CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20872

ADMINISTRATIVE DOCUMENTS

Division Director's Memorandum

Date:	Thursday, February 24, 2000
NDA:	20-872
Sponsor:	Aventis (formerly HMR/Quintiles)
Proprietary Name:	Allegra (fexofenadine HCl) tablets – 30, 60, and 180 mg.
FROM:	Robert J. Meyer, MD Director, Division of Pulmonary and Allergy Drug Products.

Action: Approval

Introduction: This submission, received on August 27th, 1999 is the response to an approvable action for NDA 20-872. This NDA is in support of multiple immediate release dosage strengths of fexofenadine tablets with new indications and proposed populations. The "approvable" action was taken July 1999 (see Div. Director's memo of July 15th, 1999), with the factors preventing approval

The sponsor resubmitted in August, removing from the NDA

It should be noted that the sponsor has stated that they may choose to try to support at a later date by providing substantial evidence of efficacy through to the end of the dosing interval (though this may have ramifications for the need for a 180 mg dose, unless a clear advantage of 180 is shown).

CMC: All approvability issues have been satisfactorily addressed, with the approval being for the 30, 60 and 180 mg immediate release tablets. While the dosage strength would likely be approvable from the CMC aspects, as well, there is no current clinical role for this dosage strength.

Pharmacology/toxicology: No new issues in this cycle, other than labeling.

Biopharmaceutics: No new issues this cycle.

Clinical / Stastical: Given the prior action, the sponsor has amended the NDA in their response to limit the claims/approval to:

- 30 mg twice daily for the treatment of SAR in children ages 6 to 11
- 30 mg twice daily for the treatment of CIU in children ages 6 to 11
- 180 mg once daily dose for the treatment of SAR in adults and adolescents aged 12 and above.
- 60 mg twice daily for the treatment of CIU in adults and adolescents aged 12 and above.

The safety update raised no new concerns that would lead to significant alterations in labeling or in approvability of the product.

Labeling - Appropriate labeling has been worked out with the sponsor's concurrence. Some of the labeling changes adopted for the tablets will also need to be applied prospectively to the capsule formulation as well, although due to the limitations of the dosage form, only the adult/adolescent CIU claim, and arguably the 180 mg once-daily dosing for SAR in adults and adolescents would be appropriately added.

EERs: The previously acceptable EERs still apply.

Conclusions: This NDA will be approved following a full review of the action package by the review team. There are no anticipated clinical phase 4 commitments.

Division Director's Memorandum

Date:	Thursday, July 15, 1999
NDA:	20-872
Sponsor:	Hoechst Marion Roussel, Inc. / Quintiles
Proprietary Name:	Allegra (fexofenadine HCl) tablets – 30, 60, 120, and 180 mg.

Introduction: This is an NDA for multiple immediate release dosage strengths of fexofenadine tablets. The NDA proposes new indications for this moiety, including seasonal allergic rhinitis and chronic urticaria in children ages 6 – 11, chronic urticaria in adults and once daily dosing in adults. Fexofenadine has previously been approved in a capsule formulation for SAR in adolescents and adults at a dose of 60 mg twice daily. A sustained-release combination product with pseudoephedrine has also previously been approved. Fexofenadine is the acid metabolite of terfenadine – the drug substance contained in the previously approved Seldane product (which is no longer marketed due to safety issues related to the QT effects of the parent moiety and the multiple drug-drug interactions with the parent).

CMC: Dr. Khorshidi was the primary reviewer for this application. Despite the sponsor's response to the Agency's IR letter of 4-26-99, unresolved issues preclude approval on this initial review cycle. These issues are detailed in Dr. Khorshidi's review of July 14, 1999.

Pharmacology/toxicology: Given the previous experience with terfenadine and with fexofenadine, and the fact that there is not a proposed indication in the very young (i.e., age less than 2 years) there were no overriding pharmacology / toxicology issues with this application.

Biopharmaceutics: The data provided by the sponsor supports the bioequivalence of the final formulation tablet to capsule, and support the dose-proportionality of the various dosage strengths (given the data from the 60 and 180 mg tablet in comparison to the 60 mg capsule and the pharmaceutics of the tablet formulations). Regarding the pediatric PK data, it appears that the 30 mg dose in the 6 – 11 year olds most approximates the systemic exposure from the adult 60 mg BID dose. Therefore, from the PK data alone, it would appear that the 30 mg BID dosing of Allegra for the treatment of SAR and CIU is most appropriate for that population.

Clinical / Stastical: Dr. Worobec and Dr. Himmel were the primary and secondary reviewers for this application (respectively), and Dr. Elashoff was the primary statistical reviewer. Drs. Worobec and Elashoff's reviews and Dr. Himmel's secondary review memo should be referenced for a detailed discussion of the pertinent issues.

The sponsor has provided sufficient data and raticnale to support the following:

- the approval of the 30 mg twice daily for the treatment of SAR in children ages 6 to 11
- the approval of the 30 mg twice daily for the treatment of CIU in children ages 6 to 11

- the approval of the 180 mg once daily dose for the treatment of SAR in adults
- the approval of 60 mg twice daily for the treatment of CIU in patients aged 12 and above.

These conclusions are based on the data from PK and clinical studies. Although the sponsor has sought the approval of higher doses of fexofenadine for children ages 6 – 11 in the treatment of SAR and CIU, they did not provide adequate data and justification to approve this higher dose (i.e., there are no data to support increased efficacy for the higher dose, and the higher dose would lead to higher systemic levels than obtained at indicated doses in adults). The sponsor also sought approval for a 120 mg once daily dosing of fexofenadine in adults with SAR. The available primary database consisted of a very large US study that did not adequately support this dose, due to a negligible end-of-dosing interval effect. While one of the non-US studies (0032) may provide support for the approval of this dose, the manner in which those data were submitted were not adequate to reliably reach an interpretation. The sponsor will be asked to address this concern in the action letter.

Auditing / Data Checking: DSI was asked to audit four study sites, one from each pivotal study. This included a 'for cause' audit of Dr. Casale, for whom deviations from GCP had been found for other drug development programs. Additionally, Dr. Edwards (who has previously been cited for significant deviations from acceptable study conduct) was a primary investigator in 3 of the pivotal studies. Data from Dr. Edward's study site were excluded from the efficacy analysis. None of the audited study sites, including Dr. Casale, revealed important problems in data handling or study conduct.

EERs were sent for the following sites: plant for drug substance (acceptable 12-21-98), HMR Cincinnati for finished dosage packaging (acceptable 10-05-98), HMR Kansas City, MO for finished drug product/packaging (acceptable 10-14-98) and for finished dosage stability testing (acceptable 10-05-98).

Labeling: Overall, the proposed labeling is largely acceptable. Some labeling comments appropriately restricting dosing and indications are to be forwarded on to the sponsor.

Conclusions: This NDA will be given an approvable action since there are significant remaining CMC issues that preclude final approval at this time. Approval will likely have some minor restrictions on dosing from what the sponsor proposed (while it appears the sponsor will not be able to offer data to support the rationale for a 60 mg BID dosing for SAR nor CIU in 6 – 11 year olds, they may well be able to support the 120 mg once daily dosing for SAR in patients aged 12 and above, providing they provide us corrected study reports and datasets). Final labeling will not be arrived at with the sponsor until such time that the CMC issues are resolved and the requested analyses

/S/

Robert J. Meyer, MD
Acting Director,

Division of Pulmonary Drug Products.

TEAM LEADER MEMORANDUM

DATE: February 22, 2000

TO: NDA 20-872 fexofenadine HCl (Allegra®) tablets

/S/ 2/22/00

FROM: Badrul A. Chowdhury, MD, PhD
Acting Medical Team Leader,
Division of Pulmonary and Allergy Drug Products, HFD-570

SUBJECT: Secondary medical review of fexofenadine tablet (Allegra®) NDA response

CC: HFD-570: Meyer, Lee, Cobbs

Administrative

NDA 20-872 for fexofenadine tablets was submitted by Hoechst Marion Rousell (now Aventis Pharmaceuticals) to the Agency on July 17, 1998, under 505 (b) of the FD&C Act. An approvable letter was sent to the sponsor on July 16, 1999. Six clinical and biopharmaceutics deficiencies, and 15 CMC deficiencies were identified in the approvable letter. In addition some preliminary labeling comments were also included. On August 27, 1999, the sponsor submitted an amendment to the NDA responding to the deficiencies, and provided safety updates from ongoing clinical studies and from post-marketing data. The user fee goal date for completion of the response review is February 27, 2000. In subsequent sections, the sponsor's submitted documents are briefly reviewed. Detail review of the submission can be found in Dr. Charles Lee's primary medical review.

Review of sponsor's response

Fexofenadine is currently approved for treatment of seasonal allergic rhinitis (SAR) in patients 12 years of age and older (NDA 20-625 for fexofenadine 60 mg capsules was approved on July 25, 1996, and NDA 20-786 for fexofenadien 60 mg plus pseudoephedrine HC 120 mg tablets was approved on January 2, 1998). The approved dose is one capsule or tablet twice-daily by mouth.

In NDA 20-872 the sponsor applied for the following:

1. Approval for two new dose strengths (120 and 180 mg tablets) for once-daily dosing in the treatment of SAR in patients 12 years of age and older
2. Approval of 30 and 60 mg (30 mg tablet, 60 mg tablet or capsule) twice-daily dose for SAR in children 6 to 11 years of age
3. Approval for treatment of chronic idiopathic urticaria (CIU) at doses of 60 mg twice-daily for adults, and 30 or 60 mg twice-daily for children 6 to 11 years of age

In addition the sponsor made health-related quality of life (HLQL) and work/activity productivity claims in their SAR and CIU indications.

Four new fexofenadine tablet formulations were in the application. These were of 30 mg, 60 mg, 120 mg, and 180 mg strengths. Currently fexofenadine is marketed as 60 mg capsule (NDA 20-625), and as 60 mg tablet in combination with 120 mg pseudoephedrine (NDA 20-768). In this memorandum distinction between the tablet and capsule formulations will not be made, as they are bioequivalent.

The major clinical deficiencies identified in the Agency's July 16, 1999, letter and the sponsor's response to these deficiencies are briefly summarized below.

We determined that the sponsor did not have adequate data to support the once-daily dosing of Specifically, efficacy at the end-of-dosing interval was not adequately demonstrated. We suggested that reanalysis of study 0032 (protocol PJP0032) might address this issue. The sponsor acknowledged the deficiency and is withdrawing the

We determined that the 60 mg twice-daily dose for children 6 to 11 years of age for SAR and for CIU provided no added advantage over the 30 mg twice-daily dose. The pharmacokinetic data show that the 30 mg twice-daily dose in children gives similar systemic exposure as the 60 mg twice-daily dose in adults. Furthermore, there are no data that a dose higher than 30 mg twice-daily provides additional benefit. The sponsor agreed with our determination and is withdrawing

On withdrawal of the claims described above the remaining claims in the application are (a) fexofenadine 180 mg once-daily for SAR in patients 12 years of age and older, (b) fexofenadine 60 mg twice-daily for CIU in patients 12 years of age and older, and (c) fexofenadine 30 mg twice-daily for SAR and CIU in patients 6 to 11 years of age. The 120 mg formulation is not needed since there is no claimed indication for that dose. The sponsor is also withdrawing

These remaining claims can be approved based on the sponsor original submission, which was reviewed by Dr. Worobec (MO review dated May 20, 1999). The sponsor had submitted data from adequate clinical studies to support the 180 mg once-daily dose for SAR in patients 12 years of age and older, the 60 mg twice-daily dose for CIU in patients 12 years of age and older, and 30 mg twice-daily dose for SAR in children 6 to 11 years of age. The CIU indication in children 6 to 11 years of age can be supported according to CFR 201.57 (f) (9) (iv) by extrapolation of the demonstrated efficacy of fexofenadine in adults and the likelihood that the course, pathophysiology, and response to fexofenadine for CIU in children are similar to that of adults. The appropriate dose for this age group for CIU should be 30 mg twice-daily, which is the same dose found to be effective for this age group for SAR. The reasoning for choosing this dose comes from extrapolation of the adult data, where 60 mg twice-daily dose was found to be effective for both SAR and CIU. Therefore, in children one dose-level should also be effective for the same two diseases. Safety of the 30 mg twice-daily dose for children 6 to 11 years of age was demonstrated in the SAR studies.

Safety update from ongoing clinical studies

The clinical studies under progress at the time of this submission are listed in Table 1. The PAR studies are typical large efficacy and safety studies and will presumable be submitted later by the sponsor to support a PAR indication for fexofenadine. The SAR studies explored the efficacy of fexofenadine in patients with SAR and asthma. The sponsor submitted clinical adverse even reports from these studies. Detail physical examination findings, ECG findings, and laboratory test results were not submitted. In subsequent sections of this memorandum adverse events are discussed by grouping the studies based on indication. The European and the single Australian study will not be included in the discussion because only serious adverse evens were submitted from those studies. Those studies were primarily marketing in nature. There were no deaths or serious and unexpected adverse events of concerns from any of these studies.

Table 1. Clinical studies included in the safety update

Study ID, location	Indication	Treatment duration	Number of subjects
MO 1104, Japan	Clinical Pharmacology study	1 day	24
MO 1105, Japan	Clinical Pharmacology study	7 days	18
JTAM 201, Japan	Chronic idiopathic urticaria	7 days	226
JTAM 202, Japan	Perennial allergic rhinitis	2 weeks	314
MO 3097, US & Canada	Perennial allergic rhinitis	8 weeks	1300
PR 0057, Canada	Perennial allergic rhinitis	4 weeks	673
MO 4049, US	Seasonal allergic rhinitis and asthma	7 days	20
MO 4092, US	Seasonal allergic rhinitis and asthma	6 weeks	350
MO 3091, US	Seasonal allergic rhinitis, pollen chamber study	1 dose	127
MO R010, Europe	Chronic idiopathic urticaria	3 months	225
MO R015, Europe	Seasonal allergic rhinitis	2 weeks	2177
MO 4073, Europe	Chronic idiopathic urticaria	6 weeks	50
AUS 001, Australia	Seasonal allergic rhinitis	7 days	646
MO C087, Europe	Seasonal allergic rhinitis	14 days	2925

Clinical pharmacology studies

The clinical pharmacology studies were done in healthy male volunteers. They included a small number of subjects. Reported adverse events were not remarkable.

Chronic idiopathic urtacaria study

The single Japanese CIU study JTAM 201 was a 7-day parallel-arm dose-ranging study. The treatment arms were fexofenadine 10 mg twice-daily, 60 mg twice-daily, and 120 mg twice-daily. There was no placebo arm in this study. Common adverse evens that had dose ordering are show in Table 2. The adverse events of somnolence and dry mouth are of interest because these are commonly seen with first generation H_1 receptor antagonists, and not expected with a second generation H_1 receptor antagonist such as fexofenadine. However, a firm conclusion on causality of these events with fexofenadine cannot be drawn from this study, because the study was relatively small, the duration of treatment was only 7 days, and there was no placebo arm in the study.

Table 2. Adverse events reported by ≥2% patients and showing dose-ordering in a CIU study*

Events	Fexo 10 mg BID (n = 78)	Fexo 60 mg BID (n = 75)	Fexo 120 mg BID (n = 73)
Somnolence	9.0 %	12.0 %	15.1 %
Abdominal pain	2.6 %	4.0 %	6.8 %
Headache	2.6 %	4.0 %	5.5 %
Dry mouth	1.3 %	2.7 %	5.5 %
Leukocytosis	0.0 %	0.0 %	2.7
* Reported as %			
Source: Volume 26.2, page 294			

Perennial allergic rhinitis studies

Common adverse events pooled from three PAR studies (JTAM 202, MO 3097, and PR 0057) are shown in Table 3. None of the adverse events occurred with a clear-cut increased frequency in the fexofenadine treated groups over the placebo group, and dose ordering was not seen for any adverse events including somnolence and dry mouth. However, differences in study design limit any conclusion from this poled analysis. Fexofenadine 120 mg was given on a BID dosing schedule in study JTAM 202, whereas in the other two studies fexofenadine 120 mg was given on a QD dosing schedule. Study JTAM 202 was not placebo controlled.

Table 3. Adverse events reported by ≥2% patients in the PAR studies*

Events	Placebo (n = 539)	Fexo 10 mg BID (n = 100)	Fexo 60 mg BID (n = 333)	Fexo 120 mg QD or BID (n = 664)	Fexo 180 mg QD (n =539)
URI	11.3 %	11.0 %	9.3 %	12.3 %	16.9 %
Headache	8.9 %	9 %	9.0 %	9.6 %	9.2 %
Pharyngitis	2.8 %	3.0 %	2.4 %	3.8 %	6.8 %
Somnolence	0.4 %	11 %	5.1 %	2.7 %	0.9 %
Influenza	4.3 %	0 %	1.8 %	3.6 %	5.5 %
Sinusitis	4.3 %	0 %	0.6 %	1.7 %	5.5 %
Back pain	1.5 %	0 %	0.6 %	1.7 %	4.9 %
Pain	2.4 %	0 %	0.3 %	1.5 %	3.7 %
Dry mouth	0.7 %	4 %	1.5 %	2.0 %	0.3 %
Myalgia	1.9 %	0 %	0 %	1.5 %	3.7 %
Tooth disorder	0.7 %	0 %	0.3 %	0.6 %	3.4 %
* Reported as %					
Source: Volume 26.2, pages 332-337					

Seasonal allergic rhinitis studies

Safety data from SAR studies MO 4049 and MO 4092 are reviewed here. Study MO 4049 was a crossover study comparing three doses of fexofenadine, 60 mg BID, 120 mg BID, and 360 mg BID, and placebo in 20 patients with SAR and asthma. Duration of treatment was 7 days. Study MO 4092 was a parallel arm study comparing the safety and efficacy of fexofenadine 180 mg QD and placebo in 350 patients with SAR and mild asthma. Duration of treatment was 6 weeks. Table 4 shows the adverse events for placebo and fexofenadine

180 mg QD groups. Placebo data is pooled from the two studies, and fexofenadine 180 BID data is from study MO 4092. Adverse events for fexofenadine 60 mg, 120 mg, and 360 mg doses are not included in the table, because only 20 patients received those doses in study MO 4049, and adverse event reporting for those doses were rare. None of the adverse events reported in the SAR studies were unique or new. As is the PAR studies, there were no signal for increased reporting of somnolence and dry mouth with fexofenadine.

Table 4. Adverse events reported by ≥2% patients and more commonly by fexofenadine treated patients in the SAR studies*

Events	Placebo (n = 198)	Fexo 180 mg QD (n = 172)
Headache	15.2 %	18.6 %
URI	4.5 %	11.6 %
Pain	4.0 %	6.4 %
Pharyngitis	3.5 %	6.4 %
Sinusitis	6.1 %	6.4 %
Back pain	0.5 %	3.5 %
Arthralgia	0.5 %	2.3 %
Bronchitis	0.5 %	2.3 %
* Reported as %		
Source: Volume 26.2, page 349-351		

Post-marketing safety update

The sponsor submitted two safety updates covering the periods from March 11, 1998, to September 10, 1988, and from September 11, 1998, to March 10, 1999. Except for a cardiac adverse event discussed below, there were no safety concerns coming out of the safety updates. We note that the sponsor has updated their core safety data sheet. The core safety data sheet lists adverse events that the sponsor considers to be of significance worth of increased attention. The new additions to the list are dizziness, insomnia, nervousness, nightmares, and hypersensitivity reactions.

One notable cardiac adverse event covered in the periodic safety updates was the report of a QTc prolongation and *Torsade de Pointes* in a 67 year male patient from Netherlands. The case was also published in Lancet (Pinto YM et al., QT lengthening and life-threatening arrhythmias associated with fexofenadine. Lancet 1999; 353:980). The patient developed syncopal episode while he was waiting in a clinic waiting room. Immediately after the syncope an ECG was done and QTc calculated on V2 and V3 leads was 532 msec. The patient was on fexofenadine 180 mg QD for about 2 months at that time. He was put on fexofenadine for pruritus, which was through to be caused by carvedilol. He was on carvedilol for hypertension. Carvidolol was stopped at the same time fexofenadine was started.

The most interesting aspect of the case report was a positive dechallenge and rechallenge with fexofenadine. The patient's QTc shortened to 489 msec the same day fexofenadine was discontinued. On rechallenge 6 days later with fexofenadine 180 mg QD in a monitored setting the QTc prolonged to 512 msec, and 5 days later while on fexofenadine the patient

developed *Torsade de Pointes*. Fexofenadine was again stopped and his QTc decreased to 482 msec. All QTc values reported in the case report were corrected for heart rate using Bazett's formula.

The sponsor looked at the case intensely and used an external consultant to further analyze the data. We also obtained detailed information on the case and analyzed the data ourselves. On reanalysis, the data appears less convincing. The case is confounded by a number of factors. The patient was on carvedilol, which was discontinued at the same time fexofenadine was started. Carvedilol is known to protect heart via its beta-blocking properties. He also has coronary artery disease based on an angiogram, history of hypertension, and mild left ventricular dysfunction. According to the sponsor's consultant's notes, the patient presumably had prolonged QTc and QTc dispersion on an ECG done about 5 months prior to fexofenadine treatment. The sponsor's consultant reanalyzed all ECGs looking at all leads and also corrected for QT interval by formulae other that Bazett's. On reanalysis, unimpressive changes in uncorrected QT and Fridercia's corrected QT were seen. Based on these additional data the sponsor concluded that preexisting cardiac disease and stopping the carvedilol possibly caused the patient to develop *Torsade de Pointes*, and fexofenadine possibly was not the causative agent (volume 26.6, pages 1793-1803). We independently reached the same conclusion by analyzing the available data. Subsequently the patient's blood was analyzed for gene mutations known to be associated with hereditary long QT syndrome. A preliminary report suggests that the patient has a mutated HERG gene. However the mutant HERG gene produced wild-type like current and was not inhibited by fexofenadine when expressed in xenopus oocyte (Biopysical Journal 2000; 78:342A). We also looked at the AERS and other data bases for QTc prolongation, *Torsade de Pointes*, and syncopal episode with fexofenadine. No clear cases were identified to incriminate fexofenadine. So far fexofenadine appears to be free of cardiac repolarization effects.

Recommendations

NDA NDA 20-872 for fexofenadine HCl (Allegra®) tablets as submitted by Hoechst Marion Rousell (now Aventis) on July 17, 1998, and modified on August 27, 1999, is recommended for approval. The modifications are withdrawals.

The sponsor had submitted adequate clinical data in the submission of July 17, 1998, to support the 180 mg once-daily dose for SAR in adults 12 years of age and older, 60 mg twice-daily dose for SAR and CIU in adults 12 years of age and older, and 30 mg twice-daily dose for SAR in children 5 to 11 years of age. The 30 mg twice-daily dose for CIU in children 5 to 11 years of age can be supported by extrapolation according to CFR 201.57 (f) (9) (iv) as discussed above. Safety review of the sponsor's ongoing clinical studies, and the post-marketing safety updates do not show any new safety concerns with fexofenadine. There are no outstanding pharmacology, toxicology, biopharmaceutics, and CMC issues. The sponsor has submitted a proposed label removing all claims related to the indications and doses that they have withdrawn. The label is being will be reviewed and comments will be forwarded to the sponsor.

13/14. Patent Information/Certification

Patent information relevant to Fexofenadine tablets is defined in Attachments A, B, and C.

These attachments are copies of Patent Information Declarations issued separately to NDA 20-872. These declarations apply to:

1. United States Patent No. 4,254,129 (Attachment A).
2. United States Patent No. 5,375,693 (Attachment B).
3. United States Patent No. 5,578,610 (Attachment C).

Attachment A: United States Patent No. 4,254,129

July 17, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Park Building, Room 2-14
12420 Parklawn Drive
Rockville, MD 20857

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail: P.O. Box 9627
Kansas City, MO 64134-0627
Telephone (816) 966-5000

Subject: Re: Original NDA Submission for Fexofenadine Tablets
Patent Information and Declaration

Dear Sir:

The undersigned submits the following patent information as relevant to Fexofenadine tablets:

PATENT NUMBER: United States Patent No. 4,254,129

EXPIRATION DATE: April 10, 1999

PATENT OWNER: Merrell Pharmaceuticals Inc.
2110 E. Galbraith Road
Cincinnati, OH 45215

Hoechst Marion Roussel, Inc.
10236 Marion Park Drive
Kansas City, MO 64137

TYPE OF PATENT: Drug substance, Drug Product Composition and Method of Use

The undersigned declares that United States Patent No. 4,254,129 covers Fexofenadine HCl, a drug substance contained in the drug product Fexofenadine tablets for which the above-referenced NDA is being submitted for approval, even date herewith, as well as the drug product (composition) containing said drug substance and a method of using said drug substance in treating allergic reactions. Merrell Pharmaceuticals Inc. is a wholly owned subsidiary of Hoechst Marion Roussel, Inc. The patent is currently the subject of a pending application for patent term extension pursuant to 35 U.S.C. § 156.

Please list the above patent in the Orange Book Publication upon approval of the NDA.

Submitted by: Elaine Waller
Elaine Waller
Vice President
North American Drug Regulatory Affairs

Attachment B: United States Patent No. 5,375,693

Hoechst Marion Roussel

July 17, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Park Building, Room 2-14
12420 Parklawn Drive
Rockville, MD 20857

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail: P.O. Box 9627
Kansas City, MO 64134-0627
Telephone (816) 966-5000

Subject: Re: Original NDA Submission for Fexofenadine Tablets
Patent Information and Declaration

Dear Sir:

The undersigned submits the following patent information as relevant to Fexofenadine tablets:

PATENT NUMBER: United States Patent No. 5,375,693

EXPIRATION DATE: August 3, 2012

PATENT OWNER: Sepracor Inc.
33 Locke Drive
Marlborough, MA 01752-1146

and

Georgetown University
Washington, D.C.

TYPE OF PATENT: Method of Use

The undersigned declares that United States Patent No. 5,375,693 covers a method of using Fexofenadine HCl, a drug substance contained in the drug product Fexofenadine tablets for which the above-referenced NDA is being submitted for approval, even date herewith, in treating allergic rhinitis. Hoechst Marion Roussel, Inc. is licensed under United States Patent No. 5,375,693 which has not been extended under 35 U.S.C. § 156.

Please list the above patent in the Orange Book Publication upon approval of the NDA.

Submitted by: Elaine Waller
Elaine Waller
Vice President
North American Drug Regulatory Affairs

Attachment C: United States Patent No. 5,578,610

July 17, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Park Building, Room 2-14
12420 Parklawn Drive
Rockville, MD 20857

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail: P.O. Box 9627
Kansas City, MO 64134-0627
Telephone (816) 966-5000

Subject: Re: Original NDA Submission for Fexofenadine Tablets
Patent Information and Declaration

Dear Sir:

The undersigned submits the following patent information as relevant to Fexofenadine tablets:

PATENT NUMBER: United States Patent No. 5,578,610

EXPIRATION DATE: November 26, 2013

PATENT OWNER: Albany Molecular Research, Inc.
21 Corporate Circle
Albany, New York 12203-5154

TYPE OF PATENT: Drug substance, Drug Product Composition and Method of Use

The undersigned declares that United States Patent No. 5,578,610 covers Fexofenadine HCl, a drug substance contained in the drug product Fexofenadine tablets for which the above-referenced NDA is being submitted for approval, even date herewith, as well as the drug product (composition) containing said drug substance and a method of using said drug substance in treating allergic reactions. Hoechst Marion Roussel, Inc. is licensed under United States Patent No. 5,578,610. The patent has not been extended under 35 U.S.C. § 156.

Please list the above patent in the Orange Book Publication upon approval of the NDA.

Submitted by: Elaine Waller
Elaine Waller
Vice President
North American Drug Regulatory Affairs

EXCLUSIVITY SUMMARY FOR NDA # __20-872__

Trade Name __Allegra Tablets__ Generic Name __fexofenadine hydrochloride

Applicant Name ___Aventis Pharmaceuticals Inc._ HFD # ___570_

Approval Date If Known _February 25, 2000_

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA?

YES /X/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /X/

If yes, what type? (SE1, SE2, etc.) __N/A__

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 /X/ NO /___/

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

_____

_____

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

_____N/A_____

_____

Form OGD-011347 Revised 10/13/98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /X/ NO /___/

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

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

___NO_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /X/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 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 /X/ NO /___/

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

NDA# __20-625____ ____20-786____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability 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 /X/ 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 /X/ 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 /X/

(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 /X/

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 /X/

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:

Protocols M016455B/3081, PJPR0067, PJPR006610077, PJPR0039

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 /X/

Investigation #2 YES /___/ NO /X/

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 /X/

Investigation #2 YES /___/ NO /X/

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"):

Protocols M016455B/3081, PJPR0067, PJPR006610077, PJPR0039

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

INDs YES /X/ ! 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 /X/

If yes, explain: _____

_____

/S/

LCDR James Lindsay Cobbs
Title: Regulatory Project Manager

February 24, 2000
Date

/S/

Robert J. Meyer, M.D.
Division Director

2/25/00
Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20872	**Trade Name:**	ALLEGRA(FEXOFENADINE HCL)TABS 30/60/~~120~~ 180mg
Supplement Number:		**Generic Name:**	FEXOFENADINE HCL
Supplement Type:		**Dosage Form:**	Tablet; Oral
Regulatory Action:	AP	**Proposed Indication:**	SAR,CIU

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)

____Children (25 Months-12 years)

____Infants (1-24 Months)

____Adolescents (13-16 Years)

_X_Other Age Groups (listed): 6-12 YEARS OF AGE

Label Adequacy	Adequate for SOME pediatric age groups
Formulation Status	NEW FORMULATION needed. Applicant in NEGOTIATIONS with FDA
Studies Needed	STUDIES needed. Applicant in NEGOTIATIONS with FDA
Study Status	Protocols are submitted and under review

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER/LINDSAY COBBS

/S/

Signature

February 24, 2000

Date

Debarment Certification

Hoechst Marion Roussel, Inc. hereby certifies that we did not and will not use in any capacity the services of any person debarred under Section 306(a) or (b) in connection with this application.

Elaine Waller

Elaine Waller, PharmD
Vice President,
North American Drug Regulatory Affairs

1 July 98
Date

Division of Pulmonary Drug Products

NDA Administrative Review

Application number: 20-872

Name of Drug: Allegra (fexofenadine HCL) Tablets (30, 60, 120, and 180 mg)

Sponsor: Hoechst Marion Roussel Inc. (HMR)

Indication: Seasonal Allergic Rhinitis/Chronic Idiopathic Urticaria.

Submission Date(s): July 16, 1998

Receipt Date: July 17, 1998

The following complete documents were submitted by HMR.

1. Form FDA 356h.
2. Form FDA 3397 (User Fee Cover Sheet).
3. Cross-References.
4. Index to the application.
    - Table of contents for each volume to include Lists of Tables and Figures.
5. Patent Information.
6. Debarment Certification.
7. Application Summary:
    a. Labels and Labeling Summary
        - Draft labeling disk provided (submitted July 21, 1998).

b. Pharmacologic class, scientific rationale, intended use and potential clinical benefits summary.

c. Foreign Marketing history.

d. Chemistry, Manufacturing and Controls Summary.

- Methods Validation and Labeling.

e. Nonclinical Pharmacology and Toxicology Summary.

f. Human Pharmacokinetic and Bioavailability Summary.

- Raw data on disk (submitted July 21, 1998).

g. Clinical Data Summary and Results of Statistical analysis.

h. Benefit/Risk Relationship and Proposed Postmarketing studies.

8. Case Report Tabulations.

The application is administratively fileable.

/S/

J. Lindsay Cobbs
Project Manager

August 3, 1998
Date

CC ORIGINAL NDA 20-872
HFD-570/DIVISION FILE
HFD-570/Cobbs

Initialed by: Schumaker/ 8/5/98

N:\My Documents\n20872AdminRev.doc

Cobbs

TELECON RECORD

Date: November 29, 1999

NDA: 20-872

Product: Allegra Tablets

FDA Participant: J. Lindsay Cobbs, Regulatory Project Manager
Shawn Khorshidi, Chemistry Reviewer

Sponsor: Faraneh Attarchi, CMC Manager, Quintiles, Inc.

Background: A brief teleconference was held to discuss the following issues regarding the CMC section of the response to the AE issued July 16, 1999.

1. The sponsor was reminded that 3 copies of the Methods Validation package (that includes the finalized specifications) should be provided.
2. The sponsor was informed that the dissolution specifications are acceptable as proposed in option 3 of the submission dated October 15, 1999.
3. The sponsor agreed to update the specification sheets for the drug substance and drug product.

Cobbs

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM

DATE: September 28, 1999

FROM: Mr. J. Lindsay Cobbs, R.Ph.
Regulatory Project Manager, DPADP

SUBJECT: HMR/Quintiles CMC Telecon (July 22, 1999)

TO: NDA 20-872 Division File

This memo will serve as an amendment to the teleconference minutes dated July 22, 1999. The teleconference was requested to discuss the CMC issues from the approvable letter dated July 16, 1999. HMR/Quintiles provided a correspondence indicating their general agreement with the minutes and noted 2 issues for the Division's consideration. Please see the general correspondence dated September 20, 1999, or Attachment 1 (copy of September 20, 1999, submission) for details.

1. Issue 1.

   a. HMR provides additional information regarding their response for item 4.a. of the July 22, 1999, minutes.

   b. HMR provides clarification of the term "future" regarding item 4.b.

2. HMR noted a typo (the number of printed cartons for physician samples should be instead of in item 5 of the minutes dated July 22, 1999.

Hoechst Marion Roussel, Inc
NDA 20-872
Allegra (fexofenadine HCL) Tablet
July 22, 1999

HMR/QUINTILES TELECONFERENCE
CHEMISTRY, MANUFACTURING & CONTROLS (CMC)

Representing **Hoechst Marion Roussel (HMR)**:

Charlie Aiman, Director, Active Ingredient Process Development & Production, NA
Alan Bina, Process Specialist, Manufacturing Operations
Matthias Baun, Project Manager-fexofenadine Technology Transfer
Marion Ceruzzi, Associate Director, Global Regulatory Specialist
Ian Davidson, Senior Director/Global Project Team Leader-fexofenadine
Greg Guthrie, Director, Dry Product Process Unit
Dan henry, Assistant Director, US Regulatory Affairs
Melinda Hester, Senior Associate Manufacturing Engineer
Michael Nicholas, Director, US Regulatory Affairs
Ernie Parente, Director of QC of Kansas City Quality Operations
John Reynolds, QC Lab Leader
Dhiren Shah, Director, US Regulatory Affairs (CMC, Marketed Products)
Steve Simmons, Head of North American Quality Operations

Representing **Quintiles**:

Faraneh Attarchi, Manager, US Regulatory Affairs (CMC, Development Product)
Cindy Brown, Senior Research Chemist, Dissolution Group Leader
John Claudius, Senior Associate Scientist, Drug Delivery Solids
Carloyn Lindsey, Senior Research CMC Specialist
Dave Pack, Senior Statistical Scientist
Gary Silvey, Director, Physicochemical Analysis
Vinh Tran, Scientist, Analytical Development

Representing the **Division of Pulmonary Drug Products**:

Lindsay Cobbs, Project Manager
Shawn Khorshidi, Chemistry Reviewer
Guirag Poochikian, Chemistry Team Leader
Brian Rogers, Chemistry Reviewer

Background: This teleconference was requested to discuss the CMC questions from the approvable letter dated July 16, 1999. Please see a copy of the approvable (AE) letter (Attachment 1) dated July 16, 1999, and the submission dated July 29, 1999, for details.

1. Question 9., of the AE letter.

   a. HMR noted that the facsimile dated July 15, 1999, in response to the Information Request (IR) for NDA 20-625/S-008 dated July 1, 1999, addressed the drug substance specifications (specs) as per the Agency's proposal to tighten the specifications, where possible, for this application (Allegra Tablet, NDA 20-872) as requested in the IR dated April 26, 1999.

   b. The Division noted that HMR should be able to produce drug substance without batch failure while tightening THE specs. Further, the data provided in various submissions do not support the proposed specs of NMT % (+/- 5 standard deviations) for Total Related Substances. Based on the data provided NMT % (+/-3 standard deviations) as stated in the AE would be acceptable. However, the Division agreed to the proposed impurity specs but stated that NMT % for Total Related Substances may be acceptable.

2. Question 14., of the AE letter.

   a. HMR requested that the specs for MDL 102,038 be increased to NMT % because HMR would like to extend the shelf life of the product past two years when the long term data are available. HMR also noted that MDL 102,038 is a non-toxic impurity/degradant and has no safety risk at the proposed limit.

   b. The Division noted that the data provided does not support the spec of NMT %. However, the Division requested that HMR provide their rationale in the response for review, as this is a review issue.

3. Question 17., of the AE letter.

   a. HMR noted that they agree to change the test time points to 10 and 30 minutes for the 60, 120 and 180 mg tablets. However, HMR felt that the proposed Q values would cause a high level of S1 dissolution failures. HMR proposed Q % in 10 mintes and Q % in 30 mintes for the 60, 120 and 180 mg tablets; and Q % in 15 minutes and Q % in 30 minutes for the 30 mg tablet.

   b. The Division also noted that a separate spec for the 30 mg tablet is not

acceptable. The Division noted that they did not see any problems with HMR's proposal for the 60, 120, and 180 mg tablets but would have to consult the biopharmaceutics division before agreeing to the proposal.

c. The Division inquired about the difference in the dissolution profiles of the two compression studies (profiles from the May 21, 1999, submission and the facsimile dated July 22, 1999). The Division further stated that because there is a difference there is some reason for the difference and recommended that HMR provide an explanation for the discrepancy, especially now with the other dosage form problems. HMR agreed to investigate the discrepancies and provide an explanation in the response.

4. Question 15., of the AE letter.

a. The Division asked why the softest tablets did not have the fastest release rate? HMR explained that the product has an optimum hardness and the softest tablets do not have the best dissolution, but could not explain why.

b. The Division expressed concern of the dissolution decreasing on stability and suggested intra-batch average as the best way to observe the dissolution rate (this would justify the *in vitro* dissolution profile). HMR agreed to do this type study in the future.

5. Question 21., of AE letter.

a. HMR inquired about a discrepancy in the How Supplied section of the package insert (PI) and the statement in Question 21.c.("protect from excessive moisture"). Also, HMR noted that they have already printed cartons for physician samples and requested permission to add this statement at the next printing.

b. The Division restated that comments for the labeling provided in the AE were preliminary comments, and that additional comments may be forthcoming. However, the Division agreed that this statement maybe added at the next printing to the physician samples.

6. Attachment 3 provides the background of the HMR/Quintiles relationship.

Attachment 1

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:

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

We acknowledge receipt of your submissions dated July 30, 31, August 13, 25, September 29, October 28, November 10, 20, 23, December 10, 16, 1998, February 16, May 6, 13, 14, 21, 24, June 4, 11, and 18, 1999.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to adequately address the following comments.

1. The changes to the trade name for the individual dosage strengths as proposed (Allegra-24 Hour) are not acceptable. The tradename and its representation on packaging and labeling as proposed in the original NDA submission should be utilized.

2. The data provided do not adequately support the once-daily dosing of 120 mg in the treatment of seasonal allergic rhinitis (SAR) in patients 12 years of age and above. Specifically, efficacy throughout the entire dosing interval was not adequately shown. In order to obtain labeling for 120 mg once-daily, provide adequate and well-controlled data to demonstrate the efficacy of this dose, including end-of-dosing interval data. A complete, corrected report of SAR Study 0032 (protocol PJPR0032), with the electronic data, may sufficiently address this issue.

3. The pharmacokinetics data for fexofenadine indicate that the 30 mg dose in children 6 to 11 years of age would provide similar systemic exposure as the 60 mg dose in adults. There are no data that a dose higher than 30 mg twice daily provides additional benefit in the treatment of SAR in children 6 to 11 years of age. Therefore, the proposed dose

Additional data and rationale must be provided if a 60 mg twice daily dosage for the treatment of SAR is sought for children 6 to 11 years of age.

4. As the pharmacokinetics data for fexofenadine indicate that the 30 mg dose in children 6 to 11 years of age provides similar systemic exposure as the 60 mg dose in adults, and the proposed dose for the treatment of chronic idiopathic urticaria (CIU) in adults is 60 mg twice daily, and given that a dose higher than 60 mg twice daily did not provide additional clinical benefit in adults and adolescents,

Additional data and rationale must be provided if a 60 mg twice daily dose for the treatment of CIU is sought for this population.

5. Our analysis of the combined data from the two trials K-98-0093-D and K-98-0119-D using population methods indicates no difference in clearance between adults and children. Since our estimate of clearance from this analysis differs from your results, the population pharmacokinetic approach should be utilized to compare the pharmacokinetics of fexofenadine in adults with that in children using the data from K-98-0093-D and K-98-0119-D.

6. The analysis of variance with terms of sequence was not performed for each pharmacokinetic parameter in Study PJPR0045. Re-analyze the data including sequence and provide the result for the study.

The following comments pertain to the drug substance.

7. Based on actual observed data (amendment dated May 21, 1999, exhibit 2, p.60), specify a reasonable range for DSC temperature in drug substance specifications (S3380).

8. Include appropriate test(s) and acceptance criteria in drug substance specifications to control the polymorphic forms.

9. Based on the stability data submitted in the amendment dated July 30, 1998, the following acceptance criteria for the related substances are proposed. In addition, refer to the Agency's correspondence dated July 1, 1999, regarding NDA 20-625/S-008.

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.

10. Establish and submit a master batch record with all appropriate tests and controls for 30 mg tablets. The manufacturing process for 30 mg tablets should be validated for full commercial scale.

11. As requested in the correspondence dated April 26, 1999, include acceptance criteria for particle size distribution in the master batch record as in-process control after the final blending step.

12. The visual observation of tablets for chipping and capping, as stated in your response, do not measure the actual resistance of the tablets against the breakage or other physical defects in use. Include a test and specification for friability as in-process control.

13. We acknowledge that MDL 46,619 is a synthetic impurity and is controlled in the drug substance specifications (S3380). For completeness of the specification sheet, include MDL 46,619 in drug product specifications. A footnote may indicate that MDL 46,619 is a synthetic impurity and does not need monitoring.

14. The proposed acceptance criteria for impurities/degradation products at release and stability are unacceptable. The following acceptance criteria based on observed data are proposed.

MDL 102,038	NMT	%
MDL 46,016	NMT	%
*MDL 46,619	NMT	%
Total other degradants	NMT	%
Total degradants	NMT	%

* Refer to comment 13. above.

15. The proposed hardness range of Kp (120 mg tablets) and Kp (180 mg tablets) is not acceptable. Provide dissolution vs. hardness data for the 120 and 180

mg tablet using 0.001M HCl (as dissolution media) and propose new hardness ranges for the 120 and 180 mg tablets, respectively.

16. Submit "hardness data" for the following batches of the tablets reported in exhibit 6, amendment dated May 21, 1999, (updated stability data). Also specify the dissolution medium used for these batches.

For 30 mg tablets:	Batch Nos. RF9713, RF9714 and RF9715
For 60 mg tablets:	Batch Nos. RC9626, RD 9619, RD9620, 98057614, 98057617 and 98057619
For 120 mg tablets:	Batch Nos. 98054478, 98054529 and 98054530
For 180 mg tablets:	Batch Nos. 98058304, 98058346 and 98058362

17. The dissolution method proposed is acceptable. However, the proposed dissolution specifications of Q % at 15 minutes and Q % at 45 minutes are not sufficiently discriminatory to adequately characterize the dissolution profiles of the tablets. The following acceptance criteria are acceptable.

Q % at 10 minutes and Q % in 30 minutes

18. Specify the criteria for "the acceptable and non-acceptable changes" for the proposed grading scales No. 1 and 2 in the stability specifications for product and package appearance.

19. As previously requested, submit method validation packages that also include all updated methods.

20. Identify all packaging presentations (i.e., blister and HDPE bottles) intended for distribution that do not have child resistance closure (CRC) features. Address and justify adequately the absence of the CRC feature for such packaging.

21. Submit revised draft labeling that incorporates the following preliminary comments as well as the preliminary revisions shown in the enclosed marked-up draft package insert.

    a. Increase the size and prominence of the established name "fexofenadine hydrochloride" on all labels and labeling for Allegra tablets.

    b. Blister labels for 60 mg tablets should prominently display the statement "store at controlled room temperature 20-25°C (68-77°C)".

    c. Include the statement "protect from excessive moisture" in prominent

lettering on all labels and labeling for Allegra tablets

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR

314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

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

Enclosure

Redacted 15

pages of trade

secret and/or

confidential

commercial

information

Draft Labeling

Record of Telephone Conversation

Date: December 16, 1998
NDA: 20-872
Product Name: Allegra Tablets
Firm Name: Hoechst Marion Roussel, INC.
Telecon Initiated by: By the Agency
Name and Title of Person with whom conversation was hold:
Faraneh Attarchi
Telephone No: (816)-966-7660

Background:

For 60 mg tablets, there are some discrepancies between released vs distributed and stability specifications (S4304) for degradation products (refer to S3-V1.4,pp. 12-25). Such discrepancies do not exist in case of 30 mg, 120 mg and 180 mg tablets. This should be clarified.
HMR has provided summary of the results for analyzed batches (S3-V1.5-pp.107-203). However, for proper evaluation of batch analysis results, the actual COA for all analyzed batches should be provided.

Content of Telecon:

Agency's Q No.1:

For 60 mg tablets, there are some discrepancies between released vs distributed and stability specifications (S4304) for degradation products (refer to S3-V1.4,pp.12-25). Such discrepancies do not exist in case of 30 mg, 120 mg and 180 mg tablets. Please explain this discrepancies.

Furthermore, provide the actual COA for all analyzed batches of 30 mg, 60 mg, 120 mg and 180 mg tablets (this include primary as well as validation batches)

Mrs. Attarchi promised to fax us the above information by facsimile as soon as possible.

/S/ 12/16/98

Hossein S. Khorshidi
HFD-570

cc:
NDA 20-872
HFD-570/Division File
HFD-570/H Khorshidi
HFD-570/GPoochikian
R/D Init. by:_____
F/T by:HKhorshidi
doc. # N:\NDA 20-872\Chem\98-12-16. Tel

Record of Telephone Conversation

Date: December 8, 1998
NDA: 20-872
Product Name: Allegra Tablets
Firm Name: Hoechst Marion Roussel, INC.
Telecon Initiated by: By the Agency
Name and Title of Person with whom conversation was hold:
Faraneh Attarchi
Telephone No: (816)-966-7660

Content of Telecon:

Agency's Q No.1:

Please provide information (in tabular forms) which include the following:

I)- List of all batches of fexofenadine hydrochloride tablets which are included in NDA 20-872 submission.
II)- Formulation numbers identifying formulation used for each batch.
III)- Batch size.
IV)- Year that the batch was manufactured.
V)- The clinical or stability studies in which the batch was used.

Mrs. Attarchi promised to fax us the above information by facsimile as soon as possible.

/S/ 12/8/98

Hossein S. Khorshidi
HFD-570

cc:
NDA 20-872
HFD-570/Division File
HFD-570/H Khorshidi
HFD-570/GPoochikian
R/D Init. by:_____
F/T by:HKhorshidi
doc. # N:\NDA 20-872\Chem\98-12-08. Tel

Record of Telephone Conversation

Date: December 5, 1998
NDA: 20-872
Product Name: Allegra Tablets
Firm Name: Hoechst Marion Roussel, INC.
Telecon Initiated by: By the Agency
Name and Title of Person with whom conversation was hold:
Faraneh Attarchi
Telephone No: (816)-966-7660

Background: Applicant is claiming that " *site was only used for stability testing of 30 mg tablets and will not be used for any future primary or commercial stability testing for this NDA. Therefore, it will not be necessary to inspect the site".* In order to make a decision on whether inspection of site is necessary or not, we asked HMR to provide the following information:

Content of Telecon:

Agency's Q No.1:

In reference to your response that is not a planned site for analytical release or stability testing, please provide details on the site in which testing for each tablet strength were performed. Also identify the planned site(s) in which the future stability tests will be performed.

Mrs. Attarchi promised to fax us the above information by facsimile as soon as possible.

/S/ 12/5/98

Hossein S. Khorshidi
HFD-570

cc:
NDA 20-872
HFD-570/Division File
HFD-570/H Khorshidi
HFD-570/GPoochikian
R/D Init. by:_____
F/T by:HKhorshidi
doc. # N:\NDA 20-872\Chem\98-12-05. Tel

Cobbs.

TELECON RECORD

Date: April 30, 1999

NDA: 20-872

Product: Allegra Tablets

FDA Participant: J. Lindsay Cobbs, R.Ph
Project Manager, DPDP

Sponsor: Wayne Vallee, R.Ph.
HMR

Background: A general correspondence dated April 15, 1999, submitted to the above application regarding the inadequacy letter dated November 24, 1998, for Pediatric Exclusivity request was provided to request that the Division reconsider the decision not to issue a written request.

1. I informed Mr. Vallee that the Division's decision to not accept a proposal referencing previously submitted data is consistent with the Agency's interpretation of Section 505A of the Federal Food, Drug and Cosmetic Act to qualify for pediatric exclusivity. In addition, I noted that for further discussion of this matter HMR should contact Center level management.

2. I also informed Mr. Vallee that the Division stands by its decision for a proposal that includes data in children under 6 years of age.

cc: NDA 20-872
HFD-570/Division File
HFD-570/Cobbs
HFD-570/ SCHUMAKER

4/30/99

DRAFTED BY: LCOBBS/April 30, 1999
N:/MY DOCUMENTS/n20872tel99-04-30.doc

MEMORANDUM OF TELECON

DATE: June 22, 1998

IND:

PRODUCT: fexofenadine HCl tablet

PARTICIPANTS:

FDA:	Brad Gillespie	Clinical Pharmacology & Biopharmaceutics Reviewer
	Brian Rogers	Chemistry Reviewer
	Gretchen Trout	Project Manager
HMR:	F. Attarchi	Regulatory Affairs
	C. Brown	Analytics
	E. Parente	Operations
	D. Shah	Regulatory Affairs
	W. Vallee	Regulatory Affairs

BACKGROUND: During a pre-NDA meeting on May 18, 1998, HMR and the Division agreed that HMR would submit additional data on drug product dissolution, and a follow-up meeting would be held to discuss this issue. Reference is made to submissions dated May 27 and June 11, 1998. Following an internal meeting, the Division requested a brief teleconference prior to the face-to-face meeting scheduled for June 25, 1998.

The Division restated to HMR, as was discussed at the May 18, 1998, meeting, that we have concerns that the media HMR has chosen is not adequately discriminating. In response to the Division's concerns, HMR has submitted data to demonstrate that their method can discriminate tablets of varying hardness.

The Division questioned if HMR has tried 0.01 N HCl with a pH of 2. HMR replied that they have only used pH 1 and 3, and that they use the 0.001 N HCl to support their international product line and for consistency would like to use it for this application.

HMR stated that the biobatch is compressed at the same hardness as the NDA stability batches. The Division pointed out that what HMR is showing is that their method is discriminating only for hardness. HMR replied that they have looked at all the critical parameters, and hardness is the only parameter that had an effect on dissolution.

Cobbs

MEMORANDUM OF TELECON

DATE: July 13, 1998

IND:

PARTICIPANTS:

FDA:	Barbara Elashoff	Biometrics Reviewer
	Gretchen Trout	Project Manager
	Steve Wilson	Biometrics Team Leader
HMR:	George Hayes	Statistics
	Roger Kew	Statistics
	Mike Mosier	Statistics
	Wayne Vallee	Regulatory Affairs

BACKGROUND: HMR requested a teleconference to discuss the status of the submission of the electronic data in support of their incoming NDA for Allegra small tablets.

HMR explained that they had originally planned to submit the entire package of data and programs with the NDA submission, however they are behind schedule on this timeline. The discussion focused on the status of the reports for: a Chronic Idiopathic Urticaria (CIU) trial, a QD seasonal allergic rhinitis (SAR) trial, and a pediatric SAR trial. HMR plans to submit physical documentation for each study. This will include all of the SAS programs, datasets, and documentation to explain the programs, datasets, etc.

- The CIU report is almost final. HMR stated that they were in the process of changing the SAS code to allow for differences between mainframe SAS and PC SAS regarding performance of the Fisher's Exact test. The Division informed HMR that it was not necessary to change the code, and a note in the documentation regarding this problem would be sufficient.

- The documentation for the QD SAR trial can be finalized in one week, the datasets will be ready in two weeks.

- For the pediatric trial, the first draft of documentation has been reviewed and should be finalized in approximately one week. The datasets are almost ready, and the programs should be ready in 1-2 weeks.

The Division thanked HMR for communicating with us the change in their timeline and encouraged HMR to stay in contact with the Division if they encounter additional problems.

CONCLUSION: The Division and HMR agreed that if everything is completed and can be submitted by the last week of July/first week of August, then HMR will submit everything simultaneously. However, if problems are encountered in finalizing any of the three reports, then HMR (keeping the Agency informed) will submit the reports, individually, as soon as they are available.

Gretchen Trout /
Project Manager

cc: IND
Div. File
HFD-570/Elashoff
HFD-570/Trout
HFD-570/Wilson
HFD 570/C0665

TELECONFERENCE

Cobbs

TELECON RECORD

Date: February 5, 1999

NDA: 20-872

Product: Allegra Tablets

FDA Participant: J. Lindsay Cobbs, R.Ph
Project Manager

Sponsor: Wayne Valle
U.S. Drug Regulatory Affairs

Background: An Inadequacy letter dated November 24, 1998, was issued in response to the request for a request dated August 28, 1998. HMR provided a response to the aforementioned correspondence in the submission dated January 21, 1999.

1. I informed HMR that their response to the Inadequacy letter remains inadequate.
   a. I restated the Division's recommendations in the Inadequacy letter dated November 24, 1998, that any proposed pediatric study request for a Written Request (WR) should address the issues as per section IV.A of the Guidance for Industry: Qualifying for pediatric Exclusivity Under Section 505A of the Federal Food, Drug and cosmetic Act.
   b. I also reminded HMR that the reports of studies already submitted to the Agency may not be referred to in a request for a request.
   c. Finally I restated that the Division would like to see data in the pediatric population below 6 years of age.
2. Wayne noted an apology for the confusion and indicated that he will convey the Division's message to the Allegra team.

Cobbs

TELECON RECORD

Date: April 30, 1999

NDA: 20-872

Product: Allegra Tablets

FDA Participant: J. Lindsay Cobbs, R.Ph
Project Manager, DPDP

Sponsor: Wayne Vallee, R.Ph.
HMR

Background: A general correspondence dated April 15, 1999, submitted to the above application regarding the inadequacy letter dated November 24, 1998, for Pediatric Exclusivity request was provided to request that the Division reconsider the decision not to issue a written request.

1. I informed Mr. Vallee that the Division's decision to not accept a proposal referencing previously submitted data is consistent with the Agency's interpretation of Section 505A of the Federal Food, Drug and Cosmetic Act to qualify for pediatric exclusivity. In addition, I noted that for further discussion of this matter HMR should contact Center level management.

2. I also informed Mr. Vallee that the Division stands by its decision for a proposal that includes data in children under 6 years of age.

cc: NDA 20-872
HFD-570/Division File
HFD-570/Cobbs
HFD-570/ SCHUMAKER

4/30/99