANT:

Name: Horizon Pharma, Inc.

Address: 520 Lake Cook Road, Suite 520, Deerfield, IL 60015

Chemistry Review Data Sheet

Representative: Timothy P. Walbert, Chairman, President, and CEO

Telephone: 224-383-3009

Fax: 847-572-1525

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Rayos (Prednisone) Delayed-Release Tablet
- b) Non-Proprietary Name (USAN): Prednisone
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NDA 505(b)(2)**10. PHARMACOL. CATEGORY: Anti-rheumatic****11. DOSAGE FORM: Tablet (delayed release)****12. STRENGTH/POTENCY: 1 mg, 2 mg, and 5 mg/tablet****13. ROUTE OF ADMINISTRATION: Oral****14. Rx/OTC DISPENSED: Rx OTC****15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)**

SPOTS product – Form Completed

Not a SPOTS product

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

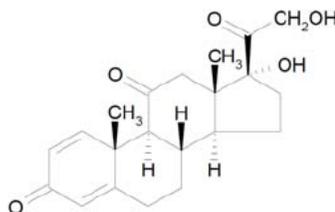
Chemistry Review Data Sheet

Chemical name: 17 α ,21-dihydroxypregna-1,4-diene-3,11,20-trione; 1,2-dehydrocortisone;
1,4-pregnadiene-17- α ,21- diol-3,11,20-trione

United States Adopted Name (USAN): Prednisone

Compendial name: Prednisone

Chemical structure:



Molecular formula: C₂₁H₂₆O₅

Molecular weight: 358.44 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCE D	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	24-Apr-2012	Adequate information to support its use are provided per MAPP 5015.5, no DMF review is required
	III			7			
	III			7			
	III			7			
	III			7			
	III			7			

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

Chemistry Review Data Sheet

- 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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA	NA	NA

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not needed	NA	NA
EES	Acceptable	25-Jul-2012	Dr. Allison Aldridge
Pharm/Tox	Adequate	18-Jun-2012	Dr. Asoke Mukherjee
Biopharm	Adequate	18-Jun-2012	Dr. Karen Riviere
LNC	NA	22-Mar-2012	NA
Methods Validation	Not needed	22-Mar-2012	Xiaobin Shen
EA	Adequate	22-Mar-2012	Xiaobin Shen
Microbiology	Not needed	22-Mar-2012	Xiaobin Shen

The Chemistry Review for NDA 202-020

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Applicable

NA.

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

Prednisone is a white to almost white, crystalline and odorless powder. It is very slightly soluble in water at 37°C. The CMC information for prednisone drug substance is referenced to DMF (b) (4).

The prednisone drug substance is manufactured by Tianjin Tianyao per DMF (b) (4) at their Tianjin, China site. DMF (b) (4) was last reviewed by Dr. Andrew J. Langowski in April, 2012 and deemed adequate. There has been no change to the DMF that affects its quality since that review.

Specifications for the prednisone drug substance include both USP and EP requirements in consideration of ICH Q3A. Collectively they include appearance, identity, assay, related substances, mutagenic impurity (b) (4), residue on ignition, water, residual solvents, and particle size. The drug substance is packaged in (b) (4). Its retest period is (b) (4).

The drug product is a round delayed release tablet for oral administration. The product strengths include 1 mg, 2 mg, and 5 mg per tablet; each strength has a unique color and strength indicating "NP1", "NP2", and "NP5" embossed on one side of the tablet. The excipients include lactose monohydrate, povidone, croscarmellose, colloidal silicon dioxide, magnesium stearate, red ferric oxide, and yellow ferric oxide. The delay in release is achieved via encasing an immediate release prednisone core tablet with an inactive tablet shell. The delay is approximately (b) (4) 4.0 hours in *in vitro* dissolution

Executive Summary Section

testing, and about 4.0 (b) (4) hours *in vivo* as demonstrated by the prednisone absorption profile.

The prednisone tablets are packaged into three packaging configurations, 7-tablet (15 mL, professional sample) bottle, 30-tablet (35 mL) bottle, and 100-tablet (75 mL) bottle. All bottles are made of HDPE resins. The (b) (4) caps are twist off round tamper evident screw on caps with integrated desiccant and desiccant insert aperture. The caps are child-resistant for the 30 and 100 tablet bottles.

The prednisone drug product specifications include appearance, identification, assay, related substances, uniformity of dosage units, dissolution, (b) (4) microbial limits and specified microorganisms. The drug product stability study was conducted on four batches per strength and per packaging size, at both long term (25°C/60% RH) and intermediate conditions (30°C/75% RH). Up to 24 months of long term and intermediate condition stability data are submitted. The average assay results of the 1 mg and 5 mg strengths showed no apparent trend over the 24 months, that of the 2 mg strength showed a slight downtrend. The time zero assay results are generally skewed to the lower side by 2% or more from the nominal target of 100% of the product label claim, this is believed to be caused by the assay method that is to be further improved. Both individual and total impurities trended up over time slightly but are well within the drug product specifications. The trend up of impurities is most apparent for the 1 mg strength. The dissolution generally slowed down with the increase of storage time, however the results are all within acceptable criteria. The provided 24 month real time data and statistical analysis results support the extrapolation of product expiry to 30 months. The drug product is known to be photo labile, the container closure system protects the product from light.

The prednisone drug product is manufactured at a proposed commercial scale of (b) (4) by Bayer Pharma AG or Aenova France SAS. Both sites have acceptable EES status. The registration stability batches were manufactured at the proposed commercial scale from both sites.

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

The product is indicated for the treatment of rheumatoid arthritis in adult patients.

The proposed treatment regimen is shown below:

- Initial dose: NP01 5 mg administered once per day at bedtime.
- Maintenance dose: lowest dosage that will maintain an adequate clinical response.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments provided acceptable information on the chemistry, manufacturing, and controls of the prednisone tablet. The product is recommended for approval from the CMC review perspective based on the following:

- The drug substance and product specifications provided adequate controls;

Executive Summary Section

- The drug product excipients are of USP/NF grade;
- The drug product container closure systems are acceptable for pharmaceutical use;
- Both drug substance and drug product are stable in the studied stability period and support the currently claimed 30 months of drug product expiry.

III. Administrative

A. Reviewer's Signature

Review is digitally signed off in DARRTS.

B. Endorsement Block

ChemistName/Date

ChemistryTeamLeaderName/Date

ProjectManagerName/Date

C. CC Block

9 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

XIAOBIN SHEN

07/25/2012

The amendment captures the overall acceptable EES status of the cGMP sites. The NDA is recommended for approval.

PRASAD PERI

07/25/2012

I concur

NDA 202-020

NP01 (Prednisone, Delayed Release) Tablet

Horizon Pharma, Inc.

Xiaobin Shen, Ph.D.

for

**Division of Pulmonary, Allergy and Rheumatology Drug
Products**

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C. CC Block	9
Chemistry Assessment	10
I. Amendment 0011 (21-Mar-2012).....	10
II. Amendment 0013 (13-Apr-2012).....	10
III. Amendment 0014 (04-May-2012)	15
VI. Amendment 0015 (09-May-2012).....	15

Chemistry Review Data Sheet

1. NDA 202-020
2. REVIEW #: 1 Amendment
3. REVIEW DATE: 19-Jun-2012
4. REVIEWER: Xiaobin Shen, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	26-Sep-2011
Amendment 0004	08-Dec-2011
Amendment 0005	12-Dec-2011
Amendment 0006	29-Dec-2011
Amendment 0007	20-Jan-2012
Amendment 0009	31-Jan-2012
Amendment 0010	02-Feb-2012

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment 0011	21-Mar-2012
Amendment 0013	13-Apr-2012
Amendment 0015	09-May-2012

Only Amendments containing CMC information are listed.

7. NAME & ADDRESS OF APPLICANT:

Name: Horizon Pharma, Inc.

Address: 520 Lake Cook Road, Suite 520, Deerfield, IL 60015

Representative: Timothy P. Walbert, Chairman, President, and CEO

Chemistry Review Data Sheet

Telephone: 224-383-3009

Fax: 847-572-1525

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Rayos (Prednisone) Delayed-Release Tablet
- b) Non-Proprietary Name (USAN): Prednisone
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Anti-rheumatic

11. DOSAGE FORM: Tablet (delayed release)

12. STRENGTH/POTENCY: 1 mg, 2 mg, and 5 mg/tablet

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#) SPOTS product – Form Completed Not a SPOTS product

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

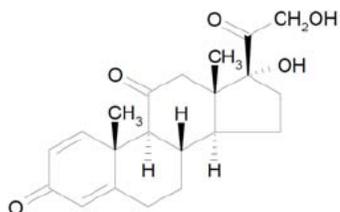
Chemical name: 17 α ,21-dihydroxypregna-1,4-diene-3,11,20-trione; 1,2-dehydrocortisone;
1,4-pregnadiene-17- α ,21- diol-3,11,20-trione

Chemistry Review Data Sheet

United States Adopted Name (USAN): Prednisone

Compendial name: Prednisone

Chemical structure:

Molecular formula: C₂₁H₂₆O₅

Molecular weight: 358.44 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCE D	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	24-Apr-2012	
	III			7			Adequate information to support its use are provided per MAPP 5015.5, no DMF review is required
	III			7			
	III			7			
	III			7			
	III			7			

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6 – DMF not available

7 – Other (explain under "Comments")

Chemistry Review Data Sheet

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA	NA	NA

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not needed	NA	NA
EES	Pending	18-Jun-2012	Dr. Allison Aldridge
Pharm/Tox	Adequate	18-Jun-2012	Dr. Asoke Mukherjee
Biopharm	Adequate	18-Jun-2012	Dr. Karen Riviere
LNC	NA	22-Mar-2012	NA
Methods Validation	Not needed	22-Mar-2012	Xiaobin Shen
EA	Adequate	22-Mar-2012	Xiaobin Shen
Microbiology	Not needed	22-Mar-2012	Xiaobin Shen

The Chemistry Review for NDA 202-020

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for approval pending a satisfactory establishment evaluation report.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Applicable

NA.

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

Prednisone is a white to almost white, crystalline and odorless powder. It is very slightly soluble in water at 37°C. The CMC information for prednisone drug substance is referenced to DMF (b) (4).

The prednisone drug substance is manufactured by Tianjin Tianyao per DMF (b) (4) at their Tianjin, China site. DMF (b) (4) was last reviewed by Dr. Andrew J. Langowski in April, 2012 and deemed adequate. There has been no change to the DMF that affects its quality since that review.

Specifications for the prednisone drug substance include both USP and EP requirements in consideration of ICH Q3A. Collectively they include appearance, identity, assay, related substances, mutagenic impurity (b) (4), residue on ignition, water, residual solvents, and particle size. The drug substance is packaged in (b) (4). Its retest period is (b) (4).

The drug product is a round delayed release tablet for oral administration. The product strengths include 1 mg, 2 mg, and 5 mg per tablet; each strength has a unique color and strength indicating “NP1”, “NP2”, and “NP5” embossed on one side of the tablet. The excipients include lactose monohydrate, povidone, croscarmellose, colloidal silicon dioxide, magnesium stearate, red ferric oxide, and yellow ferric oxide. The delay in release is achieved via encasing an immediate release prednisone core tablet with an inactive tablet shell. The delay is approximately (b) (4) – 4.0 hours in *in vitro* dissolution

Executive Summary Section

testing, and about 4.0 – (b) (4) hours *in vivo* as demonstrated by the prednisone absorption profile.

The prednisone tablets are packaged into three packaging configurations, 7-tablet (15 mL, professional sample) bottle, 30-tablet (35 mL) bottle, and 100-tablet (75 mL) bottle. All bottles are made of HDPE resins. The (b) (4) caps are twist off round tamper evident screw on caps with integrated desiccant and desiccant insert aperture. The caps are child-resistant for the 30 and 100 tablet bottles.

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The prednisone drug product is manufactured at a proposed commercial scale of (b) (4) by Bayer Pharma AG or Aenova France SAS. Both sites have acceptable EES status. The registration stability batches were manufactured at the proposed commercial scale from both sites.

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

The product is indicated for the treatment of rheumatoid arthritis in adult patients.

The proposed treatment regimen is shown below:

- Initial dose: NP01 5 mg administered once per day at bedtime.
- Maintenance dose: lowest dosage that will maintain an adequate clinical response.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments provided acceptable information on the chemistry, manufacturing, and controls of the prednisone tablet. The product is recommended for approval from the CMC review perspective based on the following:

- The drug substance and product specifications provided adequate controls;

Executive Summary Section

- The drug product excipients are of USP/NF grade;
- The drug product container closure systems are acceptable for pharmaceutical use;
- Both drug substance and drug product are stable in the studied stability period and support the currently claimed 30 months of drug product expiry.

III. Administrative

A. Reviewer's Signature

Review is digitally signed off in DARRTS.

B. Endorsement Block

ChemistName/Date

ChemistryTeamLeaderName/Date

ProjectManagerName/Date

C. CC Block

9 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

XIAOBIN SHEN

06/21/2012

Recommended for approval from CMC perspective pending acceptable EES status.

PRASAD PERI

06/22/2012

I concur

NDA 202-020

NP01 (Prednisone, Delayed Release) Tablet

Horizon Pharma, Inc.

Xiaobin Shen, Ph.D.

for

**Division of Pulmonary, Allergy and Rheumatology Drug
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II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	70
A. Labeling & Package Insert	70
B. Environmental Assessment Or Claim Of Categorical Exclusion	80

Chemistry Review Data Sheet

1. NDA 202-020
2. REVIEW #: 1
3. REVIEW DATE: 03-May-2012
4. REVIEWER: Xiaobin Shen, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

NA

Document Date

NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Amendment 0004

Amendment 0005

Amendment 0006

Amendment 0007

Amendment 0009

Amendment 0010

Document Date

26-Sep-2011

08-Dec-2011

12-Dec-2011

29-Dec-2011

20-Jan-2012

31-Jan-2012

02-Feb-2012

Only Amendments containing CMC information are listed.

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Telephone: 224-383-3009

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- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Anti-rheumatic

11. DOSAGE FORM: Tablet (delayed release)

12. STRENGTH/POTENCY: 1 mg, 2 mg, and 5 mg/tablet

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#) SPOTS product – Form Completed Not a SPOTS product

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

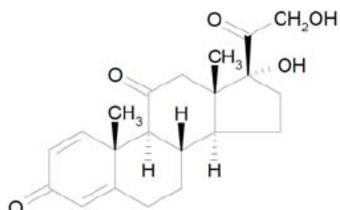
Chemical name: 17 α ,21-dihydroxypregna-1,4-diene-3,11,20-trione; 1,2-dehydrocortisone;
1,4-pregnadiene-17- α ,21- diol-3,11,20-trione

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United States Adopted Name (USAN): Prednisone

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Chemical structure:

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Molecular weight: 358.44 g/mol

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A. DMFs:

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	III			7			Adequate information to support its use are provided per MAPP 5015.5, no DMF review is required
	III			7			
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6 – DMF not available

7 – Other (explain under "Comments")

Chemistry Review Data Sheet

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA	NA	NA

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not needed	NA	NA
EES	Pending	2-May-2012	Xiaobin Shen
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LNC	NA	22-Mar-2012	NA
Methods Validation	Not needed	22-Mar-2012	Xiaobin Shen
EA	Adequate	22-Mar-2012	Xiaobin Shen
Microbiology	Not needed	22-Mar-2012	Xiaobin Shen

The Chemistry Review for NDA 202-020

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for approval pending resolution of issues listed at the end of this review and an acceptable recommendation from the Office of Compliance for the manufacturing facilities.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA.

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

Prednisone is a white to almost white, crystalline and odorless powder. It is very slightly soluble in water at 37°C. The CMC information for prednisone drug substance is referenced to DMF (b) (4).

The prednisone drug substance is manufactured by Tianjin Tianyao per DMF (b) (4) at their Tianjin, China site. DMF (b) (4) was last reviewed by Dr. Andrew J. Langowski in April, 2012 and deemed adequate. There has been no change to the DMF that affects its quality since that review.

Specifications for the prednisone drug substance include both USP and EP requirements in consideration of ICH Q3A. Collectively they include appearance, identity, assay, related substances, mutagen impurity (b) (4), residue on ignition, water, residual solvents, and particle size. The drug substance is packaged in (b) (4). Its retest period is (b) (4).

The drug product is a round delayed release tablet for oral administration. The product strengths include 1 mg, 2 mg, and 5 mg per tablet, each strength has a unique color and strength indicating "NP1", "NP2", and "NP5" embossed on one side of the tablet. The excipients include lactose monohydrate, povidone, croscarmellose, colloidal silicon dioxide, magnesium stearate, red ferric oxide, and yellow ferric oxide. The delay in release is achieved via encasing an immediate release prednisone core tablet with an

Executive Summary Section

inactive tablet shell. The delay is approximately (b) (4) 4.0 hours in *in vitro* dissolution testing, and about 4.0 (b) (4) hours *in vivo* as demonstrated by the prednisone absorption profile.

The prednisone tablets are packaged into three packaging configurations, 7-tablet (15 mL, professional sample) bottle, 30-tablet (35 mL) bottle, and 100-tablet (75 mL) bottle. All bottles are made of HDPE resins. The (b) (4) caps are twist off round tamper evident screw on caps with integrated desiccant and desiccant insert aperture. The caps are child-resistant for the 30 and 100 tablet bottles.

The prednisone drug product specifications include appearance, identification, assay, related substances, uniformity of dosage units, dissolution, (b) (4), microbial limits and specified microorganisms. The drug product stability study was conducted on four batches per strength and per packaging size, at both long term (25°C/60% RH) and intermediate conditions (30°C/75% RH). Up to 12 months of long term and intermediate condition stability data are submitted. The assay results do not appear to decrease over time, even though overall they are skewed to the lower side by 2% or more from the nominal target of 100% of the product label claim at release (An information request was sent to the applicant requesting their explanation for the skewed assay results and corrective approach). Both individual and total impurities trended up slightly but are well within the drug product specifications. The dissolution generally slowed down with the increase of storage time, however the results are all within acceptable specifications. The provided 12 month real time data and statistical analysis results support the extrapolation of product expiry to (b) (4). The drug product is known to be photo labile, the container closure system protects the product from light.

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

The product is indicated for the treatment of rheumatoid arthritis in adult patients.

The proposed treatment regimen is shown below:

- Initial dose: NP01 5 mg administered once per day at bedtime.
- Maintenance dose: Use lowest dosage that will maintain an adequate clinical response.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments provided acceptable information on the chemistry, manufacturing, and controls for the prednisone tablets. The product is recommended for approval based on the following:

- The drug substance and product specifications provided adequate controls;
- The drug product excipients are of USP/NF grade;
- The drug product container closure systems are acceptable for pharmaceutical use;
- Both drug substance and drug product are stable in the studied stability period and support the currently claimed (b) (4) of drug product expiry.

Executive Summary Section

III. Administrative**A. Reviewer's Signature**

Review is digitally signed off in DARRTS.

B. Endorsement Block

ChemistName/Date: Xiaobin Shen, Ph.D./Sign off date in DARRTS

ChemistryBranchChiefName/Date: Prasad Peri, Ph.D./Sign off date in DARRTS

ProjectManagerName/Date: Youbang Liu, Ph.D./Notification date in DARRTS

C. CC Block

72 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

XIAOBIN SHEN

06/21/2012

The NDA is recommended for approval pending resolution of issues listed at the end of the review.

PRASAD PERI

06/21/2012

I concur

**ONDQA Review for
OND Division of Pulmonary Allergy and Rheumatology Products
Initial Quality Assessment
Date: November 15, 2011**

NDA: 202020

Prednisone delayed release tablets

Applicant: Horizon Pharma Inc.

Stamp Date: 9/26/2011

PDUFA Date: 7/26/2012

ONDQA 5 month date: 2/26/12

Proposed Proprietary Name: (code NP01)

Established Name: prednisone delayed release tablets

Dosage form and strength: tablet, delayed release

Route of Administration: oral

Indications: CMC Lead: Alan C. Schroeder, Ph.D. /DNDQA III/ONDQA

Filability recommendation: Fileable (see filing review dated 10/26/11)

Review team recommendation: Single primary reviewer (Dr. Xiaobin Shen)

Recommended briefing level: Branch

Time goals:

- Initial Quality Assessment in DFS: 11/26/11
- Filing decision “Day 45”: 11/10/11 (Filing/planning meeting 11/07/11)
- Filing review issues “Day 74”: 12/09/11
- **Chemistry Review (DR/IR) letter: 5/26/11 (8 months)**
- Mid-cycle meeting “Month 5”: 2/24/2012
- Wrap Up: 6/22/2012
- **Final Chemistry Review “Month 8” in DFS: 6/21/12 (per PM)**
- PDUFA: 7/26/2012

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm	A biopharmaceutics reviewer has been assigned, e.g. to evaluate the dissolution method.
CDRH	N.A.
EA	To be assessed by Primary Reviewer
EES	EER sent to Office of Compliance on 10/13/2011
DMETS	Labeling consult request will be sent as part of DPARP’s request.
Methods Validation	Methods validation for non-compendial methods may be requested of FDA laboratories if deemed necessary by the reviewer after test methods are finalized.
Microbiology	There is a microbial limits specification for drug product but not drug substance. It is a review issue for the drug substance as to whether a microbial limits specification is necessary. Micro should also determine whether proposed future testing of every tenth lot of the drug product for micro limits is adequate.

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Pharm/Tox	DS and DP impurities/degradants to be evaluated for safety.

Background:

Prednisone delayed release tablets are proposed for treatment of rheumatoid arthritis (RA) in adult patients.

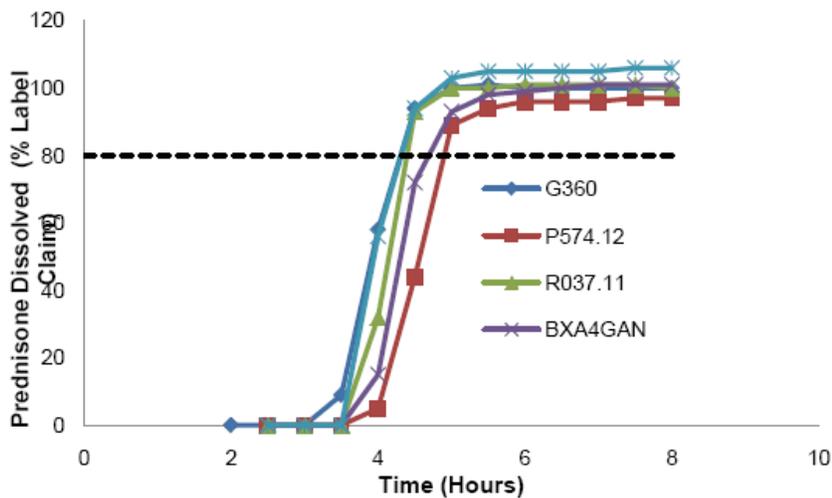
The code name for the product is “NP01.”

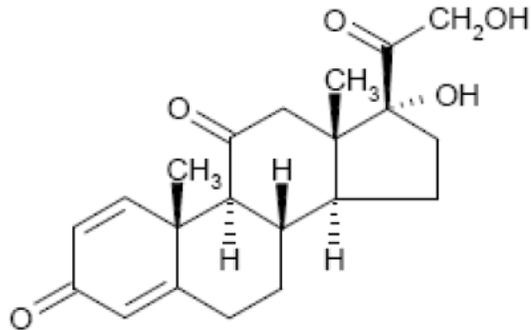
Tablet strengths are 1 mg, 2 mg and 5 mg. They are distinguished by color and debossing, although the color differences tend to be small.

Drug product is a “tablet-in-tablet” dosage form, “consisting of an immediate-release prednisone core tablet, surrounded by an inactive outer shell. Drug release is triggered by penetration of water into the tablet shell (b) (4)

Drug product dissolution profiles demonstrate delayed release characteristics:

Figure 3: Mean *In Vitro* Release Profiles for the NP01 5-mg Tablets used in the Pharmacokinetic Studies EMR 62215-005, NP01-006, NP01-013, and NP01-014



Drug substance**Figure 1: Chemical Structure of Prednisone**

Drug substance is manufactured by Tianjin Tianyao Pharmaceutical Company (DMF (b) (4))

DMF (b) (4) was last reviewed on 12/15/09 and found to be adequate for Prednisone Tablets.

The applicant's "confirmatory" specifications for drug substance comply with the USP monograph for prednisone drug substance (see below):

Table 2: Confirmatory Specification for the Prednisone Drug Substance

Test	Method	Acceptance Criteria
Appearance	Visual	White to almost white, crystalline powder
Identity – IR (A)	USP <197K>	The IR absorption spectrum of sample should match the spectrum of working standard.
Identity – Chemical test (B)	USP	Positive
Assay	USP	97.0 – 102.0%
Chromatographic purity (%w/w)	Ph. Eur. prednisone method (HPLC)	NMT (b) (4)
Specified impurity (b) (4)		
Unspecified impurity		
Total		
(b) (4)	NP-TPA-001 (HPLC)	NMT (b) (4)

(continued on next page)

Applicant’s drug substance specifications (continued):

Residue on ignition	USP <281>	NMT (b) (4)
Water	USP <921>, Method 1 (KF)	NMT (b) (4)
Residual solvents (b) (4)	TT method (GC)	NMT (b) (4)
Melting point	USP <741>	(b) (4)
Specific rotation	USP <781s>	
Particle size	Laser diffraction	
Confirmation of CoA	CoA review	Confirmation that the lot has been tested and meets the requirements of the current USP monograph for prednisone

CoA = certificate of analysis; GC = gas chromatography; HPLC = high-performance liquid chromatography; IR = infra red; KF = Karl Fischer titration; NMT = not more than; Ph. Eur. = European Pharmacopeia; TT = Tianjin Tianyao Pharmaceutical Co., Ltd; USP = United States Pharmacopeia

Solubility of prednisone in aqueous solution is as follows: 0.15-0.17 mg/mL at 37°C (over a range of pH 1.2 – 7.5).

Drug product

Tablet strengths are 1 mg, 2 mg and 5 mg. See photo below.

Figure 2: NP01 Drug Product



Drug product composition (core):

Table 1: Components and Composition of the NP01 Drug Product

Ingredient	Function	Amount per NP01 Tablet (mg)			% of NP01 Tablet (w/w) ³		
		1 mg Tablet	2 mg Tablet	5 mg Tablet	1 mg Tablet	2 mg Tablet	5 mg Tablet
Prednisone Core Tablet							
(b) (4)							

Drug product composition (outer tablet shell):

Inactive Outer Tablet							
(b) (4)							

P.2 Drug product development.

This section contains the biopharmaceutics results summary, among other information.

Most PK studies used the intended commercial tablet except for studies EMR 62215-01 and EMR 62215-002. From clinical study EMR 62215-005 forward, the clinical lots were manufactured using the same formulation and the “fully scaled process.”

The drug product dissolution has a lag time of at least (b) (4). The last sample time when mean release value was $\leq 10\%$ was in the (b) (4) hour range. After the delay, the drug is released (e.g., the time point for mean % dissolution $\geq 80\%$ ranged from (b) (4) hours). This will be assessed by the biopharmaceutics reviewer.

Drug product manufacturers:

Bayer Schering Pharma AG (Leverkusen, Germany) and (b) (4) – both produce the bulk tablets.

PHAST GmbH (Homburg, Germany) – QC, stability, release testing of drug product

Temmler Werke GmbH (München, Germany) (b) (4) – drug packaging and labeling.

Manufacturing process:

(b) (4)

The proposed commercial batch size is (b) (4) tablets.

Critical process parameters and process attributes are described in section 3.2.P.2.3.2.

Transfer of the manufacturing process to Bayer Schering Pharma is addressed in section 3.2.P.2.3.3. There are some manufacturing process differences between the Bayer site and the (b) (4) site but the applicant does not consider them to be major. Properties of the tablets (e.g., dissolution and particle size distribution) from different manufacturing sites appear to be similar. Graphs are provided in this section of the NDA. One graph shows the dissolution profile for Lot B940 of the drug product, which is the lot used for the second pharmacokinetic study (EMR 62215-002). This graph shows the “relatively high” variability in dissolution of Lot B940 which was “optimized for a new lag time target of (b) (4).” The other graph shows the variability in dissolution profiles for (b) (4) of a single lot which were intentionally manufactured using (b) (4).

In-process controls:

The manufacturing process limits the maximum hold time for prednisone core tablets to (b) (4)

The reviewer should check supporting stability data in support of this hold time and should ensure that the effect of high humidity on storage of the core tablets, is assessed in the stability study. Core tablet stability should be studied in the same container closure system as proposed in the NDA.

The maximum hold time for bulk tablets is (b) (4) **The reviewer should check stability data for this hold time, including storage under conditions of high humidity. Bulk tablet stability should be assessed in the same container-closure system as proposed in the NDA.**

Batch release data are provided. Assay results range up to 98.8% for the Bayer site and up to 100.0% for the (b) (4) site. **Each manufacturer of the drug product should assure that their release target is 100% for assay.**

Discussion of the excipient, (b) (4) .

(b) (4)

Drug product specifications – see below for 1-mg tablet specifications as an example.

Table 10: Specification for the NP01 1-mg Tablet

Test	Method	Acceptance Criteria
Appearance	Visual	Cylindrical, pale-yellowish white, tablet embossed with "NP 1" on one side
Identification	UV	UV spectrum of the sample corresponds to the reference spectrum
Identification	HPLC	Retention time of the prednisone peak in the sample is consistent with that of the reference standard
Assay	NP-TPA-001 (HPLC)	90 – 105% of LC
Related substances (%w/w)	NP-TPA-001 (HPLC)	NMT (b) (4)
Other identified impurities		NMT
Unidentified impurities		NMT
Total Impurities		NMT
Uniformity of dosage units	NP-TPA-008 (USP <905>)	Meets USP for content uniformity
Dissolution (% LC) ¹	NP-TPA-054 (USP <711>)	(b) (4)
3 Hours		(b) (4)
7 Hours		(b) (4)
Microbial enumeration test ²	USP<61>	Total aerobic microbial count: NMT (b) (4) Total combined yeasts and molds: (b) (4)
Test of specified microorganisms ²	USP <62>	<i>E. coli</i> : Absent

HPLC = high-performance liquid chromatography; LC = label claim; NLT = not less than; NMT = not more than; USP = United States Pharmacopeia; UV = ultraviolet

¹ Meets the requirements of stage testing for delayed release products per USP<711>.

² Testing is performed on every tenth lot.

Impurity/Degradant with a structure alert: (b) (4) (b) (4)

(b) (4) (b) (4) is said to have produced a positive response in the Ames assay. The applicant has taken measures to reduce (b) (4). It is limited in the drug product to NMT (b) (4). Data are provided to show that this impurity is present in marketed prednisone tablets in the US, at levels of (b) (4). **This needs to have a pharm/tox assessment.**

Container closure system:

(b) (4)

Comment: We should request samples of the drug product (core tablets, final coated tablets and the container closure system including the desiccant insert inside the cap).

Stability/Proposed Expiry:

The proposed expiry is (b) (4)

In the original submission, 12 months of primary long-term (25°C/60%RH) stability data are provided for the drug product manufactured at Bayer, and 3 months of data for the product manufactured at (b) (4) (Three lots of each strength were studied on stability for each container size at Bayer and one lot of each strength was studied on stability for the (b) (4) site.) In addition, supportive stability data in “precommercial” packaging configurations and in “European Union (EU) commercial” packaging configurations are provided.

“The NP01 tablet registration stability studies were conducted using $25 \pm 2^\circ\text{C}/60 \pm 5\%$ relative humidity (RH) as the long-term storage condition and $30 \pm 2^\circ\text{C}/75 \pm 5\%$ RH as the intermediate condition. $30 \pm 2^\circ\text{C}/75 \pm 5\%$ RH was selected as the intermediate condition (for Zone IV B) in the US commercial packaging configuration studies to account for international climate changes as specified by the World Health Organization (WHO). The pre-commercial and EU commercial packaging configuration studies used $30 \pm 2^\circ\text{C}/65 \pm 5\%$ RH for the intermediate condition. The accelerated condition ($40 \pm 2^\circ\text{C}/75 \pm 5\%$ RH) was performed for the EU commercial packaging configuration study. However, because of the rapid change in the dissolution profile of the product at the accelerated conditions, Horizon chose to discontinue performing studies using the accelerated condition for the precommercial and commercial packaging configurations.” (Section 3.2.P.8.1.1) **The reviewer should verify the data and justifications supporting the decision to not conduct primary NDA stability studies under the accelerated condition.**

Stability samples were tested at the usual time points for the following attributes: appearance, assay, total impurities, dissolution, (b) (4) and hardness (hardness is controlled in-process and studied on stability for information only). USP <61> and <62> tests (microbial limits) are performed at release and then annually (12, 24 and 36 months).

(b) (4) stability data (3 months to date): All results are said to meet acceptance criteria so far.

Bayer stability data (12 months to date): assay results were analyzed using a one-sided lower limit confidence interval of 95% to project shelf life. The lower assay acceptance criterion of 90% was used (with a p-value of 0.25). The assay was found to not be shelf-life limiting for 1 mg but 2 mg tablet analysis gave a prediction of failure @ 19 months. The assay was not indicated to be shelf life limiting for the analysis of 5 mg tablets. Similar analyses of total impurities with a (b) (4) acceptance criterion are indicated to not

be shelf life limiting over (b) (4). Other parameters (dissolution, water content) were not projected for expiry. Long term data: 2 lots did not meet dissolution stage 1 criteria but met stage 2 criteria. Water analysis showed “no discernable trend.”

Drug product stability data (12 months, 25°C, 60%RH) – the applicant indicates that the study of the 2 mg tablet in the 7 count bottle showed a decrease in assay on stability (i.e., a loss of 2.1% of Label Claim over 12 months). **The reviewer should check to see if mass balance is demonstrated for this loss.**

Stability commitment: current ongoing stability studies will be continued through protocol life (for long term at 25°C/60%RH and intermediate stability at 30°C/75%RH). Currently, these full stability studies are being conducted on three commercial scale Bayer lots and one commercial scale (b) (4) lot for each dosage strength and container.

Subsequent to the stability studies for the first three commercial scale Bayer lots and the one commercial scale (b) (4) lot for each dosage strength and container, the applicant will “place at least 2 lots representing 2 of the 3 dosage strengths in commercial packaging configurations from each supplier on annual stability at 25°C/60%RH using a bracketing scheme. **This is a review issue.**

IND for this drug product: 72569, 105868

IND Information relevant to CMC review: see 10/26/11 filing review.

Supporting DMFs:

See separate filing review in DARRTS (entered on 10/26/11)

Letters of authorization for the referenced DMFs:

DMF (b) (4) LOA dated 6/8/10
DMF (b) (4) LOA dated 6/8/10
DMF (u) (u) LOA dated 10/18/10
DMF (b) (4) LOA dated 10/18/10
DMF (b) (4) LOA dated 7/27/10
DMF (b) (4) dated 7/29/10

EES – status is pending (as of 11/3/2011). Only one site needs a compliance recommendation and that will be based on inspection (Temmler Werke GmbH for labeling and packaging)

Consult: recommend a pharm/tox consult for impurities and degradants.

Filing Check List: See separate filing review in DARRTS (10/26/11).

Certain review issues which were noted are listed below for consideration by the reviewer

See comments highlighted with bold text in the review above.

Comments for filing letter: see separate 10/26/11 DARRTS filing review. See also the additional comments below:

Provide samples of the drug product (core tablets, final coated tablets and the container closure system including the desiccant insert inside the cap

Provide assurance that the drug product release target is 100% for assay for each manufacturer of the drug product.

Recommendation:

Fileable from a CMC perspective.

Attachment A: Nanotechnology product evaluating questions:

<p>1, This review contains new information added to the table below: <input checked="" type="checkbox"/> Yes; <input type="checkbox"/> No</p> <p>Review date: _____</p>
<p>2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) Yes _____; No <input checked="" type="checkbox"/>; Maybe (please specify) _____</p>
<p>3 a) What nanomaterial is included in the product? (Examples of this are listed as search terms in Attachment B.) _____</p>
<p>3 b) What is the source of the nanomaterial? _____</p>
<p>4) Is the nanomaterial a reformulation of a previously approved product?</p> <p>Yes _____ No _____</p>
<p>5) What is the nanomaterial functionality?</p> <p>Carrier _____; Excipient _____; Packaging _____</p> <p>API _____; Other _____</p>
<p>6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble (e.g., gold nanoparticle) in an aqueous environment?</p> <p>Soluble _____; Insoluble _____</p>
<p>7) Was particle size or size range of the nanomaterial included in the application?</p> <p>Yes _____ (Complete 8); No _____ (go to 9).</p>
<p>8) What is the reported particle size?</p> <p>Mean particle size _____; Size range distribution _____; Other _____</p>
<p>9) Please indicate the reason(s) why the particle size or size range was not provided:</p> <p>_____</p> <p>_____</p>
<p>10, What other properties of the nanoparticle were reported in the application (See Attachment E)? _____</p>
<p>11) List all methods used to characterize the nanomaterial? _____</p> <p>_____</p>

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

/s/

ALAN C SCHROEDER
11/21/2011

PRASAD PERI
11/21/2011
I concur

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA (ONDQA)**

NDA Number:

202020

Supplement Number and Type:

Established/Proper Name:

prednisone delayed release tablets

Applicant:

Horizon Pharma Inc.

Letter Date:

9/27/2011

Stamp Date:

9/26/2011

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On initial overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA (ONDQA)**

4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	review issue	<p>Original IND 72569 review (7/23/07): one minor request for modifying dissolution specification and request for labeling. March 24, 2006 (pIND 72569 teleconference): no technical CMC requests. Responses to questions (12/12/07) for I72569 sent in advance of EOP2 meeting which may have been cancelled. CMC asked that ICH Q3 guidances be followed for impurities and degradants specifications, and asked for additional sampling time points and in vitro data for dissolution testing. Additional data related to lag time requested. Batch release data requested for each drug product supplier and drug substance specifications used by drug product manufacturer. Some labeling comments. Jan. 26, 2010 pNDA meeting for I72569: the Agency agreed to a matrix design for executed batch records. We agreed to a qualification protocol in the NDA to qualify Bayer as a drug product manufacturing site and we asked for site specific stability data. The amount of stability data, dissolution specifications and impurity/degradant specifications were discussed and recommendations were made. We asked for specific information for manufacturing and testing sites. Original IND 105868 review (9/23/09): no comments for sponsor, it was cross-referenced to IND 72569. Responses to pre-meeting questions for IND 105868 (sent 2/23/10): meeting was apparently cancelled. See these responses and numerous additional CMC comments in this document.</p>
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B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x for d.p.		Drug product facilities are listed on form FDA 356h, and the drug substance facility is listed in section 3.2.S.2.1.
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			N.A.

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA (ONDQA)**

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		<p>Yes, however the information is provided in section 3.2.S.2.1 rather than on form 356h.</p>
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		<p>Note that there are two manufacturers of the bulk tablets, Bayer Schering Pharma AG (Leverkusen, Germany) [REDACTED] (b) (4)</p>

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA (ONDQA)**

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		Statement is on form 356h for drug product facilities, and in section 3.2.S.2.1 for drug substance

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		section 1.12.14 (categorical exclusion request)

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA (ONDQA)**

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?		X	This information is cross-referenced to DMF (b) (4) DMF (b) (4) was last reviewed on November 17, 2009 by Anil Pendse and found to be adequate for Prednisone Tablets.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		X	This information is cross-referenced to DMF (b) (4) (see above)
14.	Does the section contain information regarding the characterization of the DS?		X	This information is cross-referenced to DMF (b) (4) (see above)
15.	Does the section contain controls for the DS?	X		It is stated that the DMF Holder for the drug substance provides USP grade material. See DMF (b) (4) for specifications. The applicant has provided "confirmatory specifications" for the d.s. Confirmatory test methods are referenced to the USP monograph and the d.s. manufacturer's DMF. Related substances testing is referenced to the Ph. Eur. monograph. Validation data for this test are provided. The impurity (b) (4) (b) (4) is quantified using an assay/HPLC method which was originally validated in 2004 (report not provided) and updated in 2005 for the optimized extraction step (report provided). Applicant should provide a copy of the Ph. Eur. related substances test used for the drug substance.
16.	Has stability data and analysis been provided for the drug substance?		X	Stability data are cross referenced to DMF (b) (4) (see above)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	to be confirmed by reviewer, during review of DMF (b) (4)
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	to be confirmed by reviewer, during review of DMF (b) (4)

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA (ONDQA)**

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		Drug product manufacturers produce the bulk drug product. Contractors are used to fill, seal and label the final container closure systems. Batch records for this final filling, sealing and labeling process do not appear to be provided, nor is this process described in the description of manufacturing.
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		The executed batch records have been translated from German (Bayer) and (b) (4) (b) (4) into English. The Bayer Masterbatch record has been translated into English. The (b) (4) masterbatch record appears to be only in (b) (4)
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		Determination of whether the linkage is adequate between the product used in clinical studies and the to be marketer product is a review issue. "From clinical Study EMR 62215-005 forward, clinical lots were manufactured using the same formulation and fully-scaled process. The manufacturing process has been in place at (b) (4) since 2003 and has remained unchanged from clinical study EMR 62215-005 through commercial production." Applicant claims that "All dissolution profiles of the batches used in all of the clinical trials of the current NP01 product conform to a proposed specification of not more than (NMT) (b) (4) release at 3 hours and not less than (b) (4) release (Q= (b) (4)) at 7 hours." Alcohol, pH, ionic strength, bile salts are said to not influence dissolution. (Section P.2.2) Bayer was added as a d.p. manufacturing site in 2009 and a comparability report of the two sites is provided (P.2.3).
23.	Have any biowaivers been requested?		x	To be verified by reviewer.

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24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
25.	Does the section contain controls of the final drug product?	x		Tablet hardness is not included in the d.p. specification, but it is part of the in-process controls for active core tablets and press coated tablets. Note the d.p. specification for (b)(4) (structure alert) at a max. of (b)(4). Reviewer should check to see if this has been qualified.
26.	Has stability data and analysis been provided to support the requested expiration date?	x		12 months of stability data are available in the original NDA for the Bayer site for drug product, and 3 months data for the (b)(4) site. An (b)(4) expiry has been proposed. The graph of assay results suggests at time zero that the tablet strength for all lots was below the 100% target. Tablets should be manufactured to target 100%.
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	To be confirmed by reviewer.
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	To be confirmed by reviewer.

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F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?		x	An MV package was not found, and should be requested if not present.

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			N.A.

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		There is a LOA to a DMF for drug substance.

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	III		(b) (4)	Jun 10	
	II		Jun 10		
	III		8 Oct 10		
	III		8 Oct 10		
	III		7 Jul 10		
			9 Jul 10		

Cross-referenced INDs: 72569 and 105868. Note that Nitec Pharma GmbH merged with Horizon Therapeutics in April, 2010 to form Horizon Pharma Inc.

I. LABELING				
	Parameter	Yes	No	Comment

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32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	x		See comments elsewhere in this table for mention of comments for forwarding to the applicant.

Comments for filing letter:

Provide a copy of the related substances test (European Pharmacopoeia) used for the drug substance.

Provide representative executed and master batch records for the final drug product filling, sealing and labeling process or provide a description of these processes using an equivalent level of detail as in a batch record.

Provide an accurate English translation of the (b) (4) masterbatch record which is provided only in (b) (4)

The graph of stability assay results suggests at time zero that the tablet strength for all lots was below the 100% target. Tablets should be manufactured to target 100%.

Provide an appropriate Methods Validation package. See the recommendations for methods validation in our draft guidance, "Analytical Procedures and Methods Validation."
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM122858.pdf>)

**PRODUCT QUALITY (Small Molecule)
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{See appended electronic signature page}

Alan C. Schroeder, Ph.D.

CMC Lead

Division of New Drug Quality Assessment III

Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Prasad Peri, Ph.D.

Branch Chief, Branch VIII

Division of New Drug Quality Assessment III

Office of New Drug Quality Assessment

Date

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

/s/

ALAN C SCHROEDER

10/26/2011

Signing for myself and for Prasad Peri, Ph.D. (Branch Chief)