CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-259

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration Rockville MD 20857

NDA 21-259

Celltech Pharmaceuticals, Inc.
Attention: Norma Cappetti
Director, Regulatory Affairs
755 Jefferson Road
P.O. Box 31710
Rochester, NY 14623

Dear Ms. Cappetti:

Please refer to your new drug application (NDA) dated March 31, 2000, received April 3, 2000, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Metadate® CD (methylphenidate hydrochloride USP) Extended-release Capsules, 20 mg.

We acknowledge receipt of your submissions dated February 13 and March 22, 2001.

Your submission of February 13, 2001 constituted a complete response to our February 2, 2001 action letter.

This new drug application provides for the use of Metadate® CD (methylphenidate hydrochloride USP) Extended-release Capsules for the treatment of attention deficit disorder.

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.

LABELING

Accompanying this letter as an attachment is the final agreed upon labeling for Metadate CD. We note your amendment dated March 22, 2001, which reflects the agreed upon labeling.

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 21-259." Approval of this submission by FDA is not required before the labeling is used.

BIOPHARMACEUTICS

The final dissolution method specifications for METADATE™ CD, 20 mg *d,l-threo*-methylphenidate HCl capsules, are as follows:

Dissolution apparatus: USP Paddle Apparatus II
Rotation speed: 50 rpm
Medium and volume: Water, 500 mL
Medium Temperature: 37 ± 0.5°C

Time Interval	Specification (% of label)
1 h	
2 h	
4 h	
8 h	
12 h	

We also remind you of your post marketing study commitment listed in your submission dated February 13, 2001. This commitment is listed below:

PHASE IV COMMITMENT

We acknowledge your commitment to conduct a study in juvenile rats to examine the effects of methylphenidate hydrochloride on developing systems with particular emphasis on neurobehavioral and reproductive parameters within 20 months following agreement on its design.

Please submit all nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

CHEMISTRY

Expiration Date

We have approved an expiration date of 24 months for the 20 mg capsule strength.

Methods Validation

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. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

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 note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies for the under six years of age group. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

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 Homonnay, R.Ph., Regulatory 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

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-259

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Issued 2/2/01

NDA 21-259

Medeva Americas, Inc.
Attention: Norma Cappetti
Director Regulatory Affairs
755 Jefferson Road
P.O. Box 1710
Rochester, NY 14603-1710

Dear Ms. Cappetti:

Please refer to your new drug application (NDA) dated March 31, 2000, received April 3, 2000, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for METADATE CD (methylphenidate hydrochloride) Extended-release Capsules.

We acknowledge receipt of your submissions dated April 27, May 17, June 9, June 14, July 6 and 7, August 11, October 17, December 15 and 27, 2000; January 2 and 11, 2001.

This new drug application provides for the use of METADATE CD Extended-release Capsules for the treatment of attention deficit disorder.

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:

Labeling Issues

Accompanying this letter as an attachment, is our labeling proposal, including explanations, for METADATE CD. We ask that you adopt this labeling for approval. If you would like to further discuss this labeling proposal, a teleconference may be arranged through the division project manager.

Worldwide Literature Update

Please provide any new information on the worldwide regulatory status of METADATE CD, including the status of all actions either taken or pending before any foreign regulatory authorities.

Biopharmaceutics Issues

1. The *in vitro-in vivo* correlation (IVIVC) that was submitted for this formulation is not acceptable. If you would like, a teleconference may be arranged through the division project manager to further discuss this issue.

2. The following revised *in vitro* dissolution specifications should be adopted for the 20 mg *(d,l-threo*-methylphenidate HCl) 30:70 IR:ER extended-release capsule:

   Dissolution apparatus: USP Paddle Apparatus II
   Rotation speed: 50 rpm
   Medium and volume: Water, 500 mL
   Medium Temperature: 37 ± 0.5°C

Time Interval	Specification (% of label)
1 h	—
2 h	—
4 h	—
8 h	—
12 h	—

The 4-hour and 12-hour time points have been revised from — % and — %, to — % and —, respectively.

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.

Chemistry Issues

1. Data provided in your January 11, 2001, amendment indicate that batches EA-623, EA-626 and PE104EA-630 all fail your proposed dissolution specification at the two hour time point at release, whereas batches EA-604, EA-688 and EA-689 remain within specification throughout full term stability. Please explain this discrepancy.

2. We recognize that ER bead batch EA-544 (page 139, Section 4, Volume 2) exhibits a mean twelve hour dissolution value of —, after six (6) months storage. However, this batch is a pilot scale batch (—) and was stored at ambient conditions in an unspecified container closure system which cannot possibly match the environment of the commercial scale system, even if those components were used.

Batch PE104EA-630 is a commercial scale batch (——— , and after eighteen (18) months storage in the proposed commercial container closure system under commercial warehouse conditions, the corresponding twelve hour dissolution value was — % (page 140, Section 4, Volume 2). Therefore, based on the data provided, the deficiency comment #3 from Agency letter dated December 28, 2000 remains. It is repeated below for your convenience. Please note that *"aforementioned batches"* refers to batches EA-623, EA626 and PE104EA-630.

> *" The proposed 12 hour dissolution specification for the ER beads is — —%. However, the 12 hour dissolution performance for the aforementioned batches is greater than —%. Please tighten this specification (e.g., ——— %) so that it is based on and reflective of the data."*

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 should have any questions, please call Ms. Anna Marie Homonnay, R.Ph., Regulatory 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

attachment