CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022571Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: **July 12, 2010**

From: **Yichun Sun, Ph.D.**
Review Chemist
Division of New Drug Quality Assessment II
ONDQA

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch IV
Division of New Drug Quality Assessment II
ONDQA

To: **CMC Review #1 of NDA 22-571**

Subject: Final CMC Recommendation

At the time when the CMC review #1 was written, the result of Establishment Evaluation was pending.

On July 12, 2010, the Office of Compliance gave an overall "Acceptable" recommendation for all the facilities involved in the manufacture and test of the drug substance and drug product (see the EER Summary Report attached).

Therefore, this NDA is now recommended for ***approval*** from the CMC perspective.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22571/000	**Sponsor:**	SHIONOGI PHARMA
Org. Code:	540		5 CONCOURSE PKY STE 1800
Priority:	3		ATLANTA, GA 30328
Stamp Date:		**Brand Name:**	GLYCOPYRROLATE ORAL SOLUTION
PDUFA Date:		**Estab. Name:**	
Action Goal:		**Generic Name:**	(b) (4)
District Goal:	29-MAY-2010	**Product Number; Dosage Form; Ingredient; Strengths**	001; LIQUID; GLYCOPYRROLATE; 1MG/5ML

Application:	NDA 22571/000	**Sponsor:**	SHIONOGI PHARMA
Org. Code:	540		5 CONCOURSE PKY STE 1800
Priority:	3		ATLANTA, GA 30328
Stamp Date:	28-SEP-2009	**Brand Name:**	GLYCOPYRROLATE ORAL SOLUTION
PDUFA Date:	28-JUL-2010	**Estab. Name:**	
Action Goal:		**Generic Name:**	(b) (4)
District Goal:	29-MAY-2010	**Product Number; Dosage Form; Ingredient; Strengths**	001; LIQUID; GLYCOPYRROLATE; 1MG/5ML

FDA Contacts:	J. DAVID	Project Manager	301-796-4247
	Y. SUN	Review Chemist	301-796-1388
	S. DING	Team Leader	301-796-1349

Overall Recommendation: ACCEPTABLE on 12-JUL-2010 by M. STOCK (HFD-320) 301-796-4753

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

(b) (4)

DMF No:

AADA: (b) (4)

Responsibilities:
DRUG SUBSTANCE LABELER
DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: NON-STERILE BULK BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 29-OCT-2009

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** 1050658 **FEI:** 1050658

MIKART INC
1750 CHATTAHOOCHEE AVE NW
ATLANTA, GA 303182112

DMF No:

AADA: N 017558
I 061716
N 012827
N 014764

Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: LIQUIDS (INCLUDES SOLUTIONS, SUSPENSIONS, ELIXIRS,

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 12-JUL-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

(b) (4)

DMF No:

AADA: (b) (4)

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 02-FEB-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22571	ORIG-1	SHIONOGI PHARMA INC	GLYCOPYRROLATE ORAL SOLUTION

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

/s/

YICHUN SUN
07/13/2010

MOO JHONG RHEE
07/13/2010
Chief, Branch IV

NDA 22-571

Cuvposa® (glycopyrrolate) oral solution

Shionogi Pharma, Inc.

Yichun Sun, Ph.D.

Review Chemist

Branch IV, Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

CMC REVIEW OF NDA 22-571
For the Division of Dermatology and Dental Products (HFD-540)

Table of Contents

Chemistry Review Data Sheet

1. NDA: #22-571

2. REVIEW #: 1

3. REVIEW DATE: 29-June-2010

4. REVIEWER: Yichun Sun, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Pre-IND meeting minutes	October 10, 2000
IND 61,716	December 29, 2000
End-of-Phase 2 meeting minutes	April 17, 2007
Pre-NDA meeting minutes	December 15, 2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	September 25, 2009
Amendment (C)	November 18, 2009
Amendment (QR)	January 21, 2010
Amendment (QR)	March 23, 2010
Amendment (BH)	April 2, 2010
Amendment (LC)	May 12, 2010
Amendment (LC)	June 8, 2010
Amendment (BH)	June 22, 2010
Amendment (EG)	June 23, 2010

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Shionogi Pharma, Inc.
Address:	Five Concourse Pkwy Suite 1800 Atlanta, GA 30328
Representative:	Marty Solberg
Telephone:	(678) 459-1616

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Cuvposa®
b) Non-Proprietary Name (USAN): Glycopyrrolate
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: Standard Review

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

10. PHARMACOL. CATEGORY: Anticholinergic (antimuscarinic)

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 16 oz (1 mg per 5 mL)

13. ROUTE OF ADMINISTRATION: Oral

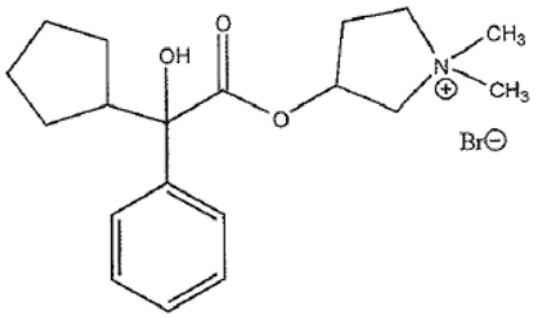
14. Rx/OTC DISPENSED: __X__ Rx ___OTC

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:

CAS: Pyrrolidinium, 3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethyl-,bromide



Empirical formula: $C_{19}H_{28}B_rNO_3$

Molecular weight: 398.33

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	June 14, 2010	Y. Sun
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			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:
N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	----	----
EES	Pending	----	----
Pharm/Tox	N/A	----	----
Biopharm	N/A	----	----
LNC	N/A	----	----
Methods Validation	To be validated per ONDQA Policy	----	----
DMET/DDMAC	N/A	----	----
EA	Categorical Exclusion Acceptable	06/29/2010	Y. Sun
Microbiology	N/A	----	----

The Chemistry Review for NDA 22-571

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. The labels have adequate information as required. However, the Office of Compliance has not issued an "Acceptable" overall recommendation on the manufacture and test sites of the drug substance and drug product as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until the site acceptability is established.

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)

Drug Substance

The drug substance used in the drug product of this NDA is glycopyrrolate USP, (b) (4) with a melting point between 193 and 198 ºC. (b) (4) Detailed CMC information was referred to DMF (b) (4) A letter of authorization dated June 24, 2009 was provided. The DMF has been reviewed and found adequate for supporting the use of glycopyrrolate USP in NDA 22-571.

Drug Product

Cuvposa® is indicated for the treatment of (b) (4) (chronic (b) (4) severe) drooling in pediatric patients. The drug product is an oral solution containing 1 mg glycopyrrolate USP per 5 mL. Glycopyrrolate oral solution is prepared (b) (4) glycopyrrolate, sorbitol solution, glycerin, citric acid, sodium citrate hydrous, saccharin sodium, propylene glycol, methylparaben, propylparaben, natural and artificial cherry flavor (b) (4), and purified water. Sixteen fluid ounces of the solution is packaged in each polyethylene (HDPE) bottle with a (b) (4) cap for marketing. The in-process controls implemented during the manufacturing process are: (b) (4) The identity, purity, strength and quality of the drug product are adequately controlled by the drug product specification. The proposed expiration dating period of 36 months is supported by the long-term stability data provided. The drug product would qualify for categorical exclusion from the preparation

of an environmental assessment according to 21 CFR 25.31(b). The carton and container labels, and package insert meet the requirements of 21 CFR 201.

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

Doses are initiated at approximately 0.01-0.02 mg/kg three times daily and titrated in increment of 0.02 mg/kg every 5 - 7 days. Most optimal doses range from approximately 0.01 to about 0.1 mg/kg three times daily. The maximum recommended dosage is 0.1 mg/kg three times daily. Glycopyrrolate is dosed at up to 15 mL per dose which is equivalent to 3 mg of glycopyrrolate per dose. The presence of high fat food reduces the oral bioavailability of Cuvposa® if taken shortly after a meal. Cuvposa® should be dosed at least one hour before or after meals as reasonably feasible.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period. All labels have the required information. However, Office of Compliance has not issued an "Acceptable" overall recommendation on the facilities involved in the manufacture and test of the drug substance and drug product.

III. Administrative

A. Reviewer's Signature

/s/ Y. Sun, Ph.D.

B. Endorsement Block

Yichun Sun, Ph.D.
Reviewer _____ Date

Moo-Jhong Rhee, Ph.D.
Branch Chief _____ Date

C. CC Block

Shulin Ding, Ph.D.
Pharmaceutical Assessment Lead _____ Date

Jeannie C. David M.S.
Project Manager _____ Date

62 pages have been withheld in full immediately following this page as B4 (CCI/ TS).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22571	ORIG-1	SHIONOGI PHARMA INC	GLYCOPYRROLATE ORAL SOLUTION

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

/s/

YICHUN SUN
06/29/2010

MOO JHONG RHEE
06/30/2010
Chief, Branch IV

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division:	Division of Dermatology and Dental Products
NDA:	22-571
Applicant:	Sciele Pharma, Inc.
Stamp Date:	Sep. 28, 2009
PDUFA Date	July 28, 2010
Trademark:	Not yet proposed
Established Name:	Glycopyrrolate
Dosage Form:	Solution
Route of Administration:	Oral
Indication:	(b) (4) (chronic, (b) (4) severe) drooling in pediatric patients
PAL:	Shulin Ding

	YES	NO
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☒	☐

Summary and Critical Issues:

A. Summary

Sciele is submitting a 505(b) (2) New Drug Application (NDA) for the prescription use of glycopyrrolate oral solution 1 mg/5 mL. The product is intended for treatment of (b) (4) (chronic, (b) (4) severe) drooling in pediatric patients, and has been designated as an orphan drug.

The applicant references DMF (b) (4) for the CMC information of the proposed drug substance, glycopyrrolate USP. (b) (4)

The proposed drug product is a clear, cherry flavored solution packaged in opaque, white, high density polyethylene bottles with white, (b) (4), child–resistant caps. (b) (4) configurations are proposed: 16 oz, (b) (4). The formulation contains 0.2 mg of glycopyrrolate in each milliliter, and has the following excipients: sorbitol solution, USP; glycerin, USP; citric acid, USP; sodium citrate, USP; saccharin sodium, USP; propylene glycol, USP; methylparaben, NF; propylparaben, NF; Natural and artifical Cherry Flavor (b) (4); and Purified water, USP. The flavoring agent, Natural and artifical Cherry Flavor (b) (4), is a novel excipient. The to-be-marketed formulation is the same formulation used in the Phase 3 clinical studies and registration stability batches.

The proposed product is manufactured (b) (4)

(b) (4)

Stability data provided in the initial submission to support an expiration dating period of 36 months at the storage temperature of 20-25°C with excursions permitted to 15-30°C include 36 months at 25°C/60% RH, and 6 months at 40°C/75% RH from five, (b) (4) batches for the configurations of 16 oz, (b) (4), respectively. Additionally, a photostability study was conducted to evaluate the sensitivity of the drug product to light exposure. All registration stability batches are (b) (4) in batch size, which is slightly above the one-tenth of the proposed commercial scale (b) (4)

B. Critical issues for review

Drug Substance DMF (b) (4)

- (b) (4)

Natural and artifical Cherry Flavor (b) (4)

- The composition and manufacturing information of this flavoring agent can not be found in the NDA, and should be sought from the applicant in order to assess its safety since this is a novel excipient. The name of the excipient indicates that the flavoring agent can be a synthetic one or an extract from a natural source. It is important to know which one (synthetic or natural) was used in the manufacture of clinical and registration stability batches. Synthetic version and natural extract bear different safety concerns.

Environment Assessment

- The applicant is also the holder of an approved glycopyrrolate NDA 12-827 (Robinul and Robinul Forte glycopyrrolate tablets). It is unclear whether the EIC-Aquatic calculation submitted to this NDA has included NDA 12-827 and its supplements.

C. Comments for 74-Day Letter:

- To support your categorical exclusion claim from the preparation of Environmental Assessment , provide 5 year forecast for the production of glycopyrrolate drug substance for this NDA and any related applications (such as NDA 12-827 and its supplements) held by you. The EIC-Aquatic calculation should use the highest quantity in a given year and should include all related applications.

- Provide representative samples packaged in the to-be-marketed container/closure system for visual examination of the product.

D. Comments/Recommendation:

The application is fileable from CMC perspective. The major CMC review issue with this NDA is inadequate drug substance DMF, and inadequate CMC information for a novel excipient.

The drug substance and drug product manufacturing sites are located in U.S. GMP inspection requests have been submitted.

Shulin Ding, Ph.D.
Pharmaceutical Assessment Lead

Moo Jhong Rhee, Ph.D.
Chief, Branch III

NDA Number: 22-571	**Supplement Number and Type:**	**Established/Proper Name: Glycopyrrolate**
Applicant: Sciele Pharma	**Letter Date: 9/26/09**	**Stamp Date: 9/28/09**

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.**			n/a

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • 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		No fax# and eMail address
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • 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		No fax# and eMail address

9.	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: • 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		No fax# and eMail address
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	Schematic is provided. The rest is referenced to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		x	Referenced to DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?		x	Referenced to DMF (b) (4)
15.	Does the section contain controls for the DS?	x		
16.	Has stability data and analysis been provided for the drug substance?		x	Referenced to DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	n/a
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	n/a

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		(b) (4) [redacted] .
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers 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?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	n/a
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	n/a

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	x		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		x	This is not a sterile product.

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		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II		(b) (4)	6/24/09	Drug Substance
	III			10/22/08	
	III			10/28/08	
	III			10/27/08	
	III			10/22/08	
	III			7/16/09	
	III			10/22/08	

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 SECTION OF THE APPLICATION FILEABLE?**	x		
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.			n/a
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	x		See p. 2 of IQA.

{See appended electronic signature page}

Shulin Ding, Ph.D.
Pharmaceutical Assessment Lead
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

Date

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

/s/

SHULIN DING
10/31/2009

MOO JHONG RHEE
11/02/2009
Chief, Branch III