CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-028

CHEMISTRY REVIEW(S)

NDA 22-028

Cosyntropin Injection

Sandoz Canada Inc.

Martin Haber, Ph.D.
Division of Pre-Marketing Assessment-I

Reviewed for
Division of Metabolic and Endocrine Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-028
2. REVIEW #2
3. REVIEW DATE: January 24, 2008
4. REVIEWER: Martin Haber, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	2/3/06
Amendment	9/7/06
Chemistry Review #1	11/15/07
FDA Approvable Letter	12/6/06

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	8/20/07
Amendment	9/17/07
Amendment	10/15/07
Amendment	12/21/07

7. NAME & ADDRESS OF APPLICANT:

Name:	Sandoz Canada Inc.
Address:	145 Jules Leger Street, Boucherville, (QC) Canada J4B 7K8
Representative:	Beth Brannan, Sandoz Inc., Broomfield, CO 80038
Telephone:	303-438-4237

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None Proposed
b) Non-Proprietary Name (USAN): Cosyntropin (Tetracosactide, INN)
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: Type 3, new formulation of previously approved drug
- Submission Priority: S

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

Reference Listed Drug: Cortrosyn™ (cosyntropin for injection), 0.25 mg, NDA 16-750, Amphastar Pharmaceuticals (originally Organon), approved 1970

10. PHARMACOL. CATEGORY: Diagnostic Agent

11. DOSAGE FORM: Sterile solution for injection

12. STRENGTH/POTENCY: 0.25 mg/mL

13. ROUTE OF ADMINISTRATION: IV Injection

14. Rx/OTC DISPENSED: _x__Rx ___OTC

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

__x___Not a SPOTS product

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

First 24 amino acid residues of the natural 39-residue adrenocorticotropic hormone (ACTH), which is also called corticotropin

Ser - Tyr - Ser - Met - Glu - His - Phe - Arg - Trp - Gly - Lys
1 2 3 4 5 6 7 8 9 10 11
Pro - Val - Gly - Lys - Lys - Arg - Arg - Pro - Val - Lys - Val
12 13 14 15 16 17 18 19 20 21 22
Tyr - Pro
23 24

Chemistry Review Data Sheet

Primary sequence in one letter code:

S-Y-S-M-E-H-F-R-W-G-K-P-V-G-K-K-R-R-P-V-K-V-Y-P

Other chemical name:

Alpha (sup 1- 24) - Corticotropin

Compendial name(s)

Cosyntropin (USAN)

Molecular formula

$C_{136}H_{210}N_{40}O_{31}S$

CAS-registry number

16960-16-0

Relative molecular mass

2933 a.m.u.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II		Drug substance, cosyntropin or tetracosactide acetate	1	Adequate	11/14/06	Review #2 by this reviewer
	III			4	Adequate		
	III			4	Adequate		
	III			3	Adequate		

b(4

Chemistry Review Data Sheet

	III			3	Adequate		b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	69,720	Supporting IND

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Required		
EES	Acceptable	10/23/07	
Pharm/Tox	Acceptable	1/16/08	Indra Antonipillai, Ph.D.
Clinical Pharmacology	NA		
Methods Validation	Not Required		
ODS	NA		
Environmental Assessment	Adequate, Exclusion requested		
Microbiology	Acceptable	1/17/08	Robert Mello, Ph.D.

The Chemistry Review for NDA 22-028

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend **Approval**

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 Product(s) and Drug Substance(s)

The drug product is a sterile aqueous solution containing 0.25 mg of the active peptide, cosyntropin, with excipients. The excipients are 10 mg mannitol, 6.4 mg sodium chloride, 1 mg acetic acid, and 0.82 mg trihydrated sodium acetate in ~ mL of water for injection. The pH of the solution is low, only ~, because the ——— Manufacturing by Sandoz Canada Inc. in Quebec, Canada begins with ——— b(4)

——— Microbiology sterility assurance was initially inadequate but after amendment review is now acceptable.

The drug product specifications include description, assay and impurities by HPLC, pH, bacterial endotoxins, particulate matter, and sterility. Drug product vials are stored under refrigeration at — C. The proposed expiration dating is 2 years and this is adequately supported by 24 months of long-term stability data. No proprietary tradename has yet been proposed.

The drug substance, Cosyntropin, is a synthetic peptide (molecular weight 2933) prepared by ——— synthesis. The sequence corresponds to the first 24 amino acid residues of the natural 39-residue adrenocorticotropic hormone (ACTH, corticotropin). The API is manufactured by ——— The referenced Drug Master File #' — for Tetracosactide (the INN name for Cosyntropin) has been reviewed twice by this reviewer and after amendment is adequate.

Drug substance specifications include description (white or yellow powder); identification, assay ( ) and impurites (%, reduced %, unspecified unidentified % each, total %) by HPLC; absorbance, amino acid composition, and optical rotation (-99° to -109°); peptide content (%), acetic acid (8-13%), %), and water (< %) content of the , and EU/μg). A bioassay has been added, the biological potency must **be 80 – 120% of the stated potency,** IU/mg, as determined by cell response using the European Pharmacopea bioassay test. The impurities determination method has been improved to increase the sensitivity and the limits for specified and unspecified impurities tightened, as requested by the Agency. The drug substance is stored under refrigeration at C in . b(4)

The inspection status of the manufacturing and testing facilities was found acceptable on 10/23/07.

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

The drug product is a diagnostic agent used in the screening of patients presumed to have adrenocortical insufficiency. Because of its rapid effect on the adrenal cortex, a 30 minute test of adrenal function (measuring the plasma cortisol increase in response to ACTH) is possible. Typically, to carry out the test, one (1) mL of the sterile solution containing 0.25 mg of Cortrosyn is injected intravenously. The solution in the drug product vial is ready for injection, no reconstitution is required. There is a of the vial to insure that an adequate amount of solution can be withdrawn and injected. To measure the response, blood samples are taken before and 30 minutes after injection. Drug product vials are intended for single use only and do not contain preservatives. The amber glass drug product vials are stored under refrigeration at C. b(4)

C. Basis for Approvability or Not-Approval Recommendation

The reviewed chemistry amendments provide adequate chemistry manufacturing and control information regarding bioassay and impurity testing. Therefore, the **applicant's proposed specifications are now** adequate to ensure the potency and purity of the product. There are no remaining chemistry deficiencies.

III. Administrative

A. Reviewer's Signature
See DFS

B. Endorsement Block
See DFS

C. CC Block
See DFS

16 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

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

/s/

Martin Haber
1/24/2008 03:56:54 PM
CHEMIST

recommends approval

Ali Al-Hakim
1/25/2008 09:55:45 AM
CHEMIST

NDA 22-028

Cosyntropin Injection

Sandoz Canada Inc.

Martin Haber, Ph.D.
Division of Pre-Marketing Assessment-I

Reviewed for
Division of Metabolic and Endocrine Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-028

2. REVIEW #1

3. REVIEW DATE: November 14, 2006

4. REVIEWER: Martin Haber, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NA	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	2/3/06
Amendment	9/7/06

7. NAME & ADDRESS OF APPLICANT:

Name:	Sandoz Canada Inc.
Address:	145 Jules Leger Street, Boucherville, (QC) Canada J4B 7K8
Representative:	Beth Brannan, Sandoz Inc., Broomfield, CO 80038
Telephone:	303-438-4237

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None Proposed

Chemistry Review Data Sheet

b) Non-Proprietary Name (USAN): Cosyntropin (Tetracosactide, INN)
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: Type 3, new formulation of previously approved drug
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)
Reference Listed Drug: Cortrosyn (cosyntropin for injection), 0.25 mg, NDA 16-750, Amphastar Pharmaceuticals, approved 1970

10. PHARMACOL. CATEGORY: Diagnostic Agent

11. DOSAGE FORM: Sterile solution for injection

12. STRENGTH/POTENCY: 0.25 mg/mL

13. ROUTE OF ADMINISTRATION: IV Injection

14. Rx/OTC DISPENSED: _x__Rx ___OTC

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

__x___Not a SPOTS product

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

First 24 amino acid residues of the natural 39-residue adrenocorticotropic hormone (ACTH), which is also called corticotropin

Ser - Tyr - Ser - Met - Glu - His - Phe - Arg - Trp - Gly - Lys
1 2 3 4 5 6 7 8 9 10 11
Pro - Val - Gly - Lys - Lys - Arg - Arg - Pro - Val - Lys - Val
12 13 14 15 16 17 18 19 20 21 22
Tyr - Pro
23 24

Chemistry Review Data Sheet

Primary sequence in one letter code:

S-Y-S-M-E-H-F-R-W-G-K-P-V-G-K-K-R-R-P-V-K-V-Y-P

Other chemical name:

Alpha (sup 1- 24) - Corticotropin

Compendial name(s)

Cosyntropin (USAN)

Molecular formula

$C_{136}H_{210}N_{40}O_{31}S$

CAS-registry number

16960-16-0

Relative molecular mass

2933 a.m.u.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	II		Drug substance, cosyntropin or tetracosactide acetate	1	Adequate	11/14/06	Review #2 by this reviewer
—	III			4	Adequate		
—	III			4	Adequate		

b(4)

	III	[redacted]		3	Adequate		
	III	[redacted]		3	Adequate		

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	69,720	Supporting IND

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Pending		
Pharm/Tox	Pending		
Biopharm	NA		

Chemistry Review Data Sheet

LNC	NA		
Methods Validation	Pending-May be requested		
ODS	NA		
EA	Adequate, Exclusion requested		
Microbiology	Pending		

The Chemistry Review for NDA 22-028

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend Approvable Action, with deficiency comments to be communicated to the applicant

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 Product(s) and Drug Substance(s)

The drug product is a sterile aqueous solution containing 0.25 mg of the active peptide, cosyntropin, with 10 mg mannitol, 6.4 mg sodium chloride, 1 mg acetic acid, and 0.82 mg trihydrated sodium acetate in 1 mL of water for injection. The applicant has not proposed a tradename. The pH of the solution is low, only — Manufacturing by Sandoz Canada Inc. in Quebec involves preparation — b(4)

Microbiology sterility assurance review is pending. There is a — of the vial to insure that an adequate amount of solution can be withdrawn and injected.

The drug product specifications include description, assay and impurities by HPLC, pH, bacterial endotoxins, particulate matter, and sterility. The drug product vials are stored under refrigeration at – C. The proposed expiration dating is 2 years and — months of long-term stability data has been submitted.

b(4)

Cosyntropin is a synthetic peptide (molecular weight 2933) prepared by — synthesis. The sequence corresponds to the first 24 amino acid residues of the natural 39-residue adrenocorticotropic hormone (ACTH, corticotropin). The API is manufactured by — Drug Master File — (INN name for Cosyntropin) has been reviewed and after amendment is adequate. Drug substance specifications include description (white or yellow powder); identification, assay (— %) and impurites

(< ———%, unspecified unidentified —% each, total —%) by HPLC; absorbance, amino acid composition, and optical rotation (-99° to -109°); peptide — %), acetic acid (8-13%), ———— %), and water (—%) content of the ———— EU/µg). There is no bioassay. The drug substance is stored under refrigeration at —C in ——— b(4)

Major NDA deficiencies are: The applicant has not provided a bioassay or any proof of the potency of their peptide other than the bioequivalence trial. In addition, the assay and characterization of impurities/degradants is inadequate for both drug substance and product. Due to the lack of meaningful impurity data, the quality of the product is unclear and no expiry period can be determined. Facilities inspection is still pending.

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

The drug product is a diagnostic agent used in the screening of patients presumed to have adrenocortical insufficiency. Because of its rapid effect on the adrenal cortex, a 30 minute test of adrenal function (measuring plasma cortisol response to ACTH) is possible. Typically, to carry out the test, one (1) mL of sterile solution containing 0.25 mg of Cortrosyn is injected intravenously. Vials are intended for single use only and do not contain preservatives. The ———— drug product vials are stored under refrigeration at - C. b(4)

C. Basis for Approvability or Not-Approval Recommendation

Adequate information regarding bioassay and impurity testing was not provided in the application. Principal deficiencies are the lack of any bioassay testing on either the drug substance or drug product and inadequate characterization of the impurity profile of the drug substance and product. Therefore, the applicant's proposed specifications are inadequate to ensure the potency and purity of the product.

III. Administrative

A. Reviewer's Signature

See DFS

B. Endorsement Block

See DFS

C. CC Block

See DFS

29 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 2

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

/s/

Martin Haber
11/15/2006 10:47:47 AM
CHEMIST

Blair Fraser
11/15/2006 10:56:46 AM
CHEMIST

Initial Quality Assessment

OND Division of Metabolism and Endocrinology Products
NDA: 22-028
Applicant: Sandoz Canada Inc.
Stamp Date: 06-FEB-2006
PDUFA Date: 06-DEC-2006
Proposed Proprietary Name: [none proposed]
Established Name: cosyntropin injection
Dosage form and strength: 0.25 mg/mL sterile solution
Route of Administration: intravenous injection [redacted]
Indications: For use as diagnostic agent in the screening of patients presumed to have adrenocortical insufficiency.

b(4)

PAL: Su (Suong) Tran, Branch II/DPA I/ONDQA

Fileability recommendation: Acceptable for filing
Review team recommendation: Single primary reviewer (Chemist Martin Haber)

Time goals:

- **Initial Quality Assessment in DFS: by 15-MAR-2006** (NDA accessible on 22-FEB-2006)
- **Chemistry filing memo in DFS: by 23-MAR-2006**
- Filing decision "Day 45": 23-MAR-2006 (tentative; to be set by Clinical Division)
- Filing review issues sent to applicant "Day 74": 21-APR-2006 (tentative; to be set by Clinical Division)
- **Chemistry Review (DR/IR) letter: by 06-JUL-2006**
- Mid-cycle meeting "Month 5": 06-JUL-2006 (tentative; to be set by DMEP)
- **Final Chemistry Review "Month 8" in DFS: by 06-OCT-2006**
- PDUFA: 06-DEC-2006

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm/ClinPharm	*Not Applicable*
CDRH	*Not Applicable*
EA	To be assessed by Primary Reviewer
EES	EER sent on 01-MAR-2006
DMETS	*Labeling consult request will be sent as part of DMEP's request.*
Methods Validation	*Validation may be requested of FDA labs after test methods are finalized.*
Microbiology	Consult request sent on 24-FEB-2006
Pharm/Tox	To be determined by Primary Reviewer

Summary:

- This is a paper NDA, delivered to PAL on 22-FEB-2006. There is a 39-page Quality Overall Summary.
- The associated IND is IND 69,720. The NDA is filed as a 505(b)(2) application. The efficacy of the product is supported by the one pharmacodynamic study (Study 50525) submitted in the NDA. This study was conducted with the drug product lot 1200503-F. Cosyntropin by a different manufacturer is approved in the U.S. as Cortrosyn (cosyntropin for injection).
- Reference is made to DMF — (holder: ————) for all chemistry information on the drug substance. The drug substance, cosyntropin (or INN: tetracosactide) acetate, is a synthetic single-chain peptide (by ——— synthesis). It represents the first 24 amino acid residues of the 39-residue natural adrenocorticotropic hormone (ACTH). The amino acid sequence is:

  Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-Pro

  There is no USP monograph for cosyntropin, but there is an EP monograph under the INN "tetracosactide". The drug substance specification in the NDA is based partly on the EP monograph (specific optical rotation, absorbance, amino acid analysis, and peptide content). The drug product manufacturer (Sandoz, same as applicant) is responsible for testing the drug substance per specification upon receipt of the material, using a reference standard from the drug substance manufacturer. The shelf life of the drug substance is the earlier of either 2 years from the date of assay by Sandoz or the expiry stated by the drug substance manufacturer. The storage container closure and conditions are the same at both sites: —% LDPE/ —% HDPE capped —— at —°C.

b(4)

b(4)

- The drug product is an injectable solution, 0.25 mg dosage strength. The drug product bulk is sterile filtered and [redacted] filled. There is no overage of the drug substance in the product formulation. The product is air-sensitive, and the filling/sealing of vials has [redacted]

Component	Function	Quantity per vial	%
Cosyntropin	Active ingredient	0.25 mg	0.025%
Trihydrated sodium acetate USP		0.82 mg	0.082%
Sodium chloride USP		6.4 mg	0.64%
Mannitol USP		10 mg	1.0%
Glacial acetic acid USP		1 mg	0.1%
Water for injection USP		q.s. to [redacted] mL	[redacted] %
[redacted]			

b(4)

- Container closure systems for product distribution: [redacted]

- The drug product is stored at 2-8 °C, protected from light and freezing. The following stability data are provided in the NDA: [redacted] month data at [redacted]

b(4)

Critical Issues:

- Has all information requested during the IND phases, and at the pre-NDA meetings been included?

Note: No chemistry information request was made during the IND phases or at the pre-NDA meeting.

- **Lack of a bioassay in either drug substance or drug product specification.**

Note: A bioassay is critical for this product because it is used as a diagnostic agent. The EP monograph for the drug substance includes a bioassay, which is not implemented by Sandoz (even though other tests in the same monograph are adopted as part of the drug substance specification). Sandoz uses a HPLC test method for both identity and assay testing. A bioassay must be included in either the drug substance or drug product specification. Alternatively, identity testing by peptide mapping must be added to the drug substance specification, and data must be submitted to demonstrate an acceptable direct correlation between the bioassay and the HPLC test method over a range of degradation of the peptide [item for the 74-day letter].

- **What is the drug substance?**

Note: The drug substance is cosyntropin acetate, with the USAN "cosyntropin" as established name. Currently the NDA has the chemical name, structure, molecular formula and mass for the free base moiety, and the drug substance specification is for "tetracosactide" (INN for the same substance as cosyntropin). The applicant should provide the chemical name, structure, molecular formula and mass for the drug substance "cosyntropin acetate" and revise the drug substance specification to state the correct name "cosyntropin acetate" [item for the 74-day letter].

- **Reference standard of the drug substance.**

Note: Sandoz uses the primary standard (lot TC0501) and working standard (lot TC0401) as supplied by the drug substance manufacturer. The potency of these reference standards should be periodically verified by a bioassay using an international reference preparation.

- **Lack of testing for residual solvents in the drug substance specification.**

Note: This issue may be covered by information in DMF [redacted] b(4)

- **Composition of the drug product.**

Note: The composition table of the drug product should include the quantity of the peptide salt per unit container [item for the 74-day letter]. In addition, this information should be stated on all the labeling (see comment below on labeling).

- **Issues concerning the drug product specification:**
  - **Lack of identity testing of the drug product.**

    Note: The drug product specification in section 3.2.P.5.1 does not include identity testing even though this test is performed on the drug product (results provided in Batch Analyses). b(4)

  - **Low pH of the drug product.**

    Note: The proposed acceptance criteria for the pH of the injectable solution is [redacted] The reviewer may consult with the Medical reviewer on the safety of this low pH.

  - **Impurities in the drug product.**

    Note: The reviewer may consult with the Pharm. Tox. reviewer on the safety of the proposed limits of [redacted] for [redacted] and [redacted] for an unidentified impurity. The applicant should revise the specification to clarify that the limit of [redacted] Total Impurities does not include tetracosactide sulfoxide content.

  - **Volume per container of the drug product.**

    Note: The applicant should revise the specification to include an upper limit in the criteria for Volume (currently having only a limit of [redacted] mL). USP allows an excess of 0.1 mL for a volume of 1.0 mL.

  - **Description of the drug product.**

    Note: The drug product specification in section 3.2.P.5.1 has the criteria "Conforms" for Description (test method is "Organoleptic".) The applicant should revise the specification to clearly state the criteria for Description.

- **Expiration dating period of the drug product.** b(4)

Note: Currently the NDA has [redacted] month stability data at [redacted]. The proposed expiry of 24-month under refrigeration is not acceptable given the limited stability data [item for the 74-day letter]. The reviewer will request additional data to be submitted no later than Month 8 of the review cycle for a final determination of the expiry of the product.

- **Drug product labeling.**

Note: Labeling (packaging labels and package insert) should include the statement "Each vial contains – mg/mL of cosyntropin acetate to deliver – mg/mL of cosyntropin."

b(4)

The following are general issues concerning the DMF — for the drug substance. Not much detail can be divulged in this IQA due to the confidentiality nature of DMFs and because this IQA is filed in DFS as part of the NDA review.

- **Established name of the drug substance.**
  Note: The DMF should be titled with the USAN "cosyntropin". Currently the DMF is titled "tetracosactide". Labeling for the drug substance should include the USAN "cosyntropin".
- **Characterization of the drug substance reference standard.**
  Note: The chiral integrity of the amino acid residues should be confirmed.
- **Reprocessing of the drug substance.**
- **Safety information on the product-contact surface of the container closure system used to store and ship the drug substance.**
  Note: References to the US food additives regulations would suffice.

Supporting NDA or IND:
IND 69,720

Supporting DMF:

DMF	TYPE	HOLDER	ITEM REFERENCED	COMMENTS
	III			
	III			
	III			
	III			

b(4)

1 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry-3

CHEMISTRY NDA FILEABILITY CHECKLIST

IS THE CMC SECTION OF APPLICATION FILEABLE? Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		All facilities are listed.
6	Has an environmental assessment report or categorical exclusion been provided?	X		Provide in Module 1 of NDA.
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Have stability data and analysis been provided to support the requested expiration date?	X		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		No information was requested.
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?	X		

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

/s/

Suong Tran
3/8/2006 10:51:13 AM
CHEMIST

paper sign-off 3/8/06

Blair Fraser
3/8/2006 12:41:20 PM
CHEMIST

(Cosyntropin) injection
NDA 22-028

Summary Basis for Recommended Action
From Chemistry, Manufacturing, and Controls

Applicant: Sandoz Canada, Inc.
145 Jules Leger Street
Boucherville, (QC) Canada J4B 7K8

Indication: The drug product is a diagnostic agent used in the screening of patients presumed to have adrenocortical insufficiency.

Presentation: Supplied as a sterile, injectable 1 mL solution, 0.25 mg dosage strength, in a single dose, [redacted] b(4)

EER Status: **Acceptable. October 23, 2007**

Consults:

Microbiology:	Acceptable
Pharm/Tox:	Acceptable
Biopharm:	N/A
Methods Validation:	Not required
DMETS:	Acceptable
EA:	Categorical exclusion granted under 21 CFR 25.31(c)
Original Submission:	08-FEB-2006
PDUFA Date:	21-FEB-2008
Post-Approval Agreements:	None

Drug Substance

Cosyntropin is a synthetic peptide (molecular weight 2933) prepared by [redacted] synthesis. The sequence corresponds to the first 24 amino acid residues (see figure below) of the natural 39-residue adrenocorticotropic hormone (ACTH, corticotropin). The drug substance is manufactured by [redacted] Drug Master File # [redacted] for Tetracosactide (INN name for Cosyntropin) has been reviewed and found adequate.

Ser	Tyr	Ser	Met	Glu	His	Phe	Arg	Trp	Gly	Lys
1	2	3	4	5	6	7	8	9	10	11
Pro	Val	Gly	Lys	Lys	Arg	Arg	Pro	Val	Lys	Val
12	13	14	15	16	17	18	19	20	21	22
Tyr	Pro									
23	24									

Drug substance specifications include description (white or yellow powder); identification, assay (%) and impurites (%, unspecified unidentified % each, total %) by HPLC; absorbance, amino acid composition, and optical rotation (-99° to -109°); peptide content (> %), acetic acid (8-13%), b(4)
%), and water (%) content of the powder; and
J/µg). A bioassay has been added, the biological potency must be 80 – 120% of the stated potency, U/mg, as determined by cell response using the European Pharmacopea bioassay test. The impurities determination method has been improved to increase the sensitivity, as requested. The drug substance is stored under refrigeration at C in
Stability studies were performed on three batches of drug substance. Stability testing protocol includes: assay, peptide content , individual impurities, water content, acetic acid content and specific rotation. At and (accelerated conditions), samples met specifications for 18 months. Under accelerated conditions, total impurities increased to about at 18 months.

Conclusion: The Drug Substance is satisfactory

Drug product
The drug product is a sterile aqueous solution containing 0.25 mg of the active peptide, cosyntropin, with excipients. The excipients are 10 mg mannitol, 6.4 mg sodium chloride, 1 mg acetic acid, and 0.82 mg trihydrated sodium acetate in mL of water for injection. The pH of the solution is low, only because
. Manufacturing by Sandoz Canada Inc. in Quebec, Canada b(4)
begins with

The drug product specifications include description, assay and impurities by HPLC, pH, bacterial endotoxins, particulate matter, and sterility. Drug product vials are stored under refrigeration at . The proposed expiration dating is 2 years and this is adequately supported by 24 months of long-term stability data. No proprietary tradename has yet been proposed.

Conclusion: The Drug Product is satisfactory

Overall Conclusion:
From the CMC perspective, the application is recommended for **approvable**.

Ali Al-Hakim, Ph.D.
Branch Chief, Branch II
DPA I/ONDQA

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

/s/

Ali Al-Hakim
1/30/2008 01:03:40 PM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 22028/000
Org Code : 510
Priority : 5S

Sponsor: SANDOZ
2555 WEST MIDWAY BLVD
BROOMFIELD, CO 800380446

Stamp Date : 06-FEB-2006
PDUFA Date : 06-DEC-2006
Action Goal :
District Goal: 07-OCT-2006

Brand Name : SYNTROPIN INJECTION 0.25MG/ML
Estab. Name:
Generic Name: COSYNTROPIN INJECTION
Dosage Form: (INJECTION)
Strength : 0.25 MG

FDA Contacts: J. WEBER Project Manager 301-796-1306
M. HABER Review Chemist 301-796-1675
S. TRAN Team Leader 301-796-1764

Overall Recommendation: ACCEPTABLE on 20-NOV-2006by S. ADAMS (HFD-322) 301-827-9051

Establishment : CFN : FEI :

b(4)

DMF No: AADA:

Responsibilities: [redacted]

b(4)

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 20-NOV-06

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI : [redacted]

[redacted]

b(4)

DMF No: AADA:

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 03-MAR-06

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : [redacted] FEI : [redacted]

[redacted]

b(4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

27-NOV-2006 FDA CDER EES

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

FINISHED DOSAGE RELEASE TESTER

Profile :	CTL	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	24-AUG-06		
Decision :	ACCEPTABLE		
Reason :	DISTRICT RECOMMENDATION		

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

DMF No: AADA:

Responsibilities: [redacted] b(4)

Profile :	CTL	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	03-MAR-06		
Decision :	ACCEPTABLE		

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9615155 FEI : 3000280957

SANDOZ CANADA

145 JULES-LEGER STREET

BOUCHERVILLE,QC, , CA j4b 7k8

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : SVS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 13-NOV-06

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : [redacted] FEI : [redacted]

b(4)

DMF No: [redacted] AADA:

Responsibilities: [redacted] b(4)

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 03-MAR-06

Decision : ACCEPTABLE

Reason : BASED ON PROFILE