

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204078Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

**PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and Composition)
and/or Method of Use*

NDA NUMBER

NAME OF APPLICANT/NDA HOLDER

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Neostigmine Methylsulfate Injection, USP

ACTIVE INGREDIENT(S)

Neostigmine

STRENGTH(S)

1 mg/mL, 0.5 mg/mL

DOSAGE FORM

Injection

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

b. Issue Date of Patent

c. Expiration Date of Patent

d. Name of Patent Owner

Address (of Patent Owner)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

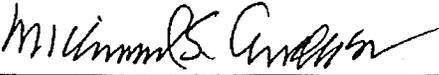
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification	
<p>6.1 <i>The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.</i></p> <p>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</p>	
6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)	Date Signed
	4/4/2012
<p>NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).</p>	
Check applicable box and provide information below.	
<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Michael S. Anderson	
Address 699 Trade Center Blvd., Suite A	City/State Chesterfield, MO
ZIP Code 63005	Telephone Number 636-449-1830
FAX Number (if available) 636-449-1850	E-Mail Address (if available) manderson@eclatpharma.com
<p>The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <p style="text-align: center;">Department of Health and Human Services Food and Drug Administration Office of Chief Information Officer 1350 Piccard Drive, Room 400 Rockville, MD 20850</p> <p style="text-align: center;"><i>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</i></p>	

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

PARAGRAPH II CERTIFICATION

Per 21 CFR 314.50(i)(1)(i)(A)(2), Éclat Pharmaceuticals certifies, to the best of its knowledge, that any patent(s) associated with Anzemet (dolasetron mesylate; NDA 020624) are expired.



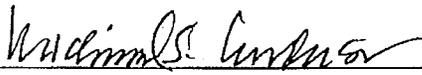
Michael S. Anderson
Chief Executive Officer
Éclat Pharmaceuticals



Date

PARAGRAPH IV CERTIFICATION

Per 21 CFR 314.50(i)(1)(i)(A)(4), Éclat Pharmaceuticals certifies, to the best of its knowledge, that Patent No. 5453510 associated with Nimbex (cisatracurium besylate; NDA 020551) will not be infringed by the manufacture, use or sale of Neostigmine Methylsulfate Injection, USP, for which this application is submitted.



Michael S. Anderson
Chief Executive Officer
Éclat Pharmaceuticals



Date

NDA 204078

EXCLUSIVITY SUMMARY

NDA # 204078

HFD # 170

Trade Name: Bloxiverz

Generic Name: neostigmine methylsulfate injection

Applicant Name: Eclat Pharmaceuticals

Approval Date, If Known: May 31, 2013

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)(2)

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

The submission contains only published literature to support the indication. The Applicant did not conduct any clinical studies to support the safety and efficacy of this product.

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?

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 204078

studies.) If 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:

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 YES NO

Investigation #2 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 YES NO

Investigation #2 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"):

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 # YES ! NO
! Explain:

Investigation #2
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
YES
Explain: ! NO
! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====

Name of person completing form: Allison Meyer
Title: Regulatory Health Project Manager
Date: May 30, 2013

Name of Office/Division Director signing form: Rigoberto Roca, Deputy Director
Title: Director, HFD-170

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

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

/s/

ALLISON MEYER
05/31/2013

RIGOBERTO A ROCA
05/31/2013

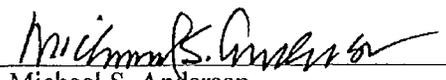
3. DEBARMENT CERTIFICATION

**CERTIFICATION PURSUANT TO SECTION 306(K)(1) OF THE GENERIC DRUG
ENFORCEMENT ACT OF 1992 [21 USC § 335A(K)(1)]**

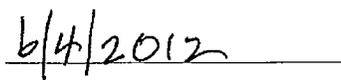
This is to certify:

- (1) that Éclat Pharmaceuticals did not use in any capacity the services of any person debarred under subsection (a) or (b) of this section in connection with the development or submission of this application;
- (2) that Éclat Pharmaceuticals will not use in any capacity the services of any person debarred under subsection (a) or (b) of this section in connection with this application;
and
- (3) that neither Éclat Pharmaceuticals nor affiliated persons responsible for the development or submission of this application have been convicted within the past five (5) years of offenses described in subsections (a) and (b) of this section.

List of convictions: None



Michael S. Anderson
President and Chief Executive Officer
Éclat Pharmaceuticals



Date

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

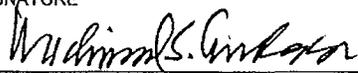
Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Michael S. Anderson	TITLE Chief Executive Officer
FIRM/ORGANIZATION Eclat Pharmaceuticals	
SIGNATURE 	DATE (mm/dd/yyyy) 06/04/2012

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right.

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 204078 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Bloxiverz Established/Proper Name: Neostigmine Methylsulfate Dosage Form: Injection		Applicant: Eclat Pharmaceuticals LLC Agent for Applicant (if applicable):
RPM: Allison Meyer		Division: DAAAP
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" 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></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>NDA 20642 Anzemet</p> <p>NDA 20551 Nimbex</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>The above products were relied upon for their data on phenol and tonicity of excipients.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input checked="" type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² 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 checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: 5/31/13</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>5/31/13</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	

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.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<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>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 3S</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 type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <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> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<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)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<p> <input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other </p>

³ 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 checked="" 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 checked="" 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 checked="" 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 checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input checked="" 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 checked="" 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 checked="" 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
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	6/4/13
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) AP 5/31/13
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. 	5/31/13
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	7/31/12
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. • Original applicant-proposed labeling • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ 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 	5/28/13
<ul style="list-style-type: none"> ❖ 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>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	5/28/13 (2)
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 10/10/12 <input checked="" type="checkbox"/> DMEPA 11/16/12, 5/14/13, 5/31/13 <input type="checkbox"/> DMPP/PLT (DRISK) <input checked="" type="checkbox"/> ODPD (DDMAC) 5/13/13 <input checked="" type="checkbox"/> SEALD 5/30/13 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	10/10/12
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2) 5/17/13 <input type="checkbox"/> Not a (b)(2) 5/31/13
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included 5/31/13
<ul style="list-style-type: none"> ❖ 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 checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>12/5/12</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ 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, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	8/3/12, 10/12/12, 11/30/12, 12/18/12, 1/8/13, 1/13/13, 1/14/13, 1/22/13, 2/1/13, 2/15/13 2/26/13, 2/27/13, 2/28/13, 3/4/13, 3/13/13, 3/14/13, 3/21/13, 3/26/13, 4/25/13, 5/24/13, 5/28/13, 5/31/13
❖ Internal memoranda, telecons, etc.	
❖ .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 checked="" 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 type="checkbox"/> No mtg 5/16/12
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	6/30/11, 9/16/11
❖ 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 5/31/13
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 5/10/13
PMR/PMC Development Templates <i>(indicate total number)</i>	<input type="checkbox"/> None 5/30/13
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	
• Clinical review(s) <i>(indicate date for each review)</i>	9/9/12, 4/26/13
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ 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>	4/26/13
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not applicable

⁶ Filing reviews should be filed with the discipline reviews.

❖ 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
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI 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 checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/10/12
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 9/12/12, 3/14/13
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
<ul style="list-style-type: none"> ADP/T Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Supervisory Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 9/14/12, 4/3/13
❖ 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 checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI 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 checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None 9/28/12, 4/26/13, 5/31/13
❖ Microbiology Reviews		<input type="checkbox"/> Not needed 9/17/12, 4/26/13
<input checked="" 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 (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		<input type="checkbox"/> None 9/11/12 (biopharm)
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		4/26/13
<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) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>		Date completed: 01/31/2013 <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) (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 type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁷ 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.

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

/s/

ALLISON MEYER
06/04/2013

505(b)(2) ASSESSMENT

Application Information		
NDA # 204078	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Bloxiverz Established/Proper Name: Neostigmine Methylsulfate Dosage Form: Injection Strengths: 0.5 mg/mL and 1.0 mg/mL		
Applicant: Eclat Pharmaceuticals		
Date of Receipt: July 31, 2012		
PDUFA Goal Date: May 31, 2013		Action Goal Date (if different):
Proposed Indication(s): indicated for reversal of non-depolarizing neuromuscular blocking agents		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)
--

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 20624 Anzemet (dolasetron)	The Applicant is referencing this NDA to justify the safety of the bolus dose of phenol via this drug product.
NDA 20551 Nimbex (cisatracurium)	The Applicant is referencing this NDA to justify the safety of the osmolality of the drug product solution.
Published literature	Pharmacology, pharmacokinetics/ADME, general toxicology, genetic toxicology, reproductive and developmental toxicology, phenol toxicology, clinical efficacy and safety

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The proposed product bridge to the published literature is a scientific justification that is supported by: data from IV studies (100% bioavailable) from published literature and the product is IV (100% bioavailable). The data are relevant without the need for a study (100% = 100%).

The proposed product bridge to the reference to NDA 20624 (Anzemet) justifies the levels of phenol in the drug product (excipient). The level of phenol in the proposed product (22.5mg) is lower than the level of phenol is the LD (25mg), so it covered. This is covered in the pharm/tox review.

The proposed product bridge to the reference to NDA 20551 (Nimbex) justifies the tonicity of the injectable product (excipient). Excerpt from pharm/tox review: “The osmolality of the solution is approximately 53-59 mOsmal/L, which is hypotonic (isotonic solutions are ~290 mOsmol). Although this drug is not isotonic, the applicant notes that the FDA approved drug Nimbex is also indicated for intravenous use and that drug has an osmolality of 8 mOsmol/L and is injected in the same volume as that proposed. Therefore, there is an FDA previous finding of safety for an intravenous hypotonic drug product

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO”, proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

N/A NO YES

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs

(approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Anzemet (dolastetron mesylate) injection	20624	Y
Nimbex (cisatracurium besylate) injection	20551	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application: 20624 and 20551

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

- d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

- i) Were the products discontinued for reasons related to safety or effectiveness?
 YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

- 9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

There are currently only marketed unapproved drugs for this product on the market.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

- 10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If “**NO**” to (a) proceed to question #11.
If “**YES**” to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
YES NO

If “**YES**” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If “**NO**”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
YES NO

If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- X 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

- 15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

ALLISON MEYER
05/31/2013

PARINDA JANI
05/31/2013



Memorandum

DATE: May 31, 2013
TO: DARRTS
FROM: Prasad Peri, Ph.D,
SUBJECT: Correction of NDA number on page 7 in Review dated April 26, 2013, Trade name/Labeling comments

Dr. Arthur Shaw placed a review in DARRTS on April 26^h recommending approval of the product from a CMC perspective. However after this review was placed it was noticed that on page 7 of the review the heading states "**The Chemistry Review for NDA 200436**". This heading on page 7 is an error and the correct number for this NDA review is 204078 as noted all other places of the document.

This memo is entered to notify the team of this error.

In addition, it was noted that the trade name of the drug product has been revised from (b) (4) to Bloxiverz which was evaluated and accepted by DMEPA recently and the established name is stated as (Neostigmine Methylsulfate Injection, USP) in the carton and container labels submitted on May 28th 2013. It is noted that the first letter of the established name is spelled in capital letters on the carton and container labels where as it is spelled out as small letter in the package insert (per email from project manager and DMEPA reviewers). The sponsor will be asked to commit to revise these to be consistent.

In addition the storage statement on the carton should be "store at 20° to 25°C (68° to 77°F) and not (b) (4) to be consistent with the Package Insert.

Prasad Peri



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

(b) (4)

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/s/

PRASAD PERI
05/31/2013

Meyer, Allison

From: Meyer, Allison
Sent: Thursday, May 30, 2013 4:59 PM
To: Marla Scarola
Subject: Carton and container labels neostigmine

Marla,

Please incorporate the following recommendations and resend the carton/container labeling.

- A. All Container Labels and Carton Labeling (5 mg/10 mL and 10 mg/10 mL)
1. Revise the presentation of the proprietary name from all upper case letters "BLOXIVERZ" to title case "Bloxiverz" to improve readability.
 2. Delete  (b) (4)
 3. Remove or decrease the size and prominence of the company name and logo so that it does not distract from important identifying drug information. The company name and logo is problematic because it is currently equally or more prominent than the established name on the container label and the proprietary and established name on the carton labeling.
- B. Container Label (5 mg/10 mL and 10 mg/10 mL)
1. Include a space between the number and unit. For example, 5 mg/10mL should read 5 mg/10 (space) mL and 10 mg/10mL should read 10 mg/10 (space) mL.
 2. Reformat the strength statement to appear in a stacked format to help with the readability of this information. The format of the strength statement should appear similar to the currently proposed format on the carton labeling.
 3. Relocate and revise the "Rx ONLY" statement from the principal display panel to the side panel and to appear as "Rx Only."
- C. Carton Labeling (5 mg/10 mL and 10 mg/10 mL)
1. Include a space between the number and unit. For example, 5 mg/10mL should read 5 mg/10 (space) mL and 10mg/10mL should read 10 (space) mg/10 (space) mL.
 2. Relocate the "Manufactured for" statement on the principal display panel to the side panel to help increase the readability of the most important information.
 3. Relocate the route of administration statement, "For Intravenous Use," to appear above the net quantity statement similar to the presentation of the statement on the container label.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

Meyer, Allison

From: Meyer, Allison
Sent: Tuesday, May 28, 2013 3:55 PM
To: Marla Scarola
Subject: 356h

Marla,

We noticed that the 356h form, while it indicates b2, it does not list the 2 listed drugs (N20624 and N20551). The next time you submit an amendment to the NDA, ensure the listed drugs are indicated on the 356h form.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
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301-796-9713 (fax)

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/s/

ALLISON MEYER
05/31/2013

Meyer, Allison

From: Meyer, Allison
Sent: Friday, May 24, 2013 2:53 PM
To: Marla Scarola
Subject: Package insert

Attachments: draft for Applicant clean.docx



draft for Applicant
clean.docx...

Marla,
Attached is our draft package insert. Please keep in mind that this has not been completely reviewed by management yet, so there may be some additional minor adjustments. We will ask that you change the tradename through the label as appropriate. There are a few comments that will need to be addressed as well as updates to the table of contents and formatting as per the PLR guidance.

Please let me know if you have any questions.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

Meyer, Allison

From: Meyer, Allison
Sent: Tuesday, May 28, 2013 9:49 AM
To: Marla Scarola
Subject: Neostigmine label

Marla,
Please see the below comments with respect to the package insert labeling:

This relates to the subsection in Section 5 titled: Serious Adverse Reactions in Patients with Certain Coexisting Conditions.

You propose to include the following statement in the Warnings and Precautions (W&P) section of the neostigmine prescribing information:

(b) (4) should be used with caution in patients with (b) (4), coronary artery disease, cardiac arrhythmias, recent acute coronary syndrome, (b) (4) myasthenia gravis, (b) (4)

However, this statement is not consistent with the W&P regulations [21 CFR 201.57(c)(6)] or 2011 *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format guidance* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf>) because it does not "describe clinically significant adverse reactions" associated with each of the listed conditions. Furthermore, the statement includes a possibly ambiguous and uninformative statement on how to prevent, mitigate, monitor for or manage the clinically significant adverse reaction (i.e., "should be used with caution"). Therefore, you need to revise the statement to include the clinically significant adverse reactions associated with each of the stated conditions and include a statement on how to prevent, mitigate, monitor for or manage each clinically significant adverse reaction if known. If there is no information to support the warning for a particular underlying condition, i.e., reports of adverse events related to the condition, that condition should be removed from this section of the label.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

Meyer, Allison

From: Meyer, Allison
Sent: Tuesday, May 28, 2013 3:55 PM
To: Marla Scarola
Subject: 356h

Marla,

We noticed that the 356h form, while it indicates b2, it does not list the 2 listed drugs (N20624 and N20551). The next time you submit an amendment to the NDA, ensure the listed drugs are indicated on the 356h form.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
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/s/

ALLISON MEYER
05/29/2013



NDA 204078

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Éclat Pharmaceuticals
c/o The Weinberg Group Inc.
1129 Twentieth St., NW, Suite 600
Washington, DC 20036

ATTENTION: Marla E. Scarola, MS
Senior Consultant and U.S. Agent

Dear Ms. Scarola:

Please refer to your New Drug Application (NDA) dated and received on July 31, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Neostigmine Methylsulfate Injection, 0.5 mg/mL and 1 mg/mL.

We also refer to your correspondence, submitted and received May 6, 2013, requesting review of your proposed proprietary name, Bloxiverz. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Bloxiverz, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. Additionally, if **any** of the proposed product characteristics as stated in your May 6, 2013 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 Teena Thomas, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796- 0549. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Allison Meyer at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Medication Error Prevention and Risk Management

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
05/23/2013



NDA 204078

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Éclat Pharmaceuticals
c/o The Weinberg Group Inc.
1129 Twentieth St., NW, Suite 600
Washington, DC 20036

ATTENTION: Marla E. Scarola, MS
Senior Consultant

Dear Ms. Scarola:

Please refer to your New Drug Application (NDA) dated and received on July 31, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Neostigmine Methylsulfate Injection, USP, 0.5 mg/mL and 1 mg/mL.

We also refer to your correspondence, dated and received August 1, 2012, requesting review of your proposed proprietary name, (b)(4). We have completed our evaluation of the proposed proprietary name and have concluded that this name is unacceptable (b)(4).

We acknowledge that this determination differs from our previous evaluation and conclusion communicated in the later dated October 25, 2012.

The reason we have reached a different determination with respect to the safety of your proposed name is based upon our re-evaluation of the misinterpretation of (b)(4) in the inpatient prescription study as well as a comment from another participant indicating that the name looked similar to (b)(4). The sample that was misinterpreted for (b)(4) is included here:



In our current evaluation of your proposed name, the review team determined that both of these products may be used in the same clinical setting of use and may be present on an inpatient medication order at the same time. For example, post-operative patients who are able to swallow may have medication orders written for oral medications that they will receive upon transfer to a step down nursing unit prior to actually being transferred. Additionally, oral medications may be initiated in a post-operative nursing unit as their stay can at times reach 24 hours or longer, especially in the case of minor surgical procedures that require extended observation but not actual admission to an inpatient nursing unit. The review team concludes that these circumstances create the possibility that both medications may be present on a patient's medication administration record (MAR) or order set, especially in the setting of a planned procedure, where any and all medications which may be given to the patient during the course of their stay will be included.

The review team notes in their evaluation that in the intensive care unit patients may undergo neuromuscular blockade for various clinical reasons. Neostigmine may be administered as a reversal agent for daily neurological testing, or for complete reversal. The review team also notes that Neostigmine is used in treatment of other disease states, including Ogilvie's syndrome. Medical literature states that there may be a range of doses administered to treat Ogilvie's syndrome with variation between 2-2.5 mg.^{1,2} Therefore, we anticipate that some orders for (b) (4) when used to treat Ogilvie's syndrome, will have a direct dose or strength overlap with (b) (4). Such circumstances may lead to confusion with (b) (4) particularly for patients who are continued on their outpatient regimen of (b) (4) while in the intensive care unit.

The review team acknowledges that (b) (4) is not proposing labeling for the treatment of Ogilvie's syndrome. However, they raise concern that this medication has been in use for decades to manage the disease, and therefore we anticipate that some off-label use of your product for this (and other) diseases may occur.³ The team concludes, therefore, based upon literature review, responses from the prescription simulation study, and current clinical practices, believe that these names are vulnerable to confusion in the usual practice setting.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

¹ Stephenson, B. M., Chir, J. R. S. M., & Wheeler, M. H. (1995). Ogilvie's syndrome: a new approach to an old problem. *Diseases of the colon & rectum*, 38(4), 424-427.

² Hutchinson, R., & Griffiths, C. (1992). Acute colonic pseudo-obstruction: a pharmacological approach. *Annals of the Royal College of Surgeons of England*, 74(5), 364.

³ Ponc, R. J., Saunders, M. D., & Kimmey, M. B. (1999). Neostigmine for the treatment of acute colonic pseudo-obstruction. *New England Journal of Medicine*, 341(3), 137-141.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Teena Thomas, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0549. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Allison Meyer at (301) 796-1258.

Sincerely,

(See appended electronic signature page)

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

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/s/

CAROL A HOLQUIST
05/01/2013

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/s/

ALLISON MEYER
05/01/2013

Rivera, Luz E (CDER)

From: Rivera, Luz E (CDER)
Sent: Thursday, April 25, 2013 10:24 AM
To: marla.scarola@weinberggroup.com
Subject: NDA 204078

Good morning Ms. Scarola,

We are reviewing your NDA 204078 and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Commit to submitting a PAS if the drug substance supplier (b) (4)
2. Commit to making (b) (4) a Critical Process Parameter.
3. Commit to amending the manufacturing directions in the master batch record to do the following:
 - a) Include (b) (4)
 - b) Include (b) (4)

Please contact me if you have any questions.

Please acknowledge the receipt of this request.

Thank you,
Luz E Rivera, Psy.D.
LCDR, USPHS
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment III
Phone (301) 796-4013

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/s/

LUZ E RIVERA
04/25/2013

Rivera, Luz E (CDER)

From: Rivera, Luz E (CDER)
Sent: Thursday, March 21, 2013 3:26 PM
To: marla.scarola@weinberggroup.com
Subject: FW: NDA 204078: Request for clarification

Good afternoon Ms. Scarola,

Please find the response to your clarification questions:

Drug Substance

3) **Provide the source and Specifications for the [REDACTED] (b) (4) used in Method ATP1255.**

We assume that this request is in reference to Method ATP1225 (P404 Drug Substance Related Substances by HPLC). Is that correct?

FDA Response: Yes

5) **Provide the results of measurement of Total Impurities for the drug substance and the [REDACTED] (b) (4) in the Batch Analysis.**

Regarding [REDACTED] (b) (4), the validation batches and all commercial batches will be manufactured using drug substance for which [REDACTED] (b) (4) levels were analyzed and reported. However, the [REDACTED] (b) (4) specification was not

included at the time of registration batch manufacture. Thus, Éclat does not have the results for the lots of drug substance used to manufacture the registration batches to add to the Batch Analysis. Results for Total Impurities will be

added to the Batch Analysis as requested and [REDACTED] (b) (4) results will be available on future batches. Is this acceptable to the Agency?

FDA Response: Yes

Drug Product

2) **Regarding the Control of the Drug Product (3.2.P.5)**

a) **Regarding Method ATP1226 for the testing for Leachables:**

iii) **Explain why the sum of the values for Assay of neostigmine methylsulfate, [REDACTED] (b) (4) and Total Impurities are greater than [REDACTED] (b) (4) in Table 6 in the Leachables Method Validation Report (REP2659).**

Is the Agency referring to REP2659 [REDACTED] (b) (4) Report or to REP2569 Leachables Method Validation Report?

2) Regarding the Control of the Drug Product (3.2.P.5)

b) Regarding Method ATP1226 for the testing for Leachables:

- ii) Explain why the procedure for calculating the Total Impurities does not specify that the areas of individual impurities should be added, rather than taking the mean.**

The data reporting section in ATP1092 instructs the analyst to

- Calculate the % Label Claim of the individual impurities in each replicate to three decimal places and the mean % Label Claim of the impurities between replicate samples to two decimal places.*
- Calculate total % Label Claim of the impurities using the two decimal place mean of individual impurities and report the total % Label Claim to one decimal place.*

Is the Agency requesting that we clarify the second bullet point to state that the two decimal place means of individual impurities should be added to report the total % Label Claim to one decimal place?

FDA Response: Yes

4) Regarding the Stability Protocols

a) Include reporting (b) (4) in the Stability protocols.

(b) (4) is currently reported in the stability data tables (3.2.P.8.3) and will continue to be reported as a related substance per the post-approval stability protocol (3.2.P.8.2). The stability testing is conducted against the current drug

specification in which the related substances specification requires testing for (b) (4). Would the Agency's request be satisfied if we simply include the drug product specification in the stability protocol?

FDA Response: Yes

4) Regarding the Stability Protocols

c) Add testing for leachables, endotoxin, and sterility as part of Stability Protocols B and D.

Stability Protocols B and D currently include testing for endotoxin and sterility. Is the Agency requesting that we add leachables testing to these protocols?

FDA Response: Yes

Thank you,

Luz E Rivera, Psy.D.
LCDR, USPHS
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment III
Phone (301) 796-4013

From: Marla Scarola [mailto:Marla.Scarola@weinberggroup.com]
Sent: Thursday, March 21, 2013 11:11 AM
To: Rivera, Luz E (CDER)
Cc: Meyer, Allison
Subject: NDA 204078: Request for clarification

LCDR Rivera,

In regards to the most recent information request (dated March 13 and emailed to me on March 16), we would like to ask for clarification on a number of the items. The Agency's requests are in bold followed by our request for clarification in red.

Drug Substance

3) **Provide the source and Specifications for the [REDACTED] (b) (4) used in Method ATP1255.**

We assume that this request is in reference to Method ATP1225 (P404 Drug Substance Related Substances by HPLC). Is that correct?

5) **Provide the results of measurement of Total Impurities for the drug substance and the [REDACTED] (b) (4) in the Batch Analysis.**

Regarding [REDACTED] (b) (4) the validation batches and all commercial batches will be manufactured using drug substance for which [REDACTED] (b) (4) levels were analyzed and reported. However, the [REDACTED] (b) (4) specification was not included at the time of registration batch manufacture. Thus, Éclat does not have the results for the lots of drug substance used to manufacture the registration batches to add to the Batch Analysis. Results for Total Impurities will be added to the Batch Analysis as requested and [REDACTED] (b) (4) results will be available on future batches. Is this acceptable to the Agency?

Drug Product

2) **Regarding the Control of the Drug Product (3.2.P.5)**

a) **Regarding Method ATP1226 for the testing for Leachables:**

iii) **Explain why the sum of the values for Assay of neostigmine methylsulfate, [REDACTED] (b) (4) and Total Impurities are greater than [REDACTED] (b) (4) in Table 6 in the Leachables Method Validation Report (REP2659).**

Is the Agency referring to REP2659 [REDACTED] (b) (4) Report or to REP2569 Leachables Method Validation Report?

2) **Regarding the Control of the Drug Product (3.2.P.5)**

b) **Regarding Method ATP1226 for the testing for Leachables:**

ii) **Explain why the procedure for calculating the Total Impurities does not specify that the areas of individual impurities should be added, rather than taking the mean.**

The data reporting section in ATP1092 instructs the analyst to

- Calculate the % Label Claim of the individual impurities in each replicate to three decimal places and the mean % Label Claim of the impurities between replicate samples to two decimal places.

- Calculate total % Label Claim of the impurities using the two decimal place mean of individual impurities and report the total % Label Claim to one decimal place.

Is the Agency requesting that we clarify the second bullet point to state that the two decimal place means of individual impurities should be added to report the total % Label Claim to one decimal place?

4) Regarding the Stability Protocols

- a) **Include reporting of (b)(4) in the Stability protocols.**

(b)(4) is currently reported in the stability data tables (3.2.P.8.3) and will continue to be reported as a related substance per the post-approval stability protocol (3.2.P.8.2). The stability testing is conducted against the current drug specification in which the related substances specification requires testing for (b)(4). Would the Agency's request be satisfied if we simply include the drug product specification in the stability protocol?

4) Regarding the Stability Protocols

- c) **Add testing for leachables, endotoxin, and sterility as part of Stability Protocols B and D.**

Stability Protocols B and D currently include testing for endotoxin and sterility. Is the Agency requesting that we add leachables testing to these protocols?

Thank you,
Marla

Marla E. Scarola, M.S., RAC
Senior Consultant
The Weinberg Group
1129 Twentieth St, NW, Suite 600
Washington, DC 20036
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F +1 202.833.7057
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/s/

LUZ E RIVERA
04/10/2013

Meyer, Allison

From: Meyer, Allison
Sent: Tuesday, January 22, 2013 10:21 AM
To: Marla Scarola
Subject: Eclat NDa 204078

Attachments: image001.gif; IR_204078_Jan10_2013.pdf



IR_204078_Jan10_2013.pdf (75 K...

Marla,

“We are contacting you with regard to the CMC IR sent to you in a letter on January 13, 2013.

We would like to inquire as to the time frame of when you would be able to provide the requested information

on DS Specifications, Drug Product Specifications etc. In addition, we would like to know if you have made drug product material for the process validation in order to confirm the proposed drug product manufacturing process”.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

Meyer, Allison

From: Meyer, Allison
Sent: Tuesday, March 26, 2013 3:03 PM
To: 'Marla Scarola'
Subject: Labeling for Neostigmine

Regarding the Carton and Container Labels: [REDACTED] (b) (4)
[REDACTED] **in the carton labels for the 0.5 and 1 mg/ml strengths, respectively.**

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

Meyer, Allison

From: Meyer, Allison
Sent: Tuesday, March 26, 2013 11:19 AM
To: 'Marla Scarola'
Subject: Neostigmine reports

FDA is has begun use of a new adverse event reporting system that identifies case reports with a new numbering system, but allows searches with the ISR numbers used for the old version of AERS. We have been able to locate 9 of the 11 cases of coma that you reference in the NDA; however, 2 cases have report numbers that are not recognized by either the old or the new system. These are C01398365 and C01695412. Please submit copies of these case reports.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258

Meyer, Allison

From: Meyer, Allison
Sent: Thursday, February 28, 2013 4:51 PM
To: 'Marla Scarola'
Subject: RE: NDA 204078 request

Attachments: image001.gif



image001.gif (2 KB)

Marla,
Provide the following:

1. The mass spectra for the following peaks found in the analysis (b) (4)

[Redacted]

[Redacted]

Peak #

RRT

Figure

(b) (4)
[Redacted]

2. Provide the analysis used to determine that the mass spectra are consistent with the proposed structure.

Thank you,

Allison

From: Marla Scarola [mailto:Marla.Scarola@weinberggroup.com]
Sent: Thursday, February 28, 2013 3:23 PM
To: Meyer, Allison
Subject: RE: NDA 204078 request

Allison,

Per Section 6.2 of the (b) (4) report, the potential leachable (b) (4) was identified (b) (4) to Gas Chromatograph with Mass Spectrometric detection. The results were compared against the NIST08 Mass Spectral Library which showed a (b) (4) confidence fit (see Table 14 of (b) (4) report).

Please let me know if this sufficiently answers the reviewer's question.

Thanks,

Marla

Marla E. Scarola, M.S., RAC

Senior Consultant

The Weinberg Group

1129 Twentieth St, NW, Suite 600

Washington, DC 20036

P +1 202.730.4129

F +1 202.833.7057

weinberggroup.com

Description: Description: Description: Logob

From: Meyer, Allison [mailto:Allison.Meyer@fda.hhs.gov]
Sent: Wednesday, February 27, 2013 9:52 AM
To: Marla Scarola
Subject: RE: NDA 204078 request

Provide the method used to confirm the identification. The “(b) (4) 2011” Report only states that the structure of (b) (4) is based on a “Most Probable Compound” analysis.

Allison

From: Marla Scarola [mailto:Marla.Scarola@weinberggroup.com]
Sent: Wednesday, February 27, 2013 9:19 AM
To: Meyer, Allison
Subject: RE: NDA 204078 request

Allison,

Would you please clarify your request? Are you looking for the structure of the leachable or the method used for identification?

Thanks,

Marla

From: Meyer, Allison [mailto:Allison.Meyer@fda.hhs.gov]
Sent: Wednesday, February 27, 2013 8:18 AM
To: Marla Scarola
Subject: NDA 204078 request

Marla,

Provide data to confirm the structure of the leachable, (b) (4)

Allison Meyer

Sr. Regulatory Health Project Manager

Division of Anesthesia, Analgesia and

Addiction Products

Office of New Drugs II

Center for Drug Evaluation and Research

10903 New Hampshire Avenue

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Silver Spring, MD 20993

301-796-1258

301-796-9713 (fax)

Meyer, Allison

From: Meyer, Allison
Sent: Thursday, February 28, 2013 3:58 PM
To: 'Marla Scarola'
Subject: RE: neostigmine

Attachments: image001.gif



image001.gif (2 KB)

[Please send us copies of these reports.](#)

From: Marla Scarola [mailto:Marla.Scarola@weinberggroup.com]
Sent: Tuesday, February 26, 2013 4:44 PM
To: Meyer, Allison
Subject: RE: neostigmine

Allison,

The 11 events of coma were identified through a search of the FDA AERS database. Please see Table 7 of the ISS.

Please let me know if you require further information.

Best,

Marla

Marla E. Scarola, M.S., RAC

Senior Consultant

The Weinberg Group

1129 Twentieth St, NW, Suite 600

Washington, DC 20036

P +1 202.730.4129

F +1 202.833.7057

weinberggroup.com

Description: Description: Description: Logob

From: Meyer, Allison [mailto:Allison.Meyer@fda.hhs.gov]

Sent: Tuesday, February 26, 2013 4:28 PM

To: Marla Scarola

Subject: neostigmine

Marla,

For Neostigmine, please identify the articles in the literature where you found the 11 events of coma?

Thanks.

Allison Meyer

Sr. Regulatory Health Project Manager

Division of Anesthesia, Analgesia and

Addiction Products

Office of New Drugs II

Center for Drug Evaluation and Research

10903 New Hampshire Avenue

Bldg. 22, Rm. 3176

Silver Spring, MD 20993

301-796-1258

301-796-9713 (fax)

Meyer, Allison

From: Meyer, Allison
Sent: Wednesday, February 27, 2013 9:52 AM
To: 'Marla Scarola'
Subject: RE: NDA 204078 request

Provide the method used to confirm the identification. The (b) (4) 2011" Report only states that the structure of (b) (4) is based on a "Most Probable Compound" analysis.

Allison

From: Marla Scarola [mailto:Marla.Scarola@weinberggroup.com]
Sent: Wednesday, February 27, 2013 9:19 AM
To: Meyer, Allison
Subject: RE: NDA 204078 request

Allison,

Would you please clarify your request? Are you looking for the structure of the leachable or the method used for identification?

Thanks,

Marla

From: Meyer, Allison [mailto:Allison.Meyer@fda.hhs.gov]
Sent: Wednesday, February 27, 2013 8:18 AM
To: Marla Scarola
Subject: NDA 204078 request

Marla,

Provide data to confirm the structure of the leachable, (b) (4)

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

Meyer, Allison

From: Meyer, Allison
Sent: Wednesday, February 27, 2013 8:18 AM
To: 'Marla Scarola'
Subject: NDA 204078 request

Marla,

Provide data to confirm the structure of the leachable,  (b) (4)

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
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Silver Spring, MD 20993
301-796-1258

301-796-9713 (fax)

Meyer, Allison

From: Meyer, Allison
Sent: Tuesday, February 26, 2013 4:28 PM
To: 'Marla Scarola'
Subject: neostigmine

Marla,

For Neostigmine, please identify the articles in the literature where you found the 11 events of coma?
Thanks.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

Meyer, Allison

From: Meyer, Allison
Sent: Friday, February 01, 2013 11:05 AM
To: 'Marla Scarola'
Subject: Neostigmine label

Marla,
Can you send me an updated word version of your label with your tradename included?
Thanks,

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

Meyer, Allison

From: Meyer, Allison
Sent: Monday, January 14, 2013 10:06 AM
To: 'Marla Scarola'
Subject: neostigmine

Marla,
Please respond by Wednesday.

In your ISE (page 10) you state the following:

More recently, recovery to a TOF ratio of 0.9 (TOF_{0.9}) or above has been shown to correlate well with adequate and safe recovery from a NMBA, providing a greater margin of safety in patients with lung disease (i.e., bronchitis or asthma) or neuromuscular disease (i.e., myasthenia gravis) ([Heier et al. 2001](#)).

That statement is not supported by the cited publication: Hemoglobin Desaturation after Succinylcholine-induced Apnea. Were you intending to cite a different reference?

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

Meyer, Allison

From: Meyer, Allison
Sent: Tuesday, January 08, 2013 11:44 AM
To: 'Marla Scarola'
Subject: RE: neostigmine

Microbiology Information Request:

We acknowledge the December 28 submission of antimicrobial effectiveness testing (AET) validation. There are additional matters that need to be addressed regarding your AET data and test method. Please address the following points:

- Your drug product specifications state an (b) (4) content of phenol as compared to the formulation. Provide data to demonstrate that undiluted

drug product with (b) (4) of phenol content is effective to adequately preserve the drug product.

- Confirm that AET is performed using methods described in USP<51> or a suitable alternative.

Allison Meyer

Sr. Regulatory Health Project Manager

Division of Anesthesia, Analgesia and

Addiction Products

Office of New Drugs II

Center for Drug Evaluation and Research

10903 New Hampshire Avenue

Bldg. 22, Rm. 3176

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301-796-1258

301-796-9713 (fax)

Meyer, Allison

From: Meyer, Allison
Sent: Tuesday, December 18, 2012 3:41 PM
To: 'Marla Scarola'
Subject: RE: NDA 204078 IR

Attachments: image001.gif



image001.gif (2 KB)

[Also, do you have any updated stability data? If so, when can we expect that submission?](#)

Thanks,
Allison

From: Marla Scarola [mailto:Marla.Scarola@weinberggroup.com]
Sent: Tuesday, December 18, 2012 3:39 PM
To: Meyer, Allison
Subject: RE: NDA 204078 IR

Allison,

We plan to submit the responses by 12/31 as requested.

Best,

Marla

From: Meyer, Allison [mailto:Allison.Meyer@fda.hhs.gov]
Sent: Tuesday, December 18, 2012 3:38 PM
To: Marla Scarola
Subject: RE: NDA 204078 IR

Marla,

When can we expect these responses?

Thanks,

Allison

From: Marla Scarola [mailto:Marla.Scarola@weinberggroup.com]
Sent: Friday, November 30, 2012 1:23 PM
To: Meyer, Allison
Subject: RE: NDA 204078 IR

Thank you, Allison. We'll be in touch if we require any clarification.

Best regards,

Marla

Marla E. Scarola, M.S., RAC

Senior Consultant

The Weinberg Group

1129 Twentieth St, NW, Suite 600

Washington, DC 20036

P +1 202.730.4129

F +1 202.833.7057

weinberggroup.com

Description: Description: Description: Logob

From: Meyer, Allison [<mailto:Allison.Meyer@fda.hhs.gov>]

Sent: Friday, November 30, 2012 1:19 PM

To: Marla Scarola

Subject: NDA 204078 IR

Marla,

These need to be addressed before 12/31/12.

· Your most recent information request response (dated November 15, 2012) contains graphical layouts of your facility. However, a higher quality graphic is needed for review. It is only necessary to submit graphical layouts of the air classification, personnel flow, and product flow of the [REDACTED] suites. (b) (4)

· Your most recent information request response (dated November 15, 2012) describes preservative efficacy testing (Section 3.2.P.2.) This section states that routine preservative effectiveness testing will be performed [REDACTED] (b) (4)

- Provide results from the most recent [REDACTED] (b) (4) loads.
- What is the [REDACTED] (b) (4) schedule for depyrogenation [REDACTED] (b) (4)
- Describe environmental monitoring procedures performed during media fills.
- Provide results from your most recent media fill on [REDACTED] (b) (4)

Allison Meyer

Sr. Regulatory Health Project Manager

Division of Anesthesia, Analgesia and

Addiction Products

Office of New Drugs II

Center for Drug Evaluation and Research

10903 New Hampshire Avenue

Bldg. 22, Rm. 3176

Silver Spring, MD 20993

301-796-1258

301-796-9713 (fax)

Meyer, Allison

From: Meyer, Allison
Sent: Friday, November 30, 2012 1:19 PM
To: 'Marla Scarola'
Subject: NDA 204078 IR

Marla,

These need to be addressed before 12/31/12.

- Your most recent information request response (dated November 15, 2012) contains graphical layouts of your facility. However, a higher quality graphic is needed for review. It is only necessary to submit graphical layouts of the air classification, personnel flow, and product flow of the (b) (4) suites.
- Your most recent information request response (dated November 15, 2012) describes preservative efficacy testing (Section 3.2.P.2.) This section states that routine preservative effectiveness testing will be performed (b) (4)
[Redacted]
- Provide results from the most recent (b) (4)
- What is the (b) (4) schedule for depyrogenation (b) (4)
- Describe environmental monitoring procedures performed during media fills.
- Provide results from your most recent media fill on (b) (4)

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
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Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

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/s/

ALLISON MEYER
03/27/2013

Rivera, Luz E (CDER)

From: Rivera, Luz E (CDER)
Sent: Thursday, March 14, 2013 5:00 PM
To: 'Marla.Scarola@weinberggroup.com'
Subject: NDA 204078

Good afternoon Ms. Scarola,

We are reviewing your NDA 204078 and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- You are advised that (b) (4) is not a synonym (b) (4) (b) (4) is of neostigmine methylsulfate. Delete (b) (4) wherever it appears in the application.
-

Please acknowledge the receipt of this request.

Thank you,
Luz E Rivera, Psy.D.
LCDR, USPHS
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment III
Phone (301) 796-4013

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/s/

LUZ E RIVERA
03/14/2013



NDA 204078

INFORMATION REQUEST

Éclat Pharmaceuticals
Attention: Marla Scarola, M.S.
Senior Consultant
The Weinberg Group Inc., 1129 Twentieth St., NW, Suite 600
Washington, DC 20036

Dear Ms. Scarola:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neostigmine Methylsulfate Injection, USP, 1 mg/mL, and 0.5 mg/mL.

We are reviewing the Chemistry, Manufacturing and Control section 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.

I. Regarding the drug substance:

1. [REDACTED] (b) (4)
2. Correct the spelling of the name [REDACTED] (b) (4)
3. Provide the source and Specifications for the [REDACTED] (b) (4)
[REDACTED] used in Method ATP1255.
4. Explain why, throughout the description of the analytical procedure and validation, [REDACTED] (b) (4) is listed as having the name [REDACTED] (u) (4)
5. Provide the results of measurement of Total Impurities for the drug substance and the [REDACTED] (b) (4) in the Batch Analysis.
6. Regarding the Methods Validation Report for the Related Substances (REP2578)
 - a. Explain why the report refers to the known impurity [REDACTED] (b) (4) rather than the known impurity [REDACTED] (b) (4). Provide data to show validation of the method using the latter rather than the former.
 - b. Provide an assessment of the precision of the assay in terms of the repeatability i.e. injecting the same sample a number of times. This information should be used to support the injection Precision in the System Suitability Test.

II. Regarding the drug product:

1. Regarding the Pharmaceutical Development Report (3.2.P.2)
 - a. Explain why the sum of the values for Assay of neostigmine methylsulfate, the Impurities at RRT (b) (4) and total Related Substances are greater than (b) (4) in the report on the effect of pH, preservative and (b) (4) in Tables 3 and 4 in Section P.2.2.1.
 - b. Provide the actual test results as specified in Table 2 in the Infusion Set Study in 3.2.P.2.6.
2. Regarding the Control of the Drug Product (3.2.P.5)
 - a. Regarding Method ATP1226 for the testing for Leachables :
 - i. Provide the source and Specifications for (b) (4) reference standard used in the procedure.
 - ii. Provide the analytical procedure and the methods validation for the test for (b) (4) in Sections 3.2.P.5.2 and 3.2.P.5.3, respectively, rather than in 3.2.P.2.4.
 - iii. Explain why the sum of the values for Assay of neostigmine methylsulfate, (b) (4) and Total Impurities are greater than (b) (4) in Table 6 in the Leachables Method Validation Report (REP2659).
 - iv. Include the Leachables in the Section 3.2.P.5.6 “Justification of Specifications.”
 - b. Regarding Method ATP1092 HPLC for Related substance:
 - i. Include a test for resolution in the System Suitability Test.
 - ii. Explain why the procedure for calculating the Total Impurities does not specify that the areas of individual impurities should be added, rather than taking the mean.
 - iii. Provide the actual changes in the (b) (4) that were used in the Robustness experiment in the Methods Validation (REP2518)
3. Explain why the sum of the assay values and the total impurities is greater than (b) (4) in the photostability studies reported in REP2691.
4. Regarding the Stability Protocols
 - a. Include reporting of (b) (4) in the Stability protocols.
 - b. Explain why Stability Protocols B and D are identical to each other and Stability Protocols C and E are identical to each other.
 - c. Add testing for leachables, endotoxin, and sterility as part of Stability Protocols B and D.
 - d. Explain why leachables will not be tested in the stability protocol for the Validation Lots and Commercial Lots.
 - e. Explain why the vials will not be stored inverted in the stability protocol for commercial lots.

We remind you of your commitment in your amendment dated February 7, 2013 to respond to our Question 2 in our January 13, 2013 Information Request Letter:

“Validate HPLC method for related substance (method 1225) to provide limit of detection (LOD), limit of quantitation (LOQ) accuracy, and precision for (b) (4) and (b) (4) and (b) (4). Revise the acceptance criterion for resolution in the system and suitability to read 'Confirm that the resolution between P404 and (b) (4) .”

If you have any questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796-4013.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

PRASAD PERI
03/13/2013



NDA 204078

INFORMATION REQUEST

Éclat Pharmaceuticals
Attention: Marla Scarola, M.S.
Senior Consultant
The Weinberg Group Inc., 1129 Twentieth St., NW, Suite 600
Washington, DC 20036

Dear Ms. Scarola:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neostigmine Methylsulfate Injection, USP, 1 mg/mL, 0.5 mg/mL.

We are reviewing the Chemistry, Manufacturing and Control section 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.

1. Your application references Drug Master File (DMF) (b)(4), submitted by (b)(4) and includes their Letter of Authorization (LOA) (April 17, 2012) referencing an amendment containing information regarding (b)(4). This information cannot be found in the DMF. The LOA states that the information was submitted on February 22, 2011. Please contact (b)(4) immediately to have them submit the information to the DMF and submit a new LOA referencing the date of that submission.
2. Regarding Method ATP1092 for measurement of neostigmine content and Related Substances:
 - a. Provide the identity of the compound responsible for the very large peak at about (b)(4) minutes
 - b. Provide information to show that there are no degradant peaks hidden under this large peak.
 - c. Include directions in the calculations to ignore this peak when calculating the Total impurities

If you have any questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796-4013.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
03/04/2013



NDA 204078

INFORMATION REQUEST

Éclat Pharmaceuticals
Attention: Marla Scarola, M.S.
Senior Consultant
The Weinberg Group Inc., 1129 Twentieth St., NW, Suite 600
Washington, DC 20036

Dear Ms. Scarola:

Please refer to your new drug application submitted under section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act for Neostigmine Methylsulfate Injection, USP, 1 mg/mL, 0.5 mg/mL.

We acknowledge receipt of your amendment dated February 7, 2013.

The February 7, 2013, amendment constituted a response to our January 13, 2013 information request letter. The response did not include revision of Section P.5 to include the revised specification, the test method for the leachable, [REDACTED] ^{(b) (4)}, a validation report for this test, or a justification for the acceptance criterion for this compound.

We request a written response by **February 21, 2013** in order to continue our evaluation of your NDA for the following:

- Revise Section P.5 to include the amended specification, a complete description of the test method for the leachable, [REDACTED] ^{(b) (4)}, a validation report for this test, and a justification for the acceptance criterion for this compound. Please note that this information cannot be only in the eCTD section 1.11 that covers “Information Not Covered in Modules 2 to 5.”

If you have questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796-4013.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
02/15/2013



NDA 204078

INFORMATION REQUEST

Éclat Pharmaceuticals
Attention: Marla Scarola, M.S.
Senior Consultant
The Weinberg Group Inc., 1129 Twentieth St., NW, Suite 600
Washington, DC 20036

Dear Ms. Scarola:

Please refer to your new drug application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Neostigmine Methylsulfate Injection, USP, 1 mg/mL, 0.5 mg/mL.

We are reviewing the Chemistry, Manufacturing and Control section 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.

- For the drug substance neostigmine methyl sulfate:
 1. Contact your drug substance supplier [REDACTED] (b) (4) and revise the specification to include controls for total impurities, residual solvents, and [REDACTED] (b) (4)
 2. Validate HPLC method for related substance (method 1225) to provide limit of detection (LOD), limit of quantitation (LOQ), accuracy, and precision for [REDACTED] (b) (4).
[REDACTED] Revise the acceptance criterion for resolution in the system suitability to read “Confirm that the resolution between P404 and [REDACTED] (b) (4) [REDACTED]”

- For the drug product neostigmine methyl sulfate injection.
 1. Provide a list of all the equipment used in the drug product manufacturing.
 2. Provide operation parameters and ranges for each step of the manufacturing.
 3. Specify the holding times between manufacturing steps and indicate how these holding times are validated.
 4. Revise the drug product specification to include control on leachable [REDACTED] (b) (4).
[REDACTED] The proposed acceptance criterion should be based on safety evaluation and stability data.

5. Tighten the proposed acceptance criterion of NMT (b) (4) for total impurities to NMT (b) (4) to be reflective of data.

If you have questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796-4013.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
01/13/2013



NDA 204078

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Éclat Pharmaceuticals
c/o The Weinberg Group Inc.
1129 Twentieth St., NW, Suite 600
Washington, DC 20036

ATTENTION: Lauren Wind, MPH
Senior Consultant

Dear Ms. Wind:

Please refer to your New Drug Application (NDA) dated and received on July 31, 2012, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Neostigmine Methylsulfate Injection, USP, 0.5 mg/mL and 1 mg/mL.

We also refer to your correspondence, dated and received August 01, 2012, requesting review of your proposed proprietary name, (b) (4). We have completed our review of the proposed proprietary name, (b) (4) and have concluded that it is acceptable.

The proposed proprietary name, (b) (4) will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. Additionally, if any of the proposed product characteristics as stated in your August 01, 2012, 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 Teena Thomas, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0549. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Allison Meyer at (301) 796-1258.

Sincerely,

{ See appended electronic signature page }

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL



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/s/

CAROL A HOLQUIST
10/26/2012



NDA 204078

FILING COMMUNICATION

Eclat Pharmaceuticals
c/o The Weinberg Group Inc.,
1129 Twentieth St., NW, Suite 600
Washington, DC 20036

Attention: Lauren Wind, MPH
Senior Consultant

Dear Ms. Wind:

Please refer to your New Drug Application (NDA) dated July 31, 2012, received July 31, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Neostigmine methylsulfate injection, USP.

We also refer to your amendments dated August 23, and September 13 and 24, 2012.

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 May 31, 2013.

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, mid-cycle, 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 May 10, 2013.

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

1. Provide the following information for the manufacturing process and process controls:
 - a. A description of container-closure integrity testing methods, (b) (4)
(b) (4) – Describe the method of
(b) (4) Provide justification that this method can

detect [REDACTED] (b) (4) into the drug product.

- b. Results from preservative effectiveness testing performed in product development
- c. An overview of the building and production facilities, including:
 - i. A facility floor plan along with an outline of product and personnel flow
 - ii. Production equipment locations
 - iii. A listing of air quality in production rooms
- d. A more thorough description of the overall manufacturing process, including:
 - i. A description of any [REDACTED] (b) (4)
 - ii. The duration of the [REDACTED] (b) (4)
- e. A description of the sterilization process for containers, closures, and production equipment
- f. A summary of environmental and personnel monitoring schedules, sites, and methods, including alert and action levels for all monitoring programs

2. Provide the following process validation information:

- a. Describe the [REDACTED] (b) (4) studies for the [REDACTED] (b) (4). For each [REDACTED] (b) (4) study, state:
 - i. [REDACTED] (b) (4) parameters
 - ii. The number [REDACTED] (b) (4) used in the study [REDACTED] (b) (4)
 - iii. [REDACTED] (b) (4)
 - iv. Acceptance criteria for these studies and most recent results
 - v. The [REDACTED] (b) (4) schedule [REDACTED] (b) (4)

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. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form

with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

If you request a full waiver, we will notify you if the full waiver is denied and a pediatric drug development plan is required.

If you have any questions, call Allison Meyer, Regulatory Project Manager, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BOB A RAPPAPORT
10/12/2012

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state “None”)
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**
 - Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”
- **Product Title**
 - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.
- **Initial U.S. Approval**
 - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.
- **Boxed Warning**
 - All text in the boxed warning is **bolded**.
 - Summary of the warning must not exceed a length of 20 lines.
 - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
 - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.
- **Recent Major Changes (RMC)**
 - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
 - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
 - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
 - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
 - Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

• General Format

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

• Boxed Warning

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

• Contraindications

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/

ALLISON MEYER
10/10/2012

PARINDA JANI
10/10/2012



NDA 204078

NDA ACKNOWLEDGMENT

Eclat Pharmaceuticals
C/O The Weinberg Group, Inc.
1129 Twentieth St. N.W. Suite # 600
Washington DC 20036

Attention: Lauren Wind, MPH
Senior Consultant, The Weinberg Group Inc.

Dear Ms. Wind:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Neostigmine methylsulfate injection, USP

Date of Application: July 31, 2012

Date of Receipt: July 31, 2012

Our Reference Number: NDA 204078

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 29, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly 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>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited 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 Anesthesia, Analgesia, and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ALLISON MEYER
08/03/2012