MidCycle Meeting Summary, August 20, 2013 - RAGWITEK

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

MID-CYCLE MEETING SUMMARY

Date and Time: August 20, 2013, 1:00 – 2:30 p.m.
Location: CBER Conf. WOC2-2330
Call-In: ----b(4)----------
Passcode: --b(4)---------
STN #: 125478/0
Submission Type: Biologics Licensure Application (BLA), Original Submission
Applicant: Merck Sharp & Dohme Corp.
Product: RAGWITEK, Short Ragweed Pollen Allergen Extract, Tablet for Sublingual Use
Meeting Chair: LCDR Elizabeth Valenti, M.P.H., R.A.C.
Meeting Recorder: Katie Rivers, M.S.

CBER/FDA Attendees

LCDR Elizabeth Valenti, M.P.H., R.A.C.
Katie Rivers, M.S.
Jennifer Bridgewater, M.P.H.,brr /> Tammy Massie, Ph.D.
Taruna Khurana, Ph.D.
Ching-Long (Joe) Sun, Ph.D.
Deborah Trout, CSO
Kristine Khuc, Pharm.D.
Patricia Rohan, M.D.
Dennis T. Cato, CSO
CAPT Julienne Vaillancourt, R.Ph., M.P.H.
Robert Fischer, M.S.N., R.N.
Daphne Stewart, CSO
Paul Richman, Ph.D.
Drusilla Burns, Ph.D.
Jay Slater, M.D.
Joseph Quander III, CSO
Karen Campbell, M.S.
CAPT Karen Farizo, M.D.
Marion Gruber, Ph.D.
Philip Krause, M.D.
Wellington Sun, M.D.

Loris McVittie, Ph.D.
LCDR Juan Lacayo, Ph.D.

1.0 PURPOSE

To discuss the milestones, review progress to date, and any significant review issues identified with management.

2.0 BACKGROUND

BLA STN # 125478/0 was submitted by Merck Sharp & Dohme Corp. (Merck) on March 08, 2013, and received by CBER on March 11, 2013. The product is a Short Ragweed Pollen Allergen Extract, tablet for sublingual use, intended for immunotherapy of individuals (>18 years) diagnosed with ragweed pollen induced allergic rhinitis, with or without conjunctivitis. The action due date for this file is March 11, 2014.

The proposed indication is based on submitted data, including five randomized, double-blinded, placebo-controlled clinical trials:

- Three 28-day safety trials in adults (RT-01, P06081, P05751) and
- Two 52-week Phase 2/3 dose-finding efficacy and safety trials in adults with allergic rhinoconjunctivitis with or without asthma (P05233, P05234).

2.1 Review Committee

Committee Member	**Review Role**	**Module Assignment**
Reviewer: LCDR Elizabeth Valenti, M.P.H., R.A.C. BC: Paul Richman, Ph.D.	Chair	All Modules
Reviewer: Katie Rivers, M.S. BC: Paul Richman, Ph.D.	Lead Regulatory Project Manager	All Modules
Reviewer: Jennifer Bridgewater, M.P.H. DD: Jay Slater, M.D.	Regulatory Coordinator	All Modules
Reviewer: Ronald L. Rabin, M.D. DD: Jay Slater, M.D.	Clinical	Modules 1, 2 & 5
Reviewer: Tammy Massie, Ph.D. BC: Dale Horne, Ph.D.	Biostatistics	Modules 1, 2 & 5
Reviewer: Patricia Rohan, M.D. BC: Christopher Jankosky, M.D., M.P.H.	Pharmacovigilence/Epidemiology	Modules 1 & 2
Reviewer: Taruna Khurana, Ph.D. BC: Ronald L. Rabin, M.D.	CMC/Product	Modules 2 & 3
Reviewer: Deborah Trout, CSO BC: Carolyn Renshaw, Ph.D.	CMC/Facility	Modules 2 & 3
Reviewer: Cheryl Hulme, CSO TL: Joseph Quander, III, CSO	CMC/Lot Release	Modules 2 & 3
Reviewer: Cherry Geronimo, B.S. BC: Ronald L. Rabin, M.D.	CMC/Lot Release	Modules 2 & 3
Reviewer: Claire Wernly, Ph.D. BC: Karen Campbell, M.S.	CMC/Lot Release	Modules 2 & 3

Reviewer: Dennis T. Cato, CSO BC: Patricia Holobaugh	Bioresearch Monitoring	Modules 2 & 5
Reviewer: Kristine Khuc, Pharm.D. BC: Lisa Stockbridge, Ph.D.	APLB/Promotional Labeling	Modules 1 & 2
Reviewer: Daphne Stewart BC: Laraine Henchal, M.S.	Carton and Container Labeling	Modules 1 & 2
Reviewer: Ching-Long (Joe) Sun, Ph.D. TL: Dave Green, Ph.D.	Toxicology/ Pharmacology	Modules 1, 2 & 5
Reviewer: LT. David Schwab, CSO BC: Laraine Henchal, M.S.	Electronic Integrity Reviewer	All Modules

2.2 Milestones & Meetings

This product is an allergen extract and is exempt from PDUFA requirements. It is on a 12-month review clock.

MILESTONES

Submitted: March 08, 2013
Received: March 11, 2013
Committee Assignment: March 25, 2013
First Committee Meeting: April 01, 2013
Filing Meeting: April 17, 2013
Filing Action: May 09, 2013
Deficiencies Identified: May 22, 2013
APAC Determination: May 24, 2013
PeRC Determination: July 23, 2013
SWG Determination: January 3, 2014
First Draft Reviews Due: June 09, 2013 [Statistical & Pharmacovigilence review draft is due by July 09, 2013]
Second Draft Reviews Due: September 02, 2013 [Statistical & Pharmacovigilence review draft is due by September 17, 2013]
Final Reviews Due: November 1, 2013
Final Review Addendum Due: January 24, 2014
Complete Inspections: N/A – Inspections waived
Finalize Lot Release Protocol: February 3, 2014
Labeling Comments to Applicant: February 8, 2014
Action Due: March 11, 2014
Action Package for Posting Due: March 11, 2014

MEETINGS

First Committee Meeting: April 17, 2013
Filing Meeting: April 17, 2013
Monthly Team Meetings: June 17, 2013, September 16, 2013, October 15, 2013, November 18, 2013 (Dec – Jan TBD)
Mid-Cycle Review Meeting: August 20, 2013
Labeling Meetings: October 09, 2013, November 20, 2013, Additional times TBD
PeRC: October 23, 2013
APAC Rehearsals: January 7, 2014, January 14, 2014, and January 21, 2014

APAC: January 28-29, 2014
SWG: TBD by January 29, 2014

2.3 Information Requests

Date Summary

April 26, 2013Request for identification of duplicate sections with BLA125473
May 13, 2013 Request for identification of duplicate portions of Module 3 with BLA125743
May 24, 2013 Request for pediatric study plan (PSP), Bioburden, confirmation that tox studies will not be reviewed under this BLA
June 18, 2013 Request for –b(4)----------testing
August 2, 2013 Request for PSP timeline justification

2.4 Amendments

Date	Amendment #	Summary
March 22, 2013	001	Request for proprietary name review
May 10, 2013	002	Response to April 26, 2013 information request
May 21, 2013	003	Response to May 13, 2013 information request
May 22, 2013	004	Submission of updated labeling based on CBER provided proper name and dosage form
June 27, 2013	005	Response to May 24, 2013 information request
July 19, 2013	006	Response to June 18, 2013 information request
August 7, 2013	007	Response to August 2, 2013 information request

2.5 Significant Telecons/Decisions

Date Summary

March 27, 2013 Discussion regarding the proper name of the product, the requirement for proprietary name to be included in the product blister packaging, and appropriate completion of Form FDA 356h for amendment submission.
April 05, 2013 Response to proposal to print blister packs, leaving a black space for the proprietary name to be later added using a sticker, so that printing of the labels is not delayed.
May 01, 2013 Discussion regarding 120-day safety update.
May0 3, 2013 Confirmation that the use of a sticker to add the proprietary name to the blister packs of the drug product is no longer required.
August 06, 2013 Communicated UNII codes.
August 08, 2013 Discussion regarding need for –b(4)---------- testing for release of drug product.

3.0 DISCUSSION TOPICS: STATUS AND ISSUES

3.1 Review Status by Discipline

3.1.1 Clinical/K. Rivers for R. Rabin – The clinical review is currently ongoing and review completion is anticipated by November 1, 2013. No substantive issues that would impact the review timeline have been identified. It was determined that the sponsor has not provided an integrated summary of effectiveness (ISE). Per regulation, an ISE is encouraged, but not required in a BLA. A clinical summary as well as associated clinical data have been provided in the application. This is acceptable for inclusion in the clinical review. In the future, a request to include an ISE should be discussed during the pre-BLA meeting. The clinical review template will be modified to note that an ISE was not included in the BLA submission.

3.1.2 Statistical/T. Massie – The statistical review is currently ongoing and there are no statistical issues to report. It is expected that the clinical study data are adequate and complete analysis will demonstrate that endpoints were met.

3.1.3 Epidemiology/Postmarketing/P. Rohan – The epidemiology review is currently ongoing and no substantive issues have been identified.

3.1.4 Toxicology – C.L. Sun – The toxicology review is currently ongoing and no substantive issues have been identified.

3.1.5 Product/CMC/T. Khurana – The product review is currently ongoing. A recent telecon was held between CBER and Merck regarding the need for –b(4)---------- testing of the final drug product based on –b(4)--------. Merck has agreed to send a proposal for inclusion of b(4) testing for CBER review.

CBER anticipates that multiple information requests (IRs) regarding both the drug product and the drug substance will be sent to the sponsor. Two issues of note include the need for validation data as well as information pertaining to source material. In addition, methods, process parameters, and SOPPs are missing and will be requested. The product reviewer anticipates that a draft information request will be available in early September. There is potential for the response to this IR to be classified as a major amendment to the file pending the sponsor response timeline.

3.1.6 CMC/Lot Release/K. Rivers and J. Bridgewater for C. Geronimo/C. Hulme/C. Wernly – DBSQC has completed the review of microbial enumeration tests and tests for specific microorganisms. The review has been finalized and uploaded to the EDR. A request for Merck to draft a lot release protocol will be included in the information request for CMC issues discussed above.

Merck recently contacted the CBER Product Release Branch in OCBQ to determine if it is acceptable to provide lot release samples in a labeled bag of blister packs versus labeling each blister pack in order to avoid crumbling of the sample tablet. CBER will follow-up with the sponsor regarding these inquiries and further advise the POC that all questions should to directed at the RPM.

Following the Mid-cycle meeting, CBER contacted Merck to request clarification regarding the issue of tablet crumbling upon removal from the blister pack for lot release samples. CBER communicated that the samples provided for lot release should be the same as the samples intended for market. Merck will provide further clarification. Please see the telecon summary for details.

3.1.7 BiMo/D. Cato – The BiMO review is currently ongoing. Two inspections have been completed; however, the establishment inspection reports have not yet been received. The findings will be reviewed and communicated to the committee upon completion of all inspections and after final review.

3.1.8 DMPQ (Facility Inspection)/D. Trout – The facility review is ongoing and no substantive issues have been identified.
3.1.9 Labeling/APLB/K. Khuc – The labeling review is ongoing and no substantive issues have been identified. Review completion is anticipated by the end of August.
3.1.10 Labeling/Carton and Container/D. Stewart – The carton and container review is ongoing. It was determined that the NDC# should be included on sample labels. The reviewer is following up to determine how the NDC# should be included.
3.2 PeRC/R. Fischer – Merck is requesting a waiver for children under the age of 5 years old and a deferral for children aged 5 to17 years. The paperwork for PeRC Meeting has been preliminarily filled out by the medical reviewer. However, the information required for the deferral request needs to be updated. Follow-up with the medical reviewer is required.
CBER previously requested justification for Merck's pediatric study timeline. Merck responded that they intend to initiate protocol design for the pediatric development of Ragwitek once the risk:benefit is evaluated in the adult population. Protocol completion is targeted for Q1 2015 and the final Clinical Study Report submission is targeted for Q2 2017. This timeline is acceptable to the review team.
3.3 APAC/E. Valenti – APAC meeting rehearsals are scheduled for
January 7, 14, and 21, 2014. The APAC meeting is scheduled for January 28-29, 2014. It was determined that only one day may be required for the APAC meeting; however, confirmation will be provided in the future due to the possible need to present other topics to the APAC.
It was determined that the CMC1 Branch Chief would assist the Clinical Reviewer with the briefing document due to workload. The briefing document should be limited to 35 pages and only contain references or addendums if necessary. Because CBER has not reviewed a new allergenic product in a number or years, there may be a need to brief Committee Members at the start of the meeting or brief the Committee Chair in the Chair's Briefing prior to the APAC meeting.
3.4 Labeling Review Plan/K. Rivers – Labeling meetings are scheduled for October 9, 2013, and November 20, 2013. Future meetings will be scheduled as needed.
The need for a black box warning on the product label was discussed. The currently licensed subcutaneously administered allergen extracts include a black box warning for anaphylaxis. There is some question of whether this applies to the sublingually administered tablets. Further discussion during labeling meetings is required.
3.5 Final Action Status –Review of the BLA is ongoing.
4.0 CONCLUSION – Review of the BLA is ongoing. The CMC issues will be communicated to the sponsor as soon as possible. The review progress will be monitored and updated on the MS Project schedule.
5.0 SUMMARY OF ACTION ITEMS –
5.1 An information request including CMC issues will be sent to the sponsor when it is available in early September.