CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-437

CHEMISTRY REVIEW(S)

NDA 22-437

Trelstar® 22.5 mg (24 weeks)

Watson Laboratories, Inc.

William M. Adams
Office of New Drug Quality Assessment (ONDQA)

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-437

2. REVIEW #2

3. REVIEW DATE: 03 Mar 2010

4. REVIEWER: William Adams

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
N-000 (original submission)	12 Sep 2008
Amendment N-001 (draft labels & labeling)	06 Oct 2008
Amendment N-002 (trade name)	23 Dec 2008
Amendment N-004 (contact info for mfg sites)	14 Jan 2009
Amendment N-005 (contact info for mfg sites)	15 Jan 2009
Amendment N-006 (partial CMC response to filing letter)	21 Jan 2009
Amendment N-007 (trade name)	30 Jan 2009
Amendment N-008 (completed CMC response to filing letter)	24 Mar 2009
Amendment N-009 (trade name)	04 Apr 2009
Amendment N-010 (type C meeting request)	07 Apr 2009
CMC IR Letter	10 Jun 2009
CMC Review #1	16 Jun 2009
CR Letter	10 Jul 2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment N-011 (draft vial/carton labels)	04 May 2009
Amendment N-013 (response to CMC IR letter)	09 Jul 2009
Amendment N-014 (draft package insert)	10 Jul 2009
Amendment N-015 (revised response to CR letter)	10 Sep 2009
Amendment N-016 (updated facility list)	29 Sep 2009
Amendment N-017 (updated facility information)	29 Oct 2009
Amendment N-018 (draft package insert)	03 Feb 2010
Amendment N-020 (draft labeling)	01 Mar 2010
Amendment N-021 (draft labels)	03 Mar 2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Watson Laboratories, Inc.
Address:	577 Chipeta Way Salt lake City, UT 84108
Representative:	Wendy DeSpain, B.S., M.B.A, R.A.C. Associate Director, Proprietary Regulatory Affairs
Telephone:	(801) 588-6200
Fax:	(801) 588-6232

8. DRUG PRODUCT NAME/CODE/TYPE:
   (a) Proprietary Name: Trelstar 22.5 mg (24 weeks)
   (b) Non-Proprietary Name: Triptorelin Pamoate for Injection Suspension, 22.5 mg
   (c) Code Name/#: D-Trp^6-LHRH
   (d) Chemical Type/Submission Priority): 3S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOLOGICAL CATEGORY: treatment of prostate cancer

11. DOSAGE FORM: Injectable suspension

12. STRENGTH/POTENCY: 22.5 mg peptide as pamoate salt

13. ROUTE OF ADMINISTRATION: Injection

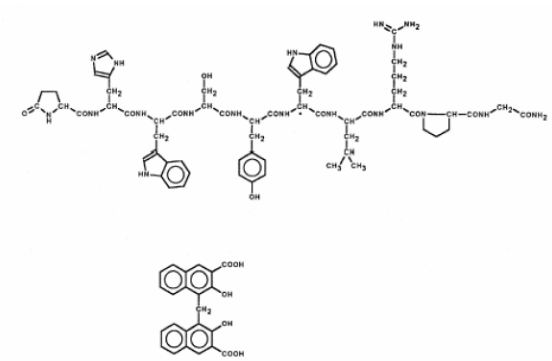
14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
   _____SPOTS product – Form Completed

   __XX__ Not a SPOTS product

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

Chemical Name	L-pyroglutamyl-L-histidyl-L-trytophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-L-prolylglycinamide pamoate salt
Chemical Name	5-oxo-Pyr-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH_2 pamoate salt
Molecular Formula	$C_{64}H_{82}N_{18}O_{13}$ (triptorelin) + $C_{23}H_{16}O_6$ (pamoate)
Molecular Weight	1699.9 amu (salt), 1311.5 amu (free base), 388.4 amu (pamoate)
Molecular Structure	



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Triptorelin	1	Acceptable	01/21/10	

			Pamoate			
[redacted]	IV	[redacted]	[redacted]	1	Acceptable	02/16/10
	IV	[redacted]	[redacted]	1	Acceptable	NDA Review #1
	III	[redacted]	[redacted]	4		
	IV	[redacted]	[redacted]	4		
	III	[redacted]	[redacted]	4		
8084	IV	Solvay	pre-filled syringe	1	Acceptable	02/16/10

[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] Acceptable, Inacceptable, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

APPLICATION	DESCRIPTION
NDA 20-715*	Trelstar® Depot (triptorelin pamoate for injectable suspension, 3.75 mg)
NDA 21-288*	Trelstar® LA (triptorelin pamoate for injectable suspension, 11.25 mg)
IND [redacted]**	Trelstar® [redacted] (triptorelin pamoate for injection suspension, 22.5 mg)

* Cross referenced to this application
** Reference is made to the MM for the EOP2 and pre-NDA meetings

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Clinical/Statistics	Acceptable	06/29/09	Y.Ning/Y.Change
ClinPharm	Acceptable	06/30/09	S.Abraham
DMEPA	Acceptable	07/23/09	S.Griffith
Biopharm	Acceptable	02/17/10	H.Mahayni
EES	Withhold	09/02/09	OC
	Pending for this review clock	3/2/10	
Methods Validation	Acceptable	NDA Review #2	M.Adams
EA	Acceptable	NDA Review #1	M.Adams
Microbiology	Acceptable	06/22/09	V.Pawar

CMC Review for NDA 22-437

The Executive Summary

I. RECOMMENDATIONS

A. RECOMMENDATION & CONCLUSION ON APPROVABILITY

The application is APPROVABLE from the Chemistry, Manufacturing and Controls (CMC) perspective pending final OC Overall Conclusion of "acceptable" (revised conclusion is awaiting the result of a GMP inspection at a drug product manufacturing site) and a minor labeling revision.

B. RECOMMENDATION ON PHASE 4 (Post-Marketing) COMMITMENTS, AGREEMENTS &/or RISK MANAGEMENT STEPS, if Approvable

None are proposed.

II. SUMMARY OF CHEMISTRY ASSESSMENTS

A. DESCRIPTION OF THE DRUG PRODUCT(S) & DRUG SUBSTANCE(S)

DRUG PRODUCT

Triptorelin, marketed as Trelstar®, is a luteinizing hormone releasing hormone agonist indicated for the palliative treatment of advanced prostate cancer. Trelstar 22.5 mg (24 weeks) is a single dose, sterile, lyophilized powder for reconstitution suspension presented in a glass vial. For administration, 2 mL sterile WFI is added to prepare a suspension for intramuscular injection in the buttocks once every 24 weeks (168 days).

The drug product is the third in a series of triptorelin extended release injectable suspension products - Trelstar 3.75 mg (4 weeks) under NDA 20-715, Trelstar 11.25 mg (12 weeks) under NDA 21-288.

The commercial presentation is either as a single vial of drug product in a non-functional carton or as a kit. The kit is a (b) (4) tray with slots for a vial of drug product, a Mixject apparatus, a syringe of sterile water for injection (WFI syringe), and a convenience pack consisting of an alcohol wipe pad, a sterile gauze pad, a band aid and a label for the patients record.

The Mixject apparatus is an FDA approved device [510(k) K963583] developed specifically for the reconstitution of lyophilized powders into injectable suspensions. It is manufactured by MediMop Medical Projects, Inc. (Ra'anana, Israel) and (b) (4) CMC information for the apparatus is accepted without review as this is an FDA approved device.

The WFI syringe is a pre-filled, pre-sterilized glass syringe containing 2.0 mL WFI manufactured by Solvay Biologicals BV (Olst, The Netherlands). CMC information supporting it is provided in type II DMF 8084. The file has been reviewed and found acceptable.

The convenience kit is provided by (b) (4) Secondary packaging is by (b) (4) (b) (4) Each item in the kit is marketed over-the-counter in the U.S, and therefore all are acceptable.

The drug product is manufactured by Debio Reserche Pharmaceutique S.A. (Martigny, Switzerland) (Debiopharm). (b) (4) Drug substance is provided by (b) (4) Contract laboratories performing specific testing on excipients, the apparatus or drug product have been identified along with their functions.

Developmental studies are provided to justify polymer identity and properties, drug product formulation, the manufacturing process and controls and key intermediate parameters. (b) (4) . An accelerated dissolution method has been developed to reduce the analysis time from 24 weeks (168 days) to 168 hours. The test, method and criteria have been accepted.

(b) (4)

(b) (4)

Specifications for acceptance of bulk drug substance and each release polymer at the drug product manufacturing site are based on the supplier's release specification. Testing addresses identity, assay, purity and key physico-chemical attributes for each material. The other excipients meet USP/NF requirements. No material is novel, or of human or animal origin. CMC information for the polymers is provided under DMF (b) (4) and DMF (b) (4) Both files have been reviewed and found acceptable.

The drug product release specification is acceptable. Testing includes appearance, identity of peptide and anion, total peptide content, content uniformity, purity (total, specified and unspecified related substances), and water content on the lyophilized powder; and pH, particle size, reconstitution time, dissolution, sterility and bacterial endotoxins on the reconstituted suspension. Analytical methods include Identity by HPLC and TLC; assays by HPLC; particle size by (b) (4) and USP methods. Dissolution uses the Trelstar 11.25 mg method (5% aqueous methanol at 37 C with apparatus II at 75 rpm), then increases medium temperature to 61^{o}C at 48 hours without changing medium. The proposed samples times and criteria have been accepted by the Biopharmaceutics Reviewer. Analytical methods for intermediate testing and drug product release are described in sufficient detail, example HPLCs are included, and acceptable method validation studies are provided. The proposed criteria are justified with batch analysis data, stability study data and product development information. With the exception of total peptide content, particle size and release profile, the proposed criteria are those approved for Trelstar 11.25 mg (12 weeks) and Trelstar 3.75 mg (4 weeks). Impurities and degradants are stated to be those present in other Trelstar products.

The reference standard is that approved for the other Trelstar products.

The primary package and components are those approved for the other Trelstar products. Provided are component descriptions and acceptance specifications.

The proposed expiry period for drug product is 36 months with storage at USP controlled room temperature and do not freeze in the Mixject device. Stability information is primary studies on clinical lots and process robustness lots; supporting studies on gamma irradiation validation lots and process validation lots; a reconstituted suspension study; and a USP Q1B photostability study. For the primary studies, vials stored at ICH LT for 24-36 months, at ICH INT

for 12 months and at ICH ACC for 6-7 months with testing for the release specification. For the supporting studies, vials are stored at ICH LT for 12 months and ICH ACC for 6 months with testing for the release specification. Data trends across time and condition were the same for primary and supportive study lots. Degradation trends are those observed for Trelstar 3.75 mg and 11.25 mg, and no lot failed. The reconstituted suspension study shows no significant potency loss in suspension stored ICH LT/24 hours, however the applicant concludes that the suspension should be administered immediately upon reconstitution for microbiological safety since the formulation contains no antimicrobial agents. The Microbiology Reviewer concurs. The photostability study shows that the glass vial provides sufficient light protection for the lyophilized powder.

The post approval stability protocol proposes to complete the primary and supportive studies through 60 months, and to place 1 annual drug product lot on stability.

The expiry period for WFI syringes is 36 months with storage at USP controlled room temperature. Submitted are completed studies on syringes stored at ICH LT for 36 months and on-going studies on syringes stored at ICH LT/3-24M. The data shows all test parameters unchanging except for pH which increases steadily, but remains within specification. The data submitted in this application and in DMF 8084 are sufficient to support the proposed expiry period and storage condition. The post approval protocol in DMF 8084 is acceptable.

The current draft package insert contains information for all 3 Trelstar products and is acceptable with regard to CMC information. Except for a minor editorial revision, the draft labels are acceptable with regard to CMC information.

The applicant has requested a categorical exclusion under 21 CFR 25.31(a). The justification was accepted.

DRUG SUBSTANCE
Reference is made to [(b) (4)] type III DMF [(b) (4)] for CMC information regarding bulk drug substance. This file has been reviewed and found acceptable to support NDA approval.

The application provides a nomenclature and structure information, a summary of the general properties of the drug substance, the Debiopharm acceptance specification, and justification of the proposed criteria. The molecule is a linear sequence of 7 amino acids, manufactured as the pamoic acid salt. The salt is practically insoluble in water and soluble in DMF.

Drug substance acceptance is based on an acceptable [(b) (4)] certificate of analysis and acceptance testing at the drug product manufacturing site. The release specification is acceptable. Testing includes appearance, identity, assay for peptide and anion, purity (total, specified and unspecified impurities), water content, particle size and bioburden. Analytical methods are assay by HPLC, particle size by [(b) (4)] and bioburden by USP <61>. The analytical methods are described, example HPLCs are included, and acceptable validation studies are provided. The proposed criteria are justified based on batch analysis data on current lots and data in DMF [(b) (4)]. The same release specification is approved for the NDA 20-715 and NDA 21-288.

B. DESCRIPTION OF HOW THE DRUG PRODUCT IS INTENDED TO BE USED

The proposed lyophilized powder is intended to be reconstituted with 2.0 mL sterile WFI into a suspension for IM injection in the buttocks at the 24 week intervals.

C. BASIS FOR APPROVABILITY OR NOT APPROVAL RECOMMENDATION

The application is considered APPROVABLE pending final overall OC conclusion of "Acceptable" (revised conclusion is pending the results from a GMP inspection of one drug product manufacturing site) and a minor revision to the labels.

III. ADMINISTRATIVE

A. REVIEWER'S SIGNATURE

_____
William M. Adams, CMC Reviewer

B. ENDORSEMENT BLOCK

ONDQA/DPMA-III/CMC Reviewer/M.Adams
ONDQA/DPMA-III/PAL/T.Ocheltree
ONDQA/DPMA III/Branch Chief/S.Pope Miksinski
ONDQA/DPMA-III/PM/D.Mesmer
HFD-150/PM/K.Robertson

C. CC BLOCK

Rik Lostritto/ONDQA/Dir DPMA III

34 page(s) have been Withheld in Full immediately following this page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22437	ORIG-1	WATSON LABORATORIES INC	TRELSTAR (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/

WILLIAM M ADAMS
03/03/2010

Sarah Pope Miksinski
03/04/2010

Memorandum

To: NDA 22-437

From: Sarah C. Pope, Ph.D.

Date: 7/9/2009

Re: Final CMC recommendation for NDA 22-437

NDA 22-437 (triptorelin pamoate for injection suspension, 22.5 mg) was initially submitted on 12-SEP-2008 and was granted a standard review by the Agency. Chemistry Review #1 (dated 16-JUN-2009) identified eleven (11) Chemistry, Manufacturing and Controls (CMC) deficiencies which were subsequently communicated to the Applicant. These deficiencies have not been resolved to date. At the time of the Chemistry Review, a final recommendation from the Office of Compliance had not yet been issued, and the microbiology review was not completed.

This memo serves to update that determination. The microbiology review recommends approval of this NDA and was finalized on 19-JUN-2009. However, the Office of Compliance issued an overall withhold recommendation for this application on 07-JUL-2009.

Several CMC deficiencies were conveyed to the Applicant in a 16-JUN-2009 letter. While the majority of these items remain as outstanding CMC issues, two (5d and 9b) were partially covered as part of the subsequent microbiology review dated 19-JUN-2009. Therefore, these two deficiencies were discussed in an informal teleconference on 08-JUL-2009 (Dr. J. McVey, Dr. V. Pawar, Dr. S. Pope, and Dr. M. Adams participating). As a result of that discussion, a decision was made to slightly revise deficiency 5d to read "Verify that the procedures and parameters for the sterilization and depyrogenation of vials and stoppers in this application are the same as those validated and approved in NDA 20-715 and NDA 21-288." Additionally, the participants collectively decided to delete deficiency 9b, as it was already covered by the microbiology review. These revisions were made in the action letter language.

Three of the proposed manufacturing sites received withhold recommendations from the Office of Compliance. While only one of the sites (Debio) was actually inspected, all three sites (Debio, (b) (4) will be mentioned in the action letter as having received withhold recommendations.

NDA 22-437 has outstanding CMC deficiencies, as well as an overall withhold recommendation from the Office of Compliance. Accordingly, from a CMC perspective, approval of NDA 22-437 cannot be recommended until any related deficiencies are resolved.

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

/s/

Sarah Pope
7/9/2009 04:02:13 PM
CHEMIST

NDA 22-437

Trelstar® 22.5 mg (24 weeks)

Watson Laboratories, Inc.

William M. Adams
Office of New Drug Quality Assurance (ONDQA)

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-437

2. REVIEW #1

3. REVIEW DATE: 16 Jun 2009

4. REVIEWER: William Adams
5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
N-000 (original submission)	12 Sep 2008
Amendment N-001 (draft labels & labeling)	06 Oct 2008
Amendment N-002 (trade name)	23 Dec 2008
Amendment N-004 (contact info for mfg sites)	14 Jan 2009
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Amendment N-006 (partial CMC response to filing letter)	21 Jan 2009
Amendment N-007 (trade name)	30 Jan 2009
Amendment N-008 (completed CMC response to filing letter)	24 Mar 2009
Amendment N-009 (trade name)	04 Apr 2009
Amendment N-010 (type C meeting request)	07 Apr 2009
Amendment N-011 (revised labels, labeling , trade name)	04 May 2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Watson Laboratories, Inc.
Address:	577 Chipeta Way Salt lake City, UT 84108
Representative:	Wendy DeSpain, B.S., M.B.A, R.A.C. Associate Director, Proprietary Regulatory Affairs
Telephone:	(801) 588-6200
Fax:	(801) 588-6232

8. DRUG PRODUCT NAME/CODE/TYPE:
   (a) Proprietary Name: Trelstar 22.5 mg (24 weeks)
   (b) Non-Proprietary Name: Triptorelin Pamoate for Injection Suspension, 22.5 mg
   (c) Code Name/#: D-Trp^{6}-LHRH
   (d) Chemical Type/Submission Priority): 3S

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOLOGICAL CATEGORY: cancer treatment

11. DOSAGE FORM: Injectable suspension

12. STRENGTH/POTENCY: 22.5 mg peptide as pamoate salt

13. ROUTE OF ADMINISTRATION: Injection

14. Rx/OTC DISPENSED: Rx

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

_____SPOTS product – Form Completed

__XX__Not a SPOTS product

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

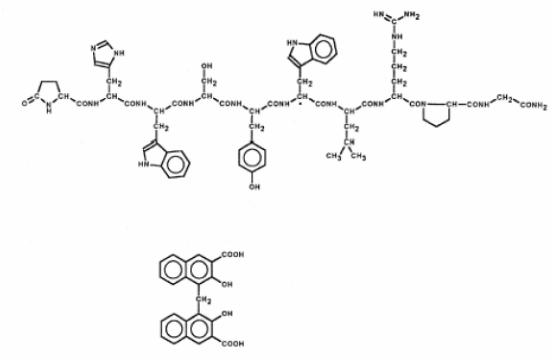
Chemical Name L-pyroglutamyl-L-histidyl-L-trytophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-L-prolylglycinamide pamoate salt

Chemical Name 5-oxo-Pyr-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH_2 pamoate salt

Molecular Formula $C_{64}H_{82}N_{18}O_{13}$ (triptorelin) + $C_{23}H_{16}O_6$ (pamoate)

Molecular Weight 1699.9 amu (salt), 1311.5 amu (free base), 388.4 amu (pamoate)

Molecular Structure



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Triptorelin Pamoate	1	Inadequate	05/19/09	
	IV	(b) (4)	(b) (4)	1	Inadequate	05/19/09	
	IV	(b) (4)	(b) (4)	1	Adequate	pending	
	III	(b) (4)	(b) (4)	4			

(b) (4)	IV	(b) (4)	(b) (4)	4			
	III	(b) (4)	(b) (4)	4			
8084	IV	Solvay	pre-filled syringe	1	Inadequate	05/19/09	

[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)

B. Other Documents:

APPLICATION	DESCRIPTION
NDA 20-715*	Trelstar® Depot (triptorelin pamoate for injectable suspension, 3.75 mg)
NDA 21-288*	Trelstar® LA (triptorelin pamoate for injectable suspension, 11.25 mg)
IND (b) (4)**	Trelstar® (b) (4) (triptorelin pamoate for injection suspension, 22.5 mg)

* Cross referenced to this application
** Reference is made to the MM for the EOP2 and pre-NDA meetings

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	pending	27 May 2009	
EES	pending	27 May 2009	
Pharm/Tox	pending	27 May 2009	
Biopharm	pending	27 May 2009	
LNC	pending	27 May 2009	
Methods Validation	pending	27 May 2009	
OPDRA	pending	27 May 2009	
EA	Acceptable	22 May 2009	M.Adams
Microbiology	pending	27 May 2009	

19. ORDER OF REVIEW: N/A

CMC Review for NDA 22-437

The Executive Summary

I. RECOMMENDATIONS

A. RECOMMENDATION & CONCLUSION ON APPROVABILITY

The application CANNOT BE APPROVED from the Chemistry, Manufacturing and Controls (CMC) perspective based on major deficiencies in the application. An acceptable and complete response to the following deficiencies is needed before approval can be recommended from a CMC perspective.

The deficiencies are summarized as follows (see exact wording to be conveyed at end of the review):

1. DMFs (b) (4) (drug substance), 8084 (WFI syringes) and (b) (4) (release polymer) are not adequate. Deficiency letters have been sent to the agent for each file.
2. Additional information is requested on the drug substance analytical methods.
3. Additional information is requested on the stopper extractables/leachables study.
4. Clarification is requested regarding the responsiblities for the proposed manufacturing and control sites.
5. Additional information is requested regarding the drug product manufacturing process.
6. Additional information is requested regarding the validation studies for the drug product analytical methods.
7. Revision and justification is requested for the proposed drug product specification for impurities.
8. Acceptance specifications for the drug product packaging components have been requested.
9. Revisions are requested for the proposed protocol for post approval stability studies.
10. The stability information supporting the proposed expiry period and label storage statement is not adequate.
11. Revisions are requested for the CMC sections of the proposed labels and labeling.

In addition, an overall recommendation has yet to be provided by the Office of Compliance on the proposed manufacturing and control sites, and the microbiology review is currently pending.

B. RECOMMENDATION ON PHASE 4 (Post-Marketing) COMMITMENTS, AGREEMENTS &/or RISK MANAGEMENT STEPS, if Approvable

None are proposed.

II. SUMMARY OF CHEMISTRY ASSESSMENTS

A. DESCRIPTION OF THE DRUG PRODUCT(S) & DRUG SUBSTANCE(S)

DRUG PRODUCT

Triptorelin, marketed as Trelstar®, is a luteinizing hormone releasing hormone agonist indicated for the palliative treatment of advanced prostate cancer. Trelstar® 22.5 mg (24 weeks) is a single dose, sterile, lyophilized powder for reconstitution suspension presented in a glass vial. For administration, 2 mL sterile WFI is added to prepare a suspension for intramuscular injection in the buttocks once every 24 weeks (168 days).

The drug product is the third in a series of triptorelin extended release injectable suspension products - Trelstar 3.75 mg (4 weeks) under NDA 20-715, Trelstar 11.25 mg (12 weeks) under NDA 21-288.

The commercial presentation is either as a single vial of drug product in a non-functional carton or as a kit. The kit is a (b) (4) tray with slots for a vial of drug product, a Mixject apparatus, a syringe of sterile water for injection (WFI syringe), and a convenience pack consisting of an alcohol wipe pad, a sterile gauze pad, a band aid and a label for the patients record.

Executive Summary Section

The Mixject apparatus is an FDA approved device [510(k) K963583] developed specifically for the reconstitution of lyophilized powders into injectable suspensions. It is manufactured by MediMop Medical Projects, Inc. (Ra'anana, Israel) and (b) (4) CMC information for the apparatus is accepted without review as this is an FDA approved device.

The WFI syringe is a pre-filled, pre-sterilized glass syringe containing 2.0 mL WFI manufactured by Solvay Biologicals BV (Olst, The Netherlands). CMC information supporting it is provided in type II DMF 8084. The file has been reviewed and found deficient. A letter detailing the deficiencies has been issued to the designated agent.

The convenience kit is provided by (b) (4) Secondary packaging is by (b) (4) (b) (4) Each item in the kit is marketed over-the-counter in the U.S, and therefore all are acceptable.

The drug product is manufactured by Debio Reserche Pharmaceutique S.A. (Martigny, Switzerland) (Debiopharm). (b) (4) Drug substance is provided by (b) (4) Other contract laboratories perform specific testing on excipients, the apparatus or drug product. Debiopharm has failed the GMP inspection requested for this application, action is pending. The function of some of the contract laboratories requires clarification.

Developmental studies are provided to justify polymer identity and properties, drug product formulation, the manufacturing process and controls and key intermediate parameters. An *in vitro* drug release profile correlation with *in vivo* drug absorption profile in rats and in humans is presented (IVIVR). (b) (4) . Based on the IVIVR, the accelerated dissolution method has been proposed as a surrogate for drug release to support future changes in the application. Based on internal discussion, the Biopharmaceutics Reviewer has concluded that the IVIVR is not sufficiently developed to support its use as a drug release surrogate; however, as of the date of this review, the final Biopharmaceutics Review is still pending. This deficiency will be deferred until the final biopharmaceutics review is available.

(b) (4)

(b) (4)

Specifications for acceptance of bulk DS and each release polymer at the drug product manufacturing site are based on the supplier's release specification. Testing addresses identity, assay, purity and key physico-chemical attributes for each material. The other excipients meet USP/NF requirements. No material is novel, or of human or animal origin. CMC information for the polymers is provided under DMF (b) (4)) and DMF (b) (4) ((b) (4) Both files have been reviewed. DMF (b) (4) was found acceptable and DMF (b) (4) was found deficient. A letter detailing the deficiencies has been issued to the designated agent for DMF (b) (4) .

Executive Summary Section

The drug product release specification includes testing for appearance, identity of peptide and anion, total peptide content, content uniformity, purity (total, specified and unspecified related substances), and water content on the lyophilized powder; and pH, particle size, reconstitution time, dissolution, sterility and bacterial endotoxins on the reconstituted suspension. Identity is by HPLC and TLC; assays are by HPLC; particle size is by (b) (4); and the other tests use USP methods. Dissolution uses the Trelstar 11.25 mg method (5% aqueous methanol at 37°C with apparatus II at 75 rpm), then increases medium temperature to 61°C at 48 hours without changing medium. The proposed samples times are 1H, 24H, 72H and 168H with USP level 2 and 3 testing. Analytical methods for intermediate testing and drug product release are described in detail and example HPLCs are included. Each method is validated per USP <1225>. The proposed criteria are justified with batch analysis data, stability study data and product development information. With the exception of total peptide content, particle size and release profile, the proposed criteria are those approved for Trelstar 11.25 mg (12 weeks) and Trelstar 3.75 mg (4 weeks). Impurities and degradants are stated to be those present in other Trelstar products. Additional information has been requested for the method descriptions and validation studies. Additional justification has been requested for the proposed criteria. The biopharmacuetics reviewer has requested changes to the proposed sampling times.

The reference standard is that approved for the other Trelstar products.

The primary package and components are those approved for the other Trelstar products, however additional information regarding component specifications and the component qualification studies has been requested.

The proposed expiry period for drug product is 36 months with storage at USP controlled room temperature. Stability information is primary studies on clinical lots and process robustness lots; supporting studies on (b) (4) (b) (4) validation lots and process validation lots; a reconstituted suspension study; and a USP Q1B photostability study. For the primary studies, vials stored at ICH LT for 12-36 months, at ICH INT for 6-12 months and at ICH ACC for 6 months with testing for the release specification. For the supporting studies, vials are stored at ICH LT for 0-6 months and ICH ACC for 0-4 months with testing for the release specification. Although no trends are observed in the primary studies there is not sufficient data from the combined primary and supporting studies to support the proposed expiry period or storage condition. The applicant has been requested to provide additional data from both the primary and supporting studies. The reconstituted suspension study shows significant potency loss in suspension stored ICH LT/24 hours, however the applicant concludes that the suspension should be administered immediately upon reconstitution for microbiological safety since the formulation contains no antimicrobial agents. The Microbiology Reviewer concurs with the need to administer the drug immediately after reconstitution. The photostability study shows that the glass vial provides sufficient light protection for the lyophilized powder.

The post approval stability protocol proposes to complete the primary studies, some of the supportive studies, and to place 1 annual drug product lot on stability with reduced testing and sampling intervals. The applicant has been requested to complete all of the primary and supportive studies since they address potential process variabilities, and to revise the sampling and testing intervals.

The expiry period for WFI syringes is 36 months with storage at USP controlled room temperature. Submitted are completed studies on syringes stored at ICH LT for 36 months and on-going studies on syringes stored at ICH LT/3-24M. The data shows all test parameters unchanging except for pH which increases steadily, but remains within specification. The data submitted in this application and in DMF 8084 are sufficient to support the proposed expiry period and storage condition. The post approval protocol in DMF 8084 is acceptable.

Recently submitted label and labeling contents are under discussion with the applicant. The CMC issues include the presentation of the drug product trade name, and justification for certain statements.

The applicant has requested a categorical exclusion under 21 CFR 25.31(a). The justification was accepted.

DRUG SUBSTANCE

Reference is made to [redacted] (b) (4) type III DMF [redacted] (b) (4) for CMC information regarding bulk drug substance. This file has been reviewed and found deficient. A letter detailing the deficiencies has been sent to the holder's designated agent.

The application provides a nomenclature and structure information, a summary of the general properties of the drug substance, the Debiopharm acceptance specification, and justification of the proposed criteria.

The molecule is a linear sequence of 7 amino acids, manufactured as the pamoic acid salt. The salt is practically insoluble in water and soluble in DMF.

Drug substance acceptance is based on an acceptable [redacted] (b) (4) and acceptance release by Debiopharm. Release testing addresses appearance, identity, assay for peptide and anion, purity (total, specified and unspecified impurities), water content, particle size and bioburden. Assays are by HPLC, particle size by [redacted] (b) (4) and bioburden by USP <61>. The analytical methods are described and example HPLCs are included; additional information has been requested. Validation studies performed per USP <1225> are provided; additional information has been requested. The proposed criteria are justified based on batch analysis data on current lots and data in DMF [redacted] (b) (4). The same specification is approved for the NDA 20-715 and NDA 21-288.

B. DESCRIPTION OF HOW THE DRUG PRODUCT IS INTENDED TO BE USED

The proposed lyophilized powder is intended to be reconstituted with 2.0 mL sterile WFI into a suspension for IM injection in the buttocks at the 24 week intervals.

C. BASIS FOR APPROVABILITY OR NOT APPROVAL RECOMMENDATION

The application is considered NOT APPROVABLE in that the supporting drug master files are deficient; the manufacturing and control sites are incorrectly listed; the manufacturing process description and drug product release specification are deficient; and inadequate stability information has been provided. See the list of deficiencies in Section IA above.

III. ADMINISTRATIVE

A. REVIEWER'S SIGNATURE

_____

William M. Adams, CMC Reviewer

B. ENDORSEMENT BLOCK

ONDQA/DPMA-III/CMC Reviewer/M.Adams
ONDQA/DPMA-III/PAL/T.Ocheltree
ONDQA/DPMA III/Branch Chief/S.Pope
ONDQA/DPMA-III/PM/D.Mesmer
HFD-150/PM/K.Robertson

C. CC BLOCK

Rik Lostritto/ONDQA/Dir DPMA III

97 page(s) have been Withheld in Full immediately following this page as B4 (CCI/TS)

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

/s/

Mike Adams
6/16/2009 03:48:15 PM
CHEMIST

Sarah Pope
6/16/2009 04:55:54 PM
CHEMIST

Initial Quality Assessment
Branch V
Pre-Marketing Assessment and Manufacturing Science Division III
Office of New Drug Quality Assessment

OND Division:	Division of Drug Oncology Products
NDA:	22-437
Applicant:	Watson Laboratories, Inc.
Stamp date:	12 SEP 2008
PDUFA Date:	12 JUL 2009
Proposed Trade Name:	Trelstar (b) (4)
Established Name:	Triptorelin pamoate
Laboratory Code:	Not applicable
Dosage Form:	Injection, Powder, For suspension, Extended Release (22.5 mg)
Route of Administration:	Injectable
Indication:	Treatment of advanced prostate cancer

Pharmaceutical Assessment Lead: Terrance Ocheltree, R.Ph., Ph.D.

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

Summary, Critical Issues and Comments

A. Summaries

Background Summary

NDA 22-437 was submitted for TRELSTAR® (b) (4) (triptorelin pamoate for injectable suspension), a sustained release formulation designed to release 22.5 mg of triptorelin over a period of 168 days (6 months). Reference is made to an active Investigational New Drug application, IND 28,547 and two new drug applications, NDAs 20-715 and 21-288.

The drug substance has been previously submitted in NDAs 20-715 (Trelstar Depot) and 21-288 (Trelstar LA), which were approved 15 JUN 2000 and 29 JUN 2001, respectively.

The following Drug Master Files (DMF) are referenced:

DMF Holder	Component	DMF Type / Number
(b) (4)	triptorelin pamoate	Type II / (b) (4)
	(b) (4)	Type IV /
		Type IV /
		Type III /
		Type V /
		Type III /
Solvay Biological BV	sterile water for injection	Type III / 8084

Triptorelin (D-Trp6-LHRH) is a synthetic decapeptide agonist analog of naturally occurring luteinizing hormone releasing hormone (LHRH) which acts as a inhibitor of gonadotropin secretion. This decapeptide is similar in structure to three approved GnRH agonists, leuprolide acetate (Lupron), goserelin acetate (Zoladex), and nafarelin acetate (Synarel). The major structural difference in the amino acid sequences is at position 6. The naturally occurring LHRH contains an L-glycine amino acid at position 6, whereas in triptorelin this position has been substituted with D-tryptophan. The substitution of a D-amino acid at position 6 provides enhanced resistance to cleavage by proteolytic enzymes relative to the native decapeptide.

Drug Substance Summary

Triptorelin pamoate is manufactured by (b) (4) who is also responsible for in-process control, drug substance testing, and stability testing. Final release of the drug substance for use in the manufacture of the drug product is preformed by the drug product manufacture Debiopharm, Martigny, Switzerland.

Reference is made to DMF (b) (4) for the pertinent information related to the manufacturing, control, analysis, and characterization of the drug substance. Reference also made to NDAs 20-715 and 21-288.

The chemical structure of triptorelin pamoate is below.

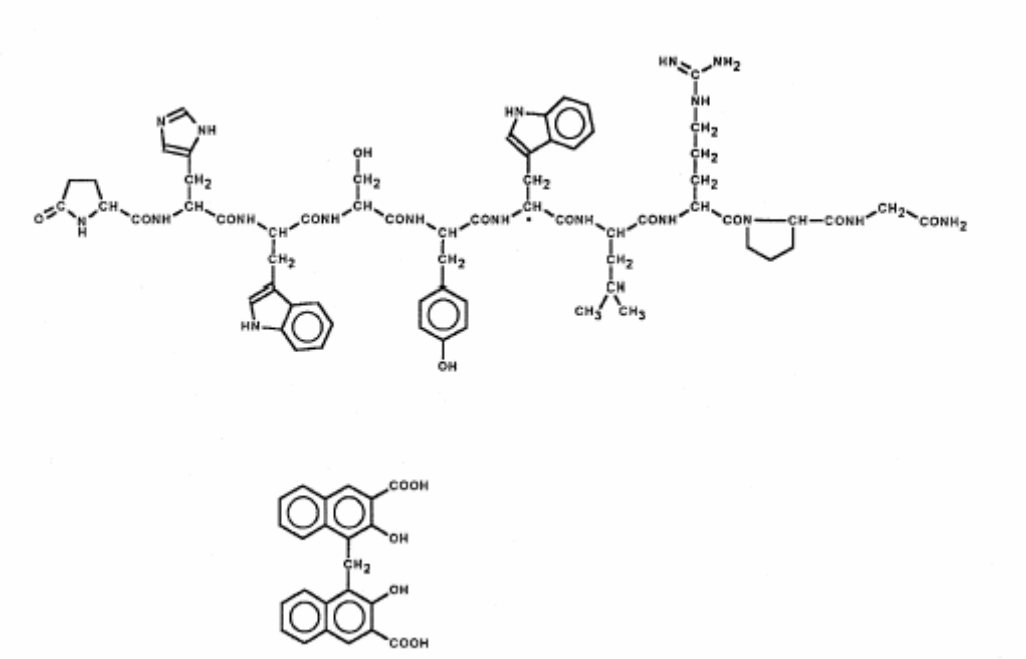


Figure 1. Triptorelin pamoate (MW= 1699.9 (triptorelin pamoate) = 1311.5 (triptorelin) + 388.4 (pamoate))

Drug Product Summary

The drug product is a long acting suspension containing triptorelin pamoate, intended to be administered intramuscularly every 168 days (6 months) as a palliative treatment of advanced prostate cancer. Formulation development was based on the knowledge and experience acquired with the FDA approved Trelstar Depot 3.75 mg (1-month sustained release) and Trelstar LA 11.25 mg (3-month sustained release) formulations and was conducted in accordance with Quality by Design principles.

Because triptorelin has a short *in-vivo* half-life, it is formulated as a sustained-release dosage form. The pamoate salt of triptorelin is [redacted] (b) (4) to form microgranules that are designed to release triptorelin over 168 days.

The Sponsor proposes a 36-month expiration dating period for the drug product.

B. Preliminary Review, Comments and Recommendations

Drug Substance Section

The Chemistry, Manufacturing and Controls information for triptorelin pamoate is referenced to DMF [redacted] (b) (4) Reference also made to NDAs 20-715 and 21-288.

Because the drug substance information is referenced to a DMF, no deficiencies are identified in this NDA for drug substance at this time. DMF [redacted] (b) (4) was last reviewed in 2000. Quality Information and Reactivation amendments were submitted in June 2008. The adequacy of these amendments and the drug substance specifications should be assessed using current Office of New Drug Quality Assessment (ONDQA) practices. It is noted that a test for residual

solvents is not included in the current specifications, but tests results are provided on the supplier certificates for analysis.

Final acceptance of the drug substance is stated to be performed by the drug product manufacture, Debiopharm, using the same specifications and methods as those described in DMF (b) (4) The Debiopharm specifications is the same as that in place for the approved Trelstar Depot 3.75mg and Trelstar LA 11.25mg drug products.

The initial CMC review for NDA 22-437 resulted in the identification of the following deficiency:

1. Provide the recommended storage conditions and retest period for the drug substance.

Drug Product Section

Triptorelin pamoate 22.5 mg injection is a sterile, lyophilized, biodegradable microgranule formulation supplied as a single-dose vial. All excipients, carboxymethylcellulose sodium, mannitol, polysorbate 80, and poly-*d*,llactide co-glycolide (PLG) (b) (4), are identical to those used for the manufacture of the FDA approved Trelstar LA 11.25 mg, except for a (b) (4) (b) (4) During a CMC pre-NDA meeting, FDA reviewers agreed that the PLG (b) (4) polymer is not a novel excipient.

Triptorelin pamoate 22.5 mg injection is packaged in a primary container closure system in one of two secondary packaging configurations. The primary container/closure is a (b) (4) Type 1 glass vial with (b) (4) closure fitted with a (b) (4) grey (b) (4) stopper and sealed with an aluminum overseal with plastic Flip-off Button. The secondary packaging configuration is either:

1. A single drug product vial packaged in a non-functional carton.
2. A single drug product vial packaged with the MIXJECT reconstitution system in a non-functional carton which includes the following:
   · The MIXJECT reconstitution system with a vial adaptor fitted with a 21-gauge stainless steel needle. The needle is sheathed by a clear plastic needle shield pre-injection and includes a plastic safety cover to sheath the needle post-injection. The vial adaptor is protected by its own (b) (4) blister pack.
   · A glass syringe containing 2 ml Sterile Water for Injection (WFI), USP, pH 6 – 8.5.
   · A plastic plunger rod for use with the glass syringe
   · A vial of triptorelin pamoate 22.5 mg drug product
   · A tray (b) (4) Two slots are molded into the tray: one slot for the MIXJECT, glass syringe, and plunger rod, which is covered and sealed with (b) (4), and one slot for a vial of drug product, which is inserted into the slot as part of the secondary packaging process.
   · A convenience kit containing:
      a. One adhesive bandage to adhere to the patient following injection of the drug
      b. One adhesive label to place on the patient's chart to document the date of injection, lot number, expiration date, administered by, and formulation used

c. One gauze pad for the purpose of applying pressure to the injection site following the injection
d. One alcohol preparation pad for the purpose of cleaning the injection site.

A [redacted] process is used to manufacture [redacted] of microgranules which constitute the drug product. The process is virtually the same as for the approved Trelstar LA 11.25 mg formulation, except for changes in the type and amounts of polymer and peptide used for preparation of the [redacted] of microgranules.

The [redacted] step used for [redacted] sterilization warrants a consult to the Office of Microbiology. The microbiology reviewer should also review the drug substance and final drug product specifications for adequacy to control/detect any microbial contamination.

The applicant provided stability data for up to 36 months at 25°C/60% RH, up to 12 months at the intermediate condition of 30°C/65% RH, and up to 6 months at the accelerated condition of 40°C/75% RH. All stability data are within proposed commercial shelf-life specifications.

The applicant has proposed a 36-month expiration dating period, when the drug product is stored at 25°C, with excursions permitted to 15 °C - 30 °C.

The initial CMC review for NDA 22-437 resulted in eight deficiencies identified by the reviewer (Mike Adams), and as stated below:

1. All impurities at or above the analytical method's limit of quantitation for each drug product lot are not listed in table 3.2.P.5.4-1.
2. Chromatograms from the specificity and robustness evaluations are requested for validation report 02-002549/01 (triptorelin assay in drug product).
3. Chromatograms from the specificity, limit of detection, limit of quantitation, and robustness evaluations are requested for validation report 02-002550/01 (related substances in drug product).
4. Chromatograms from the specificity and robustness evaluations are requested for validation report 02-002552/02 (dissolution), provide copies.
5. Chromatograms from the robustness evaluation are requested for validation report 02-002970/01 (pamoic acid assay in drug substance).
6. Chromatograms from the specificity, limit of detection and limit of quantitation evaluations, and data to establish method robustness are requested for validation report 02-002985/01 (related substances in drug substance).
7. The columns used in HPLC methods 02-002264, 02-002651, 02-002878, 02-002828, 02-002232, 02-002236 and 02-002889 should be identified.
8. A method validation study for method 02-002889 should be provided along with copies of chromatograms from the specificity and ruggedness evaluations.

C. Critical issues for review and recommendation

Drug Substance

a. DMF (b) (4) was last reviewed in 2000. Quality Information and Reactivation amendments were submitted in June 2008. The adequacy of these amendments and the drug substance specifications should be assessed using current Office of New Drug Quality Assessment (ONDQA) practices. It is noted that a test for residual solvents is not included in the current specifications. The primary reviewer should re-assess the adequacy of the currently proposed acceptance criteria. Conformance with the Agency's previous recommendations does not necessarily ensure adequacy, and the proposed criteria should also be confirmed relative to the provided drug substance batch data.

b. Based on Batch Analysis data it appears that a microbial limit test was added to the drug substance specifications. The relevance of the limits and acceptability should be evaluated during the review of DMF (b) (4)

c. The proposed storage conditions and retest period for the drug substance are not provided in the NDA. These should be included and the reviewer should confirm that they are supported by the information in DMF (b) (4)

Drug Product

1. The proposed manufacturing process is (b) (4) process for a (b) (4) (b) (4) injectable formulations. The excipients are either compendial or controlled by in house testing. The adequacy of the non-compendial testing should be determined.

2. The Pharmaceutical Development Report outlines the development of the proposed formulation including the application of quality by design (QbD) principles. During the initial review limited data was found to support this claim. However, the reviewer should be cognizant of the claim. If substantial information is found during the review, the reviewer is advised to request a QbD Consult.

3. The applicant claims an (b) (4) relationships similar to (b) (4) (b) (4) The reviewer should consider submitting a consult request to the ONDQA Biopharmaceutic group.

4. Due to the injectable nature of the formulation, all drug product manufacturing and controls information should also be consulted to the Office of Microbiology for review.

5. Letters of Authorization (LoA) have been provided for the drug substance and each of the primary packaging components (see table of LoAs above).

D. Comments for 74-day Letter:

CMC Comments for Filing Meeting

1. Provide a statement confirming that all facilities are ready for GMP inspection

2. Provide the recommended storage conditions and retest period for the drug substance.

3. Provide the profile of all impurities at or above the analytical method's limit of quantitation for each drug product lot listed in table 3.2.P.5.4-1.

4. For validation report 02-002549/01 (triptorelin assay in drug product), provide copies of chromatograms from the specificity and robustness evaluations.

5. For validation report 02-002550/01 (related substances in drug product), provide copies of chromatograms from the specificity, limit of detection, limit of quantitation, and robustness evaluations.

6. For validation report 02-002552/02 (dissolution), provide copies of chromatograms from the specificity and robustness evaluations.

7. For validation report 02-002970/01 (pamoic acid assay in drug substance), provide copies of chromatograms from the robustness evaluation.

8. For validation report 02-002985/01 (related substances in drug substance), provide copies of chromatograms from the specificity, limit of detection and limit of quantitation evaluations, and provide data to establish method robustness.

9. Identify the columns used in HPLC methods 02-002264, 02-002651, 02-002878, 02-002828, 02-002232, 02-002236 and 02-002889.

10. Provide a method validation study for method 02-002889 and include copies of chromatograms from the specificity and ruggedness evaluations.

E. Recommendation for fileability: **Fileable**

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?	√		Requested 11/12/08.
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		Referenced to DMF (b) (4)
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		Data have been provided but without analysis.
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?	√		
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?	√		
16	Have all consults been identified and initiated? (bolded items to be handled by ONDQA PM)	√ √ √	 √ √ √ √ √ 	Microbiology Pharm/Tox Biopharm Statistics (stability) CDRH LNC DMETS/ODS EER

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

DMF Holder	Component	DMF Type / Number
(b) (4)	triptorelin pamoate	Type II / (b) (4)
	(b) (4)	Type IV /
		Type IV /
		Type III /
		Type V /
		Type III /
Solvay Biological BV	sterile water for injection	Type III / 8084

Recommendation for Team Review:

This NDA does not include a significant amount of drug substance information, as most Chemistry, Manufacturing and Controls information is cross-referenced to DMF (b) (4). The drug product is a fairly complicated injectable formulation. However, it is similar, with one difference in excipients, to the FDA approved drug product Trelstar LA.

A team review approach is not recommended for this NDA even though the applicant states that quality-by-design principles are used. This is a not conventional dosage form, but due to the applicant's history with a similar product, only typical review issues are anticipated during the CMC review.

12-NOV-2008

Terrance Ocheltree, R.Ph., Ph.D.
Pharmaceutical Assessment Lead

Date

12-NOV-2008

Sarah C. Pope, Ph.D.
Branch Chief

Date

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

/s/

Terrance Ocheltree
11/12/2008 02:47:29 PM
CHEMIST

Sarah Pope
11/13/2008 11:25:08 AM
CHEMIST