CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-010

CHEMISTRY REVIEW(S)

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

OND Division:	Anesthesia, Analgesia and Rheumatology
NDA:	22010
Applicant:	Deproco, Inc.
Stamp date:	September 30, 2005
PDUFA Date:	March 30, 2005
Trademark:	Septocaine®
Established Name:	Articaine hydrochloride 4% (40mg/ml) with epinephrine 1:2000.000
Dosage Form:	Solution for Injection
Route of Administration:	injection
Indication:	Dental anesthesia

Pharmaceutical Assessment Lead: Ali Al-Hakim, Ph.D.

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

Appears This Way
On Original

Summary, Critical Issues and Comments

A. Summary

Background

This NDA (22-010) is a new formulation for an approved NDA (original NDA # 20-971 Septocaine® which was approved in April, 2000). The drug product (Septocaine®) is a sterile aqueous solution for use in dental anesthesia. It contains two active ingredients; articaine hydrochloride and epinephrine bitartrate. The drug product for this current NDA is produced in a different strength than the approved Septocaine® regarding the content of epinephrine active ingredient (see the approved and the proposed two formulations below).

The approved NDA has the following formulation:

Articaine hydrochloride 4% (40mg/ml) with Epinepherine 1:100,000 Injection (approved name: Septocaine®)

The proposed formulation for this submission is:

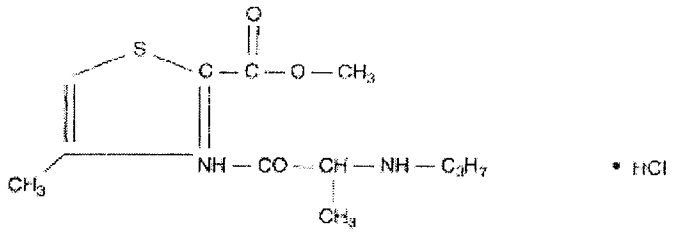
Articaine hydrochloride 4% (40mg/ml) with Epinepherine 1:200.000 Injection

Proposed name: Septocaine

Chemical names, structures and molecular weights of the active ingredients (drug substances) are provided below.

RS 4-Methyl-3-[2-proplamino)-propionamido]-2-thiophenecarboxylic acid, methyl ester hydrochloride **(Articaine HCl)**

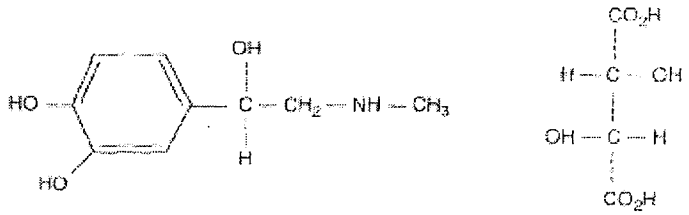
M.Wt. 320.84



$C_{13}H_{20}N_2O_3S_1 \cdot HCl$

(*R*)-1-(3,4-Dihydroxyphenyl)-2-(methylamino) ethanol bitartrate
(Epinephrine as bitartrate)

M.Wt. 333.30



$C_9H_{13}NO_3 \cdot C_4H_6O_6$

Background information for previous submissions

The above two formulations (1:100.000 and 1:200.000) were submitted in a single NDA in March, 1998. However, due to outstanding clinical issues with the formulation (1:200.000) at that time and the possibility that the sponsor might receive non-approvable letter, the sponsor decided to withdraw this formulation (1:200.000) and obtained approval for the other formulation (1:100.000). Eventually, formulation 1:100.000 was approved in April, 2000 (NDA 20-971)[1].
In September 29, 2005, the applicant re-submitted this application as a supplemental submission (prior approval supplement) and referenced the original NDA and two approved manufacturing related supplements as supportive and background information for this submission. However, the OND division (DAARP) indicated that the application can not be considered a supplement because a new formulation does not fit into a supplemental category and it had an action letter taken in April 2000. Therefore, administrative split of the NDA to new type 5 was necessary, as class 2 resubmission. The new formulation constitutes half the strength of Epinephrine in the original approved application[2].

[1] See documentation for NDA 20-971 which was submitted in March 1998 which covered both formulations and approved in April, 2000.
[2] The information regarding the administrative split of the NDA to type 5 NDA, class 2, was provided by the PM.

B. Review, Comments and Recommendations

Drug Substance Section

The NDA contains some CMC information regarding the drug substances related to physical and chemical characteristics, specifications and tests at release, certificate of analysis and analytical procedures. However, complete details of the manufacturing processes which include synthesis steps, structural elucidation, impurity profile, process controls, specifications and analytical methods, test data, stability protocol, batch records, etc, for the above drug substances were described in three different DMFs (DMF —— and DMF —— for Articaine hydrochloride and DMF —— for epinephrine[3]). These DMFs were reviewed, evaluated and found satisfactory with respect to the drug substances for NDA 20-971. However, the primary reviewer should search COMIS for any updates and/or annual reports (changes/revision) that may have been submitted to these DMFs since the last reviews, especially if such changes/revision might have an impact on the drug product quality (authorization letters for both DMFs are provided). In addition, annual stability test data for old and new manufactured batches should be reviewed and evaluated with respect to the approved expiration dating of the drug substance and the approved stability commitments.

Drug Product Section

With respect to the drug product, the active and inactive components[4] of the new formulation remained the same as the described in the original approved NDA. However, the proposed formulation for the drug product will be composed of 4% of articaine hydrochloride combined with epinephrine at strength of 1:200,000. The drug product, ——————— , is an injectable local anesthetic solution of articling hydrochloride and epinephrine bitartrate. ——————— contains 40.0 mg/mL of articling HCl and —— mg/mL of epinephrine (—— mg/mL expressed as a base). Inactive components include sodium chloride, sodium metabisulphite, sodium hydroxide solution, ——————————————— —— . The applicant provided copies of the USP/NF monograph requirements for the inactive components used in the drug product formulation. The drug product is packaged in single-use cartridge (1.7 mL solution) for use in a standard dental syringe. The finished product in its market package is ——————————————————

Drug product manufacturing process was referenced to the approved supplemental applications for NDA 20-971 (supplements 005 and 010). The reviewer needs to revisit these two supplements and any other related submissions regarding the manufacturing process and other related changes in order to compare the manufacturing process of this NDA with the approved NDA 20-971 taking into consideration the sponsor's claim that the only significant difference between the two NDAs is change in formulation (change in strength).

The manufacturing process is essentially ——— . Detailed flow diagrams are provided in the NDA which depict the manufacturing processes. However, additional manufacturing information may be found in the referenced supplements and any related documents.

---

[3] Epinephrine is listed in the USP monograph and according to the applicant; its specifications meet the current USP monograph.

[4] Composition and components table contains two strengths; quantity ——— per 1.7mL.

The NDA contains description of the in-process control procedures which include the following tests and controls:
In process control procedures includes:

- [redacted]

Assessment of the above tests which were used routinely during the drug product manufacturing process and the corresponding tests data should be evaluated with respect to the quality and safety of the injectable solution and if such tests can ensure the quality of the solutions (discussion/feedback from microbiology reviewer is encouraged due to the nature of these tests).

During reviewing and assessing the pharmaceutical development report, the reviewer may need look into the justification provided by the by the applicant with respect to the proposed specifications particularly, the justification provided for the overage in the drug product. The overage of epinephrine in the drug product solution is reported to be 15%. The applicant reported this overage is justified based on test data that [redacted][5]. The overage evaluation and subsequent conclusion should be based on test data, stability studies, USP requirements and FDA guidelines.

The drug product is an injectable solution and the sterilization process and related microbiology tests play a major role in controlling the quality of the drug product for such dosage form. Therefore, the reviewer may want to interact with the Microbiology reviewer regarding the Micro consult and related microbiological tests provided in the NDA (endotoxins, particulates matter, etc.)
Another critical aspect for this type of the drug product is the container/closure system (solution dosage form filled in cartridges, see diagram below).
The following diagram represents the container/closure system and the main areas of concern with respect to [redacted] eakage and solution contact with [redacted] plunger and cap.

A diagram of the cartridge system is provided below.

[redacted]

5- [redacted]

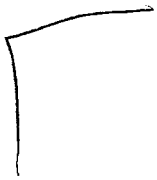
For this type of drug product the integrity of the container closure system and the sterilization process become integral part of this dosage form which might have great impact on the quality of the drug product. Therefore, assessing and evaluating process for this NDA should also concentrate on the examining closely the CMC information provided by the applicant which are related to cartridges, caps, stopper, plunger and [redacted] with respect to leakage, filling and delivering of the volume, and compatibility of drug product solution with the container/closure itself.

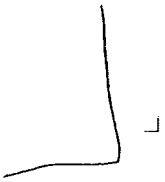
Copy of the proposed specifications and analytical tests methods is provided in this review (*batch comparison summery provided in the next page*) together with stability test data obtained from three NDA batches. Two major issues in the table need to be reviewed and assessed with emphasis on the scientific justification and available test data provided by the applicant.
The first issue is total impurities limit for epinephrine which is reported to be NMT [redacted]%, however, release and stability data indicated the amount of total impurities detected is well below the proposed limit. The second issue is the proposed limit for particulates matter USP test [redacted]. The applicant proposed specifications limits for particulate matter as [redacted]. These are maximum allowable limits in the USP monograph. However, examination of the test data from the primary production NDA batches indicated that the actual numbers of particulates found is well below the proposed limit. The reviewer may need to examine all test data obtained during the stability studies in order to determine if there is a necessity to tighten the specifications limit based on test data generated from the NDA batches and therefore, improving quality of the drug product profile.
As a background and supporting information, the reviewer may need to look briefly into the CMC information provided in NDA 20-971 and any related documents (reviewer, supplements, reports, etc) in order to obtain background science and information that may helpful for assessing the current submission.

The following table[6] contains batch comparison for the NDA batches and test data generated from stability studies. The tests were preformed as per the proposed specifications. See previous discussion regarding test data obtained from these batches with respect to epinephrine impurities and particulate matter and their proposed specifications limits.

3.7.4 Batch Comparison Summary

Finished Product Results





[6] For stability test time in months, see test data in the stability section of the NDA.

The applicant provided, in the stability section, stability protocol and the following information:

- Three NDA production batches were placed in the stability program
- Stability test data provided from the above batches included:
  - 6 months stability test data for three batches at accelerated conditions and up to 15 months of test data at recommended storage conditions.
  - 3 month of test data for one batch accelerated and up to 9 months at recommended storage conditions

In reviewing and assessing the stability data, the reviewer might want to focus on any change or trend in the test data during the stability studies especially the proposed specifications and the actual test data obtained from stability testing (see previous specifications section). In addition, assessment of the drug product quality should be performed with special emphasis on degradation and impurity profile in relation to the proposed expiry dating requested by the applicant which is 18 months. Initial assessment of the stability test data appears to indicate that the degradation products appear to increase with storage time[7].

The sponsor did not provide stability analysis (SAS program) especially the submitted real time stability data did not cover the requested expiration dating. Therefore, the reviewer may inform the project manager to issue IR letter to be sent to the sponsor requesting statistical analysis for the stability data at early stage of the reviewing process.

The NDA contains a Pharmaceutical Development report includes information regarding, choice of pharmaceutical dosage form, choice of quantitative and qualitative formulation (active ingredients and concentration and Worldwide commercial availability of the two formulations), choice of the epinephrine (as a vasoconstrictor) and its concentration, justification of the final pH in solution and overage of epinephrine in the formulation, and choice and function of inactive ingredients. The reviewer may consider examining this report with respect to early stages of the drug development and subsequent improvement of the manufacturing process. Answers to some concerns such as drug product stability, impurities/degradation product and overage may be found in the details of this report.

The analytical test methods section appears to contain the necessary test methods details concerning the drug product testing for Injectable solution. However, critique of the analytical methods and subsequent evaluation should be performed with respect to regulatory aspects of these methods and if they are suitable for regulatory purposes and if the validation report for these methods (selectivity, accuracy, repeatability, precision, etc,), supports these methods. Additionally, the sampling plan used in the above method and the justification provided by the applicant for the number of cartridges used for each test should be assessed.

Evaluation and subsequent assessment of CMC related topics in the package insert, immediate container and secondary container should be performed. These topics related but are not limited to structures, names, ingredients, name, dosage form and strength, how supply section, expiration dating, name and addresses of manufacturer/distributor, etc.

The reviewer may need to emulate and assess the methods validation package and determines if some of them should be sent to FDA laboratory for further validation based on the ONDQA MAPP.

[7] Initial evaluation of stability test data indicated that there is

C. Critical issues for review and recommendation

During reviewing and assessment of the quality of the CMC information provided in this NDA, the primary reviewer may consider performing the assessment with emphasis on the following topics and any other related issues that may have a potential impact on the quality of the drug product.

- Assess and evaluate the DMFs for the dug substances for any updates/annual reports in particular any significant changes reported for the manufacturing process. This should also involve reviewing annual stability test data for old and new manufactured batches. Data should be reviewed and evaluated with respect to relation the approved expiration dating of the drug substance and stability commitments.
- Reviewing and evaluation the referenced supplements 005, 010 and other related documents for NDA 20-971 regarding details of the drug product manufacturing process should be performed because these documents provide background information for the manufacturing process.
- Assessment of the overage issue for epinephrine in the drug product solution which is reported to be 15% should be closely examined. Evaluation and subsequent conclusion should be based on scientific justification test data, stability studies, USP requirements and FDA guidelines.
- In assessing the proposed specifications for the drug product, the reviewer may want to focus on the proposed specifications limits for drug product, which appear to be wide, compared to the actual test data provided form the NDA batches during the stability studies (e.g. proposed specification limits for particulate matter and total impurities). Consequently, the reviewer may consider requesting that the some of limits should be tightened the proposed specifications limits based on the submitted test data.
- In depth assessment and subsequent evaluation of the CMC information provided by the applicant for the container/closure system is an important issue for this type of injectable drug product. The container/closure system which included cartridges, caps, stoppers, plungers and _____ process should be assessed with respect to leakage, fill and delivery volume and compatibility of drug product solution with the container/closure itself.
- Due to the nature of the dug product solution, it is recommended that the reviewer communicates with the microbiology reviewer regarding any issue related to sterilization aspects and microbiological testing of the drug product solution.

D. Comments for 74-day Letter: IR request should be sent to the sponsor requesting analysis of the stability test data (SAS program) at early stage of the assessment.

E. Recommendation for fileability: The NDA is recommended to be filed because there is a considerable amount of CMC information and data which are suitable for evaluation and assessment based on the FDA and related ICH guidelines for submitting CMC information for New Drug Application.

- Recommendation for Team Review:

The NDA is essentially a review of the drug product (drug substances have been reviewed in the corresponding DMFs for NDA 20-971). Additionally, the drug product

is a new formulation for an approved drug product which involves one change in the content in one of the active ingredients without significant CMC changes in the manufacturing process. Moreover, the drug product is a solution dosage form and the manufacturing process is not very complex and deals mainly with [redacted]

Therefore, it is recommended that a single reviewer should review and assess the CMC information in this NDA.

- Consults

The reviewer, in conjunction with project manager, should initiate the following consults/requests as early as possible. DEMTS should be consulted regarding any confusion/medication for both proposed name for this NDA due to the similarity between the approved name for NDA 20-971 (Septocaine [redacted]) and the proposed name for the current NDA (Septocaine [redacted]).

- EER
- Microbiology
- LNC
- Biometrics/statistics
- Biopharmaceutics
- Method validation
- DEMTS
- Pharm. Tox.

Ali Al-Hakim, Ph.D.
Pharmaceutical Assessment Lead

12/07/2005
Date

Ravi Harapanhalli, Ph.D.
Branch Chief

12/07/2005
Date

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?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		Volume 6, page 155
7	Does the section contain controls for the drug substance?	√		
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?			N/A
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?	√		Volume 11
15	Is a separate microbiological section included?	√		Volumes 6-7
16	Have all consults been identified and initiated?		√ Microbiology √ Pharm/Tox √ Biopharm √ Statistics OCP/CDRH/CBER LNC √ DMETS/ODS	

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

DMF Number	Holder	Description	LOA Included	Status
			Yes	Adequate[8]
			Yes	Adequate[8]
			Yes	Adequate[8]
			Yes	
			Yes	
			Yes	
			Yes	

[8] The DMFs were reviewed with respect to the NDA 20-971 and found acceptable. However, these DMFs should be reviewed for any recent updates and annual report.

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
12/19/2005 12:28:35 PM
CHEMIST

Ravi Harapanhalli
12/22/2005 01:54:37 PM
CHEMIST

Appears This Way
On Original

__11__ Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

__X__ § 552(b)(5) Deliberative Process

NDA 22-010

Septocaine® 200

Deproco, Inc.

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

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-010

2. REVIEW #1

3. REVIEW DATE: 24-Mar-2006

4. REVIEWER: William M. Adams

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	29-Sep-2005
Amendment	10-Feb-2006
Amendment	22-Mar-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Deproco, Inc.
Address:	245-C Quigley Blvd. new Castle, DE 19720
Representative:	Wayne H. Matelski, Esq. Counsel & U.S. Agent
Telephone:	202-857-6340

8. DRUG PRODUCT NAME/CODE/TYPE:
   (a) Proprietary Name: Septocaine®
   (b) Non-Proprietary Name (USAN): Articaine HCl and Epinephrine Bitartrate Injection
   (c) Code Name/# (ONDC only): None
   (d) Chem. Type/Submission Priority (ONDC only):
   Chem. Type: 3
   Submission Priority: S

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

10. PHARMACOLOGICAL CATEGORY: nerve block or infiltration anesthetic

11. DOSAGE FORM: 708 (solution for injection)

12. STRENGTH/POTENCY: 4% articaine HCl and 1:200,000 epinephrine

13. ROUTE OF ADMINISTRATION: 109 (into soft tissue/gums)

14. Rx/OTC DISPENSED: Rx

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

_____SPOTS product – Form Completed

XXX Not a SPOTS product

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

Articaine HCl

Chemical Name	(R/S)-4-methyl-3-[2-(propylamino)-proprionamido]-2-thiophene-carboxylic acid, methyl ester hydrochloride
Molecular Formula	$C_{13}H_{20}N_2O_3S.HCl$
Molecular Weight	320.84 amu

Epinephrine Bitartrate

Chemical Name	(R)-1-(3,4-dihydroxyphenyl)-2-(methylamino)ethanol bitartrate
Molecular Formula	$C_9H_{13}NO_3$, $C_4H_6O_6$
Molecular Weight	333.30 amu

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	2			1	Adequate	pending	
	2			3	Adequate	08/27/04	
	2			1	Adequate	pending	
	3			4	N/A		
	3			4	N/A		
	3			4	N/A		
	3			4	N/A		

[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

Chemistry Review Data Sheet

NDA	20-971	Septocaine 100
IND	51,721	Articaine HCl + Epinephrine injection

18. **STATUS:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	---	---
EES	Acceptable Acceptable Pending	12/23/05 02/21/06 03/23/06	OC
Pharm/Tox	N/A	---	---
Biopharm			
LNC			
Methods Validation	N/A	---	---
OPDRA			
EA	N/A	---	---
Microbiology	Acceptable	01/11/06	B.Riley

19. **ORDER OF REVIEW:** N/A

The Chemistry Review for NDA 22-010

The Executive Summary

I. RECOMMENDATIONS

A. RECOMMENDATION & CONCLUSION ON APPROVABILITY

The application is APPROVABLE (AE) from the CMC perspective.

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

None

II. SUMMARY OF CHEMISTRY ASSESSMENTS

A. DESCRIPTION OF THE DRUG PRODUCT & DRUG SUBSTANCES

DRUG PRODUCT

Septocaine® — is 1.7mL of a ——— aqueous solution of 4% Articaine HCl with Epinephrine (1:200,000) packaged in a single-use standard dental syringe cartridge. Articaine HCl is a local anesthetic. Epinephrine is a vasoconstrictor which prolongs the anesthetic effect and reduces bleeding during the dental procedure.

Other than the concentration of Epinephrine, the proposed drug product is essentially identical to that approved under NDA 20-971 (Septocaine®, 4% Articaine HCl with Epinephrine 1:100,000). Safety information for 4% Articaine HCl solution is provided in IND 51,721. Epinephrine, formulated as the bitartrate salt, is known to be susceptible to thermal and oxidative degradation, thus the formulation includes a ——— and ——— A formulation overage is present in many approved Epinephrine products and is known to present no safety hazard. Sodium Chloride provides Sodium Hydroxide and Hydrochloric Acid are added to ——— . The initial pH and acceptable pH range were selected to ——— Metabisulfite ——— All formulation excipients are USP/NF grade materials. No excipient is novel or of animal origin.

Drug product is manufactured by Novocol Pharmaceutical of Canada using ——— technique with ——— primary packaging components followed by ——— by a ——— The application includes master production records and in-process controls for the proposed manufacturing process, and executed batch records for the ——— commercial-size primary drug product batches used for the process validation and stability studies.

The drug product manufacturing site has been found to meet current GMP requirements.

Release and stability specifications address identity, assay and impurities/degradates for both drug substances; antioxidant assay; solution pH; organic and inorganic impurities; physical and functional characteristics; and microbiological purity. All analytical methods are described in detail. Validation studies are provided for drug substance identity, assay and purity. The criteria are justified by release and stability requirements. Batch analysis data for the three primary drug product batches shows values which are within the proposed specification and consistent across lots.

The primary packaging components are a ——— type I glass standard dental syringe cartridge; a ——— cap comprised of a ——— Adequate and complete descriptions, QC specifications, qualification information and letters of authorization to the supplier's type III DMFs are provided for each component.

Stability protocols, commitments and ICH study data are provided for the three primary drug product lots. Testing addresses assay and degradates for each drug susbstance, antioxidant assay; pH, inorganic impurities,

cartridge functionality, particulates, and sterility. The study data consists of cartridges stored for — months (2 lots) and —months (1 lot) at ICH controlled room temperature conditions and for —months are ICH accelerated conditions. Data trends are consistent across lots, time and conditions, and correlate to trends observed with Septocaine® —. The developmental and stability study data is adequate to support the proposed 18 months expiry period with storage at USP controlled room temperature, protect from light and do not freeze.

The package insert, cartridge label and carton label for Septocaine® — were revised to include Septocaine® — and to delete the reference to the initial solution pH which is different for the two drug products. CMC information in the draft labels and labeling is complete and adequate to meet the requirements of 21 CFR 201.57.

Reference is made to NDA 20-971 regarding Environmental Assessment information.

DRUG SUBSTANCE

The drug substances are Articaine HCl supplied by ———————————, and Epinephrine Bitartrate supplied by ———————————. The same suppliers are approved for NDA 20-971.

Reference is made to NDA 20-971 and to the supplier's type II DMFs for all CMC information regarding bulk drug substance. Letters of authorization to the DMFs are provided. The type II DMFs have been reviewed and found to provide complete and adequate CMC information to support approval of the application.

The application includes nomenclature, general properties, release specifications, and batch analysis data.

The acceptance specifications address molecular and stereochemical identity, assay, organic and inorganic purity, residual solvents and bioburden. The analytical methods are described in detail. The criteria are based on NDA 20-971 and the PhEur monograph for Articaine HCl and on NDA 20-971 and the USP/PhEur monographs for Epinephrine Bitartrate.

The manufacturing site and all but 2 recently submitted contract testing labs have been found to meet current GMP requirements.

Batch analysis data is included for the lots used in the manufacture of the three primary drug product batches. The data is provided as certificates of analysis from the suppliers, the drug product manufacturer and the contract laboratories.

Both drug substances are known to be stable for — months when stored at USP controlled room temperature in the supplier's shipping container.

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

The drug product is a sterile injection solution in a single-use 1.7 mL prefilled glass cartridge syringe intended for use as a local infiltrative or conductive anesthetic for both simple and complex dental and periodontal procedures. The 1:200,000 strength product is preferred when it is desirable to limit the exposure of epinephrine in comparison to the 1:100,000 strength product.

Recommended dosage is based on Articaine HCl and may vary with the patient or procedure; 20-100 mg for infiltration procedures, 20-136 mg for nerve block procedures, and 40-— mg for oral surgery. Maximum daily dose for adults is 7 mg Articaine HCl per Kg body weight administered by submucosal infiltration and/or nerve block. Pediatric dosing should be determined by age and body weight to maximum of 7 mg per Kg body weight. The product is not recommended for children under 4 years of age.

Drug product is used without further dilution, but the cartridge solution should be inspected for discoloration (yellowing of solution) and formation of particulate matter immediately before use. Carpule should be sterilized with isopropanol before injection.

The proposed expiry period is 18 months with storage at USP controlled room temperature, protect from light and do not freeze.

C. BASIS FOR APPROVABILITY OR NOT APPROVAL RECOMMENDATION

The application is APPROVABLE from the CMC perspective pending establishment of the GMP status for two contract testing labs submitted in a late amendment. Complete and adequate information has been provided to address all other the CMC issues for the proposed drug substance and drug product.

III. ADMINISTRATIVE

A. REVIEWER'S SIGNATURE

William M. Adams, ONDQA

B. ENDORSEMENT BLOCK

R.Harapanhalli/ONDQA/DPA III/Chief Branch V

C. CC BLOCK

A.Meyer/PM/DAARP

Appears This Way
On Original

32 Page(s) Withheld

X § 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/

Mike Adams
3/24/2006 03:17:05 PM
CHEMIST

Ravi Harapanhalli
3/24/2006 03:26:00 PM
CHEMIST
AE pending satisfactory GMP inspections of two listed testing facilities.