

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 22-220

CHEMISTRY REVIEW(S)

NDA #22-220

TRIVARIS™

(triamcinolone acetonide injectable suspension)

80 mg/mL (8%)

Applicant: Allergan, Inc.

CMC Review

Rao V. Kambhampati, Ph.D.

Senior Regulatory Review Scientist

ONDQA, DPA II, Branch IV

Chemistry Review Data Sheet

1. NDA# 22-220

Stamp Date: August 16, 2007

PDUFA Date: June 16, 2008

OND Division: Division of Anti-Infective and Ophthalmology Products (DAIOP)

2. REVIEW #: 1

3. REVIEW DATE: 6/5/2008

4. REVIEWER: Rao V. Kambhampati, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original 0000	8/15/2007
Amendment 0002	10/11/2007
Amendment 0004	1/21/2008
Amendment 0005	2/27/2008
Amendment 0006	3/17/2008
Amendment 0007	4/4/2008
Amendment 0008	4/23/2008
Amendment 0009	5/2/2008
Amendment 0011	5/23/2008
Amendment 0012	6/4/2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Allergan, Inc.
Address:	2525 Dupont Drive P.O. Box 19534 Irvine, CA 92623-9534
Representative:	Elizabeth Bancroft Senior Director, Global Regulatory Affairs
Telephone:	714-246-4391

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: TRIVARIS™

b) Non-Proprietary Name: Triamcinolone acetonide injectable suspension

- c) Code Name/#: N/A
 d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: N/A
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2); KENALOG[®]-40 Injection (triamcinolone acetonide injectable suspension, USP), Bristol Myers Squibb Company.

10. PHARMACOL CATEGORY: Glucocorticoid

11. DOSAGE FORM: Aqueous gel suspension, sterile injectable.

12. STRENGTH/POTENCY: 80 mg/mL; 8%

13. ROUTE OF ADMINISTRATION: Intravitreal
 Indication: Sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids.

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:

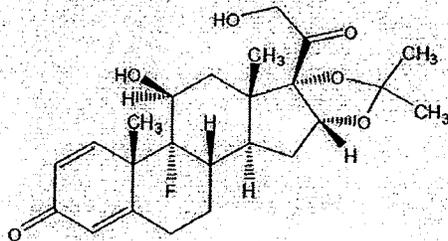
Chemical Name: 9-Fluoro-11 β ,16 α ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17 acetal with acetone

CAS Reg. No.: 76-25-5

Molecular Formula: C₂₄H₃₁FO₆

Molecular Weight: 434.50

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	COMMENTS
—	II	XXXXXXXXXX	XXXXXXXXXX	Adequate
				Adequate
—	III			Adequate
—	III			Adequate
—	III			Adequate
—	III			Adequate
—	III			Adequate
—	V			Adequate

b(4)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	14-901	Kenalog-40 Injection (triamcinolone acetonide injectable suspension, USP); Applicant: Bristol Myers Squibb Company

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EER	Acceptable	4/30/2008	S. Adams (HFD-325), DMPQ, OC
Trademark Review	Acceptable	5/29/08	Diane Smith, Pharm D., Division of Medication Error Prevention (DMEP), OSE
EA	Acceptable (Categorical Exclusion)	6/4/2008	Rao Kambhampati, Ph.D.
Methods Validation	Not necessary	6/4/2008	Rao Kambhampati, Ph.D.

The Chemistry Review for NDA 22-220

The Executive Summary

I. Recommendations

• A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls (CMC) standpoint, the NDA #22-220 is recommended for approval.

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

N/A

II. Summary of Chemistry Assessments

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

This electronic NDA# 22-220 was submitted as a 505(b)(2) application and the Reference Listed Drug Product that is the basis for the submission is KENALOG[®]-40 (triamcinolone acetonide injectable suspension, USP) of Bristol Myers Squibb (NDA# 14-901). This application relies on the Agency's previous findings of safety and effectiveness for triamcinolone acetonide under NDA# 14-901 and on published literature for safety and efficacy. To support approval for the change in route of administration to include the intravitreal route, Allergan has formulated the drug product as a sterile, preservative-free hydrogel suspension formulation presented in a pre-filled syringe. To support the safety of the drug product for intravitreal administration, this application contains literature and interim safety data from ongoing clinical trials that utilize the TRIVARIS[™] drug product. Even though the applicant requested for Priority Review status, the DAIOP accepted it as a standard NDA.

Drug Substance:

The drug substance, triamcinolone acetonide, has a USP monograph and it is presently used in the manufacturing of other FDA approved drug products including the recently approved TRISENCE[™] (triamcinolone acetonide injectable suspension, 40 mg/mL). The applicant cross-referenced the CMC information for the triamcinolone acetonide drug substance to _____, DMF _____ and provided a satisfactory Letter of Authorization (LOA) from _____. At the time of this NDA submission, the DMF _____ was determined to be inadequate by Kenneth J. Furnkranz, (OGD, Letter to Holder date 5/16/07). Later, the deficiencies were satisfactorily addressed by _____ in the DMF amendment dated 7/10/07. The DMF was then determined to be adequate by Dorota Matecka, Ph.D. (DMF Review #17, dated 10/9/07) and by Kenneth Furnkranz (DMF Review #18 dated 11/21/07). In addition to the cross-reference, the applicant provided some information directly in the NDA submission. _____

b(4)

product. Upon comment, Allergan stated that _____ was used for pre-clinical, clinical and stability batches of the drug product and it will also used for the commercial drug product manufacturing upon NDA approval.

b(4)

Triamcinolone acetonide drug substance is a white to cream-colored crystalline powder. It is practically insoluble in water; sparingly soluble in dehydrated alcohol, in chloroform and in methanol. It has a molecular formula of C₂₄H₃₁FO₆ and molecular weight of 434.50 daltons. Triamcinolone acetonide has eight chiral carbons (C8, C9, C10, C11, C13, C14, C16 and C17)

_____. s. With regard to the drug substance specifications, the initial submission contained acceptance criteria (AC) for individual impurities (NMT _____ and total impurities _____ only and they were determined by the USP method but upon comment the AC for individual specified impurities _____

b(4)

_____), total specified identified impurities (NMT _____), and individual unspecified impurities _____ were added and the determination was changed to _____ method because this method is better than the USP method. Also the initial submission did not contain test and AC for _____; but upon comment the applicant added

_____ to the drug substance specifications. In addition to the tests found in the USP monograph, specifications for particle size, endotoxin (_____ and microbial limits (_____ were included in the drug substance specifications in order to support critical quality attributes of the drug product. The initial drug substance specifications contained mean particle size (NMT _____ and particle size _____ determination only but upon comment, additional particle size determinations (particle size _____, particle size _____ were added. The revised specifications (amendment 0009, 5/2/08) are adequate and acceptable. The batch analysis results were provided for three batches which demonstrated that the drug substance can be manufactured with consistent quality and purity. For these batches, the individual impurities content and the total impurities content ranged from _____ and the assay ranged from _____. The USP Reference Standards Lot K and Lot H-1 or certified secondary reference standard are used. The _____ information was cross-referenced to the DMF# _____

Drug Product:

The TRIVARIS™ drug product is intended to be administered as an intraocular (intravitreal) injection using a prefilled glass syringe to provide 4 mg of triamcinolone acetonide (TA) for the treatment of certain ocular and non-ocular inflammation.

b(4)

Trivaris™ is a _____

_____ The formulation is _____

_____ No antimicrobial preservatives are added. The drug product is delivered with a single-use, prefilled glass syringe. The target dose of 4 mg is delivered in a 50 mg (~50 µL) intraocular injection of 8% (w/w) triamcinolone acetonide gel suspension. The applicant stated that this product conforms to all compendial requirements for triamcinolone acetonide injectable suspension, USP. The components included TA, sodium hyaluronate, sodium chloride, dibasic sodium phosphate _____ monobasic sodium phosphate _____ and Water for Injection. The drug product is manufactured at two manufacturing sites for commercial distribution, the Allergan Pharmaceutical Sciences

Operations (PSO) in Irvine, California (Allergan, Irvine) and at Allergan Pharmaceuticals Ireland in Westport, Ireland (Allergen Westport). In the initial NDA submission, the applicant stated that Allergan Irvine is used bulk drug product manufacturing only but later (amendment 0005 2/27/08) the applicant intended to use this site for filling of syringes and packaging of the drug product. The NDA batches were manufactured and packaged at Allergan Irvine. The manufacturing process includes

[redacted] A demonstration batch was manufactured at Allergan Westport as according to the proposed commercial protocol.

b(4)

The drug product

[redacted] syringe are packaged in a secondary packaging system developed to protect the filled syringe assembly from light and damage. The secondary container closure components included [redacted] syringe tray, [redacted] (seal), and carton.

b(4)

The drug product specifications included triamcinolone acetate content ([redacted]), specified identified impurity ([redacted]), individual unspecified impurity (NMT [redacted]), total impurities (NMT [redacted]), triamcinolone acetate identity (at release only), pH (7.0-7.4), viscosity ([redacted]), physical appearance [redacted], microscopic appearance ([redacted]), foreign particulate matter (USP<788>), [redacted] content uniformity (USP <905>), sterility (USP), and endotoxins (LAL). The initially submitted drug product specifications contained a single particle size determination [redacted]

b(4)

[redacted] but upon comment two additional particle size determinations were added to the specifications [redacted]

[redacted] The revised drug product specifications (amendment 0004, 1/21/08) are adequate and acceptable.

Batch analysis data were provided for two clinical and three stability lots and they were manufactured at Allergan Irvine. It was demonstrated that the drug product can be manufactured with consistent quality and purity. The total impurities content was NMT [redacted] for all batches except for the batch 12786A1 which had NMT [redacted] only.

b(4)

The container-closure system for the TRIVARIS™ drug product consists of a [redacted] glass syringe [redacted]

b(4)

The _____ prefilled syringe system is packaged in a _____ tray and sealed with a _____. The sealed tray is packaged in a _____ unit carton. All container closure components are acceptable.

b(4)

Stability studies were performed on three primary stability lots of drug product and they were compounded at a batch size of _____ and filled at Allergan Irvine. The API supplier was _____. The primary stability lots were filled at _____.

b(4)

_____ . The storage conditions included long-term (5°C) and accelerated (25°C/60% RH) conditions as well as horizontal and vertical _____ orientations. The testing of product in the vertical orientation was limited to content uniformity.

Supportive stability studies were performed at 5°C on two lots (12330 and 12697). They were compounded to the same batch size _____ as the primary stability lots, and also filled at Allergan Irvine. The supplier of _____ for lot# 12330. They were packaged similarly to the primary stability lots. The lot# 12330 was monitored for 24 months at 5°C and the lot# 12697 was monitored for 18 months at 5°C. The lot# 12697 was stored in horizontal position only.

b(4)

All refrigerated (5°C) data for primary stability lots 12785, 12786 and 12800 remained within the proposed product shelf life specifications through 12 months of study. All 5°C data for supportive lots 12330 and 12697 remained within the proposed product shelf life specification through 24 months and 18 months of study, respectively. _____ stability limiting parameter for TRIVARIS™. _____ at 5°C for both the primary and supportive stability lots exhibit a slight downward trend over time with results remaining within the proposed specifications up to 24 months of study. Out of specification _____ values were obtained for supportive stability lot 12330 at the 24 month time point with data following trend.

Based on the _____ stability profile at 5°C for the primary stability lots and supportive lots and the initial _____ results for the primary stability lots, the viscosity results for the primary lots support an 18 month expiration dating.

All 25°C/60%RH (accelerated condition) stability data for the primary lots, with exception of _____ results, remain within the proposed product shelf life specifications through 6 months of study. The _____ data at the 25°C /60%RH accelerated condition exhibit a downward trend for all primary stability lots with low out of specification _____ results obtained for all primary stability lots at the 3 month and 6 month time point. All other parameters remained relatively unchanged through 6 months of study at the 25°C/60%RH accelerated storage condition.

Based on the evaluation of 12 months of refrigerated (5°C) data and 6 months at 25°C/60%RH accelerated storage data for the primary stability lots and up to 24 months of refrigerated (5°C) data for supportive stability lots, the recommended expiration dating for TRIVARIS™ (triamcinolone acetonide injectable suspension, USP) in the proposed configuration is 18 months and a storage statement of "store refrigerated, 2°C - 8°C (36°F - 46°F)" is supported for the drug product.

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

TRIVARIS™ (triamcinolone acetonide injectable suspension) is intended to be used for intravitreal administration. Each prefilled syringe contains 8 mg (0.1 mL) of the drug product. The recommended dose is 4 mg (0.05 mL). Instructions are provided _____ regarding preparation of the syringe for the administration of 4 mg (0.05 mL) dose. In addition, in the labeling, the clinical division will be allowing the applicant to include intramuscular and intra-articular administrations for other indications on the basis of the Referenced drug product, KENALOG®-40 Injection (triamcinolone acetonide injectable suspension, USP).

C. Basis for Approvability or Not-Approval Recommendation

The original NDA submission and amendments there to, provided adequate information on the chemistry, manufacturing, and controls (CMC) for the production of TRIVARIS™ (triamcinolone acetonide injectable suspension), 80 mg/mL (8%). The DMF _____ and amendments there to found to contain adequate CMC information for triamcinolone acetonide USP drug substance. b(4)

The manufacturing and packaging processes and in-process controls used for the drug product are acceptable. Adequate batch analysis data were provided for the drug product. The specification for the drug product included adequate tests, and the revised acceptance criteria are acceptable. The stability data included 12 months real-time long-term stability data for three primary registration batches and 18 to 24 months long-term data for two supportive stability batches and, and statistical analysis which supported an expiration dating period of 18 months when stored under refrigerated conditions at 2°C - 8°C (36°F - 46°F).

The trade name, TRIVARIS™, was found to be acceptable by the Division of Medication Error Prevention (DMEP), OES. The established name (USAN) for the drug substance is triamcinolone acetonide and the USP monograph name for the drug product is triamcinolone acetonide injection suspension. Some changes were recommended to the package insert and unit carton and blister labels and those changes will be incorporated in the final printed labeling documents by the Applicant.

The drug substance manufacturing, packaging, and release testing facility _____ and the drug product manufacturing, packaging, and release testing facilities (Allergan Irvine and Allergan Ireland) were found to be acceptable and an overall recommendation of Acceptable was issued by S. Adams on 4/30/08 (DMPQ, HFD-325). As according to the current policy, the analytical methods validation is not required because the dosage form does not involve any unusual/special testing methods. The Applicant's request for an exemption from the EA requirement under categorical exclusion is acceptable. b(4)

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

Signed in DFS by Rao V. Kambhampati, Ph.D., Senior Regulatory Review Scientist (Chemist).

B. Endorsement Block

Signed in DFS by Elaine Morefield, Ph.D., Director DPA II, ONDQA.

• **C. CC Blockcc:**

Org. NDA 22-220

HFD-800/Branch Chief/NSchmuff

HFD-550/PM/RRodriquez

HFD-800/Chem Reviewer/RKambhampati

HFD-800/PAL/LNg

HFD-800/PM/SGoldie

66 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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

/s/

Rao Kambhampati
6/5/2008 05:54:01 PM
CHEMIST

Please sign off and file in DFS.

Elaine Morefield
6/5/2008 06:07:55 PM
CHEMIST
Signing for Norman Schmuff

**Initial Quality Assessment
Branch IV
Pre-Marketing Assessment Division II**

Review Date: September 27, 2007
IQA Reviewer: Rao V. Kambhampati, Ph.D.
OND Division: Division of Anti-Infective and Ophthalmology Products (DAIOP)
NDA: 22-220
Applicant: Allergan, Inc.
Stamp Date: August 16, 2007
PDUFA Date: June 16, 2008
Proposed Trademark: TRIVARIS™
Established Name: Triamcinolone acetonide injectable suspension, USP
Dosage Form: Aqueous gel suspension, sterile injectable
Route of Administration: Intravitreal Injection
Strength: 80 mg/mL (8%)
Indication: Sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids.
NDA Reviewer: Rao V. Kambhampati, Ph.D.
PAL: Linda Ng, Ph.D.
ONDQA Fileability: Yes
Comments for 74-Day Letter: None Identified

Summary and Critical Issues

Summary

This electronic NDA# 22-220 was submitted as a 505(b)(2) application and the Reference Listed Drug Product that is the basis for the submission is KENALOG®-40 (triamcinolone acetonide injectable suspension, USP) of Bristol Myers Squibb (NDA# 14-901). This application relies on the Agency's previous findings of safety and effectiveness for triamcinolone acetonide under NDA# 14-901 and on published literature for safety and efficacy. To support approval for the change in route of administration to include the intravitreal route, Allergan has formulated the drug product as a sterile, preservative-free hydrogel suspension formulation presented in a pre-filled syringe. To support the safety of the drug product for intravitreal administration, this application contains literature and interim safety data from ongoing clinical trials that utilize the TRIVARIS™ drug product. Even though the applicant requested for Priority Review status, the DAIOP accepted it as a standard NDA.

The drug substance, triamcinolone acetonide, has a USP monograph and it is presently used in the manufacturing of other FDA approved drug products. It is manufactured by _____ the CMC information was cross-referenced to — DMF# —. Even though this DMF was determined to be adequate by the previous reviewers, recently it was reviewed again by Kenneth J.

b(4)

Furnkranz (HFD-625, OGD, Letter date 5/16/07) when it was cross-referenced in the ANDA# 78-104. He stated the following reasons:

- You use two analytical methods for testing impurities in the Triamcinolone Acetonide (TA) drug substance. Both the USP method and the P&U in-house method indicate "Impurities Individual" at NMT — This is not acceptable. b(4)
- ICH Q3A as well as your in-house method indicates that "unspecified" impurities should be limited to $\leq 0.10\%$. The limits for the two methods should be comparable. The USP method limit for "unspecified" impurities should also be NMT 0.10%.
- Please also demonstrate that impurities quantitated at $>0.10\%$ by the USP method are "specified" using your in-house method, or else they should be identified and, if $>0.15\%$ should also be qualified.

The above deficiencies were satisfactorily addressed by the Holder in the DMF amendment dated 7/10/07. However, this amendment needs to be reviewed. There are _____ drug substance that are manufactured under this DMF, however, the NDA applicant did not specify the _____ that was used for the manufacturing of the NDA lots as well as for the proposed commercial drug product lots. b(4)

The TrivarisTM drug product is intended to be administered as an intraocular (intravitreal) injection using a prefilled glass syringe to provide 4 mg of triamcinolone acetonide (TA) for the treatment of certain ocular and non-ocular inflammation. TrivarisTM is _____

_____. No antimicrobial preservatives are added. The drug product is delivered with a single-use, prefilled _____ glass syringe. The target dose of 4 mg is delivered in a 50 mg (~50 μ L) intraocular injection of 8% (w/w) triamcinolone acetonide gel suspension. The applicant stated that this product conforms to all compendial requirements for triamcinolone acetonide injectable suspension, USP. The components included TA, sodium hyaluronate, sodium chloride, dibasic sodium phosphate _____ monobasic sodium phosphate _____, and Water for Injection. The drug product is manufactured at two manufacturing sites for commercial distribution. The bulk drug product is compounded in Allergan Pharmaceutical Sciences Operations (PSO) in Irvine, California (Allergan, Irvine) and shipped to Allergan Pharmaceuticals Ireland in Westport, Ireland (Allergan Westport) for filling and packaging of finished drug product. However, the NDA batches were manufactured and packaged at Allergan Irvine. The manufacturing process includes _____ b(4)

_____. A demonstration batch was manufactured at Allergan Westport as according to the proposed commercial protocol.

The drug product is _____

b(4)

_____ are packaged in a secondary packaging system developed to protect the filled syringe assembly from light and damage. The secondary container closure components included _____ syringe tray, _____ (seal), and carton.

Stability studies were performed on three primary stability lots of drug product and they were compounded at a batch size of _____ and filled at Allergan Irvine. The API supplier was _____. The primary stability lots were filled at _____

b(4)

_____ The storage conditions included long-term (5°C) and accelerated (25°C/60% RH) conditions as well as horizontal and vertical (needle down) orientations. The testing of product in the vertical orientation was limited to content uniformity.

Supportive stability studies were performed at 5°C on two lots (12330 and 12697). They were compounded to the same batch size _____ as the primary stability lots, and also filled at Allergan Irvine. The supplier of _____ for lot# 12330. They were packaged similarly to the primary stability lots. The lot# 12330 was monitored for 24 months at 5°C and the lot# 12697 was monitored for 9 months at 5°C. The lot# 12697 was stored in horizontal position only.

b(4)

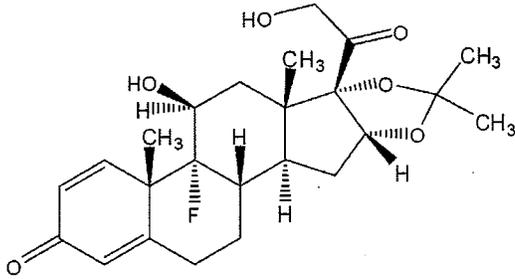
All results of the primary lots remained within the proposed shelf-life specifications through 3 months of study for the refrigerated (long-term) storage conditions. Out of specification results were observed at the 3-month time point for lots stored at 25°C/60% RH (accelerated) conditions. All supportive lots remained within the proposed product shelf-life specification through 9 months (Lot# 12330) and 18 months (Lot# 12697) of study for the refrigerated conditions. _____ is the stability limiting parameter for the drug product. _____ for both the primary and supportive stability lots exhibited a slight downward trend over time with results within the proposed specifications up to 18 months of study. Out of specification viscosity values were obtained for supportive stability lot# 12330 at the 24 month time point. The applicant proposed an expiration dating period of 18 months (when stored refrigerated at 2-8°C) on the basis of the available real time stability data and statistical analysis of the data.

b(4)

The microbiology consult, the trade name request to DMET, and the labeling consult to DDMAC have been sent by Raphael Rodriguez, DAIOP PM.

The EER was submitted on 9/10/07 by Linda Athey Mullins, ONDQA PM.

The structural formula is as follows:



Chemical Name: 9-Fluoro-11β, 16α, 17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16, 17 acetal with acetone

Molecular Formula: C₂₄H₃₁FO₆

Molecular Weight: 434.51

Critical Issues for Review:

1. Presently the DMF# _____ for triamcinolone acetonide USP drug substance is Inadequate because of the pending deficiencies regarding the impurities acceptance criteria (Letter to Holder 5/16/07). These deficiencies were satisfactorily addressed in the DMF amendment dated 7/10/07 but it needs to be reviewed. b(4)
2. The DMF Holder manufactures _____ the drug substance. Therefore, the applicant needs to clarify _____ was used for the manufacturing of pre-clinical, clinical, and stability lots of the drug product, and the grade that will be used for the manufacturing of intended commercial drug product lots. b(4)
3. The _____ should be indicated when triamcinolone acetonide is shown in the components and composition (Table 3.2.P.1.2-1) and batch formula (Table 3.2.P.3.2-1) sections in the NDA. b(4)
4. As according to ICH Q3A(R) guideline for impurities in the drug substance, the applicant needs to revise the impurities in the proposed drug substance specification, for example, by including the following: individual specified identified impurities _____ individual specified unidentified impurity, individual unspecified impurity, and total impurities. Also, in the specifications the contents of _____ should be included. b(4)
5. The batch analysis results of the demonstration batch that was _____ and packaged at the proposed commercial site, Allergan Pharmaceuticals Ireland, should be provided. b(4)
6. Only 3 months of stability data were provided for the three primary NDA stability batches that were manufactured at Allergan Inc., Irvine, CA facility but all three batches had out of specification result _____ at the 3-month time point when stored at 25°C/60%RH. Based on the currently available real time stability b(4)

study results, the expiration dating could be severely limited. Therefore, the applicant needs to provide the 6-month and 9-month stability update for these batches when available.

7. If the applicant had conducted any studies that demonstrate that the _____ of the drug product had no significant impact on the safety and efficacy of the drug product, the results of those studies should be provided.

b/c

Comments for 74-Day Letter

None recommended.

D. Review, Comments, and Recommendation:

The NDA# 22-220 is acceptable for filing. No team review is recommended. A single reviewer can review this NDA and it was assigned to Rao V. Kambhampati, Ph.D. This IQA was also assigned to Rao Kambhampati due to PAL's (Linda Ng) travel.

Rao V. Kambhampati, Ph.D.
Senior Regulatory Review Scientist

September 27, 2007
Date

Norman Schmuff, Ph.D.
Branch Chief

September 27, 2007
Date

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

/s/

Rao Kambhampati
1/8/2008 06:09:23 PM
CHEMIST

Please sign off and file.

Norman Schmuff
1/10/2008 06:28:18 AM
CHEMIST