CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-284

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

New Drug Application – Response to Approvable Letter
Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-284
Type of Submission:	N-BZ
Generic Name:	Methylphenidate Hydrochloride — Release Capsules
Formulation:	50:50 immediate release and enteric-coated, delayed release beads
Strengths:	20 mg, 30 mg, and 40 mg
Route:	PO
Brand Names	Ritalin® LA
Sponsor:	Novartis Pharmaceuticals Corporation East Hanover, NJ
Submission Date:	December 6, 2001
Related IND	—
Reviewer:	Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

I. EXECUTIVE SUMMARY

This submission contains:

a) the sponsor's response to OCPB proposed dissolution specifications from the original NDA review
b) the sponsor's response to labeling comments
c) the sponsor's verbal commitment to the final FDA recommendation for dissolution specification acceptance criteria at — hours as shown in Table 1 below

Remaining dissolution issues:

The sponsor wishes to make changes to the proposed dissolution acceptance criteria for the enteric-coated delayed-release beads at — hours. These changes entail raising the upper limits to accommodate a trend toward increasing dissolution rate of the enteric-coated beads, that is occurring with batches produced over time. A summary of proposed dissolution specifications is shown in Table 1

Table 1 Proposed Dissolution Specification Acceptance Criteria

Sampling Time	Sponsor's Initial Proposal	Initial FDA Proposal	Sponsor's Counter-Proposal	Final FDA Recommendation[a]

a Final FDA Recommendation was agreed to by the sponsor in a teleconference on April 18, 2002

The sponsor outlines a number of reasons for raising each of these limits and provides additional data from some new batches. These batches are not identified as to source, size, date of manufacture, batch number, etc. Each of the rationales for raising the dissolution limits is addressed individually in this review and each is flawed, with one exception.

Are the sponsor's proposed — acceptance criteria acceptable?

No. The overwhelming argument for keeping OCPB's — upper limit is that 138 of 140 experiments passed at the L1 testing using this limit, and the remaining 2 experiments would pass at stage 2 testing.

However, in order not to have the same upper limit at the — time point as at the — time point the upper limit at the —— time point will be raised to 58% (i.e. mean of clinical trial batches plus 10% of EC-DR beads).

Are the sponsor's proposed — acceptance criteria acceptable?

No. As per FDA guidances, the mean dissolution of the clinical trial batches — should be used to set specifications. Considering only the EC-DR bead component (——— ; and using a range of —— %, the acceptance range should be set to — of the EC-DR beads or —— % of labeled content. Consequently, the FDA upper limit is already a widening to a range of — This is even greater than the maximum range recommended with widening of — Plus, OCPB's proposed widened range already ignores the reasons given by the guidance for justifying when widening is appropriate.

Even incorporating the latest and worst data, 161/185 experiments (87%) passed at the L1 level and the remaining 13% would pass at the L2 level without widening the range any further. This is an acceptable and even desirable rate of progressing to L2 testing.

When side batches, (IVIVC data), are considered as a basis for widening the specifications, the range of dissolution rates proposed are not acceptable as the IVIVC batches were not bioequivalent since time metrics shift with dissolution rate and are of a magnitude likely to be clinically significant.

Does the data point out any other concerns?

The data presented by the sponsor indicates that the manufacturing process is not controlled and that the sources of variation should be investigated and appropriate in-process controls be implemented.

In addition, the proposed specifications could be achieved by adjusting the content of the capsules without violating the proposed limits for content uniformity. Consequently, content uniformity may need to be tightened and the data available suggests that a range of ——— is achievable. However, discussion with the Chemistry Review Team indicates that alternative measures for controlling this possibility may be more appropriate and this issue is thus referred to chemistry for recommendations (see Section II below).

II. COMMENTS TO CHEMISTRY REVIEWER:

Due to the nature of this formulation (a combination of immediate release and enteric coated/controlled release beads) it's possible for the bead ratio to be manipulated so that batches will pass dissolution specifications even when they might not pass initially. The proposed content uniformity is —— whereas data presented suggests that content uniformity could be tightened to a range of —— However, this is total content and may not adequately control for the content uniformity of each bead type. Discussions with the chemistry review team indicate that control measures other than content uniformity might be more appropriate in the present situation.

The data presented also suggest that the manufacturing process is not well controlled and that the sources of variation should be investigated and appropriate in-process controls be implemented.

These issues are referred to the chemistry reviewer for appropriate recommendations.

III. COMMENTS TO SPONSOR

1) The FDA acknowledges the sponsor's commitment to develop a single point dissolution specification for the immediate release bead component. To accomplish this, dissolution profiles for the acid dissolution phase will be determined. Acceptability of any proposed specification will be a matter of review and assumes that the next 10 lots of drug are acceptable to FDA.

2) FDA acknowledges that method specifications should state:

'Acceptance criteria for —— hours as per USP XXIV – NF 19 <724> Drug Release Acceptance Table 1'

3) The Office of Clinical Pharmacology and Biopharmaceutics has carefully considered each reason given for widening the dissolution specification acceptance criteria at — hours.

In order to allow an increase in percent dissolved from the —— hour time points, the upper limit on the — time point shall be set to —, i.e. mean of clinical trial batches plus 10% of the EC-DR beads.

Data presented does not justify raising the acceptance criteria for the — time point above ——. Based upon FDA guidances, acceptance criteria should be based upon clinical trial batches. Based upon these batches alone a range of —— is appropriate. However, the range was raised previously without being based on the clinical trial batches, and in spite of *in vivo* data showing bioinequivalence with various dissolution rates due to differences in time metrics. Even if the most recent process validation and demonstration batch data are considered; 127 of 140 experiments (91%) would pass at the L1 testing stage using a criteria of —%. Additionally, the remaining 13 dissolution experiments (9%) would likely pass upon stage 2 testing. Finally, raising the acceptance level at —— would essentially eliminate any dissolution profile mid-range criteria for a delayed release product, which is unacceptable.

Dissolution ranges of —— % at —, and —— at — were accepted by the sponsor in a teleconference on April 18, 2002.

4) The sponsor is requested to adopt the following method and specifications for all strengths of Ritalin LA capsules:

Table 2 Dissolution Method and Specifications

Parameter	Description
Apparatus type:	USP Apparatus I (basket)
Media:	Medium I: —— Medium II: 3
Volume (ml):	—— for both medium I and medium II
Temperature	——
Speed of rotation (rpm):	100 rpm.
Sample times (hours):	——
Specifications (% of Label Claim)	——

IV. DISSOLUTION ISSUES

A. FDA Proposed Regulatory Method (excluding specifications and acceptance criteria)

Sponsor agrees.

B. Acceptance Criteria for FDA Proposed Regulatory Specifications

FDA agrees with sponsor's clarification (see Table 3).

Table 3 Proposed Acceptance Criteria for Regulatory Dissolution Specifications

FDA Proposal	Sponsor's Counterproposal
Acceptance criteria for — hours as per USP XXIV – NF 19 <724> Drug Release Acceptance Table 1	Acceptance criteria for — hours as per USP XXIV – NF 19 <724> Drug Release Acceptance Table 1

n.b. specifications will be discussed in following sections

C. Dissolution Specification for IR Bead Component of Ritalin® LA

The sponsor agrees to develop a dissolution specification for the IR bead component. The sponsor commits to develop this specification based upon the next 10 lots of drug product produced.

FDA Comment:

The sponsor's commitment assumes that the next 10 lots of drug are acceptable to FDA. As the acceptance criteria are currently under discussion, it is recommended that a single point dissolution specification with an acceptance criteria of — of label claim[1] be targeted. In addition, the sampling time that this criteria is achieved should be —, as previous information suggests that at — the IR beads should be totally dissolved. Thus a specification of less than — dissolution should be achieved before —

D. 4 Hour Specification

The sponsor proposes widening the proposed acceptance criteria for the —— specification as per Table 4:

Table 4 Proposed Specification Acceptance Criteria

FDA Proposal	Sponsor's Counter-Proposal
——	

The sponsor's rationale for widening the acceptance criteria includes:

a) A range of ± 5% is tighter than the ±10% range from clinical trial batches recommended in the 'ER guidance'[2].

b) Does not allow for additional drug release from DR component at — as compared to — as proposed acceptance criteria are identical.

c) USP <905> Content Uniformity Range of —— for the IR component alone would translate into a range of — of total labeled content.

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[1] ——

[2] Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations (Issued 9/1997, Posted 9/26/1997)

d) A range of — —— would frequently necessitate 'S2' level testing and a compliance burden.

e) Stability data indicates a slight increase in dissolution rate with age. The — upper limit would thus be too restrictive.

f) A — upper limit would be too restrictive based upon the capability of the manufacturing process.

FDA Comments:

OCPB recommends a range of — at ——

a) A range of ±10% assumes that release is based upon the total content of the dosage unit. For the present formulation only the 50% of the total labeled content that is attributable to the IR component should be considered. Consequently, ± 10% of 50% is ± 5% of the total labeled content.

b) Allowance for additional drug release is counter to the design intent, where release from the delayed release component should not begin until 4 hours after administration. However, for practical reasons an increase from earlier time point needs to be incorporated in the acceptance criteria.

For enteric coated products, the % dissolved at the time point (at the end of incubation in —— medium) must be ——

The mean percent dissolved at — —— hours for 24 experiments for pivotal clinical trial batches of biobatch are shown in Table 5.

Table 5 Mean Percent Dissolved at 2 and 4 Hours for Pivotal Clinical Trial Batches[a]

	Percent Dissolved (% LC)
Time	——
Overall Mean	——
Range	——

a n = 24 experiments

In Table 6 two different ways of obtaining upper limits for dissolution at — hours are calculated. In the first the 95% UL of the CI is shown. Since, at both —— hours this is less than the 10% allowed for EC formulations, the mean percent dissolved plus 10% of the EC-DR beads is also calculated. A proposed acceptance criteria is then listed, i.e. dissolved at —— hours and a — hours the mean percent dissolved plus 10% of the EC-DR beads rounded to the nearest whole percent. Using these limits, z-scores were calculated. Based upon the z-scores the failure rate is expected to be <<1:10,000 experiments for each of these limits.

Table 6 Alternative Upper Dissolution Limits at —— hours

	—— hours	— hours
UL 95% CI	——	
Mean + 10% of EC-DR Beads		——
Proposed Upper Limit for Acceptance Criteria		
Z-score for Proposed Upper Limit[a]	4.71	7.57

a z score of 3.80 is a failure rate of 1/10,000

c) The 85% - 115% Content Uniformity Range per USP <905> applies only if stricter ranges for the product have not been set. In addition, it also requires a CV of ≤6 %. For the IR component alone this would translate into a 95% confidence interval of — In additiondata provided indicates that the content uniformity achievable is —

d) Using a range of — hours, only 2 of 140 dissolution experiments utilizing presumed full-scale batches of the final market-image required testing at the L2 level to meet the proposed FDA criteria. 138 of 140 experiments passed at the L1 testing stage.

Specifically:
- 4 of 4 clinical trial batches passed at L1
- 7 of 9 stability batches passed at L1 at the initial time point (2 of 9 passed at L2)
- 97 of 97 stability experiments for the above 9 batches passed at L1 at times ranging from 3 to 18 months
- 9 of 9 EU 'process validation' batches passed at L1 at the initial time point
- 18 of 18 stability experiments for the 'process validation' batches passed at L1 at 12 months
- 3 of 3 EU 'demonstration' batches passed at L1

e) As mentioned above all experiments conducted under stability experiments after long term storage passed the FDA proposed criteria at the L1 level

f) A —% upper limit at — hours is achievable based upon data provided. A — limit would give a z-score of 3.29 and a failure rate of 1:1000

E. 6 Hour Specification

The sponsor proposes widening the proposed acceptance criteria for the — specification as per Table 7:

Table 7 Proposed 6-hour Specification Acceptance Criteria

FDA Proposal	Sponsor's Counter-Proposal
—	

The sponsor's rationale for widening the acceptance criteria includes:

a) A range of ± 7.5% is tighter than the ±10% range from clinical trial batches recommended in the 'ER guidance'. Consequently, the range should be —

b) Side batches with mean dissolution of approximately — at — are bioequivalent.

c) Additional data from additional 'process validation' and 'demonstration batches for the EU' is provided.

Specifically dissolution rate means and ranges are provided for:

- 3 'process validation' batches at each strength, (20 mg, 30 mg, and 40 mg), at initial release and after 12 months of storage at 25 °C / 60% RH in 30 and 100 count — bottles.
- 1 'demonstration' batch at each strength, (20 mg, 30 mg, and 40 mg), at initial release

d) Stability data indicates a slight increase in dissolution rate with age. The upper limit of — would thus be too restrictive.

tightened rather than loosened. This is because with faster elimination in children a tighter specification would be needed to maintain the Tmax2 for future commercial batches close to the Tmax2 from the clinical trial batches and to Ritalin IR.

c) Regarding the additional data from the EU stability and 'demonstration' batches. These are not clinical or bioavailability batches and thus should not impact the acceptance criteria. Secondly, insufficient information is presented to evaluate these batches, i.e. manufacturing site, batch size, COA, dissolution method or full dissolution data. Even if this data were considered all batches and stability experiments would likely meet the FDA proposed specifications at the L2 level.

d) The increase in dissolution upon long term storage in the stability experiments was considered in the original FDA evaluation and proposal. The data suggests that there may be some failure of some of the packaging, otherwise dissolution rate is relatively stable over time. Even with this 'failure' or dissolution rate creep with storage 91 of 97 (94%) of the original stability experiments can meet the proposed [redacted] upper limit at [redacted] hours at the L1 level, and the remaining 6 of 97 (6%) meet the acceptance criteria at the L2 level. For the additional 'process validation' batches 15 of 18 stability batches (83%) pass at the L1 level and the remaining 3 (17%) would pass at the L2 level. Since we usually like to see at least 1/9 (11%) of stability batches at initial testing pass at the L2 level when setting specifications, the FDA proposal is not excessively restrictive.

e) The data provided does raise concerns regarding the quality of the manufacturing process. However, this is not a reason to widen specifications. Inspection of the dissolution profiles shows that there is a steady increase in rate of dissolution for batches produced over time (see Figure 2 and Figure 3). This coupled with the tightness of the individual data points within each batch suggests a lack of control in the manufacturing process, ingredients, or in storage prior to testing. Consequently, rather than widen the specifications the source of this lack of control should be investigated and appropriate in-process controls should be implemented.

Additional Concerns:

Increasing the [redacted] hours time point to [redacted] % does not allow any differentiation from the [redacted] hour time point and in essence is allowing almost complete dissolution by [redacted]. Since no enteric beads are dissolved at 4 hours, this would in essence result in a single-point dissolution criteria for a delayed release substance, without a mid-point dissolution specification.

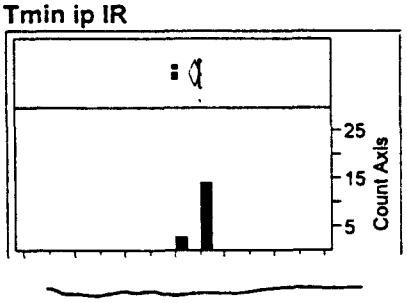
The tightness of the individual data points within each batch and the tightness of the content uniformity indicate that the proposed FDA [redacted] hour dissolution specification could readily be achieved by altering the drug content of the capsules. This could be done by decreasing the amount of enteric coated beads by up to ~20% (10% of total drug content) while still staying within the sponsor's proposed total content uniformity specification of [redacted], and without altering the amount of immediate release beads. However, this would mean the second dose of drug would be low. To avoid this, the content uniformity specifications should be tightened. The COAs from the 9 stability batches indicate that a content uniformity specification of [redacted] should be achievable (See Table 8).

Table 8 Content Uniformity of Stability and Pivotal Clinical Trial Batches

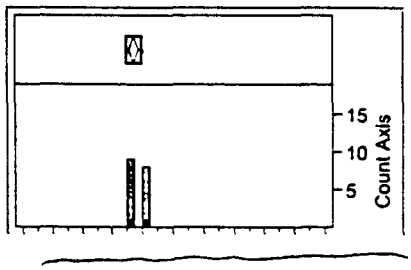
Stability Batches			Pivotal Clinical Trial Batches		
Batch	**Strength**	**Content (%)**	**Batch**	**Strength**	**Content (%)**
RD09905	20 MG		RD109908	20 MG	
RD09906	20 MG		RD109909	30 MG	
RD09907	20 MG		RD109906	40 MG	
RD09908	30 MG				
RD109901	30 MG				
RD109902	30 MG				
RD109903	40 MG				
RD109904	40 MG				
RD109905	40 MG				
Mean ± SD (CV) Min - Max		99.4 ± 1.2 (1.2)			97.2 ± 1.0 (1.0)
% EC-DR Beads (Estimated)		49.4			47.2
% Difference Compared to Pivotal Clinical Trial Batch		4.6			

Figure 1 Comparison of Time Metric Distributions for Ritalin IR, Ritalin LA in Children, and Side Batches in Adults

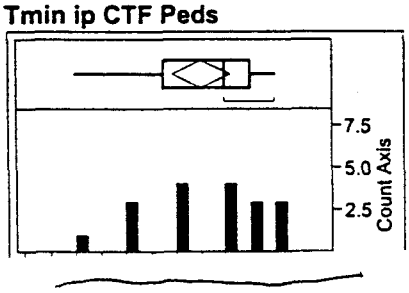
Tmin ip IR



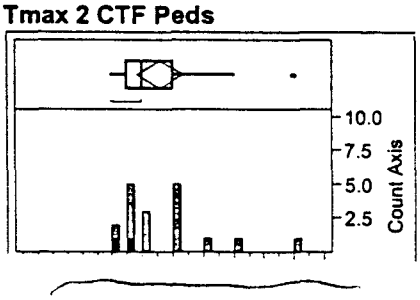
Tmax 2 IR



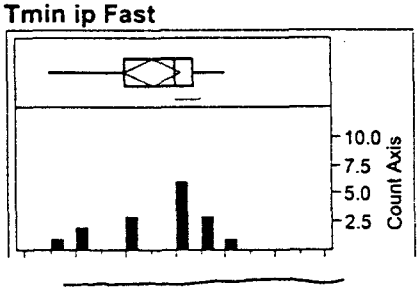
Tmin ip CTF Peds



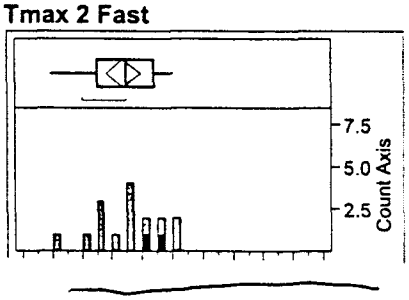
Tmax 2 CTF Peds



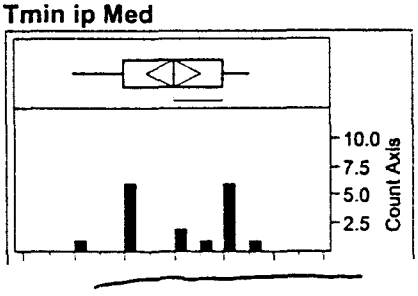
Tmin ip Fast



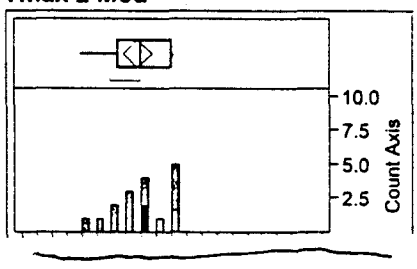
Tmax 2 Fast



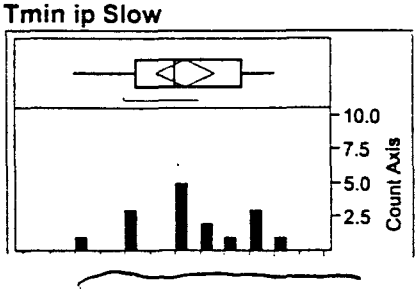
Tmin ip Med



Tmax 2 Med



Tmin ip Slow



Tmax 2 Slow

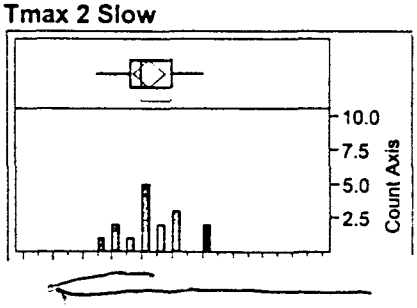
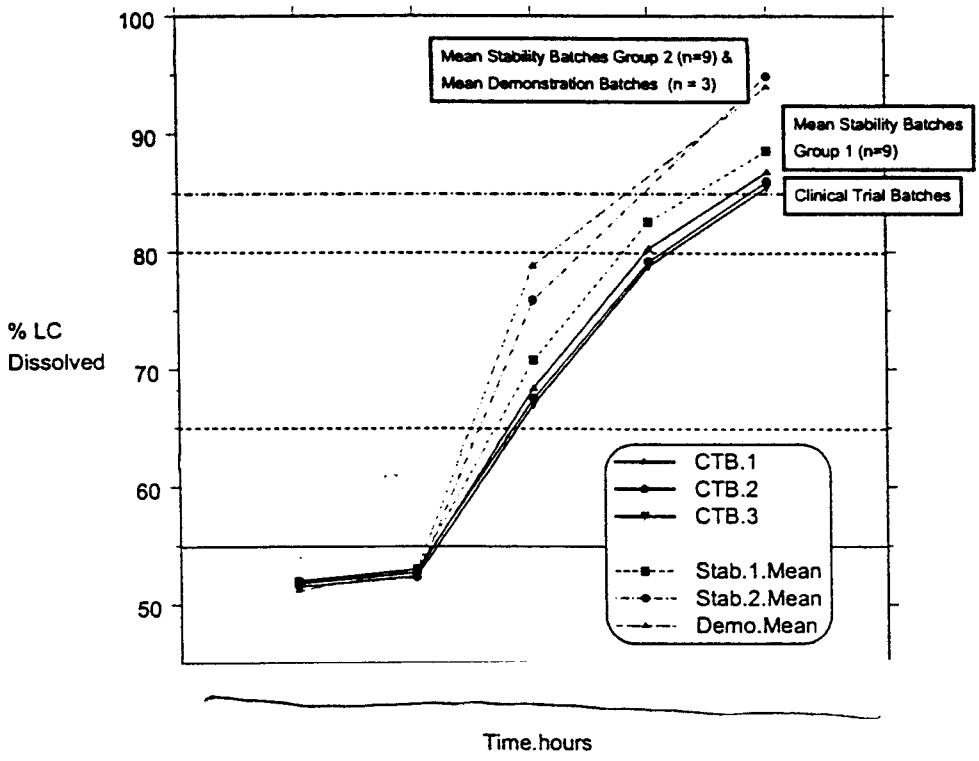


Figure 2 Dissolution Profiles - Trend by Batch Grouping Over Time and Side Batches (IVIVC)

[redacted]

Figure 3 Trend of Group Mean Dissolution Profiles Over Time in Comparison to Clinical Trial Batches



V. SIGNATURES

Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D. — Date

Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

Ray Baweja, Ph.D. — Date

Team Leader
Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

CC: NDA 21-284 (orig., 1 copy)
HFD-120 (Mosholder, Laughren, Homonnay, Gill Sangha)
HFD-860 (Kavanagh, Baweja, Mehta)
Central Document Room (Barbara Murphy)

VI. LABELING COMMENTS

Each of the following comments was discussed with the medical review team in an internal conference on April 11, 2002. The final version of the labeling will be written by the medical review team and will incorporate some but not all of these comments.

Proposed deletions are marked by addition a single line ~~strikeout~~ to text to be deleted.

Proposed additions are marked by addition of a single underline to proposed additions.

OCPB additions and deletions are marked in red.

32 pages redacted from this section of the approval package consisted of draft labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ron Kavanagh
5/6/02 01:45:48 PM
BIOPHARMACEUTICS

Raman Baweja
5/6/02 02:24:17 PM
BIOPHARMACEUTICS

New Drug Application
Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-284
Types of Submissions:	NDA S N-BB
Generic Name:	Methylphenidate Hydrochloride ——— Release Capsules
Formulation:	50:50 immediate release and enteric-coated, delayed release beads
Strengths:	20 mg, 30 mg, and 40 mg
Route:	PO
Brand Names	Ritalin® LA
Sponsor:	Novartis Pharmaceuticals Corporation East Hanover, NJ
Submission Dates:	November 29, 2000 June 22, 2001
Related IND	———
Reviewer:	Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

I. REVIEW ISSUES / QUESTIONS

[n.b. questions with double asterixes (**) are the major issues identified by OCPB]

What are the proposed products?

Ritalin® LA capsules contain a 50:50 proportion of immediate release (IR) and enteric-coated, delayed-release beads (EC-DR) encased in a hard gelatin capsule. However, the product does not act as a typical enteric-coated product. Instead it behaves as a delayed release product.

There are three proposed strengths for marketing. A 20 mg capsule, a 30 mg capsule and a 40 mg capsule. The 20 mg capsule contains 10 mg of immediate release beads and 10 mg of enteric coated delayed release beads, the 30 mg capsule contains 15 mg of each, and the 40 mg capsule contains 20 mg of each.

** **What is the proposed indication?**

The proposed indication is *'for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD)'*.

In contrast to Ritalin® IR and SR tablets, Ritalin® LA is not being proposed for narcolepsy.

Based upon the proposed labeling for dosage and administration and the clinical studies. ***Consideration should be given whether to*** [redacted]

** **How does the proposed *Dosage and Administration* compare to Ritalin IR labeling?**

The dosage and administration labeling for Ritalin® IR tablets clearly indicates that Ritalin is for 'Children (6 years and over)'. In contrast, the proposed dosage and administration labeling for *Ritalin® LA* does not.

In addition, although the Ritalin® LA labeling implies that it is for patients currently on a stable dose of Ritalin IR or Ritalin SR there is no unambiguous statement to that effect.

It's noteworthy that the recommended as well as the practicality of dosage adjustments are different between the 2 formulations, as Ritalin IR is available in 5 mg tablets and thus allows dosage increments of 5 mg, but Ritalin LA is only proposed in 10 mg increments.

Is the clinical trial formulation the same as the to-be-marketed formulation?

Yes.

Is the bioanalysis acceptable?

The assay was acceptable for the 4 studies in adults including the IVIVC study and the 2 food effect studies. However, the assay for the samples from the PK/PD study in children had a consistent average bias of 10%. Consequently, the quantitation of pharmacokinetic / pharmacodynamic parameters in children are likely to be slightly off. However, the overall conclusions should not change. As the source and direction of the bias, or whether it is spurious, cannot be determined, the pharmacokinetic metrics in children cannot be adjusted by a correction factor.

What are the bioavailability and pharmacokinetic characteristics of Ritalin® LA?

Ritalin® LA demonstrates a ***bi-modal release*** pattern. There is an ***initial lag phase of ~0.5 hours*** followed by the ***first peak at about 2 hours***. This lag phase and first peak is attributable to the immediate release beads.

The second peak from the enteric coated delayed release beads occurs on average at 6.5 hours in children and at around 5.5 hours in adults. The variability for the second peak is much greater with a range of [redacted] hours observed in children. The second peak is much lower than the first peak, and inter-peak minimum remains fairly high. This patterns suggests that typically ***absorption from the enteric coated delayed release beads begins well before a second dose of Ritalin IR tablets would be dosed at 4 hours and continues for a longer duration.***

** **How does the bioavailability of one Ritalin® LA capsule compare to two Ritalin® IR tablets administered 4 hours apart?**

The ***initial lag phase and the first peak*** from the Ritalin® LA capsules ***are comparable*** in both timing and concentration to what is seen with a similar dose from the first Ritalin IR tablet.

The ***inter-peak minimum is higher*** with the LA capsules as drug was always measurable between peaks with the LA capsules, whereas many subjects had undetectable concentrations of methylphenidate between the two doses of the Ritalin IR tablets.

In children, both daily doses of Ritalin IR tablets exhibit similar pharmacokinetics. Both doses exhibit peak concentrations 2 hours after administration. When the second mid-day dose is administered 4 hours after the morning dose this peak is approximately 6 hours after administration of the morning dose.

Although the inter-peak minimum for the Ritalin IR tablets was frequently undetectable, sufficient numbers of subjects had high enough concentrations such that superpositioning from the second dose resulted in mean second peak concentrations with Ritalin IR tablets approximately 50% higher than the first peak. In comparison the second peak from the Ritalin LA capsules was generally slightly lower than the first peak and didn't occur until slightly later than with the second dose from the Ritalin IR tablets. Consequently, ***the second peak with Ritalin LA capsules is lower than with Ritalin IR tablets.***

Due to the differences in the inter-peak minimums and second peak concentrations between the two dosage forms, ***the peak trough fluctuation is lower with Ritalin LA capsules.***

The total amount absorbed from Ritalin LA capsules is similar to the amount from Ritalin IR tablets.

** **Is there any 'dose dumping'?**

No. None of the pharmacokinetic studies showed any evidence of dose dumping either in the presence or absence of food.

Is there dose linearity?

There is dose linearity up to 40 mg, the highest strength proposed for marketing. However, based upon immediate release methylphenidate there is a possibility of nonlinearity at 60 mg. Since equal doses of Ritalin LA will be substituted for Ritalin IR, doses of Ritalin LA greater than 40 mg may be administered.

** **Is there an age effect?**

There is a slight age effect, with volume of distribution normalized to body weight being linearly related to age. This results in a slightly faster half-life in children compared to adults (2.64 ± 1.03 hours vs. ~3.4 hours) as clearance normalized to body weight is independent of age.

Consequently, a particular mg/kg dose in children should produce similar exposures to the same mg/kg dose in adults.

However, it should be noted that ***only 3 of the children studied were less than 10 years old.***

Is there a gender effect?

There appears to be a gender effect in adults, but ***it's clinically insignificant.*** (The sponsor claims there is no gender effect.) The gender effect appears to be a higher weight normalized volume of distribution and clearance in women. However, the net effect is very similar plasma concentration profiles in men and women.

Are there pharmacokinetic differences by ethnicity?

This cannot be conclusively determined from the data presented studies. However, it ***seems unlikely*** based up the pharmacokinetic properties of the drug.

** **Is there a food effect?**

The sponsor has concluded that there is ——————————————————————————— However, the data shows a ***there is a clear food effect with a high fat breakfast resulting in a delay in absorption (Tlag) and time to peak concentrations (Tmax1 and Tmax2),*** with no evidence of dose dumping.

The delay in both the lag time and the time to first peak is likely due to a delay in gastric emptying, and is thus likely related to the active ingredient and not the formulation. The delay and lower concentrations observed for the second peak, with Tmax2 occurring as late as — hours, suggests that there may also be some effect on the delay release properties due to changes in the intestinal milieu. Consequently, there might also be a food effect with a mid-day meal. However this was not examined.

No food effect was observed when the capsule beads were sprinkled on applesauce. However, this does not mean there will be no food effect with other soft foods, especially those with a high fat content.

The data with Ritalin LA also suggest the possibility of a food effect with methylphenidate immediate release tablets. Upon examination it was found that the studies in the literature reporting no food effect or a slightly more rapid absorption have seriously flawed designs. The studies used low-calorie, low-fat meals with very few subjects and had inadequate blood sampling. The inadequate blood sampling probably gave rise to the erroneous conclusion of a possible more rapid absorption in the presence of food.

** **Are there any special instructions for Ritalin® LA?**

According to the sponsor Ritalin® LA capsules may be opened and the beads sprinkled over soft food (i.e. applesauce). ***If sprinkled over applesauce, the applesauce should not be warm*** and the mixture should be consumed immediately in its entirety.

In addition, Ritalin LA capsules and/or their contents ——————————————————————

Both of these instructions are to minimize the possibility that the enteric coating may be destroyed.

** **Is there a pharmacokinetic / pharmacodynamic relationship?**

Yes.

The sponsor only performed simplistic analyses for a PK-PD relationship. These included analysis of variance on PD metrics in the presence of 4 different dose/formulation combinations vs. placebo, and regression analysis of 192 different combinations of pharmacodynamic measures vs. various measures of exposure, and plasma concentrations obtained with several different doses of methylphenidate. Even so both of these analyses suggest a PK-PD relationship.

Although formal fitting of a PK-PD model to the data was not performed, plots of mean effect vs. time by dose and concentration vs. time profiles suggest that:

a) There is a dose response relationship
b) There's a possible maximum effect above approximately 7 ng/ml
c) There appears to be a lag time for effect
d) There may be an acute tolerance resulting in a different PK-PD relationship in the morning vs. afternoon.

Possible explanations for the acute tolerance include changes in the underlying symptoms during the course of a day, and depletion of neurotransmitters, both of which will make fitting a formal PK-PD model to the data difficult.

The PK/PD data suggests that an initial dose in children of 0.3 mg/kg may be acceptable, as this would provide those children with the highest exposures for a particular mg/kg dose with concentrations near the Emax. However, upward titration to approximately 0.45 mg/kg or higher would likely be needed for the vast majority of patients to achieve maximally efficacious exposures. Additional work in the form of simulations would be needed to further clarify any dosage recommendations.

** **Are the proposed drug product dissolution method and specifications acceptable?**

The sponsor's proposed two-stage ***dissolution method*** for the enteric-coated drug product ***is acceptable***, however the ***drug release specifications need to be modified***.

Ritalin LA is a combination of an immediate release product and an enteric coated delayed release product. Consequently, a separate set of specifications is needed for each component.

The sponsor proposes sampling times of ——— ;. The first time point is at the end of the incubation (i.e – hours). Fifty-percent dissolution at this time point only indicates that the immediate release beads have totally dissolved and that the enteric beads are still intact. ***A separate earlier specification is needed for the immediate release beads***. However, currently there is no data to set a specification at an earlier time point.

After – hours the beads are transferred to ——— . As the enteric coated (EC) beads likely pass fairly quickly into the small intestine (< 1 hr) and since absorption from these beads should not begin until a couple of hours after dosing, the ***EC beads need to be stable in intestinal fluids for several hours.*** The proposed sampling time at – hours does not allow assessment of the initial stability in a more alkaline environment, whereas ***a – hour time point*** should also indicate that the EC beads have not begun to dissolve.

Finally, ***the acceptance criteria are too wide***. The sponsor uses the % of the total labeled content. Since each component accounts for 50% of the dose, using ± 10% of the total labeled amount of active drug, as is normal, is actually ± 20% relative to each component.

The sponsor based dissolution specifications upon dissolution of the to-be-marketed formulation as well as fast and slow release formulations used in the IVIVC study. OCPB proposals are based upon data from bio-batches (i.e. ≥10% of commercial batch size) used in clinical pharmacokinetic and efficacy studies and confirmed by stability studies on 3 additional bio-batches stored at 25 °C / 60% RH over 18 months.

Dissolution specifications proposed by the sponsor and OCPB follow:

	Proposed Acceptance Criteria	
Time	Sponsor's	Reviewer's
— hours	[redacted]	
— hours		
— hours		
— hours		

** **Is there an *in vitro – in vivo* correlation?**

An IVIVC was not demonstrated, although it may be possible with additional data and reanalysis.

The more significant deficiencies include:

- 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.
- Point to point prediction errors were excessive and ranged from -4.3% to 93.9% for the to-be-marketed formulation.
- Estimates of the fraction absorbed *in vivo* are considerably greater than the fraction of the dose dissolved.
- The dissolution model used in the IVIVC method provides dissolution values in excess of 140% of the labeled content
- The prediction method requires *in vivo* concentration data from the formulation being predicted and therefore does not have any utility.

Is product performance consistent across time?

No indication of changes in product performance was observed in the pharmacokinetic studies. Dosage units in these studies ranged in age from 2 - 10 months and in the phase III efficacy study (protocol 07) up to 16 months. In addition, stability studies up to 18 months did not indicate a stability problem.

** **Are the probable major marketing claims acceptable?**

Based upon the Sponsor's proposed labeling, the probable major marketing claims and their acceptability follow:

Probable Claims	Reviewer's Conclusions
[redacted]	➢ Unacceptable. The sponsor may state that there's a bimodal release
[redacted]	➢ Misleading. Total AUC is comparable but concentration profiles are dissimilar and are likely more important
• Ritalin® LA, is orally administered once daily in the morning.	➢ Acceptable - but once daily dosing may not be sufficient.
• [redacted]	➢ Unacceptable – may not be true (see above).
• Ritalin® LA, is [redacted] and has smaller peak trough fluctuations.	➢ [redacted] is unacceptable, although smaller peak-trough fluctuations are acceptable.
• Ritalin® LA, may be administered with or without food.	➢ There is a food effect, but a specific recommendation is difficult to make. Descriptive labeling may be appropriate.
• [redacted]	➢ Unacceptable. Only applesauce has been studied. High-fat soft foods have not.

** **What are the overall clinical implications with this formulation?**

Switching from twice daily to once daily administration is likely to have different implications for compliance in different patients.

Compliance is dependent upon the personal characteristics of the individual(s) administering the medication and other factors such as external distractions, rather than simply being dependent upon the number of times per day a medication is administered. By going to qd dosing, we eliminate the mid-day (school) dose and the issues associated with it, such as an unreliable drug administrator, substitute teachers, social stigmas, distractions from other students, lack of time or procedures, security of the drug etc.. On the negative side, by going to a single daily dose, if the morning dose is missed then the entire dose for the day may be missed. Unless based upon the child's behavior the teacher becomes suspicious and a make-up dose is given. Whereas with bid dosing, no matter which dose is missed the student is still likely to receive at least some medication.

The net effect of the different concentration vs. time profile with this formulation is hard to predict in any individual patient. However, higher inter-peak troughs may result in better symptomatic control in the late morning, whereas lower second peaks (Cmax2) may result in deterioration in symptom control in the afternoon compared to Ritalin IR. Consequently, some patients may get the best response with a Ritalin LA dose in the morning supplemented by a small dose of Ritalin IR at mid-day.

Making a specific recommendation regarding dosing with respect to meals is probably not appropriate. The types of meals eaten and the effect of food can both be variable. These along with when the onset of effect is desired suggests that the food effect simply be explained as best as possible with titration with respect to meals in individual patient as appropriate, but only if meals are consistent and their effects seem consistent.

II. RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation I (OCPB/DPE-1) has reviewed NDA #21-284 submitted November 29, 2000.

OCPB finds this application acceptable provided that currently outstanding issues are adequately resolved. Comments should be communicated to the sponsor as appropriate (see Section III Comments to the Sponsor on page 9). Labeling comments should also be communicated to the sponsor as appropriate (see Section V Labeling Comments on page 12).

III. COMMENTS TO THE SPONSOR

A. Dissolution

- 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: [redacted] Medium II: [redacted]	
Volume (ml):	for both medium I and medium II	
Temperature		
Speed of rotation (rpm):	100 rpm.	
Sample times (hours):		
Specifications (% of Label Claim)	[redacted]	Acceptance criteria for [redacted] hours as per USP XXIV – NF 19 <724> Drug Release Acceptance Table 1

- The proposals are based upon data from bio-batches (i.e. ≥10% of commercial batch size) used in 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.
- The sponsor is requested to 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 [redacted] of label claim[1] may be an appropriate target. This earlier sampling time may be able to replace the [redacted] hour time point.

B. In Vitro – In Vivo Correlation

- The proposed *in vitro* dissolution to *in vivo* bioavailability correlation is unacceptable. Reasons include the following points:
  - 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.
  - Point to point prediction errors were excessive and ranged from -4.3% to 93.9% for the to-be-marketed formulation.
  - Estimates of the fraction absorbed *in vivo* are considerably greater than the fraction of the dose dissolved.

[redacted]

- The dissolution model used in the IVIVC method provides dissolution values in excess of 140% of the labeled content
- The prediction method requires *in vivo* concentration data from the formulation being predicted and therefore does not have any utility.

- IVIVC data is therefore not being relied upon to set dissolution specifications.
- If the sponsor desires to pursue an *in vitro – in vivo* correlation, the sponsor may wish to contact OCPB for suggestions.

C. Labeling Comments

- The sponsor is requested to adopt OCPB proposed labeling as outlined.

IV. SIGNATURES

/S/ 9/7/01

Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D. Date

Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

/S/ 9/7/01

Ray Baweja, Ph.D. Date

Team Leader
Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

OCPB Briefing Meeting:

Date:	Thursday	September 6, 2001
Time:	10:00 – 11:30 AM	
Location:	WOC2 - Conference Room C – 3rd Floor	
Level:	Optional - Interdivisional	
Attendees:	Kavanagh, Baweja, Mehta, Sahajwalla, Malinowski, Selen, HuangS, Mosholder, Laughren, Gill Sangha, Seevers, Sunzel, Uppoor	

CC: NDA 21-284 (orig., 1 copy)
HFD-120 (Mosholder, Laughren, Homonnay, Gill Sangha, Seevers, Rosloff)
HFD-860 (Kavanagh, Baweja, Mehta)
Central Document Room (Barbara Murphy)

V. LABELING COMMENTS

Proposed deletions are marked by addition a single line ~~strikeout~~ to text to be deleted.

Proposed additions are marked by addition of a single underline to proposed additions.

OCPB additions and deletions are marked in red.

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