CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20872

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-872

Hoechst Marion Roussel, Inc.
c/o Quintiles, Inc.
P.O. Box 9708, H3-M2516
Kansas City, Mo. 64134-0708

JUL 16 1999

Attention: Wayne F. Vallee, R.Ph.
Manager
Drug Regulatory Affairs

Dear Mr. Vallee:

Please refer to your pending July 17, 1998, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Allegra (fexofenadine hydrochloride) Tablets.

We have completed our review of your submission and have the following comments and information requests.

1. The instruments utilized in the chronic idiopathic urticaria (CIU) studies included the Dermatology Quality of Life Index (DLQI) and the Work Productivity and Activity Impairment (WPAI). The seasonal allergic rhinitis (SAR) studies utilized the Juniper Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) and the Pediatric RQLQ (PRQLQ), respectively. The adult SAR study (M0164455B/3004) also utilized the WPAI and the SF-36. Review of these studies does not support HRQL or productivity claims in approved labeling as proposed and we have the following comments.

   a. A priori specification of a clinically meaningful treatment effect size or adjustment for multiple comparisons is needed.

   b. The dermatology index should be validated in the CIU population.

   c. Several studies lack a detectable significant difference between study medication and placebo (e.g., the adult SAR study where a point difference in overall RQLQ scores when compared to placebo was not demonstrated for either the 180 mg or 120 mg dose of fexofenadine and in the combined pediatric study where no significant difference was demonstrated between either of the 3 doses of study drug and placebo for the

primary endpoint—the overall DLQI score).

Furthermore, from the labeling perspective, the HRQL assessments do not add information to the labeling that differs importantly from the patient symptom score data referenced in the label. Therefore, the studies reviewed do not support HRQL or productivity claims in approved labeling as proposed. In addition, the same considerations would apply to the use of these data to substantiate promotional labeling.

2. Further analyze the data obtained from the protocol PJPR 0037 entitled "Pharmacokinetics and pharmacodynamics of fexofenadine HCl in patients 6 to 12 years of age with allergic rhinitis" utilizing pharmacokinetic-pharmacodynamic modeling technique to establish the fexofenadine concentration vs. effect relationship.

3. Acceptance criteria for related substances similar to NDA 20-872 may apply across the Allegra® product line including NDA 20-625 (Allegra Capsule) and NDA 20-786 (Allegra-D Tablets). Such changes may be submitted via a Changes Being Effected (CBE) supplement.

If you have any questions, contact Mr. J. Lindsay Cobbs, R. Ph., Project Manager, at (301) 827-1051.

Sincerely,

/S/

Robert J. Meyer, M.D.
Acting Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cobbs

NDA 20-872

OCT -5 1999

Hoechst Marion Roussel, Inc.
c/o Quintiles, Inc.
P.O. Box 9708, H3-M2516
Kansas City, Mo. 64134-0708

Attention: Wayne F. Vallee, R.Ph.
Manager
Drug Regulatory Affairs

Dear Mr. Vallee:

We acknowledge receipt on August 27, 1999, of your August 26, 1999, resubmission to your new drug application (NDA) for Allegra 30, 60, and 180 mg (fexofenadine hydrochloride) Tablets.

This resubmission contains responses to the clinical, chemistry, manufacturing, & controls (CMC), biopharmaceutics, and labeling deficiencies submitted in response to our July 16, 1999 action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is February 27, 1999.

If you have any questions, contact Mr. J. Lindsay Cobbs, R.Ph., Regulatory Project Manager, at (301) 827-1051.

Sincerely,

Cathie Schumaker, R.Ph.
Chief, Project Management Staff
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 20-872

APR 30 1999

Hoechst Marion Roussel, Inc.
c/o Quintiles Inc.
P.O. Box 9708, Mailstop H-3-M2516
Kansas City, MO 64134-0708

Attention: Mr. Wayne F. Vallee, R.Ph.
Manager, Regulatory Affairs

Dear Mr. Vallee:

Please refer to your July 17, 1998, new drug application for Allegra (fexofenadine) Tablets.

We also refer to your submission dated January 25, 1999.

As discussed by telephone on April 28, 1999, between Mr. Wayne Vallee, R.Ph. and Mr. J. Lindsay Cobbs, R.Ph. of this Division, the proposal for the product names
is unacceptable.

If you have any questions, contact J. Lindsay Cobbs, Project Manager, at (301) 827-1051.

Sincerely,

John K. Jenkins, M.D., F.C.C.P.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-872

APR 26 1999

Hoechst Marion Roussel Inc.
c/o Quintiles Inc.
P.O. Box 9708, Mailstop H-3-M2516
Kansas City, MO 64134-0708

Attention: Mr. Wayne F. Vallee, R.Ph.
Manager, Regulatory Affairs

Dear Mr. Vallee:

Please refer to your pending July 17, 1998, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Allegra (fexofenadine hydrochloride) Tablets, 30, 60, 120, and 180 mg.

We also refer to your submissions dated July 30, November 4, 9, 20, and 23, and December 10, and 16, 1998.

We have completed our review of the Chemistry, Manufacturing, & Controls (CMC) section of your submission and have the following comments and information requests.

The following comments pertain to the drug substance.

1. Provide data on an adequate number of batches of the drug substance to establish the ratio of various polymorphic forms under various stability conditions and at different time intervals. Also, demonstrate various experimental conditions under which such conversion may take place.

2. Provide updated stability protocol for the drug substance. The protocol should include test parameters, methods number, approved acceptance criteria, testing intervals, and stability storage conditions, etc.

3. The stability protocol and specifications should reflect the approved specification for the drug substance.

4. The proposed level of impurities (NMT % for each of impurities MDL 102,038, MDL 46,016, MDL 46,619 and NMT % for total related substance of the submission dated July 30, 1998, pp. 118-141) are high and need to be tightened. Based on actual and updated stability data, the following acceptance criteria are proposed:

MDL 102,038	NMT	%
MDL 46,016	NMT	%
MDL 46,619	NMT	%
Individual Unknown	LT	%
Total related substance	NMT	%

The following comments pertain to the drug product.

5. Specify the dimensions of each of the proposed tablets (30, 60, 120, and 180 mg).

6. Provide a certificate of analysis (COA) for pink iron oxide and yellow iron oxide blends. The COA should represent the actual values for assay and other attributes rather than stating "confirm."

7. In the manufacturing process of the drug product (Volume S3-1.2, page 18), you have stated that "the commercial manufacturing will be based on a Kg granulation batch size, which is a combination of two Kg granulation batches." Provide the master batch record that governs the manufacturing details of the proposed commercial batch size Kg). Information regarding weighing of raw materials, their mixing/blending and combination of granulates should also be clearly specified in the same master batch record. Note that it would not be acceptable to manufacture granulation at different times or from different lots of raw materials for use as needed.

8. In of the granulation process, it has been stated
Provide the criteria in the master batch record under which such screening are required to be performed and specify the size(s) of the screen(s) to be used. The updated master batch record should also be provided.

9. As part of the in-process controls during granulation, include the acceptance criteria for particle size after drying, milling and final blending steps in the master batch record.

10. Based on X-ray diffraction data provided (Volume S3-1.2, page 224) it is evident that during granulation, the drug substance exists in two polymorphic forms (I and II). Demonstrate with adequate data the ratio of the polymorphs. Also include a test

and specification for control of polymorphic forms in drug product specifications.

11. As part of the in-process controls (during the compression process), include acceptance criteria for moisture content of the tablets at the beginning and the end of compression run.

12. The in-process controls should include a test and specification for friability of the compressed tablets (30, 60, 120 and 180 mg). Alternatively, you may provide friability versus proposed ranges of hardness data to substantiate your claim (Volume S3-1.2, page 27) that "fexofenadine hydrochloride tablets are not friable at the optimized hardness range."

13. Tighten the proposed hardness range for each tablet. In addition, for each strength of tablet, hardness specification should be based on individual rather than average hardness of 3 tablets. Additionally, acceptance criteria for hardness should be included in the finish product specifications. However, a footnote may indicate that hardness is part of in-process control and need not be monitored.

14. The master batch record should include all in-process controls and criteria for each tablet strength. Moreover, the tablet strength should be reflected on all pages of corresponding batch records e.g., Volume 1.6, pp. 42-46.

15. Reflect the proposed unique identifier for the different strengths of tablets in all relevant statements, specification sheets, COAs and corresponding manufacturing batch records.

16. The acceptance criteria for impurities and degradation products at release and stability are unacceptable. The following acceptance criteria based on actual observed data, are proposed:

MDL 102,038	NMT	%
MDL 46,016	NMT	%
Total other degradants	NMT	%
Total degradant	NMT	%

17. Update the drug product specifications sheet to include an acceptance criterion for impurity MDL 46,619. A footnote may indicate that MDL 46,619 is an in-process impurity and need not be monitored.

18. Include test and control for friability of tablets in drug product specifications.

19. The IR specification should indicate that the relative intensities of the observed

maxima must be the same as the prepared analytical reference standard in addition to the requirement for exhibiting maxima only at the same wavelengths as the standard.

20. In analysis of the impurities, the proposed resolution factor (NLT between two peaks of MDL 16,455A (drug substance) and impurity MDL 102,038 should be revised. Separation between MDL 16,455A and impurity MDL 47,397 (closest peak) should be considered. Please specify a new resolution factor and include in all relevant documents.

21. Provide dissolution versus hardness data for all strengths of tablets. These studies should be performed in identical media (for example, 0.001M HCl) for all strengths of tablets.

22. To ensure batch to batch consistency, tighten the hardness acceptance criteria for the 120 and 180 mg tablets. Based on the observed data, we propose the following specifications:

For 120 mg tablets:	KP
For 180 mg tablets:	KP

23. In the stability specifications, the word "conform" is not acceptable for the product and package appearance. Describe the actual acceptance criteria for these attributes.

24. Post-approval stability testing should be performed on each strength of tablets with all approved container/closure systems and up to the approved expiration period.

25. The proposed shelf life of 18 months for the 30 mg tablets and 30 months for the 60, 120 and 180 mg tablets is not justified at this time. Submit updated stability data including all modified specifications and criteria (as indicated above) to support the proposed shelf life.

26. Revise the post-approval commitment to state that the expiration dating period may be extended in annual reports only if the criteria set forth in the approved stability protocol are met in obtaining and analyzing data, including statistical analysis.

27. As per your consolidation program (changes of primary HDPE bottles supplier from , any compositional or dimensional changes should be identified and reported appropriately to the Agency.

28. Perform light transmission, thermal analysis, heavy metals and nonvolatile residue test as per USP <661> for polyethylene containers or provide a COA for these tests obtained from the suppliers. The latter option would necessitate the performance of

identity testing as per 21CFR 211.84(d)(3).

29. The letter of authorization (LOA) for DMF (Volume S3-1.3, page 185) has referenced as polyethylene resin for manufacturing of HDPE bottles while you specified as utilized resin. Identify which of these two resins was used in manufacturing of HDPE bottles. Also obtain and submit an updated LOA from the DMF holder.

30. The LOA for DMF (volume S3-1.3, page 187) has referenced ' as polyethylene resin used in manufacturing of the HDPE bottles. However, the application specified two resins ' " Identify which of the two resins was used in the manufacturing of the HDPE bottles. Also, obtain and submit an updated LOA from the DMF holder which indicates the specific location (page number, submission date, etc.) for the following information:

    a. Composition of the resins
    b. Physico-chemical and other characteristics of the above resins.
    c. Reference to appropriate food and additive regulations.

31. The holder of DMFs reviewed in support of this application were issued an information request letter dated April 7, and 8, 1999, respectively.

32. Submit separate method validation packages once all the method-related issues are resolved.

33. Specify the labeling details and the package design for the blister packaging of the 30, 120, and 180 mg tablets as these strengths are to be marketed.

34. Provide mock-up presentations in actual color for all to-be-marketed push-through blister and bottle labeling.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Mr. J. Lindsay Cobbs, Project Manager, at (301) 827-1051.

Sincerely,

/S/

Guirag Poochikian, Ph.D.
Chemistry Team Leader
Division of Pulmonary Drug Products, (HFD-570)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

NDA 20-872

NOV 2 4 1998

Hoechst Marion Roussel, INC.
10236 Marion Park Drive
Kansas City, MO. 64134-0627

Attention: Wayne F. Vallee, R.Ph.
Manager
U.S. Drug Regulatory Affairs

Dear Mr. Vallee:

Reference is made to your correspondence dated August 28, 1998, requesting that FDA issue a Written Request under Section 505A of the Food, Drug, and Cosmetic Act for Allegra (fexofenadine HCl) Tablets.

We have reviewed your proposed pediatric study request and are unable to issue a Written Request based on your submission.

We recommend that you resubmit your proposed pediatric study request addressing all of the issues outlined below.

1. At a minimum, any proposed pediatric study request for a Written Request should address the issues identified in section IV.A of the Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug and Cosmetic Act available at http://www.fda.gov/cder/guidance/index.htm.

2. We also remind you that the reports of studies should be submitted after the Agency makes the Written Request.

3. The proposal should address the pediatric population below 6 years of age.

Please clearly mark your submission **"PROPOSED PEDIATRIC STUDY REQUEST"** in large font, bolded type at the beginning of the cover letter of the submission.

We look forward to working with you on this matter to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, contact Mr. J. Lindsay Cobbs, Project manager, at (301) 827-1051.

Sincerely yours,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 20-872

Hoechst Marion Roussel, Inc.
F3-M3032
P.O. Box 9627
Kansas City, MO 64134-0627

Attention: Elaine Waller, PharmD.
Vice President, North American
Drug Regulatory Affairs

Dear Dr.Waller:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Allegra (fexofenadine HCl) Tablet
Therapeutic Classification:	Standard
Date of Application:	July 17, 1998
Date of Receipt:	July 17, 1998
Our Reference Number:	NDA 20-872

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 15, 1998, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 17, 1999.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

If you have any questions, contact J. Lindsay Cobbs, Project Manager, at (301) 827-1051.

Sincerely,

/S/ 8/13/02

Cathie Schumaker, R.Ph.
Chief, Project Management Staff
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

QUINTILES

Quintiles, Inc.
Post Office Box 9708
Kansas City, MO 64134-0708
(816) 767-6000

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NEW CORRESP

DUPLICATE

September 20, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary Drug Products (HFD-570)
Document Control Room 10-03
5600 Fishers Lane
Rockville, MD 20857-1706

Subject: **NDA 20-872** **General Correspondence:**
Allegra® Tablets Response to FDA Minutes
Dated September 8, 1999

Dear Mr. Cobbs:

Reference is made to FDA's minutes dated September 8, 1999 of the teleconference, July 22, 1999 regarding the CMC questions included in the Allegra tablets NDA 20-872 approvable letter dated July 16, 1999. The purpose of this letter is to acknowledge receipt of the above referenced meeting minutes. HMR would also like to inform the Division that the content of the minutes is in general agreement with the minutes prepared by Quintiles on behalf of HMR, with the following correction and clarifications:

1. Item 4 of FDA minutes (Question No. 15 of the Approvable letter) - Part (a):

   HMR does have an explanation for Allegra tablets possessing an optimum hardness. This explanation was not provided during the teleconference due to the time constraints and because the question was not asked. For the benefit of the reviewers, the explanation is provided below:

   The soft Allegra tablets, due to their high porosity, float on the top of the dissolution vessel and don't get wetted properly; this causes delayed disintegration and slow release. The slow release of the hardest tablets is caused because the porosity is decreased due to the plastically-deforming excipients such as microcrystalline cellulose (a common occurrence for most tablet dosage forms).

Item 4 of FDA minutes (Question No. 15 of the Approvable letter) - Part (b):

HMR wants to clarify that the word "future", used at the end of the sentence in part (b), means during the development of future products and not for Allegra tablets.

2. Item 5 of FDA minutes (Question No. 21 of the Approvable letter) - Part (a):

HMR would like to request that the number of printed cartons be corrected to This is the number discussed in the meeting, however, the number was recorded as due to a typing error.

If you should have any questions, please contact me at:

Quintiles, Inc.
P. O. box 9708
Kansas City, MO 64134-0708
(816) 767-6483
(816) 767-7375 (Fax)

Sincerely,

Faraneh Attarchi

Faraneh Attarchi, Ph.D.
Manager
Drug Regulatory Affairs

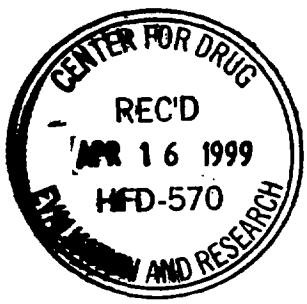
c.c. Lindsay Cobb
Project Mgr. Pulmonary
Hoechst Marion Roussel

April 15, 1999

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail P.O. Box 9627
Kansas City, MO 64134-0627
Telephone (816) 966-5000
U.S. Web site: www.hmri.com

PROPOSED PEDIATRIC STUDY REQUEST



John Jenkins, MD
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary Drug Products (HFD-570)
Document Control Room 10B-03
5600 Fishers Lane
Rockville, MD 20857-1706

Subject:	**NDA 20-872** Allegra Tablet (Fexofenidine HCl)	**GENERAL CORRESPONDENCE** Request for Agency Written Request For Pediatric Studies

Dear Dr Jenkins:

This supplements our letter of January 21, 1999 in response to your fax of November 24, 1998. We also refer to Lindsay Cobb's telephone conversation with Wayne Vallee on February 5, 1999 during which we were informed that there would be no official written response to our January 21, 1999 letter.

Mr Cobb indicated during the above referenced telephone conversation that the Pulmonary Pediatric Exclusivity Committee had found our request was inadequate for two reasons: (1) data cannot be referred to if submitted prior to FDA issuance of a written request and (2) the lack of studies in pediatric patients under 6. We will address each of these reasons below.

I. Previously Submitted Data

FDA in its fax of November 24, 1998 and in the February 5, 1999 telephone communication from Lindsay Cobb states that data submitted to FDA prior to issuance of a written request cannot be referred to. The agency thus appears to be taking the position that such data cannot be the basis for pediatric exclusivity, even if the agency were to issue a written request. We disagree with the agency's position in this regard.

Section 505A of the Federal Food, Drug and Cosmetic Act, which is the statutory basis for pediatric exclusivity, does not contain any language which directly addresses this issue. However, the legislative history does indicate that data available before issuance of a written request can be used. In the "Joint Explanatory Statement" as to Section 111 (Pediatric Studies of Drugs) contained in the Conference Report on the Food and Drug Modernization Act of 1997 is the following statement:

> With respect to any requested studies under this provision, the conferees intend that data collected prior to a request or requirement by the Secretary may be used, in addition to data collected after such request or requirement in satisfying the provisions of this section.
>
> H.R. Rept. No 105-399, 105th Cong., 1st Sess. At 93.

The FDA guidance entitled "Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug and Cosmetic Act" contains the following relevant statements on Page 4:

> Data collected prior to or after FDA issues a written request may be used to respond to the request. FDA does not believe that it would be consistent with the intent of the statute to accept data collected prior to the Written Request if such data are already known to provide no useful information. Therefore, FDA will not accept studies conducted prior to issuance of a Written Request unless the studies would potentially support a change to the label to incorporate pediatric information....

Based on the above language in the guidance, HMR submits that its previously submitted studies should be accepted by FDA as appropriate to respond to a Written Request because this data would support a label change incorporating pediatric information into the label for Allegra.

HMR is aware that the same Guidance also contains the statement later on page 4, as follows:

> Studies submitted before FDA issued a Written Request should *not* be used to request pediatric exclusivity.

We are not aware of the basis for this last sentence and believe it is inconsistent with statutory intent as expressed in the legislative history. Also, it has the effect of rewarding a sponsor who does not submit data until requested by FDA and not offering an equal reward to a sponsor who voluntarily submitted its data before receiving a request. HMR believes that an FDA position refusing to consider valid data which supports requested pediatric labeling simply because it was previously submitted to the agency is incorrect both in terms of statutory intent and appropriate policy and should be reconsidered.

II. Data on Younger Children

FDA also has taken the position that it will not issue a Written Request unless data covering younger children (under 6 years of age) is to be included.

This issue is not addressed directly in either Section 505A or in the legislative history. The only place in which the issue is directly discussed is in MAPP 6020.6 (Process for Handling Pediatric Exclusivity) which states in its fourth policy bullet on page 5:

> The Written Request should request all pediatric information needed to a particular active moiety except when there is a scientific justification for asking only for a particular use or pediatric age group.

HMR submits that there is, at this time, in this case a scientific justification for only asking for data for children over 6 years of age because there have been scientific and technical difficulties in formulating fexofenadine HCl into a dosage form appropriate for children under 6 years of age.

For example, the formulation that is the subject of the NDA under review is a 30mg tablet formulation. This tablet formulation is intended for children. As you are aware, children under the age of 6 have difficulty in swallowing tablets of any size. Children under 6 also have a tendency to chew tablets which would not be the intended use of the tablet formulation. At this time, a suitable formulation for children under 6 is still being evaluated.

Because a suitable dosage form is not available at this time for children under 6 years of age and thus cannot be studied, it is appropriate for the agency to make a Written Request for data for older children for whom an appropriate dosage form is available.

For the foregoing reasons, we request that the Pulmonary Pediatric Exclusivity Committee reconsider its position concerning this request.

Sincerely,

J. Michael Nicholas, PhD
Director, Marketed Product
US Regulatory Affairs

CC: Lindsay Cobbs