

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205410Orig1s000

CHEMISTRY REVIEW(S)

TO: CMC MEMO-TO-FILE

FROM: P. Shiromani, Ph.D

**SUBJECT: NDA 205410: Propranolol Hydrochloride Oral Solution,
4.28 mg/mL-** (b) (4)

DATE: 7-Feb-2014

The following Summary Report from the Office of Compliance was received on 07-Feb-2014, with an 'Acceptable' overall recommendation. There are no other CMC pending issues. Accordingly, this NDA is recommended for approval from a CMC perspective. The CMC Review was submitted to DARRTS on 31-Dec-2013.

**FDA CDER EES ESTABLISHMENT
EVALUATION REQUEST SUMMARY
REPORT**

Application: NDA 205410/000
Org. Code: 110
Priority: 5
Stamp Date: 17-MAY-2013
PDUFA Date: 17-MAR-2014
Action Goal:
District Goal: 18-SEP-2013

Sponsor: PIERRE FABRE DERMA
8 CAMPUS DR 2ND FL
PARSIPPANY, NJ 07054
Brand Name: (b) (4)
Estab. Name:
Generic Name: PROPRANOLOL ORAL SOLUTION 3.75MG/ML
Product Number; Dosage Form; Ingredient; Strengths
001; SOLUTION; PROPRANOLOL; 3.75MG

FDA Contacts: P. SHIROMANI	Prod Qual Reviewer	(HF-10)	3017962133
E. PFEILER	Micro Reviewer	(HF-22)	3017960642
Y. KNIGHT	Product Quality PM		3017962133
Q. NGUYEN	Regulatory Project Mgr	(HFD-110)	3017960510
K. SRINIVASACHAR	Team Leader		3017961760

Overall Recommendation: ACCEPTABLE on 07-MAR-2014 by C. CAPACCI-DANIEL () 3017963532
PENDING on 10-JUN-2013 by EES_PROD
PENDING on 10-JUN-2013 by EES_PROD

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: NON-STERILE LIQUID (OTHER THAN SUSP & EMULSIONS)

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 07-MAR-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 13-JUN-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

/s/

PRAFULL K SHIROMANI
03/07/2014

OLEN M STEPHENS
03/07/2014

NDA 205410

Propranolol Hydrochloride Oral Solution, 4.28 mg/mL

Each 1 mL contains 4.28 mg of propranolol hydrochloride equivalent to 3.75 mg/mL of propranolol.

Pierre Fabre Dermatologics

Division of Cardio-Renal Products, HFD 110

Prafull Shiromani Ph.D.

Division of Pre-Marketing Assessment 1

Office of New Drug Quality Assessment

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	8
B. Description of How the Drug Product is Intended to be Used.....	10
C. Basis for Approvability or Not-Approval Recommendation.....	11
III. Administrative.....	11
A. Reviewer's Signature.....	11
B. Endorsement Block.....	11
C. CC Block	11
Chemistry Assessment	12
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	12
S DRUG SUBSTANCE [Name, Manufacturer].....	12
P DRUG PRODUCT [Name, Dosage form].....	35
A APPENDICES	180
R REGIONAL INFORMATION	180
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	183
A. Labeling & Package Insert	183
B. Environmental Assessment Or Claim Of Categorical Exclusion	191
III. List Of Deficiencies To Be Communicated.....	191

Chemistry Review Data Sheet

1. NDA 205410
2. REVIEW #: 1
3. REVIEW DATE: 31-Dec-2013
4. REVIEWER: Prafull Shiromani Ph.D.
5. PREVIOUS DOCUMENTS: N/A

Previous DocumentsDocument Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

NDA 205410-Original
Applicant's Response to IR Letter-SN. 0006
Applicant's Response To IR-Label-SN. 0010

17-May-2013
05-Sep-2013
03-Dec-2013

7. NAME & ADDRESS OF APPLICANT:

Name: Pierre Fabre Dermatologie

Address: 45 place Abel Gance Boulogne, France 92100

Representative: John C. Kim

Chemistry Review Data Sheet

Telephone: 973-647-1640

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: (b)(4)
- b) Non-Proprietary Name (USAN): Propranolol Hydrochloride
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 5
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment for proliferating infantile hemangioma (IH) requiring systemic therapy

11. DOSAGE FORM: Oral Solution

12. STRENGTH/POTENCY: Each 1 mL contains 4.28 mg of propranolol hydrochloride equivalent to 3.75 mg/mL of propranolol.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

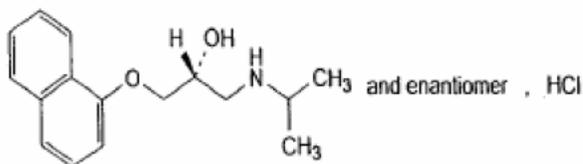
Not a SPOTS product

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

Chemistry Review Data Sheet

(2RS)-1-[(1-methylethyl)amino]-3-(naphthalen-1-yloxy)propan-2-ol hydrochloride

Structural Formula

 $C_{16}H_{21}NO_2$ HCl

Molecular Mass: 295.8 [259.3-propranolol base + 36.5 (hydrochloric acid)]

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS LOA
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	11-Sep-2013	21-Apr-2012
	IV			1	Adequate	17-Sep-2013	21-Aug-2013
				4			04-Jul-2012
				4			13-Nov-2013

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")

Chemistry Review Data Sheet

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: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox			
Biopharm	Pending		
LNC			
Methods Validation	Samples of the DP are available	10/29/13	P. Shiromani: Validation is not required since the analytical methods are conventional.
OPDRA			
EA	Their claim for categorical exclusion is acceptable		P. Shiromani
Microbiology	Recommended for approval	12/15/13	E. Pfeiler

The Chemistry Review for NDA 205410

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has provided adequate responses to the FDA CMC IR letter. However, the completion of the ONDQA Biopharm review is pending. Additionally, OC's overall acceptable recommendation based on site inspection is pending. When these items are completed they will be entered into DARRTS as a Memo-to-file. Pending acceptable recommendations from the OC and ONDQA biopharmaceutics, this NDA will be recommended for approval from a Quality perspective.

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

N/A

II. Summary of Chemistry Assessments

Propranolol hydrochloride is a well known active substance from which capsule, tablet, oral solution and intravenous formulations are approved in both Europe and US for use in adults in cardiovascular diseases. The applicant submitted an e-CTD 505(b)(2) NDA under the PDUFA V Program for (b)(4) (propranolol) oral solution, 3.75 mg/mL. The applicant has accepted FDA's recommendation to label the product as (b)(4) propranolol hydrochloride oral solution 4.28 mg/mL (equivalent to 3.75 mg/mL propranolol); reflected in the revised label (refer to Item II-Review of Common Technical Document – Quality in the body of this review). This recommendation was made to prevent any medication errors, which may have resulted with the original label since there are other propranolol hydrochloride solutions in the market.

Propranolol is a non-selective beta-blocking agent which is developed for the treatment of proliferating infantile hemangioma (IH) requiring systemic therapy. This treatment is to be initiated in infants aged 5 weeks to 5 months. The recommended therapeutic dose of propranolol is (b)(4) to be administered

Executive Summary Section

into two separate doses of (b) (4). The reference listed drug product (RLD) that is the basis for this submission is INDERAL® (propranolol hydrochloride), NDA 16-418 (b) (4) was granted an orphan designation by the FDA on 05-Sep-2008 (#08-667). Clinical Development of this drug was carried out under IND #104,390 (submit date 01-Jul-2009). A pre-NDA meeting was held on 4/6/12; however, no CMC issues were discussed at this meeting...

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

The CMC information for the drug substance was cross-referenced to the DMF # (b) (4) that was filed by (b) (4). A Letter of Authorization was provided in section 1.4.1 of the NDA. The latest amendments for this DMF were reviewed by this reviewer and the DMF determined to be adequate to support this NDA.

Propranolol hydrochloride is described in the US Pharmacopeia. The molecule has one chiral center. The synthetic route produces the racemic mixture. The drug substance is manufactured, packaged, labeled and tested at (b) (4). The process involves (b) (4) steps, described in this review.

The starting material, (b) (4), and the intermediate, (b) (4), have a structural alert for genotoxicity, which prompted an information request that was sent to the applicant. The applicant responded by providing analytical data generated by employing new LC/MS and GC/MS analytical methods. The data demonstrate that the content of these materials in several batches of the drug substance is well below the TTC of (b) (4) ppm., thereby obviating any safety concern.

The drug is manufactured as polymorph (b) (4). The characterization and proof-of-structure is based on IR, proton-NMR, MS, and elemental analyses. The drug substance is controlled by the drug product manufacturer according to USP monograph and the additional test "Related substances by LC" based on PH. Eur. Batch analysis information is provided for three production scale batches, which complies with the USP specification.

Executive Summary Section

The drug substance is packaged in (b) (4).
Based on satisfactory stability data in the DMF, the drug substance is assigned a (b) (4) months re-test period.

The applicant has provided adequate responses to IR comments on the drug substance.

DRUG PRODUCT

The drug product is an oral solution. Each mL of propranolol (V0400) oral solution contains 4.28 mg of propranolol hydrochloride, which is equivalent to 3.75 mg of propranolol free base. The solution is supplied in a 125 mL type III amber glass bottle containing 120 mL of a colorless to slightly yellow, clear solution with a fruity odor. The bottle is fitted with with an insert and closed by a white (b) (4) cap (b) (4).

The drug product information includes formulation development (definition of Quality Target Product Profile, identification of CQAs, determination of critical quality attributes of the drug substance and selection of appropriate excipients), formulation and optimization of oral solution and initial risk assessment of the manufacturing process. A risk assessment of the drug substance attributes led to the following cautions for further development:

- Selection of a pH \leq (b) (4) for enhanced stability
- Selection of an amber glass bottle as primary package to protect from light induced degradation.

The formulation comprises of hydroxyethyl cellulose (b) (4) saccharin sodium (b) (4), flavors (strawberry and vanilla), citric acid monohydrate (b) (4) and (b) (4) water. The flavors' DMF (b) (4)) was reviewed by this applicant to be adequate to support this NDA.

The manufacturing process for the oral solution is a typical process. Batch analysis data on three batches manufactured by (b) (4) were provided. The total degradation products content was $<$ (b) (4) % and each unspecified degradation products was (b) (4) %.

The drug product specification is generally acceptable as it conforms to ICH Q6A.

Executive Summary Section

Container closure system studies include justification of the choice of primary packaging components and measuring device, compatibility studies with container closure system, compatibility study between oral solution and the immediate packaging materials and also the oral syringe. Compatibility studies also included in use stability study in milk and fruit juices.

Satisfactory product stability is demonstrated after 18 months of long-term storage and 6 months at accelerated storage. Based on the data the applicant proposes a shelf-life of (b) (4) months when stored at 25°C. Satisfactory stability is also demonstrated in an in-use stability study after 60 days under the conditions of administration (twice-a-day).

The applicant states that this submission qualifies for a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR § 25.31(b) since the expected introduction concentration (EIC) at the point of entry into the aquatic environment is below 1 part per billion (ppb)/day limit. Their request is granted by this reviewer.

The applicant has provided adequate responses to comments in the CMC IR Letter. They have provided updated 24 and 30 months stability data at 25°C/60% RH and 30°C//75% RH, which were reviewed to be satisfactory. Based on these data they propose a shelf-life of 36 months for the drug product; their proposal is acceptable based on ICH Q1E, 2.4.1.1.

The applicant's updated label and labeling comply with FDA's recommendation that the strength of their product should be consistent with the HCl salt, which is allowed under the exception clause of the USP <1121> Nomenclature Policy. This is to prevent any medication errors since there are other propranolol hydrochloride solutions in the market. The equivalency statement, "Each 1 mL contains 4.28 mg of propranolol hydrochloride equivalent to 3.75 mg/mL of propranolol," is stated on the label.

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

(b) (4) oral solution (3.75 mg/mL) is a beta-blocker indicated for the treatment of proliferating infantile hemangioma requiring systemic therapy, to be initiated in patients aged 5 weeks to 5 months.

Executive Summary Section

The product should be stored at 25°C (77°F); excursions permitted to 15° - 30° C (59° - 86°F). The product has a shelf-life of 36 months. The product should be discarded after two months from opening.

.....***DOSAGE AND ADMINISTRATION***.....



C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided adequate responses to the FDA CMC IR letter. However, the completion of the ONDQA Biopharm review is pending. Additionally, OC's overall acceptable recommendation based on site inspection is pending. When these items are completed they will be entered into DARRTS as a Memo-to-file. Pending acceptable recommendations from the OC and ONDQA biopharmaceutics, this NDA will be recommended for approval from a Quality perspective.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Prafull Shiromani Ph.D.
ChemistryTeamLeaderName/Date: Olen Stephens Ph.D.
ProjectManagerName/Date: Nguyen Quiynh

C. CC Block

180 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

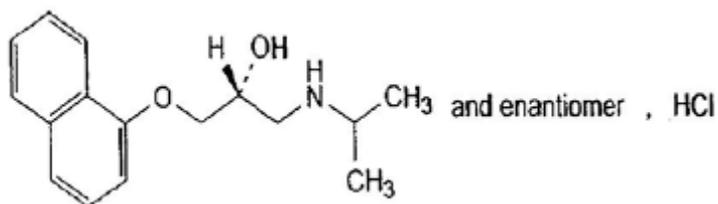
/s/

PRAFULL K SHIROMANI
12/31/2013

OLEN M STEPHENS
12/31/2013

Initial Quality Assessment (IQA)
ONDQA/Branch I

OND Division: Division of Cardiovascular and Renal Products
NDA: 205410
Applicant: Pierre Fabre Dermatologie
Letter Date: May 17, 2013
Stamp Date: May 17, 2013
PDUFA Goal Date: March 17, 2014
Tradename: (b) (4)® (proposed)
Established Name: Propranolol
Dosage Form: Oral Solution, 3.75 mg/mL
Route of Administration: Oral
Indication: Treatment of proliferating infantile hemangioma (IH) requiring systemic therapy
Assessed by: Rao V. Kambhampati, Ph.D.
ONDQA Fileability: Yes
Structural Formula:



Summary

Propranolol hydrochloride is a well-known active substance for which capsule, tablet, oral solution and intravenous formulations are approved in both Europe and US for use in adults in cardiovascular diseases.

The applicant submitted an e-CTD 505(b)(2) NDA under the PDUFA V Program for (b) (4) (propranolol) oral solution, 3.75 mg/mL. Propranolol is a non selective beta-blocking agent which is developed for the treatment of proliferating infantile hemangioma (IH) requiring systemic therapy. This treatment is to be initiated in infants aged 5 weeks to 5 months. The recommended therapeutic dose of propranolol is (b) (4) to be administered into 2 separate doses of (b) (4). The reference listed drug product (RLD) that is the basis for this submission is INDERAL® (propranolol hydrochloride), NDA 16-418.

The active substance is propranolol hydrochloride (4.28 mg/mL equivalent to 3.75 mg/mL of propranolol), a non-selective beta-adrenergic receptor blocking agent.

(b) (4) oral solution is to be administered using a dedicated oral dosage syringe as dose delivery device. (b) (4) was granted an orphan designation by the FDA on September 05, 2008 (#08-667). Clinical development of this drug was carried out under IND# 104,390 (submit date 7/1/09). Pre-NDA meeting was held on 4/26/12. No CMC issues were discussed at the meeting. On 10/15/12, the applicant was granted conditional approval of the proprietary name “(b) (4)”. Top-line results meeting was held on 12/7/12 and at this meeting DMEPA encouraged the sponsor to submit their risk analysis for the oral dosing syringe calibrated in mg (versus mL) prior to NDA submission (i.e., to IND 104390) because the sponsor indicated that they want to commercialize an oral dose syringe calibrated in mg rather than mL. In an email dated 1/9/13, the sponsor indicated to the division that they are not planning to submit the risk analysis and in the subsequent email dated 1/16/13, they decided to not pursue marketing of an oral syringe in mg and will follow the previous recommendation by the FDA to use a syringe calibrated in mL.

Drug Substance

The CMC information for the drug substance was cross-referenced to the DMF# (b) (4) that was filed by (b) (4). A Letter of Authorization from (b) (4) was provided in section 1.4.1 of the NDA. Propranolol hydrochloride is described in the US Pharmacopeia. It has a molecular formula of $C_{16}H_{22}ClNO_2$ and molecular weight of 295.8. The molecular weight of the free base is 259.3. The molecule has one chiral center. The synthetic route produces the racemic mixture. Propranolol hydrochloride is a white to off-white, crystalline powder and it is odorless and has a bitter taste. It is soluble in water and in alcohol, slightly soluble in chloroform, and practically insoluble in ether. It has melting range of 162°-165°C. It is manufactured as polymorph (b) (4). The drug substance is manufactured, packaged, labeled, and tested as according to GMP at (b) (4).

(b) (4). The process involves (b) (4) steps. The first step involves (b) (4). The characterization and proof-of-structure is based on the IR, proton-NMR, MS, and elemental analysis. The description for impurities included related substance ((b) (4), a starting material), process related impurity ((b) (4)), degradation/byproduct impurities ((b) (4)). All the impurities are controlled by appropriate validated LC methods. (b) (4) are used in the manufacturing process and they are controlled by the validated GC method. The drug substance specification included appearance, identification by IR (USP <197M>), LC, and (b) (4).

(b) (4) assay for propranolol hydrochloride by LC, and impurities determination by LC. The identified individual impurities (b) (4), any single unidentified impurity has an acceptance criterion of (b) (4)% and total impurities content has an acceptance criterion of (b) (4)%. The drug substance is controlled by the drug product manufacturer according to USP monograph and the additional test “Related substances by LC” based on the Ph. Eur. The analytical procedures were cross-referenced to the DMF# (b) (4) except the related substances test which is performed by the applicant as according to Ph.

Eur. monograph and described in section 3.2.S.4.2. The validation of analytical procedures also cross-referenced to the DMF# (b) (4) except the related substances which was performed by the applicant. Batch analysis information was provided for three production size batches and they comply with the USP specification. The batch size was in the range of (b) (4). The assay ranged from 99.7 to 100.4%. None of the impurities was greater than (u) (4) % and the total impurities content was greater than (b) (4) %. This indicates that the manufacturing process is adequately controlled to produce the drug substance with consistent quality and purity. The proposed limits for residual solvents and related substances by the DMF Holder are based on trend data, ICH guidelines and in-house validated methods (DMF# (b) (4)). Specifications set by the applicant are the same as the DMF Holder for related substances and in accordance with Ph Eur Monograph for propranolol hydrochloride. Information for the reference standard was cross-referenced to DMF# (b) (4) and the applicant conducts the IR identification and assay tests. The drug substance is packaged (b) (4).
(b) (4) Stability information was cross-referenced to the DMF# (u) (4). The applicant proposed a re-test period of (b) (4) months when stored in the proposed container/closure system but stated that no specific storage conditions (temperature and humidity) are required.

Drug Product

The drug product is an oral solution. Each mL of propranolol (V0400) oral solution contains 4.28 mg of propranolol hydrochloride, which is equivalent to 3.75 mg of propranolol free base. The solution is supplied in a 125 mL type III amber glass bottle containing 120 mL of a colorless to slightly yellow, clear solution with a fruity odor. The bottle is fitted with an insert and closed by a white (b) (4) screw cap (b) (4). A specific 5 mL oral syringe, graduated in mL, is provided for administration. The secondary packaging consists of a cardboard box. The components and composition of the drug product are summarized in the Table 6 below:

Table 6: Composition of the drug product

Component	Quantity per mL	Quantity per bottle (120 mL filled)	Function	Reference to Quality Standard
Drug substance Propranolol base (corresponding to propranolol hydrochloride) ⁽¹⁾	3.75 mg (4.28 mg)	(b) (4)	(b) (4)	USP
Excipients				
Hydroxyethyl Cellulose (b) (4)	(b) (4)			USP/NF USP
Saccharin sodium				
Strawberry flavour (b) (4)				In-house specification (MMP-17884-C)
Vanilla flavour (b) (4)				In-house specification (MMP-18371-C)
Citric acid monohydrate				USP
Water (b) (4)				USP
(b) (4)				

⁽¹⁾Theoretical value taking into account a ratio of: $\frac{\text{molecular mass of propranolol hydrochloride}}{\text{molecular mass of propranolol}} = (b) (4)$

The composition of the strawberry flavor and vanilla flavor were provided in the CMC section. The drug substance, citric acid monohydrate, and (b) (4) water are of USP grade and hydroxyethyl cellulose is of USP/NF grade. No novel excipients are used in the formulation.

The submission contained some elements of QbD in the process development section. A QbD approach was proposed as according to ICH Q8 (R2) Guideline. The information is related to the following:

1. Definition of the Quality Target Product Profile (QTPP) as it relates to quality, safety and efficacy,
2. Identification of potential Critical Quality Attributes (CQAs) of the drug product, so that those product characteristics having an impact on product quality can be studied and controlled,
3. Determination of critical quality attributes of the drug substance and selection of the appropriate excipients to deliver drug product of the desired quality,
4. Selection of an appropriate manufacturing process,
5. Definition of a control strategy to guarantee the quality of the drug product.

The drug substance information included initial risk assessment of drug substance attributes, updated risk assessment of drug substance attributes, drug substance supplier comparability, and comparability of propranolol hydrochloride with the excipients used in the formulation.

The drug product information included formulation development, formulation and optimization of oral solution, initial risk assessment of oral solution manufacturing process, oral solution

process development, hydroxyethyl cellulose solubilization process development, active substance and components solubilization, and updated risk assessment.

Container closure system studies included justification of the choice of primary packaging components and measuring device, compatibility studies with container closure system, compatibility study between oral solution and the immediate packaging materials and also the oral syringe. Compatibility studies also included in use stability study in the milk and fruits juice.

The applicant provided justification for the proposed concentration of 3.75 mg/mL. In the Module 3, section 3.2.P.2 (Tables 7 and 9), the applicant provided Quality Target Product Profile information and Critical Quality Attributes of V0400 3.75 mg/mL oral solution. The drug substance material attributes (MA) which can have an impact on the drug product quality were identified: (b) (4)

(b) (4) A risk assessment of the drug substance material attributes was performed to evaluate the impact that each material attribute could have on the drug product quality. This evaluation led to the following cautions for further pharmaceutical development of V0400 3.75 mg/mL oral solution:

- selection of a pH \leq (b) (4) for the drug product V0400 3.75 mg/mL oral solution,
- selection of an amber glass bottle as primary packaging, in order to avoid any characteristics' changes and degradation products which could appear under light exposure.

The proposed manufacture, packaging, testing, and release of V0400 3.75 mg/mL oral solution is conducted in accordance with cGMP at the following facility: (b) (4)

(b) (4) The commercial batch size for the bulk solution of V0400 3.75 mg/mL oral solution is (b) (4) and a table was provided for the batch formula. The bottles are filled with a volume of V0400 3.75 mg/mL oral solution sufficient to permit the withdrawal of the nominal volume declared on the label i.e. 120 mL. Based on the minimal filling volume of (b) (4) mL, the theoretical batch size expressed in number of bottles is (b) (4) bottles.

The manufacturing process for V0400 oral solution is a standard process and consists of the following main operations:

(b) (4)



The flow diagram of the manufacturing process and in-process controls of V0400 3.75 mg/mL oral solution were provided in table format. This table also included the controls of critical steps applied during the manufacturing process. The process validation studies will be conducted on 3 production-scale batches ([redacted]).

The proposed specification for the drug product is as follows:

Table 15: Specifications for V0400 3.75 mg/mL oral solution

TESTS PERFORMED	Acceptance criteria	Reference method
CHARACTERISTICS	Colourless to slightly yellow, clear solution with a fruity odour	MPF DEV-20286-C
IDENTIFICATION Propranolol by LC (USP<621>) Propranolol by UV spectrum (USP<851>)*	(b) (4)	MPF DEV-20286-C
TESTS		
pH		Ph. Eur.2.2.3
Deliverable volume (mL)*		MPF DEV-20286-C
Degradation products by LC (in relative %) (USP<621>) - Total - Unspecified degradation product (each)		MPF DEV-20286-C
Microbiological examination - Microbial enumeration tests (CFU/mL) (USP<61>) . Total aerobic microbial count . Total yeasts and moulds count - Specified microorganism (/mL) (USP<62>)* . <i>Escherichia coli</i>		MPF DEV-20286-C
ASSAY Propranolol by LC (mg/mL) (USP<621>)		MPF DEV-20286-C

*tests only performed at release

Analytical test methods were developed and validated by INSTITUT DE RECHERCHE PIERRE FABRE (IRPF) for the release and stability testing of V0400 3.75 mg/mL oral solution. These analytical test methods were transferred to (b) (4). IRPF and (b) (4) test methods of the specified tests are equivalent. Compendial methods are used where applicable and are referenced in the drug product specification. Detailed information and results of the validation of respective methods are documented in the validation reports provided in Module 3, section 3.2.R.2. The applicant stated that concerning the deliverable volume, no further validation is required. A summary of the validation results were provided in the submission.

Batch analyses data on three industrial-scale batches manufactured by (b) (4) were provided. The results are pretty consistent. The total degradation products content was (b) (4) %. The unspecified degradation products (each) content was < (b) (4) % for two batches but for the third batch (SB0796/B), the degradant was identified by RRT ((b) (4)) and its level was (b) (4)%. The applicant stated that the degradation products are detected only after light exposure of the

unprotected product. The only impurity observed by LC has a RRT (relative retention time) of (b) (4) and reaches only (b) (4)% under ICH stress conditions in clear glass vial. No further identification has been performed taking into account that no related substances appear in V0400 3.75 mg/mL oral solution packaged in amber glass bottle and exposed to light.

The reference standard complies with the Ph.Eur. specifications for propranolol hydrochloride.

The drug product is packaged in a 125 mL amber glass type III bottle, with a (b) (4) with a white (b) (4) cap with a (b) (4) (b) (4) A specific measuring device, 5 mL (b) (4) oral syringe graduated from 0.3 to 5 mL (0.1 mL gradation step) with (b) (4) plunger is supplied for oral administration. The graduated oral syringe and the bottle containing the drug product are packaged together in the same secondary packaging, thus meeting the combination product definition under 21 CFR 3.2(e)(2). The suitability of the proposed packaging and its intended use was provided in Module 3, section 3.2.P.2.4. All primary packaging components are commonly used in marketed oral pharmaceutical solutions.

The primary stability batches (see Module 3, section 3.2.P.8.1.) were packaged in the same container closure system intended for marketing. Detailed descriptions of the primary packaging components, their materials of constructions, specifications, dimensions and manufacturers were provided in Module 3, section 3.2.P.7. (b) (4) effectiveness of the primary packaging have been tested according to requirements for a multi-dose container. The description of the measuring device components, material of constructions, specifications, critical dimensions and manufacturers were provided in Module 3, section 3.2.P.7. The secondary packaging is a cardboard box.

Stability studies were conducted on V0400 3.75 mg/mL oral solution to evaluate the quality over time under the influence of the temperature and light and to establish the drug product specification, shelf-life, and recommended labeled storage conditions. The studies included the following:

Forced degradation studies:

- Heat stress: 12 days at 80°C
- Photostability testing according to ICHQ1B conditions

Stability study under freezing conditions

Stability study in the refrigerator: 3 months at +5°C

In-use stability study

ICH stability studies under accelerated (40°C/75%RH) and long-term condition (25°C/60%RH and 30°C/75%RH) conducted on industrial scale batches produced by (b) (4).

The compatibility studies between V0400 3.75 mg/mL oral solution, the immediate packaging materials and the oral syringe were provided in Module 3, section 3.2.P.2.4. The compatibility studies of V0400 3.75 mg/mL oral solution in milk and in fruits juice were provided in Module 3, section 3.2.P.2.6.

The applicant stated that all batches complied with the proposed acceptance criteria during the stability study and have the same behavior.

Slight coloration of the formulation upon storage was found to be due to the presence of flavors in the formulation which did not impact on the safety and efficacy according to the applicant. A slight increase ^{(b) (4)} of the pH values, according to temperature was observed after 6 months at 40°C/75%RH and 18 months at 30°C/75%RH but the pH always remained in the specifications (^{(b) (4)}). No degradation of the propranolol was observed after 6 months at 40°C/75%RH and 18 months at 30°C/75%RH or 25°C/60%RH. At release, the microbial enumeration test (TAMC and TYMC) were below the current specifications and no specified microorganism is detected. After 6 months at 40°C/75%RH and 12 months at 30°C/75%RH or at 25°C/60%RH, no change occurred on the microbial contamination. After 6 months at 40°C/75%RH and 12 months at 30°C/75%RH and 25°C/60%RH, the drug product met the requirements of efficacy of antimicrobial preservation according to USP <51> for oral preparation. A slight variability was observed on the propranolol assay results without significant trend and the assay always remained in the specifications (^{(b) (4)}).

V0400 3.75 mg/mL oral solution is not sensitive to temperature exposure.

V0400 3.75 mg/mL oral solution is sensitive to light exposure.

V0400 3.75 mg/mL oral solution packaged in amber glass bottle and in its secondary packaging is well protected from light.

The drug product does not support storage under freezing condition.

After 3 months at 5°C±3°C, no change was observed. Storage in refrigerator is allowed.

Under in-use stability conditions, no significant change was observed.

After 18 months under long term conditions (25°C/60%RH or 30°C/75%RH) and 6 months under accelerated condition (40°C/75%RH), the stability results obtained show the good stability of V0400 3.75 mg/mL oral solution which complies with the specifications proposed.

The applicant proposed a shelf-life of ^{(b) (4)} months when stored at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) and in-use stability period of 60 days under the conditions of administration (twice a day) without a requirement to store the bottle out of its secondary packaging.

Master Batch records were provided for stability batches, clinical batches, and commercial batches. Executed batch records were provided for three stability batches and three clinical batches.

Analytical validation reports were provided for identification and assay by LC; degradation products test by LC; and microbiological examination method.

Critical Review Issues:

Drug Substance

1. The CMC information for the drug substance was cross-referenced to DMF# (b) (4). The DMF was last reviewed by Jennifer Liang (OGD) and it was found to be adequate as of 3/26/13 and the review was filed in DARRTS on 4/1/13. Later, the Holder submitted two annual reports (4/25/13 and 5/9/13) and one amendment (5/2/13). These three documents need to be reviewed.
2. The synthesis produces (b) (4).
3. Solubility of drug substance in water in mg/mL should be provided.
4. Polymorph (b) (4) is produced by the synthesis and the applicant stated that the IR is the specific method for determination. Does the IR method able to detect, if the drug substance is contaminated with other polymorphic forms?
5. Did the applicant evaluate the genotoxic potential of the starting materials, reagents, byproducts, intermediates, and impurities?
6. Provide justification for the proposed acceptance criterion for specific rotation as between (b) (4).
7. The applicant stated that the reference standard complies with the Ph.Eur. specifications for propranolol hydrochloride. It needs to be compared with the USP reference standard specifications also.

Drug Product

8. Applicant stated that the manufacturing processes implemented for the phase 2/3 clinical batches and commercial batches are not significantly different. It is advised to compare both the processes and if any critical differences exist, they should be clarified with the applicant.
9. Pivotal clinical trial formulations contained (b) (4), however, it has been deleted in the commercial formulation. It should be evaluated if deletion of (b) (4) in commercial formulation has any impact on the quality of the drug product.
10. In the drug product specification, acceptance criteria for pH and total degradation products content could be tightened and the acceptance criteria for deliverable volume and assay could be changed to a range.
11. For the stability batch, after light exposure, when protected from light with aluminum foil, the drug product remained colorless, however, in clear glass bottle, yellowish-brown and opalescent coloration was observed in the chromatogram of the placebo exposed to light. Three degradants were formed. The applicant stated that two of these degradants

were due to (b) (4) and the third degradant (RRT = (b) (4)) is due to (b) (4) degradation. Characterization of the (b) (4) degradant should be requested.

12. The applicant stated that the presence of (b) (4)
13. On the basis of 18 months of long term and intermediate term data and 6 months of accelerated stability data, applicant requested an expiration dating period of (b) (4) months. Based on the real time data, expiration dating period of (b) (4) months seems high.
14. Under accelerated storage conditions, there was a gradual increase of assay values probably due to loss of water.
15. Control of critical steps and intermediates (section 3.2.P.3.4; Table 1: In-process controls) did not contain any method for assay of active ingredient.
16. The applicant stated that concerning the deliverable volume, no further validation is required. This claim needs to be checked.

Comments and Recommendations

From the quality (CMC) stand point, the NDA is fileable -- see attached Filing Check List. All necessary facilities were entered into EES but the quality reviewer should confirm the completeness and accuracy of the entries. Methods Validation (MV) by DPA is not deemed necessary based on a preliminary review since the 7 criteria in IQP 5105 are not met, however, the reviewer may choose to initiate MV if the in-depth review reveals concerns with any of the analytical methods. A categorical exclusion from the environmental assessment requirement has been requested by the applicant. The drug substance has been approved previously under several NDAs and ANDAs and the cross-referenced DMF was reviewed previously and it was found to be adequate. The NDA submission contains some elements of the QbD in the Process Development section. The applicant requested (b) (4) months expiration dating period on the basis of 18 months of long-term and intermediate term and 6 months of accelerated stability data. The dosage form is a simple oral solution and the NDA requires standard review, therefore, a single CMC reviewer is recommended.

Rao V. Kambhampati, Ph.D., Chemist, Branch I/DNDQA I

Ramesh Sood, Ph.D., Branch Chief I/DNDQA I

PRODUCT QUALITY -- CMC and BIOPHARMACEUTICS

FILING REVIEW FOR NDA

NDA Number:
205410

NDA Type: 505 (b)(2)

Original NDA, N-000

Established/Proper Name:
(b) (4) ® (propranolol) oral
solution, 3.75 mg/mL

Applicant: Pierre
Fabre Dermatologie

Letter Date: 5/17/13

Stamp Date: 5/17/13

PDUFA Goal: 3/17/14

CMC Reviewer: Prafull K. Shiromani, Ph.D.

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	Yes	No	Comment

5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			Not applicable
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 			Not applicable
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		Cross-referenced to DMF # (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Cross-referenced to DMF # (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Cross-referenced to DMF # (b) (4)
15.	Does the section contain controls for the DS?	X		Cross-referenced to DMF # (b) (4)
16.	Has stability data and analysis been provided for the drug substance?	X		Cross-referenced to DMF # (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?	X		Only some elements of QbD present.
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?		X	Clinical trial formulations contained (b) (4) however, it has been deleted in the commercial formulation because it was found unnecessary.
23.	Have any Comparability Protocols been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?			18 Months of long-term and intermediate term data and 6-months of accelerated data were provided and applicant requested (b) (4) months of expiration dating period.
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	X		Only some elements of QbD present.
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment

29.	Is there a methods validation package?	X		Only method validation reports were provided.
-----	--	---	--	---

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		Information for drug product packaging components was provided in the NDA.

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		Fileable for Product Quality. See Biopharmaceutics Filing Review for fileability of the Biopharmaceutics Section.

35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not applicable.
36.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			See Biopharmaceutics filing review.
37.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	X		The amount of stability data submitted in the NDA does not support (b) (4) months expiration dating period for the drug product. The actual duration will be determined after a complete review of the submitted stability data.

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

/s/

RAO V KAMBHAMPATI
06/21/2013

RAMESH K SOOD
06/24/2013