CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-780

CHEMISTRY REVIEW(S)

NDA 21-780

Nitro Mist
Nitroglycerin Lingual Aerosol (LA)

NovaDel Pharma, Inc.

Prafull Shiromani

Division of Pre-Marketing Assessment
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-780

2. REVIEW #: 3

3. REVIEW DATE: 11-Aug-06

4. REVIEWER: Prafull Shiromani, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Chemistry Review #2	18-May-2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 21-780 Amendments 22 and 23	4/28/06 and 6/29/06

7. NAME & ADDRESS OF APPLICANT:

Name:	Novadel Pharma, Inc.
Address:	25 Minneakoning Road
Representative:	Ms. Mary lou Zett, Ph. D., CQE
Telephone:	908-782-3431 ext 2150

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Nitro Mist
b) Non-Proprietary Name (USAN): Nitroglycerin lingual aerosol
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: Type 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Chronic Stable Angina Pectoris

11. DOSAGE FORM: Nitroglycerin Lingual aerosol

12. STRENGTH/POTENCY 0.4 mg/actuation

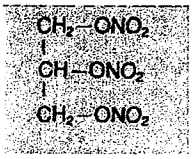
13. ROUTE OF ADMINISTRATION: Lingual spray application

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, 1,2,3-propanetriol trinitrate
STRUCTURAL FORMULA



MOLECULAR FORMULA $C_3H_5N_3O_9$
MOLECULAR WEIGHT: 227.09

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
					Review Completed (P. Shiromani)	6/15/06	Adequate
					Review Completed (P. Shiromani)	6/15/06	Adequate

[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

18. STATUS:

ONDC:

Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	None
EES	Pending	8/11/06	
Pharm/Tox	N/A	N/A	None
Biopharm	N/A	N/A	None
LNC	N/A	N/A	None
Methods Validation	N/A-samples NOT sent to Lab.	N/A	None
OPDRA	N/A	N/A	None
EA	Acceptable (Categorical Exclusion)	5/18/05	S. Zimmerman
Microbiology	N/A	N/A	None

The Chemistry Review for A/NDA 21-780

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for approval from CMC perspective pending satisfactory recommendations from the Office of Compliance for Facilities.

The following stability comments should be included in the Action Letter:

1. The formal stability study of the GTN Basic Solution failed to monitor the degradants, accordingly, the GTN Basic Solution should be tested prior to each use, until an extended holding period is established based on appropriate stability data, which includes monitoring of the degradation products.

2. The formal stability study of the drug product indicated a steady decline (decrease to the lower limit of acceptability) in the level of DS (measured as assay of nitroglycerin) with time and temperature and hence, a 18-month shelf-life is being recommended.

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

N/A

II. Summary of Chemistry Assessments

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

The basis for the use of the drug substance is that nitroglycerin is produced commercially by a process that affords a USP grade drug substance as defined by the USP monograph for Diluted Nitroglycerin. Nitroglycerin is manufactured by [redacted]. The active ingredient is glycerin trinitrate (GTN). [redacted]

The basis for the design of this product is the understanding that the drug substance is better absorbed through the oral mucosa than through other routes of administration, such as through the stomach or intestine. The aerosol solution droplet size is controlled so that there is no significant influx into the lungs as that is not the desired target. [redacted]

[redacted] Optimum priming (10 primes) and re-priming (2 primes after 6 weeks of inactivity) have been established to deliver the correct dose of the drug.

A related drug product has been marketed for many years by Horizon whereby a spray pump packaging system is approved for NDA 18-705. The sponsor of this NDA 21-780 has designed a drug product that is akin to that for NDA 18-705.

The formal stability study of the GTN solution failed to monitor the degradants, accordingly, the GTN Basic Solution should be tested prior to each use, until an expiration dating is established based on appropriate stability data, which includes monitoring of the degradation products. The applicant had proposed a [redacted] expiration dating with a [redacted]
The formal stability study of the drug product indicated a steady decline (decrease to the lower limit of acceptability) in the level of DS (measured as assay of nitroglycerin) with time and temperature and hence, a 18-month shelf-life is to be given to the product as against a [redacted] shelf-life requested by the sponsor.

The extractables from the metering valve components are unlikely to pose a toxicological hazard at the maximum calculated human exposure levels based on review of the available safety data in the literature by [redacted], the [redacted]

Satisfactory data to support the use of INyRX, Peurto Rico, as the manufacturing site has been provided in the form of satisfactory test results from [redacted] consecutive, process validation batches manufactured at this facility.

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

This drug is administered as an aerosol spray using a metered dose spray device designed to deliver a target label claim amount of the drug of 0.4 mg in each spray actuation. There are instructions in the package insert and on the carton that detail the number of spray puffs that are to be taken at any one time and the manner of administration of the dosing (e. g., how to position the device and to deliver a spray puff by actuating the valve by finger control). The maximum is three spray jets for each administration. Instructions are provided for the number of initial primes of the pump and re-primes after 6 weeks of

inactivity. The product is designed to deliver 230 metered sprays. There are also precautions to take concerning certain disposal risks relating to the presence of butane, such as would be expected if the device was thrown into a fire.
The sponsor has been requested to add the statement 'Store Upright' to the bottle label, similar to the carton label.

C. Basis for Approvability or Not-Approval Recommendation

All CMC deficiencies have to be adequately addressed.
The OC recommendation for facilities is still pending at the time of this review.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review: Prafull Shiromani/11-Aug-06
Branch Chief's Name/Date: Ramesh Sood/11-Aug-06
ProjectManager Name/Date: John David/

C. CC Block

57 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Prafull Shiromani
8/14/2006 01:25:54 PM
CHEMIST

Ramesh Sood
8/14/2006 02:09:38 PM
CHEMIST

Chemistry Review Data Sheet

NDA 21-780

Nitro Mist

Nitroglycerin Lingual Aerosol

NovaDel Pharma, Inc.

Stuart Zimmerman
Division of Cardio-Renal Drug products

Appears This Way
On Original

Table of Contents

Appears This Way
On Original

I. Chemistry Review Data Sheet

1. NDA 21-780

2. REVIEW # 2:

3. REVIEW DATE: 18-May-2005

4. REVIEWER: Stuart Zimmerman, Ph.D.

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed /Last Relevant Reviews:

- Chemistry Review #1

Submission(s) Previously Reviewed in ChemistryReview #1 /Document Date:

Document	Date	Status Date
Initial NDA	6/17/04	8/4/04
Amendment	7/29/04	7/30/04
Amendment	8/12/04	8/17/04
Amendment	10/26/04	11/01/04
Amendment	11/5/04	11/08/04
Amendment	11/15/04	11/16/04
Amendment	12/06/04	12/07/04
Amendment	1/11/05	1/12/05
Amendment	2/11/05	2/14/05

6. SUBMISSION(S) BEING REVIEWED:

Document	Date	Status Date
e-mail (Dr. Zett via. John David)	5-17-05	same
e-mail (Dr. Dugger via. Mr. David)	5/11/05	same
Amendment	5/3/05	5/4/05
Amendment	4/15/05	4/18/05

7. NAME & ADDRESS OF APPLICANT:

Name: NovaDel Pharma, Inc.

Address: 25 Minneakoning Road Flemington, NJ 08822

Representative: Ms. Mary Lou Zett, PhD., CQE

Telephone: 908-782-3431 ext 2150

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Nitro Mist
b) Non-Proprietary Name (USAN): Nitroglycerin lingual aerosol
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: Type 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Chronic Stable Angina Pectoris

11. DOSAGE FORM: Nitroglycerin Lingual aerosol

12. STRENGTH/POTENCY: 0.4 mg/actuation

13. ROUTE OF ADMINISTRATION: Lingual spray application

14. Rx/OTC DISPENSED: x Rx ___OTC

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

____SPOTS product – Form Completed

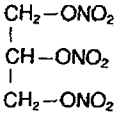
__x__Not a SPOTS product

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

Chemical Name:

1,2,3- propanetriol trinitrate

Molecular Formula: $C_3H_5N_3O_9$
Molecular Weight: 227.09
CAS # 55-63-0 (2/11/05 submission, p. 71)
Structural Formula (Chemical Structure)



17 RELATED/SUPPORTING DOCUMENTS:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
					Review Completed (S. Zimmerman)	5/18/05	Deficiency Issues identified that need resolution
					Review Completed (S.Zimmerman)	5/18/05	Certain issues to be voiced to the DMF holder
					Review Completed (S.Zimmerman)	5/18/05	Deficiency Issues identified that need resolution
					No review necessary	NA	There is a nested DMF — or the —
					Review completed (S. Zimmerman)	5/18/05	Deficiency Issues identified that need resolution
					Review Completed (S.Zimmerman)	5/18/05	No deficiency issues noted since parts do not contact drug product.

[1] Action codes for DMF Table:

1 – DMF Reviewed DMF — has been reviewed in the past for nitroglycerin but not with respect to the specific diluent formulation that is identified in NDA 21-780. In this regard, Joe Piechocki conducted a review dated 7/14/92 relating to the GTN in — but there was no indication that the current — were present in this diluent. Hence, it becomes necessary to conduct another updated review to better assess this more recognized control change. Also, an other reviewer conducted a more updated review (i.e., 2/3/98) with regard to ANDA — — and found it satisfactory with respect to the GTN drug substance.

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": (a) [redacted]

B. Other Documents:

Document	Date	Receipt Date
Chemistry Review #1 of IND 64,596 conducted by Stuart Zimmerman	8/24/04	NA
Original IND 64,596 for this drug product	4/22/02	4/25/02

17. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	None
EES	Acceptable	12/27/04	J. Dambrogio
Pharm/Tox	Informal verbal consult for DMF [redacted] No problem is noted concerning the use of the [redacted]	4/22/05	Albert Defelice
Biopharmaceutics	N/A since a solution formulation- no consult	N/A	None
Methods Validation	To be submitted		
DMETS	Trade name "Nitro-Mist" Acceptable. Other labeling issues raised as noted in this review. (Review in DFS)	12/10/04	Kristina Arnwine
EA	Acceptable (categorical Exclusion) (informal consult)	7/23/04	Florian Zielinski
Nomenclature Committee (LNC)	Established name has been determined (e-mail consult)	4/7/05	G. Poochikian
Microbiology: (1) GTN [redacted]olution (2) Drug product solution	No micro assessment required	N/A	None

The Chemistry Review for NDA 21-438

II. The Executive Summary

III. Recommendations

A. Recommendation and Conclusion on Approvability:

This NDA 21-780 is not approvable because of certain chemistry and manufacturing control aspects that are detailed in the draft letter section of this review. The Office of Compliance further needs to inspect a newly proposed testing facility for microbiological testing.

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

N/A

IV. Summary of Chemistry Assessments

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

The basis for the use of the drug substance is that nitroglycerin is produced commercially by a process that affords a USP grade drug substance as defined by the USP monograph for Diluted Nitroglycerin. Nitroglycerin is manufactured by a [redacted]. It is, however, very explosive in its pure form so it is used in commerce as a diluted solution that is prepared by the manufacturer at the same site A USP monograph has been developed in terms of a "Diluted Nitroglycerin" substance. In this case, [redacted] This specific diluent formulation is closely controlled with respect to its composition and impurity profile. It is considered to be stable if prevented from coming into contact with water and lipase containing organisms that cause hydrolysis.

The basis for the design of this drug product is the understanding that the active drug substance is better absorbed through the oral mucosa than through other routes of administration, such as through the stomach or intestine. The subject drug product, a lingual aerosol spray using a non-polar solvent, has now been developed which provides nitroglycerin for rapid absorption through the oral mucosa. resulting in fast onset of effect.. [redacted]

The aerosol solution droplet distribution size is controlled to be large enough so that there is not to be any significant influx into the lungs as that is not the desired target. To closely control the administration of a predetermined dose of the drug a metered valve is utilized that is suitable for releasing the target amount of the nitroglycerin solution.

A related drug product has been marketed for many years by Horizon whereby a spray pump packaging system is approved for NDA 18-705. The applicant of this NDA 21-780 has designed a drug product that is akin to that for NDA 18-705. Hence, there is a high correspondence between the critical delivery features that are expected to assure interchangeability for dosing between this Horizon drug product and the one that is the subject of this NDA. The amount of active drug substance delivered in a single actuation is similarly formulated to be 0.4 mg for each actuation and those control attributes that are considered to be critical to maintain equivalent absorption- performance are also designed to be comparable to the approved drug product (e.g., spray pattern, droplet size distribution, etc.).

While currently available information concerning the manufacturing process assures that each batch of the drug product can be consistently manufactured to acceptable performance standards, it is realized that there is no data demonstrating that the actual site selected for commercial manufacture can adequately produce the drug product in accord with currently proposed specifications. While it appears that the chemical impurities and degradation products are tightly controlled to very low limits throughout the entire manufacturing process train, there are outstanding questions concerning what results will be for lots manufactured commercially since the applicant is in the process of and its validation is not available for assessment. The drug product solution formulation, Nitroglycerin Basic Solution, is manufactured and in a manner that is consistent with the USP monograph for Diluted Nitroglycerin except for the fact that an Hence, there is an outstanding validation question that should be addressed.

The impurity/degradant profiles for both the drug substance and the drug product are well- known since the degradation mechanisms involve [redacted] in clearly defined manners. While currently utilized analytical control methods have been developed to monitor known impurities, it is recognized that certain degradants are not resolved from each other so that interpretation of results is ambiguous in terms of monitoring for potential trending effects in stability studies. Plans are underway to correct this matter , but this work is not yet complete.

Attention is given to the control of the spray jets in terms of assessing for consistency of each spray jet with respect to the normal aerosol control considerations expected of a metered dose delivery system, such as in terms of label claim for dose, content uniformity, spray pattern, droplet size distribution, and spray angle. These controls appear to be adequate provided that proper priming is conducted so sprays reach a steady state level for consistency of dosing. More work is needed, however, to determine optimum priming and re-priming as needed for administration of the drug product (i.e., between attacks). Hence, adequate priming instructions to be utilized by the patient are not in place to assure that dosing will deliver the expected label claim of nitroglycerin. Adequate controls are in place to allow the patient to determine when to discard the system after the label claim number of spray jets are utilized in a manner that prevent the possibility to administer sub-potent doses. This involves see-through holes in the plastic coating so the solution fill level can be observed. The safety of the system that contains butane gas has been adequately demonstrated.

While packaging configurations have been appropriately designed to adequately protect the drug product's performance characteristics against changes for the shelf-life of the product, there is no documented batch or stability data available from the proposed manufacturing site for commercial production of the drug product. Currently designed stability protocols for both the Nitroglycerin Basic Solution and the drug product need to be revised in accord with the [redacted]

The applicant proposes a [redacted] expiry date for the drug product that is currently supported by [redacted] of real-time ambient stability data on [redacted] batches of the drug product that have been packaged in the container-closure configuration that corresponds to the one to be commercially marketed except for the place of manufacture. Six months of accelerated stability data also provided as additional support as well as 33 months of supporting data from an earlier development lot. Of primary importance, however, is the lack of any stability data derived from the proposed commercial manufacturing site that is normally expected in terms of site specific considerations.

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

This drug is administered as an aerosol spray using a metered dose spray device designed to delivery a target label claim amount of the drug of 0.4 mg in each spray actuation. There are instructions in the package insert that detail the number of spray puffs that are to be taken at any one time and the manner of administration of the dosing (e.g., how to position the device and to deliver a spray puff by actuating the valve by finger control. The maximum dose is three spray jets for each administration event. Since the drug product is designed to deliver 240 doses at the label claim level, attention is given to the design of holes in the outer plastic bottle coating at a level that serves as a signal to the patient that the spray device should not be used since any residual doses are expected to be sub-potent. At this point the patient is expected to discard the spray device. There are also precautions to take concerning certain disposal risks relating to the presence of butane, such as would be expected if the device was thrown into a fire.

C. Basis for Approvability or Not-Approval Recommendation:

The NDA 21-780 is not approvable since there are certain critical control aspects that are cited in the draft letter section referenced in the Table of Contents section for 'Draft Deficiency Issues'. These issues include topics relating to [redacted] One critical issue is that the applicant intends to [redacted] There is, however, no understanding if this change can be completed and validated in a timely manner. Also, [redacted]

D. Reviewer's Signature

E. Endorsement Block

Chemist Name/Date:
Chemistry Team Leader Name / Date
Project Manager Name / Date

31 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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

/s/

Stuart Zimmerman
5/20/05 10:10:11 AM
CHEMIST

Kasturi Srinivasachar
5/20/05 01:13:48 PM
CHEMIST

NDA 21-780

Nitro Mist

Nitroglycerin Lingual Aerosol

NovaDel Pharma, Inc.

Stuart Zimmerman
Division of Cardio-Renal Drug products

Table of Contents

I. Chemistry Review Data Sheet

1. NDA 21-780

2. REVIEW # 1:

3. REVIEW DATE: 12-May-2005

4. REVIEWER: Stuart Zimmerman, Ph.D.

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed /Last Relevant Reviews:

- No previous NDA reviews.
- A 74 Day CMC Letter was drafted based on an initial draft of this current review.

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed /Document Date:

Document	Date	Status Date
Initial NDA	6/17/04	8/4/04
Amendment	7/29/04	7/30/04
Amendment	8/12/04	8/17/04
Amendment	10/26/04	11/01/04
Amendment	11/5/04	11/08/04
Amendment	11/15/04	11/16/04
Amendment	12/06/04	12/07/04
Amendment	1/11/05	1/12/05
Amendment	2/11/05	2/14/05

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name: NovaDel Pharma, Inc.

Address: 25 Minneakoning Road Flemington, NJ 08822

Representative: Ms. Mary Lou Zett, PhD., CQE

Telephone: 908-782-3431 ext 2150

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Nitro Mist
b) Non-Proprietary Name (USAN): Nitroglycerin lingual aerosol
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: Type 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Chronic Stable Angina Pectoris

11. DOSAGE FORM: Nitroglycerin Lingual aerosol

12. STRENGTH/POTENCY: 0.4 mg/actuation

13. ROUTE OF ADMINISTRATION: Lingual spray application

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:

Chemical Name:

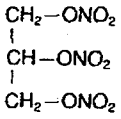
1,2,3- propanetriol trinitrate

Molecular Formula: $C_3H_5N_3O_9$

Molecular Weight: 227.09

CAS # 55-63-0 (2/11/05 submission, p. 71)

Structural Formula (Chemical Structure)



17 RELATED/SUPPORTING DOCUMENTS:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
					Under Review on a NDA specific basis	Pending Update	Refer to review comments relating to drug substance.
					Under review since this type of oil has not been reviewed	Pending specific component review	The reviewer will be Stuart Zimmerman
					Under review by two chemists	Pending Update	Refer to container – closure section
					No review necessary	NA	There is a noted DMF [redacted]
					Under review by two chemists	Pending Update	See this review for status comments

[1] Action codes for DMF Table:

1 – DMF Reviewed DMF [redacted] nas been reviewed in the past for nitroglycerin but not with respect to the specific diluent formulation that is identified in NDA 21-780. In this regard, Joe Piechocki conducted a review dated 7/14/92 relating to the GTN in [redacted] out there was no indication that the current [redacted] were present in this diluent. Hence, it becomes necessary to conduct another updated review to better assess this more recognized control change. Also. another reviewer conducted a more updated review (i.e., 2/3/98) with regard to [redacted] and found it satisfactory with respect to the GTN drug substance.

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; The LOA was not included in the original NDA but review began for the NDA 21-780 specific valve in spite of this. It was found that this DMF was also under review for another drug product, having a related but somewhat different valve for a MDI application whereby FDA queries are still outstanding. The chemist, Stuart Zimmerman, will review NDA 21-780 with respect to what information is specific to the subject valve since it has not been reviewed before.

6 – DMF not available

7 – Other (explain under "Comments": (a) [redacted]

B. Other Documents:

Document	Date	Receipt Date
Chemistry Review #1 of IND 64,596 conducted by Stuart Zimmerman	8/24/04	NA
Original IND 64,596 for this drug product	4/22/02	4/25/02

17. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	None
EES	Acceptable	12/27/04	J. Dambrogio
Pharm/Tox	Inform[redacted] verbal consult for DMF [redacted]lo problem is noted concerning the use of the [redacted]	4/22/05	Albert Defelice
Biopharmaceutics	N/A since a solution formulation- no consult	N/A	None
Methods Validation	To be submitted		
DMETS	Trade name "Nitro-Mist" Acceptable. Other labeling issues raised as noted in this review. (Review in DFS)	12/10/04	Kristina Arnwine
EA	Acceptable (categorical Exclusion) (informal consult)	7/23/04	Florian Zielinski
Nomenclature Committee (LNC)	Established name has been determined (e-mail consult)	4/7/05	G. Poochikian
Microbiology: (1) GTN [redacted]olution (2) Drug product solution	No micro assessment required	N/A	None

The Chemistry Review for NDA 21-438

II. The Executive Summary

III. Recommendations

A. Recommendation and Conclusion on Approvability:

This NDA 21-780 is not approvable because of certain chemistry and manufacturing control aspects that are detailed in the draft letter section of this review. The Office of Compliance has given an "Acceptable" recommendation for the CGMP status for all the facilities.

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

N/A

IV. Summary of Chemistry Assessments

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

The basis for the use of the drug substance is that nitroglycerin is produced commercially by a process that affords a USP grade drug substance as defined by the USP monograph for Diluted Nitroglycerin. Nitroglycerin is manufactured by a [redacted]. It is, however, very explosive in its pure form so it is used in commerce as a diluted solution that is prepared by the manufacturer at the same site A USP monograph has been developed in terms of a "Diluted Nitroglycerin" substance. In this case [redacted] This specific diluent formulation is closely controlled with respect to its composition and impurity profile. It is considered to be stable if prevented from coming into contact with water and lipase containing organisms that cause hydrolysis.

The basis for the design of this drug product is the understanding that the active drug substance is better absorbed through the oral mucosa than through other routes of administration, such as through the stomach or intestine. The subject drug product, a lingual aerosol spray using a non-polar solvent, has now been developed which provides nitroglycerin for rapid absorption through the oral mucosa resulting in fast onset of effect.. [redacted] The

aerosol solution droplet distribution size is controlled to be large enough so that there is not to be any significant influx into the lungs as that is not the desired target. To closely control the administration of a predetermined dose of the drug a metered valve is utilized that is suitable for releasing the target amount of the nitroglycerin solution.

A related drug product has been marketed for many years by Horizon whereby a spray pump packaging system is approved for NDA 18-705. The applicant of this NDA 21-780 has designed a drug product that is akin to that for NDA 18-705. Hence, there is a high correspondence between the critical delivery features that are expected to assure interchangeability for dosing between this Horizon drug product and the one that is the subject of this NDA. The amount of active drug substance delivered in a single actuation is similarly formulated to be 0.4 mg for each actuation and those control attributes that are considered to be critical to maintain equivalent absorption- performance are also designed to be comparable to the approved drug product (e.g., spray pattern, droplet size distribution, etc.).

While currently available information concerning the manufacturing process assures that each batch of the drug product can be consistently manufactured to acceptable performance standards, it is realized that there is no data demonstrating that the actual site selected for commercial manufacture can adequately produce the drug product in accord with currently proposed specifications. While it appears that the chemical impurities and degradation products are tightly controlled to very low limits throughout the entire manufacturing process train, there are outstanding questions concerning what results will be for lots manufactured commercially since the applicant is in the process of and its validation is not available for assessment. The drug product solution formulation, Nitroglycerin Basic Solution, is manufactured in a manner that is consistent with the USP monograph for Diluted Nitroglycerin except for the fact that Hence, there is an outstanding validation question that should be addressed

The impurity/degradant profiles for both the drug substance and the drug product are well- known since the degradation mechanisms involve

in clearly defined manners. While currently utilized analytical control methods have been developed to monitor known impurities, it is recognized that certain degradants are not resolved from each other so that interpretation of results is ambiguous in terms of monitoring for potential trending effects in stability studies. Plans are underway to correct this matter , but this work is not yet complete.

Attention is given to the control of the spray jets in terms of assessing for consistency of each spray jet with respect to the normal aerosol control considerations expected of a metered dose delivery system, such as in terms of label claim for dose, content uniformity, spray pattern, droplet size distribution, and spray angle. These controls appear to be adequate provided that proper priming is conducted so sprays reach a steady state level for consistency of dosing. More work is needed, however, to determine optimum priming and re-priming as needed for proper administration of the drug product (i.e., between attacks). Hence, adequate priming instructions to be utilized by the patient are not in place to assure that dosing will deliver the expected label claim of nitroglycerin. Adequate controls are in place to allow the patient to determine when to discard the system after the label claim number of spray jets are utilized in a manner that prevent the possibility to administer sub-potent doses. This involves see-through holes in the plastic coating so the solution fill level can be observed. The safety of the system that contains butane gas has been adequately demonstrated.

While packaging configurations have been appropriately designed to adequately protect the drug product's performance characteristics against changes for the shelf-life of the product, there is no documented batch or stability data available from the proposed manufacturing site for commercial production of the drug product. Currently designed stability protocols for both the Nitroglycerin Basic Solution and the drug product need to be revised in accord with the

The applicant proposes a ——— expiry date for the drug product that is currently supported by ———, of real-time ambient stability data on ——batches of the drug product that have been packaged in the container-closure configuration that corresponds to the one to be commercially marketed except for the place of manufacture. Six months of accelerated stability data also provided as additional support as well as 33 months of supporting data from an earlier development lot. Of primary importance, however, is the lack of any stability data derived from the proposed commercial manufacturing site that is normally expected in terms of site specific considerations.

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

This drug is administered as an aerosol spray using a metered dose spray device designed to delivery a target label claim amount of the drug of 0.4 mg in each spray actuation. There are instructions in the package insert that detail the number of spray

puffs that are to be taken at any one time and the manner of administration of the dosing (e.g., how to position the device and to deliver a spray puff by actuating the valve by finger control. The maximum dose is three spray jets for each administration event. Since the drug product is designed to deliver 240 doses at the label claim level, attention is given to the design of holes in the outer plastic bottle coating at a level that serves as a signal to the patient that the spray device should not be used since any residual doses are expected to be sub-potent. At this point the patient is expected to discard the spray device. There are also precautions to take concerning certain disposal risks relating to the presence of butane, such as would be expected if the device was thrown into a fire.

C. Basis for Approvability or Not-Approval Recommendation:

The applicant is not approvable since there are certain critical control aspects that are cited in the draft letter section referenced in the Table of Contents section for 'Draft Deficiency Issues'.. These issues include topics relating to [redacted] One critical issue is that the applicant intends to [redacted] There is, however, no understanding if this can be completed and validated in a timely manner. Also [redacted]

D. Reviewer's Signature

E. Endorsement Block

Chemist Name/Date: Same date as draft review
Chemistry Team Leader Name / Date
Project Manager Name / Date

F. CC Block

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