

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022571Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022571

SUPPL #

HFD # 540

Trade Name TRADENAME

Generic Name glycopyrrolate

Applicant Name Shionogi Pharma, Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

7 Years (orphan designation)

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study FH-00-01 and Study SC-GLYCO-06-01

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 Study FH-00-01 YES NO

Investigation #2 Study SC-GLYCO-06-01 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 Study FH-00-01 YES NO

Investigation #2 Study SC-GLYCO-06-01

YES

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study FH-00-01 and Study SC-GLYCO-06-01

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 061716

YES

!

!

! NO

! Explain:

The sponsor purchased the IND from First Horizon who was listed on the 1571 for the IND at the time of the investigations.

Investigation #2

IND # 061716

YES

!

!

! NO

! Explain:

The sponsor purchased the IND from First Horizon who was listed on the 1571 for the IND at the time fo the investigations.

Name of person completing form: Dawn Williams
Title: RPM
Date: 6/24/2010

Name of Division Director signing form: Susan J. Walker, M.D., F.A.A.D.
Title: Director, DDDP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/

DAWN WILLIAMS
07/28/2010

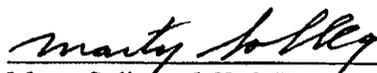
SUSAN J WALKER
07/28/2010



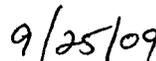
 **A SHIONOGI COMPANY**

Debarment Certification

Sciele Pharma Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic act in connection with this application.



Marty Solberg, MS, MBA
VP, Regulatory Affairs & Quality Assurance



Date

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

DA : 022571 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____
Division Name: DDDP PDUFA Goal Date: _____ Stamp Date: 8/28/2009
7/28/2010

Proprietary Name: TRADENAME
Established/Generic Name: glycopyrrolate oral solution
Dosage Form: liquid
Applicant/Sponsor: Sciele Pharma, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):
(1) Treatment of peptic ulcer disease
(2) Used as a preoperative or intraoperative medication in adults and children two years of age and older. Preoperatively it is used to inhibit salivation and excessive secretions of the respiratory tract.
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Treatment of (b) (4); (chronic (b) (4), severe) drooling in pediatric patients aged 3-16 with cerebral palsy, (b) (4) or other neurologic conditions associated with problem drooling

1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?
 Yes. Please proceed to Section D.
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

*** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?
 Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 - No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):
Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):			
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

- Are the indicated age ranges (above) based on weight (kg)? No; Yes.
- Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief**

justification):**# Not feasible:**

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

*** Not meaningful therapeutic benefit:**

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

⌋ Justification attached.

or those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation? Yes. PREA does not apply. **Skip to signature block.** No. Please proceed to the next question.**Q2:** Is there a full waiver for all pediatric age groups for this indication (check one)? Yes: (Complete Section A.) No: Please check all that apply: Partial Waiver for selected pediatric subpopulations (Complete Sections B) Deferred for some or all pediatric subpopulations (Complete Sections C) Completed for some or all pediatric subpopulations (Complete Sections D) Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E) Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**) Necessary studies would be impossible or highly impracticable because: Disease/condition does not exist in children Too few children with disease/condition to study Other (e.g., patients geographically dispersed): _____ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients. Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*) Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*) Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*) Justification attached.*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):
ote: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the eRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

ote: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 022571 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: TRADENAME Established/Proper Name: glycopyrrolate oral solution Dosage Form: solution		Applicant: Shionogi Pharma, Inc. Agent for Applicant (if applicable):
RPM: Dawn Williams		Division: DDDP
<p><u>NDA's:</u> NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check box and explain:</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>N/A- exempt Orphan Designation</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None
<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>		<input type="checkbox"/> Received

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics ²	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>Comments:</p>	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "**No**," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "**No**," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
---	--

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval- July 28, 2010
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	7/28/2010
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	9/28/2009
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A

³ Fill in blanks with dates of reviews, letters, etc.
Version: 6/8/10

❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in ttrack-changes format. 	7/28/2010
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	9/28/2009
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	7/23/2010
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	Proprietary Name Accepted- July 20, 2010 Proprietary Name Denied Letter- 3/26/2010 Proprietary Name Review- March 9, 2010
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 5/28/2010; 7/23/2010; 7/28/2010 <input checked="" type="checkbox"/> DRISK 6/4/2010 <input checked="" type="checkbox"/> DDMAC 4/14/2010 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	5/27/2010
❖ 505(b)(2) Assessment (<i>indicate date</i>)	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>exempt- Orphan Designation</u> If PeRC review not necessary, explain: <u>exempt- Orphan Designation</u> • Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	Proprietary Name Accepted-

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
Version: 6/8/10

	7/22/2010 Information Request- 7/21/2010 Proprietary Name Request Withdrawn- 5/10/2010 Acknowledge Corporate Name Change- 5/10/2010 Information Request- 4/21/2010 Proprietary Name Request Unacceptable- 3/26/2010 Information Request- 3/10/2010 Information Request- 3/2/2010 Information Request- 2/16/2010 Proprietary Name Request Withdrawn- 1/15/2010 Filing Communication- 12/8/2009
❖ Internal memoranda, telecons, etc.	CMC Telecon- 10/27/2009
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	Guidance Meeting- 12/15/2008 Guidance Meeting- 3/20/2007 Guidance Meeting- 8/20/2001 Pre-IND Meeting- 9/6/2000
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/28/2010
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 6
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	
• Clinical review(s) (<i>indicate date for each review</i>)	Clinical Review- 5/29/2010 Clinical Filing Review- 11/25/2009
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None

⁵ Filing reviews should be filed with the discipline reviews.
Version: 6/8/10

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Page 16 of the 5/29/2010 Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None DEPI- 6/17/2010 DPV I- 4/29/2010 SEALD- 4/14/2010 QT/IRT- 4/6/2010
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Statistical Review- 5/20/2010 Statistical Filing Review- 10/28/2009
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Clinical Pharmacology Review- 6/23/2010 Clinical Pharmacology Filing Review- 7/27/2010
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None

Nonclinical		<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None 5/24/2010
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)		<input type="checkbox"/> None Pharm/tox Review-5/20/2010 Pharm/tox Filing Review-10/29/2009
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting		<input type="checkbox"/> None Included in P/T review, page40 Final CAC Report 2/1/2010
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)		<input checked="" type="checkbox"/> None requested
Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)		<input type="checkbox"/> None Addendum 2-7/22/2010 Addendum 1- 7/13/2010 Product Quality Review-6/29/2010 Product Quality Filing Review-10/31/2009
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)		<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)		<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)		6/29/2010 Product Quality Review, page 70
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)		
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)		

❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>)	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/

DAWN WILLIAMS
07/29/2010



NDA 022571

**PROPRIETARY NAME REQUEST
ACCEPTABLE**

Shionogi Pharma Inc.
5 Concourse Parkway
Suite 1800
Atlanta, Georgia 30328

ATTENTION: Allison Lowry, RAC
Director, Regulatory Affairs

Dear Ms. Lowry:

Please refer to your New Drug Application (NDA) dated September 26, 2009, received September 28, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glycopyrrolate Oral Solution, 1 mg/5 mL.

We also refer to your April 28, 2010, correspondence, received April 29, 2010, requesting review of your proposed proprietary name, Cuvposa. We have completed our review of the proposed proprietary name, Cuvposa, and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your April 28, 2010, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Dawn Williams at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/

CAROL A HOLQUIST
07/22/2010

Attinello, Cristina

From: Attinello, Cristina
Sent: Wednesday, July 21, 2010 11:14 AM
To: 'alowry@shionogipharma.com'
Cc: Gould, Barbara; Williams, Dawn
Subject: NDA 022571
Follow Up Flag: Follow up
Flag Status: Red

Good Morning,

As you have been informed, a determination has been made that the name Cuvposa is acceptable. In addition to revising your container and carton labels to reflect this, the Agency has the following comments:

A. Container Label (1 mg/5 mL; 16 oz. retail and sample container)

1. We note the established name is ½ the size of the proprietary name, but it lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10 (g)(2). In addition, the gray font used in the presentation of the established name makes it difficult to read. We recommend the font color of the established name be changed to a more prominent color that is easier to read.
2. Increase the prominence of the product strength statement by increasing the font size and color to be commensurate with the proprietary name.
3. The prominence of the net quantity statement on the principal display panel may distract from other important information. Revise the label to decrease the prominence of the net quantity statement by using non bold lettering and removing the colored band highlighting the net quantity. In addition, relocate the statement to a less prominent section of the label away from the product strength.
4. Revise the presentations of the strengths and volumes by adding a space between the number and the unit of measure (i.e., 1 mg/5 mL rather than 1mg/5 mL).
5. For ease of dosage calculation in pediatric patients, we recommend adding a secondary expression of strength 0.2 mg/mL below the 1 mg/5 mL. The secondary strength expression should have decreased prominence than the 1 mg/5 mL expression.
6. In accordance to 21 CFR 201.25, provide a barcode on the container label.
7. Revise the statement, "Dosage: See package insert for full prescribing information" to read "Usual Dosage: See package insert for full prescribing information."
8. Since glycopyrrolate is also available in an Injection formulation, to avoid any potential confusion, add a statement "For Oral Use Only" below the "RX Only" statement.
9. The size of the company logo and distributor information is more prominent than the strength and established name. Decrease the size of the company logo and distributor information.
10. Separate the statement "Store between ..." and the statement (b) (4) by using bold letters or space in between to increase the prominence of the (b) (4) statement.

B. Carton Labeling (1 mg/5 mL 16 oz. container)

1. See comments A1- A8.

2. In accordance with 21 CFR 201.17, ensure the carton label incorporates the expiration date and lot number.

Please revise your carton and container labeling to reflect the above comments and provide a response no later than **COB Thursday, July 22, 2010**.

Please let me know if you have any questions.

Thank you,

Cristina Petruccelli Attinello, MPH

Regulatory Project Manager

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Dermatology & Dental Products

White Oak, Bldg. 22, Room 5181

Phone: 301-796-3986

Fax: 301-796-9895

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/

CRISTINA Petruccelli Attinello
07/21/2010



NDA 22571

**ACKNOWLEDGE CORPORATE
NAME/ADDRESS CHANGE**

Shionogi Pharma, Inc.
Attention: Allison Lowry, RAC
Sr. Manager, Regulatory Affairs
Five Concourse Parkway
Suite 1800
Atlanta, GA 30328

Dear Ms. Lowery:

We acknowledge receipt on January 22, 2010 of your January 20, 2010 correspondence notifying the Food and Drug Administration that the corporate name and/or address has been changed from

Sciele™ Pharma, Inc.

to

Shionogi Pharma, Inc
Five Concourse Parkway
Suite 1800
Atlanta, GA 30328

for the following new drug application:

NDA 22571 for Glycopyrrolate Oral Solution 1 mg/5 mL.

We have revised our records to reflect this change.

We request that you notify your suppliers and contractors who have DMFs referenced by your application of the change so that they can submit a new letter of authorization (LOA) to their Drug Master File(s).

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Dermatology and Dental Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Lt. Dawn Williams, R.N., B.S.N.,
U.S.P.H.S.
Regulatory Health Project Manager
Division of Dermatology and Dental
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22571

GI-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/

DAWN WILLIAMS
05/10/2010



NDA 022571

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Shionogi Pharma Inc.
5 Concourse Parkway
Suite 1800
Atlanta, Georgia 30328

ATTENTION: Allison Lowry, RAC
Director, Regulatory Affairs

Dear Ms. Lowry:

Please refer to your New Drug Application (NDA) dated September 26, 2009 received September 28, 2009, submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Glycopyrrolate Oral Solution, 1 mg/5 mL.

We acknowledge receipt of your April 28, 2010 correspondence, on April 29, 2010, notifying us that you are withdrawing your April 20, 2010 request for a review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of April 29, 2010.

We note that you have proposed an alternate proprietary name in your submission dated April 20, 2010. In order to initiate the review of the alternate proprietary name, Cuvposa, submit a new complete request for proprietary name review within 14 days of this letter. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Janet L. Anderson, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Dawn Williams at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/

CAROL A HOLQUIST
05/10/2010



NDA 022571

INFORMATION REQUEST

Shionogi Pharma, Inc.
Attention: Alison Lowry
Senior Manager, Regulatory Affairs
Five Concourse Pkwy, Suite 1800
Atlanta, GA 30328

Dear Ms. Lowry:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (glycopyrrolate) Oral Solution, 1 mg/mL, for the treatment of (b) (4) (chronic (b) (4) severe) drooling in pediatric patients.

We also refer to your March 9, 2010 submission.

We are in the process of reviewing the referenced material and have the following requests for information. We request response by April 27, 2010.

1. Verify the vital status of all participants in protocol Sc-GLYCO-06-01 up to day 198, in order to more accurately estimate the mortality rate in this protocol. The vital status of all participants, including those who withdrew or were lost to follow-up, should be ascertained in order to minimize any biases. Day 198 corresponds to thirty days after a participant's last dose of the study drug dose. This time frame was chosen since the three deaths observed in this protocol occurred in the thirty day period after the last dose of the study drug. All appropriate documentation should accompany additional deaths discovered as a result of this request, in addition to a report and dataset with the updated vital status of all participants.
2. Provide a copy of the pre- and post-test that was provided to the caregivers during study FH-00-01. Table 14.3.3 provides a summary of change in the training manual scores. However, for completeness, submit a table that contains the individual pre-test and post-test scores for each caregiver.

If you have any questions, call Dawn Williams, Regulatory Health Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/

SUSAN J WALKER
04/21/2010



NDA 022571

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Sciele Pharma Inc.
5 Concourse Parkway
Suite 1800
Atlanta, Georgia 30328

ATTENTION: Allison Lowry, RAC
Senior Manager, Regulatory Affairs

Dear Ms. Lowry:

Please refer to your New Drug Application (NDA) dated September 26, 2009, received September 28, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glycopyrrolate Solution 1 mg/5 mL.

We also refer to your December 31, 2009, correspondence, received December 31, 2009, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons.

(b) (4)

We recognize that this conclusion differs from the conclusion reached by your independent study submitted in support of the name. However, [REDACTED] (b) (4)

We note that you have proposed an alternate proprietary name in your submission dated December 31, 2009. In order to initiate the review of the alternate proprietary name, [REDACTED] (b) (4) submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Dawn Williams at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22571	----- ORIG-1	----- SCIELE 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/

CAROL A HOLQUIST
03/26/2010



NDA 22-571

INFORMATION REQUEST

Shionogi Pharma, Inc.
Attention: Allison Lowry, RAC
Director, Regulatory Affairs
Five Concourse Pkwy, Suite 1800
Atlanta, GA 30328

Dear Ms. Lowry:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (glycopyrrolate) Oral Solution, 1 mg/mL for the treatment of (b) (4) (chronic (b) (4) severe) drooling in pediatric patients.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA. Please provide your response within 8 - 10 business days.

1. Provide information related to the composition, manufacturing process and specification for the Natural and Artificial Cherry Flavor (b) (4).
2. Provide peak purity results for (b) (4) in the degradation study presented in the HPLC method validation.
3. Provide information regarding the determination of the relative response factor for (b) (4).
4. Provide validation results regarding linearity of (b) (4) for the HPLC method used to quantitate the related substances in the drug product.
5. Provide the procedure used to test packaging integrity of the drug product.
6. Provide characterization information for (b) (4) standard used in the HPLC method validation.
7. Clarify if photostability study on the drug product has been conducted according to ICH Q1B. If yes, please provide data.

8. Recalculate the Expected Introduction Concentration to include the forecast consumption of the drug substance in the drug products of NDA 12-827 and NDA 22-571.
9. We have also issued a DMF Deficiency Letter on March 9, 2010, for DMF (b) (4) in support of NDA 22-571.

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (Jeannie.David@fda.hhs.gov), and Dawn Williams, Regulatory Project Manager the Office of New Drugs (Dawn.Williams@fda.hhs.gov).

If you have any questions regarding this letter, call Jeannie David, Regulatory Project Manager, at (301) 796-4247.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22571	ORIG-1	SCIELE 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/

MOO JHONG RHEE
03/10/2010
Chief, Branch III

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: OSE/DPV		FROM: Dawn Williams, RPM, DDDP 6-5376 Fred Hyman, Clinical Reviewer, DDDP 6-0922		
DATE 3/9/2010	IND NO.	NDA NO. Pending NDA 022571	TYPE OF DOCUMENT Pending NDA	DATE OF DOCUMENT September 28, 2009
NAME OF DRUG TRADENAME (glycopyrrolate) Oral Solution, 1mg/5mL		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Xerostomia Agent (6030503)	DESIRED COMPLETION DATE May 1, 2010
NAME OF FIRM: Shionogi Pharma, Inc.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS:				
<p>DDDP is currently reviewing NDA 22-571, TRADENMAE (glycopyrrolate) Oral Solution for treatment of excessive drooling in children with cerebral palsy. Glycopyrrolate (glycopyrrolate bromide) is a synthetic quaternary ammonium antimuscarinic, structurally related to atropine. Following oral administration, the anticholinergic effects of glycopyrrolate may persist for up to 8 to 12 hours. The current submission contains the results of two clinical trials; the first is a phase 3 placebo controlled double-blinded trial of 8 weeks duration consisting of 36 subjects. The second study is an open label trial of 24 weeks duration consisting of 137 subjects.</p>				

Note that Glycopyrrolate is the subject of two approved NDA's:

- 1) NDA 12-827, Robinul (1 MG Glycopyrrolate oral tablet) and Robinul Forte (2 mg oral tablet) for the adjunctive treatment of peptic ulcer disease in adults
- 2) NDA 17-558 (Glycopyrrolate .2 mg/ml injectable) as a preoperative or intraoperative medication in adults and children two years of age and older. As a preoperative medication, it has been used to inhibit salivation and excessive secretions of the respiratory tract.

Robinul tablets were approved in 1961 and the injectable was approved in 1975. Since those first approvals, there have been 17 ANDA's approved for generic versions of both the tablets and injectable solution. Furthermore, there is widespread literature citing the off label use of Robinul for controlling excessive drooling, the subject of this NDA.

Because glycopyrrolate is an anticholinergic, with effects on multiple organ systems other than just the salivary glands, AE's were uncovered during the trial. Most were related to the anticholinergic activity such as constipation and lack of sweating. Because the subjects were non-communicative, several AE's rose to the level of serious and are believed to be related to the drug: nystagmus, esophageal candidiasis, dehydration, and gastrointestinal motility. During the course of the 24-week open label trial of 137 subjects, 3 subjects died within 30 days of the completion of the trial. DDDP will be closely examining autopsy reports and other data to help determine if glycopyrrolate use could have contributed to any of these deaths, although preliminary review indicates no causal association.

According to the submission, over [REDACTED] ^{(b) (4)} tablets of Robinul were dispensed during the period 2002 to 2007. During that period, the sponsor reports that no AE's were identified through the AERS system or in the sponsor's database for that same time period. We have sent a consult to DEPI, who will be reviewing these and other databases to determine how many of the dispensed Robinul tablets were used in children with CP. **It is our hope that DPV can verify for us that the sponsor's determination of AE's associated with the marketed glycopyrrolate is correct.**

Upon assignment of this consult, please have the reviewer contact the medical officer for further discussion to develop a strategy which would have the best chance of providing meaningful data.

SIGNATURE OF REQUESTER Dawn Williams, RPM	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DARRTS <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22571

ORIG-1

SCIELE 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/

DAWN WILLIAMS
03/09/2010



NDA 022571

INFORMATION REQUEST

Shionogi Pharma, Inc.
Attention: Alison Lowry
Senior Manager, Regulatory Affairs
Five Concourse Pkwy, Suite 1800
Atlanta, GA 30328

Dear Ms. Lowry:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (glycopyrrolate) Oral Solution, 1 mg/mL for the treatment of (b) (4) (chronic (b) (4) severe) drooling in pediatric patients.

We are reviewing the clinical pharmacology section of your submission and have the following information requests. We request a written response by Friday, March 12, 2010, in order to continue our evaluation of your NDA. Provide the following information regarding your population PK analyses:

1. NONMEM datasets used for model development and validation whose file names match with datasets appearing in the control stream files. The names of NONMEM datasets in the current submission do not match with files in the control stream files.
2. NONMEM control stream files used for the analysis as ASCII files that are ready to be run without additional clean-up. Submit those files only for the optimal models from each table (Tables 17-21) of the population PK report.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Dawn Williams, B.S.N.
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22571	ORIG-1	SCIELE 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/

DAWN WILLIAMS
03/02/2010



NDA 022571

INFORMATION REQUEST

Shionogi Pharma, Inc.
Attention: Alison Lowry
Senior Manager, Regulatory Affairs
Five Concourse Pkwy, Suite 1800
Atlanta, GA 30328

Dear Ms. Lowry:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (glycopyrrolate) Oral Solution, 1 mg/mL for the treatment of (b) (4) (chronic (b) (4) severe) drooling in pediatric patients.

We also refer to your January 22, 2010 submission, containing a response to our December 8, 2009 Filing Communication letter.

We are reviewing the biostatistics section of your submission and have the following comments and information requests. We request a prompt written response in order to continue evaluation of your NDA.

1. In the December 8, 2009 Filing Communication letter, we requested information on subjects who may have participated in both Studies FH-00-01 and SC-GLYCO-06-01. In your January 21, 2010 response, you stated that no subjects participated in both studies. However, by matching birthdates and subject initials, we have identified 12 subjects that appear to have been enrolled in both studies. Confirm whether or not the following subject identifications represent subjects who participated in both studies and whether any additional subjects participated in both studies.

FH-00-01 ID	06-01 ID	Site	Birthdate	Sex	Race	Initials
02-004	02-01					(b) (4)
04-003	24-03					
05-001	05-01					
05-003	05-02					
06-001	06-06					
06-002	06-04					
06-003	06-08					
06-004	06-01					
06-005	06-02					
06-007	06-03					
06-010	06-09					
08-003	08-01					

2. The original submission contained 21 Case Report Forms from Study FH-00-01. Submit the remaining 17 Case Report Forms so that the complete set is available for review.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301)796-5376.

Sincerely,

{See appended electronic signature page}

Dawn Williams, B.S.N.
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22571

ORIG-1

SCIELE 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/

DAWN WILLIAMS
02/16/2010

REQUEST FOR Patient Reported Outcomes (PRO) ENDPOINTS CONSULTATION

TO: Study Endpoints and Labeling Development (SEALD) CDER/OND-IO White Oak Bldg 22, Mail Drop 6411 SEALD.ENDPOINTS@FDA.HHS.GOV	FROM: Review Division: DDDP Medical Reviewer: Fred Hyman, Clinical Reviewer, 6-0922 Project Manager: Dawn Williams, RPM; 6-5376
---	--

DATE OF CONSULT REQUEST February 2, 2010	Application# IND/NDA/BLA# Pending NDA 022571	LETTER # OR SUBMISSION #	TYPE OF DOCUMENT (Meeting; Protocol/SPA; PDUFA Product Review) Pending NDA- Caregiver Manual	REQUESTED SEALD COMPLETION DATE* April 5, 2010
--	---	---------------------------------	---	--

DRUG ESTABLISHED NAME glycopyrrolate	DRUG TRADE NAME TRADENAME	NAME OF SPONSOR Shionogi Pharma, Inc. (formerly Sciele Pharma, Inc.)	SPONSOR SUBMIT DATE September 28, 2009
--	-------------------------------------	---	--

DEVELOPMENT PHASE (E.G., pre-IND/NDA/BLA; IND/BB-IND Phase 1, 2, 3; NDA/BLA): Pending NDA

GOAL DATE (if NDA/BLA./SPA): July 14, 2010

ELECTRONIC LINK (if applicable): The discussion of the manual and its results can be found in the EDR under NDA 022571. Open 5.3.5.1.3 (Study Report Body FH-00-01)

For the manual, see Section 9.1.2 for Caregiver Training, 9.5.6 and 9.7.1.5 for the training manual assessment; Appendix 16.1.1/Table 14.3.2.3 for the data.

For the BMRS data, see Section 9.7.1.4 for an analysis of BMRS data, 11.4.1.5 for an assessment of the BMRS Instrument, Section 12.2.3/Table 17 for BMRS results.

For TDS: See Section 9.5.2 and 9.5.3

PLEASE make certain the background-briefing package is included with this consult. It should contain the following applicable information needed to start Study Endpoints Review: Protocol or Study ID; Endpoint Concept(s); Instrument(s); Indication(s); Study population(s); Prior related reviews. Division PM, please provide the following specific information on this consult form:

DDDP is currently reviewing NDA 22-571, glycopyrrolate for treatment of excessive drooling in children with cerebral palsy. Glycopyrrolate (glycopyrrolate bromide) is a synthetic quaternary ammonium antimuscarinic, structurally related to atropine. Following oral administration, the anticholinergic effects of glycopyrrolate may persist for up to 8 to 12 hours. The results of the trials submitted to this NDA demonstrated highly significant efficacy in support of reduction of drooling, as is expected of an anticholinergic drug. However, other expected but undesirable anticholinergic activity also occurs, including constipation, urinary retention, flushing, and increased heart rate. In addition, the dosing is to be titrated per individual to balance the reduction of drooling against the severity of these anticholinergic adverse events. One of the key elements to achieve this goal was the development of a training manual for the caregiver who would be administering the glycopyrrolate. Towards that end, a manual was developed by the sponsor and assessed during the clinical trials for its validity. The manual was reviewed in 2002 by CDER reviewers in the former Office of Drug Safety and comments on this were implemented – all minutes and comments on this topic were documented in DARRTS under the IND, 61,716. The sponsor accepted the comments from the Agency in refining the manual. There was a pre-test and a post-test for comprehension of the manual administered as a part of the clinical trial, and the data is submitted in the NDA submission.

The current submission contains the results of two clinical trials; the first is a phase 3 placebo controlled double-blinded trial of 8 weeks duration consisting of 36 subjects. The second study is an open label trial of 24 weeks duration consisting of 137 subjects. There are several elements of this trial that would benefit from SEALD input:

- 1) Of most importance is assistance with interpreting the data in this NDA submission that the sponsor submitted as validation of the manual to be an acceptable guide to caregivers who will be administering the drug. (Concomitantly, a consult has been sent to DRISK about how to best require this manual to become a part of the labeling.)

- 2) In addition, one of the safety assessments was the Behavior Modification Scale (BMS), used to assess adverse events in uncommunicative patients. One of the main reasons that it is important to verify that the BMS was an acceptable measure of adverse events (and that the caregiver manual adequately trained the caregivers) is that most of the patients who will be using this chronic treatment have multiple disabilities, usually including mental retardation. The sponsor states that the BMRS is not a validated instrument, but that they used it at the recommendation of the Pediatric subcommittee recommendations during a public hearing on glycopyrrolate.
- 3) The major efficacy assessment was the Teachers Drooling Scale (TDS), a 9-point scale used to assess the degree of drooling. The sponsor states in the submission that the TDS is a validated instrument. Although it has been widely used in these types of studies and has appeared in in the literature, no comments were made by the Agency about the validity of this scale during the IND phase of development.

Instrument(s): Caregiver’s Manual

Indication(s): treatment of (b) (4) (chronic (b) (4) severe) drooling in pediatric patients

Specific Questions/Comments for SEALD:

DDDP would appreciate any comments about the acceptance of the BMRS, TDS scales and the Caregiver’s Manual.

Upon assignment of this consult, please have the reviewer contact the clinical reviewer for further discussion to develop a strategy which would have the best chance of providing meaningful data on the validity of the measurements in question.

Thank you!

Requester

Dawn Williams, RPM; 6-5376

dawn.williams@fda.hhs.gov

DDDP, Building 22, Room 5183

Name/Phone number/email address/office location

Glossary:

Concept: The specific goal of a measurement (i.e. the *thing* that is to be measured by a PRO instrument).

Instrument: A means to capture data (e.g. questionnaire, diary) plus all the information and documentation that supports its use. Generally, that includes clearly defined methods and instructions for administration or responding, a standard format for data collection, and well-documented methods for scoring, analysis, and interpretation of results.

*For voluminous study endpoint submissions (e.g. PRO “dossier” or content validity documentation greater than 50 pages), SEALD requests 60 days after receiving the background/briefing package document to complete the review.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22571

ORIG-1

SCIELE 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/

DAWN WILLIAMS
02/03/2010



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs**

FACSIMILE TRANSMITTAL SHEET

DATE: February 1, 2010

To: Allison Lowry, RAC	From: Adele Seifried
Company: Sciele Pharma, Inc.	OND IO
Fax number: (678) 992-1020	Fax number: 301-796-9855
Phone number: (678) 341-1486	Phone number: 301-796-0535
Subject: Response to Carcinogenicity Protocol Assessment Request - Final CAC Report - NDA 22,571	

Total no. of pages including cover: 5

Comments:

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-0535. Thank you.

Executive CAC

Date of Meeting: January 26, 2010

Committee:

Abby Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
Lois Freed, Ph.D., DNP, Alternate Member
Barbara Hill, Ph.D., DDDP, Supervisor
Norman See, Ph.D., DDDP, Presenting Reviewer

Author of Draft: Norman See, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

The Committee did not address the sponsor's proposed statistical evaluation for the carcinogenicity bioassays, as this does not affect the sponsor's ability to initiate the bioassays. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following the CDER/CBER Guidance for Industry, Providing Regulatory Submission in Electronic Format- Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008) and the associated Study Data Specifications document.

NDA 22-571

Drug Name: Glycopyrrolate

Sponsor: Shionogi Pharma, Inc.

Protocols for proposed carcinogenicity studies to be conducted with glycopyrrolate in mice and in rats were discussed.

(b) (4)

oral Mouse Carcinogenicity Study Protocol and Dosage Selection:

The sponsor agreed to conduct a (b) (4) carcinogenicity study in CD-1 mice post-approval to support, in part, marketing of an oral product that contains glycopyrrolate. (b) (4)

(b) (4)

(b) (4)

oral Rat Carcinogenicity Study Protocol and Dosage Selection:

(b) (4)

Executive CAC Recommendations and Conclusions

Mice:

1. The Committee did not concur with the dosages proposed by the sponsor. The Committee recommended dosages of 0, 0, 2.5, 7, and 20 mg/kg/day, based on body weight effects.
2. The Committee noted that toxicokinetic data obtained in the 13-week study (“A 13-week oral gavage dose range-finding toxicity study of glycopyrrolate in CD-1 mice”, study No. (b) (4)-714003) did not appear to document a clear dose-related increase in systemic exposure to glycopyrrolate. The Committee recommended that the sponsor further investigate this issue prior to analysis of toxicokinetic samples collected in the two-year study.
3. The Committee recommended that blood samples for toxicokinetic analysis be collected at 6 months, (b) (4)
4. The Committee recommended that the sponsor contact the division for guidance if the number of surviving animals of a given gender in any group should reach 25.

Rats:

1. The Committee did not concur with the dosages proposed by the sponsor. The Committee recommended dosages of 0, 0, 5, 15, and 40 mg/kg/day. The high dose was based on body weight effects.
2. The Committee noted that toxicokinetic data obtained in the 13-week study (“A 13-week oral gavage dose range-finding toxicity study of glycopyrrolate in the Sprague-Dawley rat,” study No. (b) (4)-714004) did not appear to document a clear dose-related increase in systemic exposure to glycopyrrolate. The Committee recommended that the sponsor further investigate this issue prior to analysis of toxicokinetic samples collected in the two-year study.
3. The Committee recommended that blood samples for toxicokinetic analysis be collected at 6 months, (b) (4)
4. The Committee recommended that the sponsor contact the division for guidance if the number of surviving animals of a given gender in any group should reach 25.

Abby Jacobs, Ph.D.
Acting Chair, Executive CAC

cc:

/Division File, DDDP

/B Hill/Supervisor, DDDP

/N See/Reviewer, DDDP

/D Williams/PM, DDDP

/A Seifried, OND IO

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22571	ORIG-1	SCIELE 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/

ABIGAIL ABBY C C JACOBS
02/01/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: OSE/DEPI		FROM: Dawn Williams, RPM, DDDP; 6-5376 Fred Hyman, Clinical Reviewer, DDDP; 6-0922		
DATE January 29, 2010	IND NO.	NDA NO. 022571	TYPE OF DOCUMENT Pending NDA	DATE OF DOCUMENT September 28, 2009
NAME OF DRUG TRADENAME (glycopyrrolate) Oral Solution, 1mg/5mL		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Xerostomia Agent (6030503)	DESIRED COMPLETION DATE April 1, 2010
NAME OF FIRM: Shionogi Pharma, Inc. (formerly Sciele Pharma, Inc.)				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: DDDP is currently reviewing NDA 022571, TRADENAME (glycopyrrolate) Oral Solution for treatment of excessive drooling in children with cerebral palsy. Glycopyrrolate (glycopyrrolate bromide) is a synthetic quaternary ammonium antimuscarinic, structurally related to atropine. Following oral administration, the anticholinergic effects of glycopyrrolate may persist for up to 8 to 12 hours. The current submission contains the results of two clinical trials; the first is a phase 3 placebo controlled double-blinded trial of 8 weeks duration consisting of 36 subjects. The second study is an open label trial of 24 weeks duration consisting of 137 subjects. During the course of the 24-week open label trial of 137 subjects, 3 subjects died within 30 days of the completion of the trial. DDDP will be closely examining autopsy reports and other data to help determine if glycopyrrolate use could have contributed to any of these deaths. Although this was a population with multiple medical conditions - 100% were mentally retarded, many had seizure disorders, and all had sufficient impairment that resulted in moderate to severe drooling – the deaths in this population must be addressed prior to approval. Because there was				

no placebo group in this trial for comparison, it is important to determine a background mortality rate for a population with a similar health profile. **It is our hope that DEPI can help us to determine if the deaths shown in the open label study submitted to this NDA is within an expected range of comparable individuals, or not.**

Note also that Glycopyrrolate is the subject of two approved NDA's:

- 1) NDA 12-827, Robinul (1 MG Glycopyrrolate oral tablet) and Robinul Forte (2 mg oral tablet) for the adjunctive treatment of peptic ulcer disease in adults
- 2) NDA 17-558 (Glycopyrrolate .2 mg/ml injectable) as a preoperative or intraoperative medication in adults and children two years of age and older. As a preoperative medication, it has been used to inhibit salivation and excessive secretions of the respiratory tract.

Robinul tablets were approved in 1961 and the injectable was approved in 1975. Since those first approvals, there have been 17 ANDA's approved for generic versions of both the tablets and injectable solution. Furthermore, there is widespread literature citing the off label use of Robinul for controlling excessive drooling, the subject of this NDA.

Based upon the availability of glycopyrrolate for almost 40 years, **it is our hope that DEPI can also examine user experience with glycopyrrolate through drug use databases.** In particular, if the data can help identify patients with cerebral palsy who have used the drug, it may add to our safety profile.

Upon assignment of this consult, please have the reviewer contact Fred Hyman, Clinical Reviewer, DDDP; 6-0922 for further discussion to develop a strategy which would have the best chance of providing meaningful data.

This is an electronic submission.

Thank you!

SIGNATURE OF REQUESTER
Dawn Williams, RPM

METHOD OF DELIVERY (Check one)
X EMAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22571	ORIG-1	SCIELE 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/

DAWN WILLIAMS
01/29/2010

REQUEST FOR CONSULTATION

TO (Office/Division): DCRP/IRT/QT Review

FROM (Name, Office/Division, and Phone Number of Requestor):

Dawn Williams, RPM, DDDP; 6-5376

Fred Hyman, Clinical Reviewer, DDDP; 6-0922

DATE
January 29, 2010

IND NO.

NDA NO.
022571

TYPE OF DOCUMENT
Pending NDA

DATE OF DOCUMENT
September 28, 2009

NAME OF DRUG
TRADENAME
(glycopyrrolate) Oral
Solution

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
Xerostomia Agent
(6030503)

DESIRED COMPLETION DATE
April 1, 2010

NAME OF FIRM: Shionogi Pharma, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS:

DDDP is currently reviewing NDA 022571, TRADENAME (glycopyrrolate) Oral Solution for treatment of excessive drooling in children with cerebral palsy. Glycopyrrolate (glycopyrrolate bromide) is a synthetic quaternary ammonium antimuscarinic, structurally related to atropine. Following oral administration, the anticholinergic effects of glycopyrrolate may persist for up to 8 to 12 hours. The current submission contains the results of two clinical trials; the first is a phase 3 placebo controlled double-blinded trial of 8 weeks duration consisting of 36 subjects. The second study is an open label trial of 24 weeks duration consisting of 137 subjects.

The results of the trials submitted to this NDA demonstrated highly significant efficacy in support of reduction of drooling, as is expected of an anticholinergic drug. However, other expected but undesirable anticholinergic activity also occurs, including constipation, urinary retention, and flushing. Also of concern are potential cardiac events associated with anticholinergic activity, most notably increased heart rate. Therefore, as a part of the controlled study of 36 subjects, the sponsor included a cardiac evaluation that consisted of obtaining 12-lead ECGs using site

recorders at Screening and then at the end of the study on Day 56. The ECGs were then retrospectively sent to a core ECG laboratory. Manual measurements of the RR, PR, QRS, and QT interval durations were performed; heart rate, QTcF and QTcB were derived. (Note that there was a cardiac-related exclusion to the study's entrance criteria which rejected patients who have medical conditions contraindicating anticholinergic therapy including: cardiac arrhythmias and/or tachycardia, and/or clinically significant ECG abnormalities as determined by the investigator).

A separate report that focused exclusively on cardiac safety was submitted to the NDA, and is available through the EDR. To open it, choose NDA 22-571 and retrieve Serial 0000 (original application – 9/2/2009), Section 5.3.5.1., which is entitled, FH-00-01-ECG-REPORT. The sponsor concludes from the study results that the heart rate was significantly increased, but there is no evidence of changes in PR duration, QRS duration, QT interval. Within the report, the sponsor provided the following conclusion, “this trial demonstrated no ECG effects of glycopyrrolate except for a clinically relevant increase in heart rate. Caution should be exercised in interpreting these data in light of the small sample sizes and the minimal ECG frequency employed. Nevertheless, the data do not suggest that glycopyrrolate should have a clinically marked increase in QTc duration.”

Specific review request:

Please review this study report for comment on the sponsor's above stated conclusion. Specifically, does DCRP agree that the data do not suggest a further need for monitoring through a PMC or PMR? Please also review the following sections of the proposed PI pertaining to cardiac events: 1) Section 4, Contraindications; 2) Section 5.5 General Anticholinergic Effects; and 3) Table 1: Adverse events, which includes “Heart Rate Increased.” The proposed package insert can be found in the same EDR submission, under section 1.14.1.2.

Upon assignment of this consult, please have the reviewer contact the medical officer for further discussion to develop a strategy which would have the best chance of providing meaningful data on cardiovascular risk.

SIGNATURE OF REQUESTOR Dawn Williams, RPM	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DARRTS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22571	ORIG-1	SCIELE 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/

DAWN WILLIAMS
02/03/2010

REQUEST FOR CONSULTATION

TO (Office/Division): DMEPA

FROM (Name, Office/Division, and Phone Number of Requestor): DDDP
Dawn Williams, RPM; 6-5376
Fred Hyman, Clinical Reviewer; 6-0859

DATE
January 25, 2010

IND NO.

NDA NO.
022571

TYPE OF DOCUMENT
Pending NDA

DATE OF DOCUMENT
September 28, 2009

NAME OF DRUG
TRADENAME
(glycopyrrolate) Oral
Solution, 1mg/5 ml

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
Xerostomia Agent
(6030503)

DESIRED COMPLETION DATE
June 1, 2010

NAME OF FIRM: (b) (4)

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review the attached Package Insert (PI and PPI) and carton and container labels. Labeling meetings have been scheduled for March 11 and 23, 2010. This is an electronic submission.
EDR Location: http://edr.fda.gov:7777/edr/EDR_Main.jsp
eRoom Location of Labeling:
http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofDermatologyandDentalProducts/0_12703
We are targeting action on this NDA on July 14, 2010.

SIGNATURE OF REQUESTOR
Dawn Williams, RPM

METHOD OF DELIVERY (Check one)
 DARTS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22571	ORIG-1	SCIELE 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/

DAWN WILLIAMS
01/27/2010

REQUEST FOR CONSULTATION

TO (Office/Division): **DDMAC**

FROM (Name, Office/Division, and Phone Number of Requestor): **DDDP**
Dawn Williams, RPM; 6-5376
Fred Hyman, Clinical Reviewer; 6-0859

DATE
January 19, 2010

IND NO.

NDA NO.
022571

TYPE OF DOCUMENT
Pending NDA

DATE OF DOCUMENT
September 28, 2009

NAME OF DRUG
TRADENAME
(glycopyrrolate) Oral
Solution, 1mg/5 ml

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
Xerostomia Agent
(6030503)

DESIRED COMPLETION DATE
June 1, 2010

NAME OF FIRM: (b) (4)

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END-OF-PHASE 2a MEETING
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY / EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|---|--|

II. BIOMETRICS

- | | |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|--|

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

IV. DRUG SAFETY

- | | |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review the Package Insert (PI and PPI) and carton and container labels regarding whether the content is promotional in nature. We are targeting action on this NDA on July 14, 2010.

Please use the link to the eRoom below to access the Package Insert and carton and container labels.

http://erom.fda.gov/eRoom/CDER3/CDERDivisionofDermatologyandDentalProducts/0_12703

First Labeling Meeting: March 11, 2010, 1:00PM, Room 5266

Second Labeling Meeting: March 23, 2010, 10:00AM, Room 5201

Thanks!

SIGNATURE OF REQUESTOR
Dawn Williams, RPM

METHOD OF DELIVERY (Check one)
 DARRTS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22571	ORIG-1	SCIELE 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/

DAWN WILLIAMS
01/27/2010



NDA 022571

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Sciele Pharma, Inc.
Five Concourse Parkway
Suite 1800
Atlanta, Georgia 30328

ATTENTION: Allison Lowry, RAC
Senior Manager, Regulatory Affairs

Dear Ms. Lowry:

Please refer to your New Drug Application (NDA) dated September 25, 2009, received September 28, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glycopyrrolate Oral Solution, 1 mg/5 mL.

We acknowledge receipt of your December 29, 2009 correspondence, received on December 29, 2009, notifying us that you are withdrawing your December 10, 2009 request for a review of the proposed proprietary names [REDACTED] (b) (4). This proposed proprietary name request is considered withdrawn as of December 29, 2009.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager Dawn Williams at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22571	ORIG-1	SCIELE 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/

CAROL A HOLQUIST
01/15/2010



NDA 022571

FILING COMMUNICATION

Sciele Pharma, Inc.
Attention: Alison Lowry
Senior Manager, Regulatory Affairs
Five Concourse Pkwy.
Suite 1800
Atlanta, GA 30328

Dear Ms. Lowry:

Please refer to your new drug application (NDA) dated September 25, 2009, received September 28, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for TRADENAME (glycopyrrolate) Oral Solution, 1 mg/mL.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is July 28, 2010.

You submitted this application pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act and identified Robinul Injection (NDAs 017558 and 014764) and Robinul Tablets (NDA 012827) as the listed drugs upon which you are relying. We note that your application does not contain comparative bioavailability data on your proposed product and Robinul Injection nor do you include any information about Robinul Injection in your proposed labeling. In addition, the conditions of use of Robinul Injection are not applicable to your proposed product and therefore reliance on Robinul Injection for approval of your proposed product is not scientifically justified. We also note that you own NDA 012827, Robinul Tablets. Therefore, because you are relying only on data that you own for approval, this NDA is considered a 505(b)(1) application.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by July 5, 2010.

During our filing review of your application, we identified the following potential review issues:

Chemistry, Manufacturing and Controls (CMC)

It is unclear whether the EIC-Aquatic calculation submitted in this application has included other glycopyrrolate NDAs/supplements held by you. To support your categorical exclusion claim from the preparation of an Environmental Assessment, provide a 5 year forecast for the production of glycopyrrolate drug substance for this NDA and any related applications held by you (such as NDA 012827 and its supplements). The EIC-Aquatic calculation should use the highest quantity in a given year and should include all related applications.

Pharmacology/Toxicology

1. The NDA contains draft protocols for teratology studies with rats and rabbits, a fertility study to be conducted with rats, and a perinatal development study to be conducted with rats. These protocols are not supported by data from dose-range finding studies (the NDA proposed that dose-range finding studies for the reproductive toxicology studies would be conducted post-approval). No provision was made to obtain or submit toxicokinetic (TK) data that would necessarily be relevant to the dosages that may be used in the reproductive toxicology studies, and such TK data would be needed to support labeling of the product. While TK data were obtained in a 90-day repeat-dose toxicology study conducted with rats, it is unclear if those data would encompass the exposures that would be achieved in the reproductive toxicology studies. No TK data from studies conducted with rabbits are available, and the rabbit teratology studies proposed for conduct post-approval make no provision for obtaining TK data. Therefore, apparent deficiencies in the NDA include a lack of complete protocols for appropriate reproductive toxicology studies (including specific dosages to be evaluated, and data from dose-range finding studies that support those dosage proposals), and a failure to address the need for suitable TK data. However, since the Division has agreed that reproductive toxicology issues may be addressed as Post Marketing Commitments under certain conditions, the adequacy of your proposals regarding reproductive toxicology issues has not been determined. The pivotal reproductive toxicology data, when submitted, should be acceptably supported by toxicokinetic data. This includes both rats and rabbits at the dosages used in the pivotal studies.
2. The NDA includes draft protocols for two-year carcinogenicity studies to be conducted in rats and mice, and data from GLP-compliant dose-ranging (90-day repeat-dose toxicology) studies. The suitability of these carcinogenicity protocols has not been determined.
3. You have been informed (see minutes of meeting on December 15, 2008) that an application that is not acceptably based upon an appropriate prior finding of safety and efficacy of a listed drug by the Agency must be supported by complete information, which would include (without limitation) fully adequate data that concerned repeat-dose toxicology. Since your product is proposed for chronic administration, the NDA should acceptably address the chronic toxicology of glycopyrrolate. While the Division has previously stated that it may be possible to address this matter through generation of a suitable clinical bridge to Robinul Tablets (NDA 012827), it has been determined that a

suitable clinical bridge to Robinul Tablets can not be established since you own the Robinul Tablets NDA. Therefore, your application appears to be deficient with respect to data which concern the chronic toxicology of glycopyrrolate (typically, repeat-dose toxicology studies involving six and nine months of administration to appropriate rodent and nonrodent species, respectively, would be expected). Some repeat-dose toxicology data are available, as well as some clinical safety data but it is unclear whether these data will be sufficient.

4. It is unclear whether your application contains data which adequately qualify the proposed exposures to excipients and impurities.

Clinical/Biostatistics

1. In Study FH-00-01, the method for calculating endpoints based on mean mTDS values (change from baseline and responders) is not clear. The mean values appear to be calculated differently for the original study report and the ISE. The results from the study report for Study FH-00-01 cannot be replicated from the analysis datasets provided. It is difficult to interpret study findings when an endpoint is not clearly or uniquely defined.
2. The integrated summary of safety does not provide information on or account for subjects who may have participated in both Studies FH-00-01 and SC-GLYCO-06-01.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We request that you submit the following information:

1. Representative samples packaged in the to-be-marketed container/closure system for visual examination of the product.
2. Detailed information concerning the impurity profiles of the lots of drug substances used in the nonclinical studies conducted by Sciele Pharma, Inc., including the 14-day and 90-day repeat-dose toxicology studies conducted with rats and mice and the genetic toxicology studies.
3. Detailed information concerning the impurity profiles of the lots of drug substance used in the pivotal clinical trials that are associated with NDA 022571.
4. A detailed algorithm for how mean daily mTDS values (both the baseline value and for follow-up visits), change from baseline values, and responders were calculated for the Study Report for Study FH-00-01 and the ISE. Include the rules for handling missing data. Provide an analysis dataset (in SAS transport format) for Study FH-00-01 (similar to the submitted datasets ade2.xpt and adef.xpt) that uses the definitions of mean mTDS and responders used in the study report (including baseline). Include the treatment

assignments. This dataset should be suitable for replicating the analyses based on mTDS for each visit as reported in the study report.

5. A dataset (in SAS transport format) that includes a unique subject identifier that identifies subjects who participated in both Studies FH-00-01 and SC-GLYCO-06-01 using a single subject ID. The dataset should include, at a minimum, the current variables USUBJID and STUDYID, and a new variable that is unique to each subject and links subjects that participated in both studies.
6. All earlier versions of Protocol FH-00-01 (Original, Amendment 1, and Amendment 2).
7. A listing which links the investigator names to the investigator numbers in Study FH-00-01 (or identify where to find this information in this submission).

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22571	ORIG-1	SCIELE 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/

SUSAN J WALKER
12/08/2009

MEMORANDUM

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

DATE: 10/27/09, 1:30 pm

TO: Alison Lowry, Regulatory Affairs
Sciele Pharma, Inc., Ph: 687-341-1486

THROUGH : Jeannie David, Regulatory Project Manager, ONDQA

FROM: Jeannie David, Regulatory Project Manager, ONDQA

SUBJECT: Memo of Telecon: Request for information on establishments information

APPLICATION/DRUG: NDA 22-571 / Glycopyrrolate Oral Solution, 1 mg/5 ml

**Memo of Telecon:

Information was provided from Alison Lowry (on behalf of Marty Solberg, VP Regulatory Affairs/Quality Assurance), Sciele Pharma, to Jeannie David, RPM, ONDQA, regarding establishment information submitted to the original NDA, on the Attachment to Form FDA 356h, in response to a voicemail from Jeannie David to Marty Solberg:

1) Submit fax numbers for the contact information for each establishment provided.

Applicant Response: the applicant referenced the fax numbers provided in 3.2.S.2.1 and 3.2.P.3.1.

2) Clarify the relationship of the (b) (4) of Mikart, Inc. which have the same Establishment Registration number: (b) (4) (e.g., (b) (4) performed at (b) (4) was the inspection from 3/2/2009 - 3/9/2009 (b) (4), as indicated)

Applicant Response: the applicant stated that (b) (4) The applicant further stated that the single registration number is indeed the same (b) (4) and confirmed that (b) (4) were inspected 3/2/2009 - 3/9/2009 under this single number.

The applicant committed to providing these responses as a amendment to the NDA.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22571

ORIG-1

SCIELE TM
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/

JEANNIE C DAVID
10/27/2009