CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-121/S-004

APPROVAL LETTER
NDA 21-121/S-004

ALZA Corporation
Attention: Tracy Lin
Associate Director, Regulatory Affairs
1900 Charleston Road
P.O. Box 7210
Mountain View, CA 94039-7210

Dear Ms. Lin:


We acknowledge receipt of your submissions dated February 14, March 1 and 4, 2002

This supplemental new drug application provides for an additional 27 mg dosage strength to be manufactured at the Vacaville manufacturing site and the requisite changes in the labeling for this new strength. In addition, the phrase, 'esophageal motility disorders' has been added to 'Potential for Gastrointestinal Obstruction' in the WARNINGS section of the labeling.

We have completed the review of this supplemental 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 submitted labeling text dated November 30, 2001. Accordingly, this supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted November 30, 2001).

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDAs (January 1999). For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-121/S-004". Approval of this submission by FDA is not required before the labeling is used.
BIOPHARMACEUTICS

The previously approved in vitro specifications are also recommended for the 27 mg methylphenidate HCl OROS® formulation. The recommended in vitro specifications are as follows:

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Specification of label claim(%range)</th>
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<tr>
<td>at 1 h</td>
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The in vitro testing is performed with USP Type VII dissolution apparatus with oral extended release tablet holder (spring holder) in pH 3 water with a fixed agitation rate of 30 cycles per minute, maintained at a temperature of 37±0.5°C.

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, Regulatory Project Manager, at (301) 594-5535.

Sincerely,

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
4/1/02 08:29:50 AM
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-121/S-004

FINAL PRINTED LABELING
CONCERTA®
(methylphenidate HCI)
Extended-release Tablets

DESCRIPTION
CONCERTA® is a once-a-day treatment for Attention Deficit Hyperactivity Disorder, or ADHD. CONCERTA® contains the drug methylphenidate, a central nervous system stimulant that has been used to treat ADHD for more than 20 years. CONCERTA® is taken by mouth, once each day in the morning.

What is Attention Deficit Hyperactivity Disorder?
ADHD has three main types of symptoms: inattention, hyperactivity, and impulsiveness. Symptoms of inattention include not paying attention, making careless mistakes, not finishing tasks, and being easily distracted. Symptoms of hyperactivity and impulsiveness include fidgeting, acting out, and being less concerned with possible consequences of actions. Some patients have more symptoms of hyperactivity and impulsiveness while others have more symptoms of inattention. Some patients have all three types of symptoms.

Many people have symptoms like these from time to time, but patients with ADHD have these symptoms more often than their age. Symptoms must be present for at least 5 months to be certain of the diagnosis.

How does CONCERTA® work?
Part of the CONCERTA® tablet dissolves right after you swallow it in the morning, giving you a dose all day. The remaining drug is slowly released during the day to continue helping the symptoms of ADHD. Methylphenidate, the active ingredient in CONCERTA®, helps increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

Who should not take CONCERTA®?
You should not take CONCERTA® if:
• You have significant anxiety, tension, or agitation since these conditions may be worsened by this medication.
• You are allergic to methylphenidate or any of the other ingredients in CONCERTA®.
• You have glaucoma, an eye disease.
• You have a family history of Tourette's syndrome, or a family history of Tourette's syndrome.

Talk to your doctor if you believe any of these conditions apply to you.

How should I take CONCERTA®?
Do not chew, crush, or divide the tablets. Swallow CONCERTA® tablets whole with the help of water or other liquids, such as milk or juice.

Take CONCERTA® once each day in the morning.

You may take CONCERTA® before or after you eat.

Take the dose prescribed by your doctor. Your doctor may adjust the amount of drug you take if it is not right for you. From time to time, your doctor may adjust your treatment to check your symptoms while you are not taking the drug.

What are the possible side effects of CONCERTA®?
In the clinical trials with patients using CONCERTA®, the most common side effects were headache, stomach pain, dry mouth, decreased appetite, and decreased appetite. Other side effects seen with methylphenidate, such as weight loss, mood changes, irritability, seizures, mood changes, memory changes, hallucinations, and nightmares, were rare.

If you experience any side effect, talk to your doctor.

What must I discuss with my doctor before taking CONCERTA®?
Talk to your doctor before taking CONCERTA® if you:
• Are being treated for depression or have symptoms of depression such as sadness, hopelessness, and hopelessness.

INDICATIONS AND USAGE
CONCERTA® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children, adolescents, and adults. The safety and effectiveness of CONCERTA® in children and adolescents have been established by controlled trials in children and adolescents with ADHD.

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In the clinical trials with patients using CONCERTA®, the most common side effects were headache, stomach pain, dry mouth, decreased appetite, and decreased appetite. Other side effects seen with methylphenidate, such as weight loss, mood changes, irritability, seizures, mood changes, memory changes, hallucinations, and nightmares, were rare.

If you experience any side effect, talk to your doctor.

Pregnancy
CONCERTA® should not be used in pregnant women.

CONCERTA® contains methylphenidate. It is not known if methylphenidate crosses the placenta or affects the fetus.

Lactation
It is not known whether methylphenidate is excreted in human milk. CONCERTA® should not be used in breastfeeding women.

Children
CONCERTA® tablets are not recommended for use in children under 6 years of age. Safety and effectiveness have not been established in this age group.

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NURSING MOTHERS
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INFORMATION FOR PATIENTS TAKING CONCERTA® OR THEIR PARENTS OR CAREGIVERS

CONCERTA®
(methylphenidate HCl)
Extended-release Tablets

This information is for patients taking CONCERTA® Extended-release Tablets CII for the treatment of Attention Deficit Hyperactivity Disorder, or their parents or caregivers.

Please read this before you start taking CONCERTA®. Remember, this information does not take the place of your doctor's instructions. If you have any questions about this information or about CONCERTA®, talk to your doctor or pharmacist.

What is CONCERTA®?
CONCERTA® is a once-a-day treatment for Attention Deficit Hyperactivity Disorder, or ADHD. CONCERTA® contains the drug methylphenidate, a central nervous system stimulant that has been used to treat ADHD for more than 30 years. CONCERTA® is taken by mouth, once each day in the morning.

What is Attention Deficit Hyperactivity Disorder?
ADHD has three main types of symptoms: inattention, hyperactivity, and impulsiveness. Symptoms of inattention include not paying attention, making careless mistakes, not listening, not finishing tasks, not following directions, and being easily distracted. Symptoms of hyperactivity and impulsiveness include fidgeting, talking excessively, running around at inappropriate times, and interrupting others. Some patients have more symptoms of hyperactivity and impulsiveness while others have more symptoms of inattention. Some patients have all three types of symptoms.

Many people have symptoms like these from time to time, but patients with ADHD have these symptoms more than others their age. Symptoms must be present for at least 6 months to be certain of the diagnosis.

How does CONCERTA® work?
Part of the CONCERTA® tablet dissolves right after you swallow it in the morning, giving you an initial dose of methylphenidate. The remaining drug is slowly released during the day to continue to help lessen the symptoms of ADHD. Methylphenidate, the active ingredient in CONCERTA®, helps increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

Who should NOT take CONCERTA®?
You should NOT take CONCERTA® if:

• You have significant anxiety, tension, or agitation since CONCERTA® may make these conditions worse.
• You are allergic to methylphenidate or any of the other ingredients in CONCERTA®.
• You have glaucoma, an eye disease.
• You have tics or Tourette's syndrome, or a family history of Tourette's syndrome.

Talk to your doctor if you believe any of these conditions apply to you.

How should I take CONCERTA®?
Do not chew, crush, or divide the tablets. Swallow CONCERTA® tablets whole with the help of water or other liquids, such as milk or juice.

Take CONCERTA® once each day in the morning.
You may take CONCERTA® before or after you eat.
Take the dose prescribed by your doctor. Your doctor may adjust the amount of drug you take until it is right for you. From time to time, your doctor may interrupt your treatment to check your symptoms while you are not taking the drug.

What are the possible side effects of CONCERTA®?
In the clinical studies with patients using CONCERTA®, the most common side effects were headache, stomach pain, sleeplessness, and decreased appetite. Other side effects seen with methylphenidate, the active ingredient in CONCERTA®, include nausea, vomiting, dizziness, nervousness, tics, allergic reactions, increased blood pressure and psychosis (abnormal thinking or hallucinations).

This is not a complete list of possible side effects. Ask your doctor about other side effects. If you develop any side effect, talk to your doctor.

What must I discuss with my doctor before taking CONCERTA®?
Talk to your doctor before taking CONCERTA® if you:

• Are being treated for depression or have symptoms of depression such as feelings of sadness, worthlessness, and hopelessness.
• Have motion tics (hard-to-control, repeated twitching of any parts of your body) or verbal tics (hard-to-control repeating of sounds or words).
• Have someone in your family with motion tics, verbal tics, or Tourette's syndrome.
• Have abnormal thoughts or visions, hear abnormal sounds, or have been diagnosed with psychosis.
• Have had seizures (convulsions, epilepsy) or abnormal EEGs (electroencephalograms).
• Have high blood pressure.
• Have a narrowing or blockage of your gastrointestinal tract (your esophagus, stomach, or small or large intestine).

Tell your doctor immediately if you develop any of the above conditions or symptoms while taking CONCERTA®.

Can I take CONCERTA® with other medicines?

Tell your doctor about all medicines that you are taking. Your doctor should decide whether you can take CONCERTA® with other medicines. These include:

Other medicines that a doctor has prescribed.
Medicines that you buy yourself without a prescription.
Any herbal remedies that you may be taking.
You should not take CONCERTA® with monoamine oxidase (MAO) inhibitors.
While on CONCERTA®, do not start taking a new medicine or herbal remedy before checking with your doctor.
CONCERTA® may change the way your body reacts to certain medicines. These include medicines used to treat depression, prevent seizures, or prevent blood clots (commonly called “blood thinners”). Your doctor may need to change your dose of these medicines if you are taking them with CONCERTA®.

Other Important Safety Information

Abuse of methylphenidate can lead to dependence.
Tell your doctor if you have ever abused or been dependent on alcohol or drugs, or if you are now abusing or dependent on alcohol or drugs.

Before taking CONCERTA®, tell your doctor if you are pregnant or plan on becoming pregnant. If you take methylphenidate, it may be in your breast milk. Tell your doctor if you are nursing a baby.
Tell your doctor if you have blurred vision when taking CONCERTA®.
Slower growth (weight gain and/or height) has been reported with long-term use of methylphenidate in children. Your doctor will be carefully watching your height and weight. If you are not growing or gaining weight as your doctor expects, your doctor may stop your CONCERTA® treatment.

Call your doctor immediately if you take more than the amount of CONCERTA® prescribed by your doctor.

What else should I know about CONCERTA®?

CONCERTA® has not been studied in children under 6 years of age.
The CONCERTA® tablet does not dissolve completely after all the drug has been released, and you may sometimes notice it in your stool. This is normal.

CONCERTA® may be a part of your overall treatment for ADHD. Your doctor may also recommend that you have counseling or other therapy.

As with all medicines, never share CONCERTA® with anyone else and take only the number of CONCERTA® tablets prescribed by your doctor.

CONCERTA® should be stored in a safe place at room temperature (between 59°-86° F). Do not store this medicine in hot, damp, or humid places.

Keep out of the reach of children.

For more information call 1-888-440-7903 or visit www.concerta.net

Manufactured by
ALZA Corporation, Mountain View, CA 94043.

Distributed and marketed by
McNeil Consumer & Specialty Pharmaceuticals,
Fort Washington, PA 19034.

McNeil

By ALZA OROS® Technology Product

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-121/S-004

MEDICAL REVIEW
REVIEW AND EVALUATION OF CLINICAL DATA

NDA 21-121
SPONSOR: ALZA
DRUG: CONCERTA (METHYLPHENIDATE)
MATERIAL SUBMITTED: SCM-004 (SUPPLEMENT FOR NEW 27 MG STRENGTH)
DATE SUBMITTED: 11-30-01
DATE RECEIVED: 12-3-01
USER FEE DUE DATE: 4-3-02

This supplement provides for a new 27 mg strength. The sponsor has proposed some corresponding changes to the Dosage and Administration section, and an entirely unrelated change to the Warnings section that I will comment upon here. Originally Alza planned to make the change in the Warnings section under a separate “changes being effected” supplement, but for the sake of expediency has included it in this submission.

Labeling changes

Related to new dosage strength

Under Dosage and Administration, for the sections on patients new to methylphenidate and patients currently using methylphenidate, the following sentence has been edited as shown:

Dosage may be adjusted to a maximum of 54 mg/day taken once daily in the morning.

Also, under Table 3 (“Recommended Dose Conversion from Methylphenidate Regimens to CONCERTA”), the following statement has been added:

A 27 mg dosage strength is available for physicians who wish to prescribe between the 18 mg and 36 mg dosages.

Additionally, the How Supplied and Description sections have been revised to reflect the availability of the new dosage strength.

Reviewer Comment: In my opinion these labeling changes are appropriate and may be approved.

Additional labeling change

In the Warnings section, under the heading, “Potential for gastrointestinal obstruction,” there is a list of conditions causing gastrointestinal narrowing, and the labeling states that Concerta should not ordinarily be administered to patients with such conditions. Alza has added the term “esophageal motility disorders” to the list of such conditions. This change is based upon a MedWatch report of a 16 year old boy who had a Concerta 36 mg tablet “wedged in the spasm of the cricopharyngeus muscle.” The tablet had to be removed by direct laryngoscopy/esophagoscopy. The patient apparently had a long history of trouble swallowing.

Reviewer Comment: It is not entirely clear to me that this subject had an esophageal motility disorder; nonetheless, I see no harm in adding this term as proposed by the sponsor.

Andrew D. Mosholder, M.D., M.P.H.
Medical Officer, HFD-120
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
________________________
Andy Mosholder
3/7/02 01:31:12 PM
MEDICAL OFFICER

Thomas Laughren
3/10/02 08:44:05 PM
MEDICAL OFFICER
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-121/S-004

CHEMISTRY REVIEW
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-121

DATE REVIEWED: 3/21/02

REVIEW #: 1

REVIEWER: Donald N. Klein, Ph.D.

SUBMISSION TYPE DOCUMENT DATE CDER DATE ASSIGNED DATE
Prior-Approval 11/30/01 12/3/01 12/13/01
(BC) Amendment 2/14/02 2/15/02 2/22/02
(BC) Amendment 3/1/02 3/4/02 3/6/02

NAME & ADDRESS OF APPLICANT:
ALZA Corporation
1900 Charleston Road
P.O. Box 7210
Mountain View, CA 94039-7210

DRUG PRODUCT NAME:
Proprietary: CONCERTA®
Established(USAN): methylphenidate hydrochloride, USP

PHARMACOL. CATEGORY/INDICATION: Attention Deficit Hyperactivity Disorder (ADHD)

DOSAGE FORM: Osmotic Tablet
STRENGTHS: 27mg
ROUTE OF ADMINISTRATION: Oral
Rx/OTC: Rx

SPECIAL PRODUCTS: Yes  No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Chemical Name: 2-piperidineacetic acid, α-phenyl-, methylester, hydrochloride, (R*,R*)-(±)-
Molecular formula: C₁₄H₁₉NO₃ . HCl
MW: 269.77
CAS Registry Number: CAS-298-59-9

![Chemical Structure Image]
RELATED APPLICATIONS:  N21-121, approved 8/1/00 for the 18mg and 36mg tablets; N21-121, SCM-001, approved on 12/8/00 for the 54mg tablet; N21-121, SCM-003, approved on 3/4/02 for alternate drug substance source;

CONSULT: BioPharmaceutics submitted on 12/17/01; completed 3/8/02.

SUPPLEMENT PROVIDES FOR: 27mg dosage strength.

CONCLUSIONS: Recommend Approval of the CMC section of N21-121, SCM-004.

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/s/

Donald Klein
3/21/02 01:59:19 PM
CHEMIST

revisions made as discussed this morning

Hasmukh Patel
3/21/02 03:29:22 PM
CHEMIST
OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

OCPB Reviewer received: Dec. 17, 2001

Brand Name  Concerta®
Generic Name  d,l-threeo-methylphenidate
Reviewer  Maria Sunzel, Ph.D.
Team Leader (acting)  Vanitha Sekar, Ph.D.
OCPB Division  HFD-860
ORM Division  HFD-120
Sponsor  Alza Corporation, 1900 Charleston Rd, Mountain View, CA 94039-7210
Relevant IND(s)  54,575
Submission Type; Code  SCM-004 Supplement (new dosage strength)
Formulation; Strength  Extended release tablet (OROS®); 27 mg
Indication  Attention Deficit - Hyperactivity Disorder (ADHD)

1 EXECUTIVE SUMMARY

This review evaluates the approved in vitro-in vivo correlation (Type A IVIVC) applied to in vitro dissolution data to support a biowaiver for a new tablet strength of 27 mg of Concerta extended release tablets (d,l-threeo-methylphenidate), and finds the IVIVC prediction acceptable.

Therefore, the sponsor’s bioavailability waiver request for the 27-mg Concerta tablet is granted, and the Office of Clinical Pharmacology and Biopharmaceutics recommends approval of the new Concerta tablet strength of 27 mg methylphenidate, manufactured at the site in Vacaville, CA.

The sponsor has withdrawn the second manufacturing site from the current supplement (submission dated March 1, 2002).

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds the IVIVC predictions acceptable for the 27-mg Concerta tablet and recommends approval of the new tablet strength, manufactured at the site in Vacaville, CA.

The sponsor’s proposed label changes regarding the label sections ‘Description’, ‘Dosage and Administration’ and ‘How Supplied’ are acceptable. However, the acceptability of the proposed label change to the WARNINGS section is deferred to the Medical Division.

The currently approved in vitro dissolution specifications for all marketed Concerta tablets (18 mg, 36 mg, and 54 mg) are also applicable for the new Concerta tablet strength of 27 mg.
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3 SUMMARY OF CPB FINDINGS

3.1 Background

Racemic d,l-threo-methylphenidate hydrochloride (d,l-MPH), a mild CNS stimulant, has been marketed in the US since 1955 for various indications. It is currently marketed for treatment of attention deficit/hyperactivity disorders (ADHD) and narcolepsy, in daily doses up to 60 mg as immediate and sustained release formulations.

The sponsor is currently marketing three different approved dose strengths of Concerta tablets (d,l-MPH HCl - 18 mg, 36 mg, and 54 mg), an OROS® (osmotic drug delivery system) extended release (ER) formulation. The OROS system delivers methylphenidate by a combined process of aqueous dissolution of the drug overcoat (immediate release) and osmotic delivery of the core drug (extended release).

The 18 mg and 36 mg Concerta tablets manufactured by ALZA were approved for the treatment of ADHD on Aug. 1, 2000. The full Clinical Pharmacology and Biopharmaceutics (CPB) reviews of the original NDA 21-121 are dated Feb. 10, and Apr. 17, 2000, where the latter is an addendum that contains the dissolution specifications based on the approved Type A in vitro-in vivo correlation. A higher strength, the 54 mg Concerta tablet, was approved in December 2000 (CPB review dated 11/27/00). These are extended release formulations intended for once daily oral dosing, with an approved maximal daily dose of 54 mg.

The earlier submissions have shown that methylphenidate has dose-proportional pharmacokinetics (18-54 mg Concerta tablets), and that the pharmacokinetics are not altered with concomitant food intake (36 mg and 54 mg tablets).

3.2 Current Submission

The sponsor has submitted this prior approval supplement (NDA 21-121/SCM-004) for a new, 27 mg, strength of the Concerta extended release (ER) tablet. Two earlier OCPB reviews regarding a biowaiver request (review dated Jun. 7, 2001), and a bioequivalence study protocol (review dated Aug. 31, 2001) have been completed with regard to the 27 mg Concerta tablet strength. The current submission contains information regarding CMC (both development and final processes and validation), as well as an application of the approved Type A in vitro-in vivo correlation based on the in vitro dissolution data from the 27 mg Concerta tablet. The IVIVC is the basis for a biowaiver request for the new 27 mg strength.

The submission contains information stating that the 27 mg tablet:
- has the same rate-controlling membrane as the other approved tablets
- is formulated to specifically achieve the required release profile for a 27 mg dose, which has been verified by release rate testing
- has the same release mechanism as the other approved strengths
- has a similar dissolution profile as the other approved strengths in the approved medium
- is manufactured by use of the same process, equipment and site as the other approved strengths

The sponsor proposed two manufacturing sites for the new 27 mg MPH HCl Concerta tablets, namely Vacaville, CA, and __________________. The two sites have different batch quantities due to a difference in the coating equipment used at the two sites. Both manufacturing sites are approved for manufacturing of the 18 mg, 36 mg, and 54 mg Concerta tablets. In the current application for the 27-mg tablet strength, the in vitro dissolution data and thereby the IVIVC is based on data from one lot produced at the Vacaville site. No 27-mg Concerta tablet batches
have been manufactured at the __________ to date. A teleconference was held between Alza and CDER representatives on March 1, 2002. The OCPB representatives (Drs Sekar and Sunzel) requested the sponsor to submit a full in vitro release profile in the compendial medium from one batch __________ manufactured at the __________. Following the teleconference, the sponsor chose to withdraw the manufacturing site (__________) from NDA 21-121/SCM-004 on March 1, 2002.

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds the IVIVC predictions acceptable for the 27-mg Concerta tablet and recommends approval of the new tablet strength, manufactured at the site in Vacaville, CA.

The sponsor’s proposed label changes regarding the label sections ‘Description’, ‘Dosage and Administration’ and ‘How Supplied’ are acceptable. However, the acceptability of the proposed label change in the WARNINGS section is deferred to the Medical Division.

The currently approved in vitro dissolution specifications for all marketed Concerta tablets (18, 36, and 54 mg) are also applicable for the new Concerta tablet strength of 27 mg.

4 QUESTION BASED REVIEW

4.1 General Biopharmaceutics

4.1.1 Formulations

How is the Concerta extended release formulation constructed and how does it function?

<table>
<thead>
<tr>
<th>OROS (MPH HCl)</th>
<th>18 mg</th>
<th>27 mg</th>
<th>36 mg</th>
<th>54 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>268 mg</td>
<td>283 mg</td>
<td>515 mg</td>
<td>526 mg</td>
</tr>
<tr>
<td>Diameter</td>
<td>5.3 mm</td>
<td>5.3 mm</td>
<td>6.8 mm</td>
<td>6.8 mm</td>
</tr>
<tr>
<td>Length</td>
<td>12 mm</td>
<td>12.2 mm</td>
<td>15 mm</td>
<td>15.4 mm</td>
</tr>
</tbody>
</table>

The OROS® systems deliver MPH HCl by a combined process of aqueous dissolution of the drug overcoat and osmotic delivery of the core drug. The system resembles a conventional tablet in appearance, is comprised by an osmotically active tri-layer core surrounded by a semi-permeable membrane with an immediate release drug overcoat (see figure and table above). The tri-layer core is composed of two drug layers containing the drug and excipients, and a push layer containing osmotically active components. There is a precision-drilled orifice on the drug-layer end of the tablet.

When the OROS system is ingested, the drug in the overcoat is quickly released and is available for absorption. After the dissolution of the drug overcoat, an osmotic gradient is established across the rate-controlling membrane, and water is imbibed into the system at a controlled rate, yielding controlled delivery of MPH for approximately __________. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the stool as the tablet-shell along with insoluble core components.
Is the new 27 mg dose strength compositionally similar to the approved strengths and did the sponsor perform adequate comparative tests?

The composition of the 27 mg OROS formulation is within the limits of the approved strengths of 18 mg and 54 mg MPH HCl, with respect to components, membrane, drug overcoat and clear overcoat, as shown in Appendix, subsection 7.1. The 27 mg tablet is gray, and has ‘ALZA 27’ imprinted on the tablet.

A series of experiments were conducted to establish the manufacturing processes that would yield comparable performance between all dose strengths of the OROS delivery system. The equivalency of the four different strengths was assessed (drug layer weights, push layer weights, drug particle size, orifice diameter, final compression force, receptor media and agitation rate) and were found functionally comparable, according to the sponsor.

What manufacturing sites are proposed for the production of the new 27 mg Concerta tablets?

The sponsor proposes two manufacturing sites for the new 27 mg OROS formulation, namely Vacaville, CA and __________. The two sites have different batch quantities due to a difference in the __________ coating equipment used at the two sites. Both manufacturing sites are approved for manufacturing of the 18 mg, 36 mg, and 54 mg Concerta tablets.

The sponsor has only produced one batch at the manufacturing site at Vacaville, CA. This batch was used for the in vitro drug release profiles and the IVIVC calculations. The sponsor has not manufactured the 27-mg Concerta tablets at the second site __________, and therefore no in vitro drug release data is available from that site. A teleconference was held between Alza and CDER representatives on March 1, 2002. The OCPB representatives (Drs Sekar and Sunzel) requested the sponsor to submit a full in vitro release profile in the compendial medium from one batch __________ for the 27-mg Concerta tablet manufactured at the __________ site. Following the teleconference, the sponsor chose to withdraw the second manufacturing site __________ from NDA 21-121/SCM-004 on March 1, 2002.

4.2 In vitro dissolution comparisons

Do all strengths of the Concerta tablets containing MPH HCl give similar in vitro dissolution profiles?

The cumulative in vitro dissolution/release profiles of all Concerta tablet strengths, including the new 27 mg strength, manufactured at the Vacaville site, were similar, as depicted in Figure 1 (by use of approved method). See Section 4.4, for details regarding the method. The tabulated values for the mean (n=24) cumulative in vitro drug release profile of the 27 mg MPH HCl tablet strength are shown in the Appendix, Subsection 7.2.
NDA 21-121/SCM-004
27 mg Concerta® tablet (d,l-threo-methylphenidate HCl)
M Sunzel

![Graph](image)

**FIGURE 1.** Comparative cumulative *in vitro* drug release curves (x-axis: 0-10 h; y-axis: mean % cumulative drug release) for all Concerta tablet strengths (27 mg denoted as large solid squares).

The sponsor also compared the 27 mg strength to the approved 18 mg, 36 mg, and 54 mg strengths by calculating the similarity factor ($f_2$ values; 27 mg vs. each approved strength) from the data depicted in Figure 1. The $f_2$ values were within acceptance criteria (50 ≤ $f_2$ ≤ 100), and the % drug released at 1, 4, and 10 h, were similar between all tablet strengths, as shown in Table 1.

**TABLE 1.** Comparisons of cumulative *in vitro* drug release of all Concerta tablet strengths at the time points in the approved dissolution method (1, 4, and 10 h), and the calculated $f_2$ values.

<table>
<thead>
<tr>
<th>Dosage Strength (mg)</th>
<th>I.D. No.</th>
<th>Similarity Factor, $f_2$</th>
<th>1h</th>
<th>4h</th>
<th>10h</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>MV9800306</td>
<td>83</td>
<td>22.8</td>
<td>51.2</td>
<td>101.4</td>
</tr>
<tr>
<td>27</td>
<td>0108221</td>
<td>-</td>
<td>22.9</td>
<td>48.0</td>
<td>100.1</td>
</tr>
<tr>
<td>36</td>
<td>9901790</td>
<td>70</td>
<td>22.7</td>
<td>45.3</td>
<td>97.3</td>
</tr>
<tr>
<td>54</td>
<td>9909642</td>
<td>84</td>
<td>22.8</td>
<td>46.7</td>
<td>99.2</td>
</tr>
</tbody>
</table>

In conclusion, the *in vitro* dissolution data showed that the new Concerta 27 mg tablet strength of methylphenidate HCl, manufactured at the Vacaville site, has similar *in vitro* drug release properties to the approved Concerta tablets (18, 36, and 54 mg strengths).

### 4.3 In vitro – in vivo correlation

*What method was used for the approved Type A *in vitro – in vivo correlation* (IVIVC)?*

A Type A *in vitro–in vivo* correlation by the use of a convolution method was approved in the original NDA 21-121 in 2000. The convolution method is a robust method, since it does not rely
TABLE 2. The sponsor’s summary of the prediction errors (%PE) of the 27-mg Concerta tablet for C<sub>max</sub> and AUC predictions. The values depicted as actual are the C<sub>max</sub> and AUC values predicted in the original IVIVC. (%PE calculated as [(actual-predicted)/actual x 100] in each case).

<table>
<thead>
<tr>
<th>Strength (ng/mL)</th>
<th>Study</th>
<th>Actual</th>
<th>Predicted&lt;sup&gt;a&lt;/sup&gt;</th>
<th>%PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>18 mg</td>
<td>C-98-024</td>
<td>3.65</td>
<td>3.91</td>
</tr>
<tr>
<td></td>
<td>18 mg</td>
<td>C-99-001</td>
<td>3.76</td>
<td>3.91</td>
</tr>
<tr>
<td></td>
<td>18 mg</td>
<td>C-98-002</td>
<td>3.60</td>
<td>3.91</td>
</tr>
<tr>
<td></td>
<td>36 mg</td>
<td>C-99-005</td>
<td>7.27</td>
<td>7.82</td>
</tr>
<tr>
<td></td>
<td>36 mg</td>
<td>C-99-005</td>
<td>8.27</td>
<td>7.82</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td>-4.4</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;inf&lt;/sub&gt;</td>
<td>18 mg</td>
<td>C-98-024</td>
<td>40.2</td>
<td>39.8</td>
</tr>
<tr>
<td>(ng.h/mL)</td>
<td>18 mg</td>
<td>C-99-001</td>
<td>40.8</td>
<td>39.8</td>
</tr>
<tr>
<td></td>
<td>18 mg</td>
<td>C-98-002</td>
<td>40.1</td>
<td>39.8</td>
</tr>
<tr>
<td></td>
<td>36 mg</td>
<td>C-99-005</td>
<td>79.1</td>
<td>79.6</td>
</tr>
<tr>
<td></td>
<td>36 mg</td>
<td>C-99-005</td>
<td>80.2</td>
<td>79.6</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td>0.6</td>
</tr>
</tbody>
</table>

<sup>a</sup>Data for 27 mg are scaled proportionally to appropriate dose (18 or 36 mg)

Although the mean prediction errors in Table 2 were not calculated as the mean of the absolute values, this does not change the conclusion that the PE% is less than 10% for both C<sub>max</sub> and AUC (mean of absolute values for %PE of C<sub>max</sub>: 6.6%; mean of absolute values for %PE of AUC: 1.1%).

In conclusion, the results of the application of the IVIVC were within the acceptance criteria, and indicate that a biowaiver can be granted for the 27-mg Concerta tablet strength.

4.4 In vitro dissolution method and specifications

Are the currently approved in vitro dissolution method and specifications also applicable to the new 27 mg dosage strength?

The previously approved in vitro dissolution specifications for the 18 mg, 36 mg, and 54 mg MPH HCl Concerta tablets are also recommended for the 27 mg dosage strength manufactured at the Vacaville site. The recommended in vitro dissolution specifications are as follows:

The in vitro dissolution testing is to be performed with USP Type VII dissolution apparatus with oral extended release tablet holder (spring holder) in pH 3 water with a fixed agitation rate of 30 cycles per minute, maintained at temperature of 37 ± 0.5°C.
4.5 Supportive in vivo data

Has the sponsor investigated the in vivo performance of the 27-mg Concerta tablet strength? What were the results of the in vivo study?

The sponsor has also performed an in vivo bioequivalence (BE) study, to fulfill regulatory requirements in countries outside the U.S. An in vivo BE study is not a regulatory requirement in the U.S., since a Type A IVIVC has been approved for the Concerta tablets. However, the sponsor submitted a study protocol for a bioequivalence study in 2001. Therefore, this reviewer contacted the sponsor and requested the summary findings from the study, if available. The sponsor submitted a study summary with the pharmacokinetic data (submission to IND 54,575 dated Feb. 12, 2002), which showed that the 27 mg MPH HCl Concerta tablet was bioequivalent to the approved Concerta tablets (2x27 mg test tablets vs. 3x18 mg reference tablets).

5 LABELING

What changes have been made to the approved label? Are these changes acceptable?

The Sponsor has proposed minor editorial revisions to the approved label. New information is included in the Sections ‘Description’, ‘Dosage and Administration’ and ‘How Supplied’. In addition, Concerta is now a registered trademark, and that has been inserted throughout the label (i.e. TM has been replaced by ®). In addition, the sponsor has made a change in the WARNINGS section of the label, the review of that change is deferred to the Medical Division. A summary of the proposed label revisions can be found in the Appendix (subsection 7.3).

The Office of Clinical Pharmacology and Biopharmaceutics finds the sponsor’s proposed label changes regarding the label sections ‘Description’, ‘Dosage and Administration’ and ‘How Supplied’ acceptable.

6 SIGNATURES

Maria Sunzel, Ph.D.

RD/FT initialed by Vanitha Sekar, Ph.D.

Division of Pharmaceutical Evaluation I,
Office of Clinical Pharmacology and Biopharmaceutics
c.c.: NDA 21-121/SCM-004, HFD-120 (Homonnay, Klein, Mosholder, Laughren), HFD-860 (Mehta, Marroum, Sekar, Upoor, Sunzel)
Page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.
7.3 The sponsor's proposed labeling changes

Volume 38.1

**LABELING**
Changes have been made to the labeling for Concerta® to reflect the addition of the 27 mg dosage strength. Additionally, a change to the WARNINGS section (addition of "esophageal motility disorders" to the "Potential for Gastrointestinal Obstruction" section) is reflected and will be submitted to the NDA separately in a CBE labeling supplement. McNeil Consumer & Specialty Pharmaceuticals (formerly McNeil Consumer Healthcare) Distribution/Marketing information and logo have also been added to the physician insert and container labels. McNeil Consumer & Specialty Pharmaceuticals is a partner company to ALZA (Johnson & Johnson being the parent company for both). Finally, Concerta is now a registered trademark, so all ™ symbols have been replaced with © symbols throughout. These changes are outlined below. The revised labeling components: bottle labels (text and layout), physician and patient insert (both a strikethrough version and a clean copy), are provided immediately following the description of changes. A diskette containing the electronic files for the physician insert is provided for the reviewers' convenience.

**Container Labels**
The dosage strength, NDC number, and color bar have been changed in the labels for the 27 mg bottles —— 100 count). McNeil Consumer & Specialty Pharmaceuticals (formerly McNeil Consumer Healthcare) Distribution/Marketing information and logo have been also been update in the container labels. While approval is sought for both —— and 100 count bottle configurations, initial marketing will only be in the 100 count bottles. This is reflected in the Physician Insert "HOW SUPPLIED" section. The Physician Insert will be updated to include the —— bottles when they are introduced to the market.

**Physician Insert**
The additions/changes to the affected portions of the physician insert are shown below in **bold/double underline** for additions and strikethrough mode for deletions.

**Section: Description**
CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in —— four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCI USP and is designed to have a 12-hour duration of effect. Chemically, methylphenidate HCI is d,l (racemic) methyl alpha-phenyl-2-piperidineacetate hydrochloride. Its empirical formula is C_{14}H_{19}NO_{2}HCl.

**Section: WARNINGS - Potential for Gastrointestinal Obstruction**
Because the CONCERTA® tablet is nondeformable and does not appreciably change in shape in the GI tract, CONCERTA® should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in
patients with known strictures in association with the ingestion of other drugs in nondeformable controlled-release formulations. Due to the controlled-release design of the tablet, CONCERTA® should only be used in patients who are able to swallow the tablet whole (see PRECAUTIONS: Information for Patients).

Section: Dosage and Administration (Patients New to Methylphenidate)
Dosage may be adjusted to a maximum of 54 mg/day taken once daily in the morning. In general, dosage adjustment may proceed at approximately weekly intervals.

Section: Dosage and Administration (Patients Currently Using Methylphenidate)
Dosage may be adjusted to a maximum of 54 mg/day taken once daily in the morning. In general, dosage adjustment may proceed at approximately weekly intervals.

Section: Dosage and Administration (Text below TABLE 3)
A 27 mg dosage strength is available for physicians who wish to prescribe between the 18 mg and 36 mg dosages. Daily dosage above 54 mg is not recommended.

Section: How Supplied
CONCERTA® (methylphenidate HCl) Extended-release Tablets are available in 18 mg, 27 mg, 36 mg, and 54 mg dosage strengths. The 18 mg tablets are yellow and imprinted with "alza 18". The 27 mg tablets are gray and imprinted with "alza 27". The 36 mg tablets are white and imprinted with "alza 36". The 54 mg tablets are brownish-red and imprinted with "alza 54". All four dosage strengths are supplied in bottles containing 100 tablets.

18 mg 100 count bottle NDC 17314-5850-2
27 mg 100 count bottle NDC 17314-5853-2
36 mg 100 count bottle NDC 17314-5851-2
54 mg 100 count bottle NDC 17314-5852-2

Manufactured by
ALZA Corporation, Mountain View, CA 94043.

Distributed and marketed by

[ALZA logo] [McNeil Consumer & Specialty Pharmaceuticals logo]

Edition: XX/2001
NDA 21-121/SCM-004
27 mg Concerta® tablet (d,l-threo-methylphenidate HCl)
M Sunzel

**Patient Insert**
The following changes have been made to the end of the Patient Insert:

Manufactured by
ALZA Corporation, Mountain View, CA 94043.

Distributed and marketed by

[ALZA logo] [McNeil Consumer & Specialty Pharmaceuticals logo]

XXXXXXX-X PI

Edition: XX/2001
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
---------------------
Maria Sunzel
3/8/02 03:35:33 PM
BIOPHARMACEUTICS

Vanitha Sekar
3/8/02 03:39:37 PM
BIOPHARMACEUTICS
MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 29, 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for new 27 mg strength tablet for Concerta extended release tablets (methylphenidate)

TO: File NDA 21-121/S-004
[Note: This memo should be filed with the 11-30-01 original submission.]

Concerta is an approved drug product, for the treatment of ADHD, currently available in 18, 36 and 54 mg OROS formulation tablet strengths. This supplement provides for a new 27 mg strength tablet for this formulation, that would permit more refined titration, i.e., between 18 and 36 mg and between 36 and 54 (you could give 27 + 18 = 45).

This supplement included CMC information, along with dissolution data, for the 27 mg tablet, and a request for a biowaiver for this strength, based on IVIVC for the dissolution data.

The biowaiver request was considered by Maria Sunzel, Ph.D. from OCPB. The sponsor had proposed two manufacturing sites for the 27 mg tablet, but provided dissolution data from only the Vacaville, CA site. Following a request for dissolution data from the other site, the sponsor chose to withdraw the request. OCPB has found the IVIVC predictions acceptable for the 27 mg strength and recommends approval of this strength from the Vacaville site. They also found the labeling changes in the Description, D&A, and How Supplied sections acceptable, and recommended the same dissolution specifications for this strength as for the other three marketed strengths.

Dr. Klein from chemistry has reviewed the CMC information, to include the following: drug substance; drug product; manufacturing process; container closure system; stability; establishment inspection; labeling; and analytical methods. He recommended approval of this tablet, along with a 24 month expiry.

The only clinical issues for this application were labeling changes in the D&A section, and an unrelated change in Warnings. The Warning change involved the addition of “esophageal motility disorders” to the
list of comorbid conditions for which Concerta would ordinarily be avoided. Dr. Mosholder agreed with changes in both sections, and I do as well.

**Recommendation**

I agree with the recommendations of all reviewers that this supplement can be approved, with the agreed upon dissolution method and specifications and proposed labeling.

cc:
Orig NDA 21-121/S-004
HFD-120/DivFile
HFD-120/TLaughren/RKatz/AHomonnay

**DOC:** NDA21121.03
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/s/

Thomas Laughren
3/29/02 11:00:42 AM
MEDICAL OFFICER
MEMORANDUM OF TELECON

NDA: 21-121

DRUG: Concerta

SPONSOR: Alza Corp

DATE: 3/13/02

TELEPHONE NUMBER: (650) 564-4135

CONVERSATION WITH: Tracy Lin

CONVERSATION:

I contacted Tracy Lin to convey some additional advice from OCPB concerning their planned supplement to add the ——— as a manufacturer of the 27 mg strength. I told her that their proposal as outlined in the March 6, 2002, fax to Dr. Klein, was acceptable. In addition, I reminded her that the pilot lot should be at least — the commercial batch size and that they should also include in the supplement predictions of AUC and Cmax utilizing the IVIVC and the in vitro dissolution data from the ———.

Anna Marie Homonnay, R.Ph.
Regulatory Health Project Manager
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/s/

Anna-Marie Homonnay
3/13/02 02:17:56 PM
CSO
April 15, 2002

NDA 21-121/S-004

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
1451 Rockville Pike
Rockville, MD 20852-1420

Attention: Russell Katz, MD, Director
Division of Neuropharmacological Drug Products

Re: Final Printed Labeling for Approved Supplement NDA 21-121/S-004
Concerta® (methylphenidate HCl) Extended-release Tablets

Dear Dr. Katz:

In response to your approval letter dated April 1, 2002 and in accordance with 21 CFR 314.70 (b)(3), ALZA is submitting the Final Printed Labeling for the approved physician/patient combined insert and 27mg bottle label as well as labeling for the 18mg, 36mg and 54mg container (bottle) labels and patient insert for Concerta® (methylphenidate HCl) Extended-release Tablets.

This submission is submitted in electronic format. Both the cover letter and FDA form 356h are also accompanied by a paper copy, which includes the original signature.

The electronic submission consists of the approved physician/patient package insert and 27mg container (bottle) label; the patient insert; the 18, 36 and 54 container (bottle) labels. The submission is approximately 2.5 MB in size. One CDROM is provided as the archive copy.

The CDROM has been screened for viruses using McAfee VirusScan v 4.5.1 SP1, using virus definitions 4.0.4196 and scan engine 4.1.60.

If you have any questions concerning this matter, please call me at (650) 564-4282 or via facsimile at (650) 564-2581. In the event you are unable to contact me, please contact Sue Rinne, Vice President of Regulatory Affairs at (650) 564-2523. We share the same facsimile number.

Sincerely,

Steve Kethum
Sr. Vice President, Operations

Enclosures: (1) Archival Copy
NDA 21-121

PRIOR APPROVAL SUPPLEMENT

Alza Corporation
Attention: Tracey Lin, Associate Director, Regulatory Affairs
1900 Charleston Road
P.O. Box 7210
Mountain View, CA 94039-7210

Dear Ms. Lin:

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

Name of Drug Product: Concerta™ (methylphenidate HCl) Extended Release Tablets

NDA Number: 21-121

Supplement number: 004

Date of supplement: November 30, 2001

Date of receipt: December 3, 2001

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act February 2, 2002 in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room, 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room, 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420
If you have any questions, call Anna Marie Homonnay, Regulatory Project Manager, at (301) 594-5535

Sincerely yours,

Robert H. Seevers, Ph.D.  
Chemistry Team Leader  
Psychiatric Drugs for the  
Division of Neuropharmacological Drug Products  
HFD-120  
DNDC 1, Office of New Drug Chemistry  
Center for Drug Evaluation and Research
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/s/

Robert H. Seevers
12/13/01 01:30:11 PM