CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-284

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-284

Novartis Pharmaceuticals Corporation
Attention: Mara Stiles
Associate Director, Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Ms. Stiles:

Please refer to your new drug application (NDA) dated November 28, 2000, received November 29, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ritalin® LA (methylphenidate hydrochloride) Extended-release Capsules.

We acknowledge receipt of your submissions dated October 18 and December 6, 2001; February 28, March 21 (juvenile animal study), April 16, May 6, 13 and 23, 2002. Your submission of December 6, 2001 constituted a complete response to our October 1, 2001 action letter.

This new drug application provides for the use of Ritalin® LA (methylphenidate hydrochloride) Extended-release Capsules for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD) for children aged 6 to 12.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDA (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-284." Approval of this submission by FDA is not required before the labeling is used.

The following agreed upon dissolution specifications have been approved for all strengths of Ritalin® LA Extended-release Capsules:

Table 1 Dissolution Method and Specifications

Parameter	Description
Apparatus type:	USP Apparatus I (basket)
Media:	Medium I: Medium II:
Volume (ml):	500 ml for both medium I and medium II
Temperature	
Speed of rotation (rpm):	
Sample times (hours):	
Specifications (% of Label Claim)	
Acceptance criteria for 2 – 10 hours	As per USP XXIV – NF 19 <724> Drug Release Acceptance Table 1

We have approved an expiration date of two years for this drug product.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated.

Please be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We are waiving the pediatric study requirement for this action on this application.

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-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you should have any questions, please call Ms. Anna Marie H. Weikel, R.Ph., Regulatory Health Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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APPROVABLE LETTER

Novartis Pharmaceuticals Corporation
Attention: Mara Stiles
Associate Director, Drug Regulatory Affairs
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Dear Ms. Stiles:

Please refer to your new drug application (NDA) dated November 28, 2000, received November 29, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ritalin® LA (methylphenidate hydrochloride) Extended-release Capsules.

We acknowledge receipt of your submissions dated February 28 (2), March 23 and 27, April 24, and June 22, 2001.

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 address the following:

Chemistry Issues

1. The drug product manufacturing site, Elan Holdings, is subject to a Consent Decree based on a history of non-conformance with current good manufacturing practices (cGMP). Elan's unacceptable cGMP status cannot be changed until Elan requests an inspection to verify that agreed upon remedies are in place. Elan Holdings did not request such an inspection in time to provide results for this review of your application. A satisfactory inspection will be required before this application may be approved.

2. [redacted] is proposed to be [redacted] in the final Ritalin® LA formulation. For example, the 20 mg capsule contains [redacted] g each of [redacted] Please explain in detail the derivation of the [redacted] value for [redacted] each dosage strength.

3. The in-process controls for the IR and DR beads formation are inadequate. Please provide detailed in-process controls at every step of manufacturing to ensure quality control. The dissolution specifications for the DR (delayed release) beads at the in-process controls should be identical to the proposed specifications for the final drug product.

4. Reprocessing operations on page 4-78, Vol. 1.3, state that "The times, temperatures, etc., stated in the summary of production are valid for a given batch size provided in the drug product – Manufacturing Formula and using the stated equipment. In the case of minor variations in batch size or use of other equipment of the same type (while maintaining the same basic production steps), these values may vary for technical reasons to ensure that the final product fulfills the requirements and corresponds to the established

specifications." The statement is unacceptable based on the Guidance for Changes to an Approved NDA or ANDA. Please commit to reporting the changes in conditions and equipment related to reprocessing appropriately in a supplement or annual report as per the Guidance for Changes to an Approved NDA or ANDA, November 1999.

5. The specifications for related impurities should be reflective of the release and stability data. It is recommended that the specifications are modified to: Individual Unknown Impurities: — Total Unknown Impurities: NMT —, and Total Impurities: — based on sufficient data from 9 batches for 12 months.

6. The analytical methods section is not very well organized. Please resubmit the information in a more organized manner for a complete review of your application. The analytical methods for identification b: —, determination of assay and related substances, dissolution and residual solvents must include: 1) a final method code, 2) specifications, 3) sampling plan, and 4) detailed analytical method. The sampling plan must include the final parameters used, such as, mobile phase, sample solvent, column type, sample concentration, flow rate, detector wavelength, injection volume, run time, column temperature, wash and equilibrium conditions for an —

7. — from — — for — is inadequate. — from —) are therefore unacceptable as a — for Ritalin ®LA until adequate information is provided for an acceptable —

8. You have proposed an equivalency protocol to qualify new container closure suppliers (Vol. 1.5 pages 4-33 - 4-34), using USP <661> and <671> testing. Please submit acceptance criteria for this protocol that are commensurate with the expected shelf-life of the drug product.

9. Please clarify the information regarding container closures in the stability protocol by correlating the suppliers of materials with reference to their DMF numbers with the to-be-marketed packages on stability. Please summarize in a tabular form which supplier's materials for bottles, CR closures, and induction seals were used in the stability studies.

10. You have provided 12 months acceptable stability data at 25°C/60%RH for Ritalin® LA. The 6 month stability data at 40 °C/75%RH shows that eight of the eighteen batch package combinations failed the dissolution test at the — time point. Expiry period of — is acceptable for Ritalin® LA reflective of the stability data. The expiry period may be extended based on additional real-time data through a Prior Approval Supplement.

11. The container labels include the dosage strength written in : — 20, 30 and 40 mg of Ritalin® LA. Please change to three distinct colors to depict the dosage strength on container labels to increase clarity.

Pharmacology/Toxicology Issues

Please provide a written commitment , including a targeted submission date, to conduct a Phase IV study in juvenile rats to examine the effects of methylphenidate on developing systems, with particular emphasis on neurobehavioral and reproductive parameters. A proposed protocol for such a study may be submitted for our review.

Biopharmaceutics Issues

1. Please adopt the following dissolution method and specifications for all strengths of Ritalin® LA capsules:

Table 1 Proposed Regulatory Dissolution Method and Specifications

Parameter	Description
Dosage Form:	Capsule, hard gelatin
Strengths:	20, 30, 40 mg
Apparatus type:	USP Apparatus I (basket)
Media:	Medium I: Medium II:
Volume (ml):	500 ml for both medium I and medium II
Temperature	
Speed of rotation (rpm):	
Sample times (hours)	
Specifications (% of Label Claim)	Acceptance criteria for as per USP XXIV – NF 19 <724> Drug Release Acceptance Table 1

2. The dissolution proposals are based upon data from bio-batches (i.e. >10% of commercial batch size) used in the clinical pharmacokinetic and efficacy studies and confirmed by data from stability studies on 3 additional bio-batches stored at 25° C / 60% RH over 18 months.

3. Please develop a dissolution specification for the immediate release bead component of the formulation at an earlier time point. A single point dissolution specification with an acceptance criteria of —— of label claim may be an appropriate target. This earlier sampling time may be able to replace the —— time point.

4. The proposed in vitro dissolution to in vivo bioavailability correlation is unacceptable for the following reasons and the data is therefore not being relied upon to set dissolution specifications:

a) The concentration time profile is not adequately predicted. Specifically a lack of prediction of absorption from the immediate release beads results in a concentration vs. time profile with a single peak concentration instead of the double peaked profile actually seen; neither is there a prediction of an initial lag phase.

b) Point to point prediction errors were excessive and ranged from -4.3% to 93.9% for the to-be-marketed formulation.

c) Estimates of the fraction absorbed in vivo are considerably greater than the fraction of the dose dissolved.

d) The dissolution model used in the IVIVC method provides dissolution values in excess of 140% of the labeled content.

e) The prediction method requires in vivo concentration data from the formulation being predicted and therefore does not have any utility.

f) If you desire to pursue an in vitro – in vivo correlation, you may wish to contact the Office of Clinical Pharmacology through the division project manager for suggestions.

Clinical Issues

1. Please provide a more detailed analysis of the weight data from Protocol 07; i.e., a presentation of mean weight by week of the trial, and by age and gender subgroups, along with hypothesis testing for the difference between treatment groups. In addition, descriptive statistics for vital signs, height and weight in Protocol 07E should be provided.

2. Under 21 CFR 314.50(d)(vi)(b), we request that you provide a final safety update for Ritalin® LA.

Labeling

Accompanying this letter as an attachment is our proposal for the labeling of Ritalin® LA Extended-release Capsules. Please submit revised draft labeling identical in content to the enclosed labeling (text for the package insert). Explanations for our proposed changes are provided in the bracketed comments embedded within the proposed text. We would be happy to discuss these proposed changes in more detail through a teleconference if you wish.

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.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

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

If you should have any questions, please call Ms. Anna Marie Homonnay, R.Ph., Regulatory Health Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research