CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-284

CHEMISTRY REVIEW(S)

CDER CHEMISTRY REVIEW CDER

NDA 21-284

Ritalin® LA Capsules
(methylphenidate HCl extended release capsules)

Novartis Pharmaceuticals Corporation

Gurpreet Gill-Sangha, Ph.D.

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-284

2. REVIEW #: 2

3. REVIEW DATE: May 9, 2002

4. REVIEWER: Gurpreet Gill-Sangha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	November 28, 2000
N (BC) Amendment	February 28, 2001

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
N (BZ) Amendment	October 18, 2001
N (AC) Amendment	December 6, 2001
N (BC) Amendment	February 28, 2002
N(BC) Amendment	April 16, 2002
Electronic Label	May 3, 2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Novartis Pharmaceuticals Corporation
Address:	One Health Plaza, East Hanover, NJ 07936
Representative:	Mara Stiles, Associate Director, Drug Regulatory Affairs
Telephone:	(973) 781-3771

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ritalin LA
b) Non-Proprietary Name (USAN): Methylphenidate HCl

c) Code Name/# (ONDC only): RITI24D, Ritalin

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) 1

10. PHARMACOL. CATEGORY: ADHD

11. DOSAGE FORM: Extended Release Capsules

12. STRENGTH/POTENCY: 20, 30 and 40 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____ SPOTS product – Form Completed

_X_ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

CA Name:
USAN Name: Methylphenidate Hydrochloride
Chemical Formula:
Molecular Weight: 269.77
CAS registry #: 298-59-9
Structure:

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: Pertinent only to the response to Approvable letter. For the DMF's relevant for the original NDA submission refer to CMC review #1.

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENT
				1	Adequate	December 15, 1999	NA
				1	Adequate	July 15, 1999	NA
				1	Adequate	October 14, 1993	NA

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: NA

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	March 11, 2002	FDA Compliance
Pharm/Tox	Review Pending		
Biopharm	Acceptable	May 6, 2002	Ron Kavanagh, Ph.D.
LNC	USAN available	NA	NA
Methods Validation	Pending	Pending	Gurpreet Gill-Sangha,

Chemistry Review Data Sheet

			Ph.D.
OPDRA	"Ritalin LA" acceptable	9/25/01	Jennifer Fan, Pharm.D.
EA	Categorical Exclusion granted in CR #1 based on information provided by Novartis	8/17/01	Gurpreet Gill-Sangha, Ph.D.
Microbiology	NA		

The Chemistry Review for NDA 21-284

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The major CMC deficiencies in the original submission for this NDA were inadequate in-process controls and analytical methods and OAI alert from FDA Compliance for the contract drug product manufacturer, packager and tester, Elan Holding Inc. The response submission from Novartis dated December 6, 2001 provided detailed in-process controls (with batch data) and analytical methods for the manufacture of IR and DR beads. All the chemistry, manufacturing and controls deficiencies including the inadequate in-process and analytical methods identified in review #1 have been adequately addressed as evaluated in this review. In addition, Elan Holdings site has been found acceptable by FDA Compliance for this NDA on March 11, 2002. The FDA Compliance has issued an overall acceptable recommendation for all the manufacturing, packaging and testing sites for N21-284 on March 11, 2002. Therefore, the NDA is recommended for approval from CMC standpoint.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Ritalin® LA (methylphenidate HCl extended release) capsules for the treatment of ADHD is to be marketed in 20, 30 and 40 mg strengths. Ritalin® LA is an extended release formulation of methylphenidate HCl with a bi-modal release profile due to equivalent amounts of IR and DR beads. The capsule colors are: 20 mg – white imprinted with NVR R20, 30 mg – yellow imprinted with NVR R30, and 40 mg – light brown imprinted with NVR R40. The three strengths are packaged for 30 and 100 count in 90 and 175 cc white square — bottles respectively with plastic 38 mm child resistant closure with — induction seal. Ritalin® LA capsules are composed of 1:1 ratio of immediate release beads and enteric coated delayed release beads. The inactive ingredients including — — sugar spheres, PEG (polyethylene glycol —, talc, and triethyl citrate are USP/NF. The only non-compendial excipient used is the . The — are described in DMF — and are adequate for use per review of DMF

The drug substance is methylphenidate HCl commonly known as Ritalin HCl. Methylphenidate HCl is a white, odorless, fine crystalline powder freely soluble in water and methanol with a molecular weight of 269.77. Methylphenidate HCl is manufactured by Novartis Pharmaceuticals Corp., NJ. N10-187 by Novartis (approved on December 5, 1955) is referenced for the drug substance. The drug substance release specifications provide adequate control of identity, quality and purity of methylphenidate HCl used to manufacture Ritalin® LA capsules.

The bead formulation of all dose strengths used in the pre-clinical and clinical studies is same as the commercial capsules. The batch data for all the clinical batches are within proposed specifications and are also evaluated in the stability protocol.

B. Description of How the Drug Product is Intended to be Used

The recommended dose for Ritalin LA for the initial treatment is a starting dose of 20 mg once daily. Dosage may be adjusted in weekly 10 mg increments to a maximum of 60 mg/day taken once daily in the morning, depending on tolerability and degree of efficacy observed. Daily dosage above 60 mg is not recommended. The patients currently taking methylphenidate b.i.d. or Ritalin SR should remain with the equivalent dose strength with Ritalin® LA. For other methylphenidate regimens, clinical judgement should be used when selecting the starting dose.

Based on 24 month real time (25 °C/60% relative humidity) and 26 month at 30 °C/60% relative humidity stability data, a 24 month expiration period (shelf-life) is acceptable for Ritalin LA packaged in 30 and 100 counts in 90 and 175 cc square white —— bottles respectively with child resistant closure and ——— induction seal. The storage condition for the bottles is to store at 25 °C (77 °F), excursions permitted to 15-30 °C (59-86 °F).

C. Basis for Approvability or Not-Approval Recommendation

N21-284 (Ritalin LA capsules) is recommended for approval from CMC standpoint based on the following:

- Novartis has adequately addressed all the CMC deficiencies listed in the approvable letter dated October 1, 2001.
- Adequate information is provided to assure identity, strength, quality and purity of the drug product. The FDA Compliance issued an overall acceptable cGMP for all the manufacturing, packaging and testing sites for drug substance and drug product on March 11, 2002.

III. Administrative

Reviewer – Gurpreet Gill-Sangha, Ph.D.
Chemistry Team Leader – Hasmukh Patel, Ph.D.
Project Manager – Anna Marie Homonnay

Chemistry Assessment

N21-284 was recommended NOT APPROVAL from CMC standpoint on August 17, 2001 due to withhold recommendation from FDA Compliance for the drug product manufacturing, testing and packaging site (Elan Holdings, GA). The withhold recommendation revealed laboratory and data integrity issues at Elan site. It has not been known whether the integrity issues specifically affect data submitted for this NDA. The NDA was recommended NOT APPROVAL due to withhold recommendation for the drug product manufacturing site and also other deficiencies identified in various sections of drug product. However, an approvable letter was sent on October 1, 2001 by the Division of Neuropharmacological Drugs. Dr. Russ Katz, Division Director of Neuropharmacological drugs explains in a memo dated September 27, 2001 the rationale for approvable versus not approval recommendation.

The following review includes evaluation of responses in amendments dated October 18, 2001 and December 7, 2001 to FDA approvable letter dated October 1, 2001. The deficiencies relate only to the drug product section and there was no deficiency for the drug substance. The review also includes the February 28, 2002 amendment for the contract testing laboratories for excipients, updated 24 month stability data, and a corrected stability commitment. The responses to Q3 and 6 are evaluated only from December 6, 2001 amendment since the responses in the October 18, 2001 amendment for these questions were incomplete as noted in the two memos written to the NDA file dated October 31, 2001 and November 16, 2001 by Dr. Gurpreet Gill-Sangha.

The questions (as Q1, Q2, etc.) refer to the CMC questions in the FDA approvable letter, and the responses are listed as A1, A2, etc. The responses are evaluated and comment for the sponsor is noted where applicable.

Q1. The drug product manufacturing site, Elan Holdings, is subject to a Consent Decree based on a history of non-conformance with current good manufacturing practices (cGMP). Elan's unacceptable cGMP status cannot be changed until Elan requests an inspection to verify that agreed upon remedies are in place. Elan Holdings did not request such an inspection in time to provide results for this review of your application. A satisfactory inspection will be required before this application may be approved.

A1. Elan Holdings has contacted the Atlanta District Office of FDA and has indicated its readiness for an inspection.

Evaluation: Acceptable since Elan site was resubmitted to FDA Compliance on EES on December 14, 2001 and an overall acceptable recommendation was sent on March 11, 2002 by FDA Compliance.

_____ is proposed to be — in the final Ritalin® LA formulation. For example, the 20 mg capsule contains — mg each of _____

Please explain in detail the derivation of — value for — in each dosage strength.

A2. Ritalin LA capsules are composed of equal proportions of immediate release (IR) and delayed release (DR) beads containing the drug substance methylphenidate hydrochloride. The DR beads are manufactured

The following table provided on page 3, Section chemistry response, Vol. 5.2 of October 18, 2001 amendment shows the derivation of · with respect to the IR beads weight per dosage form.

Table 1: Amount of — per Ritalin LA capsule

Dosage strength (mg)	Quantity of IR beads per capsule (mg)[1]	Quantity of — per capsule (mg)	Quantity of — per capsule (mg)
20			
30			
40			

[1] See table 3-2 'Nominal IR and DR bead quantities in each capsule strength', page 4-40, Volume 3, original NDA

Evaluation: — represents of each — to the IR bead weight. However, the separate composition of the IR and DR beads is unclear from the Table of composition presented in Vol. 1.3, page 4-41, Table 4-1, of the original submission since the table does not list the individual formulation of IR and DR beads per capsule. Novartis is requested to provide an updated Table of Composition to reflect the separate composition of IR and DR beads per dosage strength. The following question was addressed in an IR letter to Novartis on April 3, 2002.

FDA DEFICIENCY 1. The Table of Composition of the Ritalin LA (Vol. 1.3, page 4-41, Table 4-1 of the original submission) as presented does not provide detailed information on individual composition of IR and DR beads for each dosage strength. Please provide the updated Table of Composition to reflect the composition of the IR and DR beads for each dosage strength.

NOVARTIS RESPONSE ARIL 16, 2002 – An updated Table of Composition that represents the composition for the finished capsule dosage form as the sub-parts of IR and DR beads is provided as shown below (page 3, April 16, 2002 amendment):

Table 2: Composition of Ritalin LA capsules 20, 30 and 40 mg as IR and DR bead sub-part

Ingredient	Amount per capsule (mg)			Function	Reference to standards
Strengths	20 mg	30 mg	40 mg		
IR beads					
Methylphenidate hydrochloride				Active ingredient	USP
Sugar spheres					NF/Ph. Eur.
Polyethylene glycol					NF/Ph. Eur.
					USP/Ph. Eur.
IR bead weight (theoretical)					
DR beads (IR beads coated with DR coating solution)					
Methylphenidate hydrochloride				Active ingredient	USP
Sugar spheres					NF/Ph. Eur.
Polyethylene glycol					NF/Ph. Eur.
Ammonio methacrylate copolymer					NF
Methacrylic acid copolymer					NF/Ph. Eur.
Talc					USP/Ph. Eur.
Triethyl citrate					NF/Ph. Eur.
					USP/Ph. Eur.
DR bead weight (theoretical)					
Capsule fill weight IR + DR beads (theoretical)					
Total capsule weight (theoretical)					

*brand name ——— supplied as ———

**brand name ——— supplied as ———

***removed during processing

Please note that quantities of sugar spheres and polyethylene glycol for the 30 mg capsule have been rounded to two decimal places in this tabular presentation

Evaluation to the response: Acceptable since the updated table of composition clearly reflects the composition of IR and DR beads for the finished capsule dosage form.

Q3. The in-process controls for IR and DR beads formation are inadequate. Please provide detailed in-process controls at every step of manufacturing to ensure quality control. The dissolution specifications for the DR (delayed release) beads at the in-process controls should be identical to the proposed specifications for the final drug product.

The Q3 was finally asked as following after two memo responding to response to Q3 in the NDA Approvable letter.

Final Q3. ***We note that in the table of contents in the faxed response to FDA Q6, the dissolution specifications for the DR beads are provided on page 68 of the resubmission dated October 18, 2001. You imply that these are the dissolution specifications for the DR beads. You had responded in the earlier resubmission dated October 18, 2001 that the DR beads specifications for the in-process controls would be provided after NDA approval, which is unacceptable. There is still no batch data for the IR or DR beads in-process specifications. In order for a complete response to the FDA approvable letter, please provide the following:***

- ***Confirm the DR dissolution specifications provided on page 68 of the resubmission are the same as that of the in-process dissolution specifications for the DR beads.***
- ***Provide data on 3 batches of IR and DR beads in-process specifications including the tests, acceptance criteria and the batch results.***

A3. Novartis apologizes for the administrative error in which blank tables were submitted in the October 18, 2001 response, necessitating the addition of completed pages by fax on October 30, 2001, and any resultant confusion this may have caused the FDA reviewer.

Novartis now clarifies that the dissolution specifications for the DR beads provided on page 68 of the resubmission dated October 18, 2001 are the same as the in-process specifications for the DR beads.

Data are provided on the IR and DR bead batches used in three primary stability batches manufactured in 1999, three validation batches manufactured in 2000, and the batches used in Protocol 06, the bioequivalence study. These latter batches were shown to produce bioequivalent drug products suggesting that the in-process dissolution specifications for DR beads (slow, target commercial, fast) support the dissolution ranges studied for the product formulations. The following table illustrates the batches for which IR and DR bead in-process data is provided.

Table 3: Batch numbers of IR and DR beads for in-process data

Bead type	Batch Type	Batch Number
IR bead	Primary Stability	RD039913, RD079902, RD079904
	Validation	OC901, OC903, OD904
	Biobatch	RD129904
DR bead	Primary Stability	RD039916, RD099902, RD099904
	Validation	OC905, OC907, OF903
	Biobatch	RD030004 (fast polymer), RD129908 (target polymer), RD030006 (slow polymer)

Evaluation:

The in-process specifications for IR and DR beads as provided in the December 6, 2001 amendment are summarized as follows:

In-process Specification	IR beads	DR beads
Description	White to off-white beads free from visible impurities	White to off-white beads free from visible impurities
Identification	Must Comply with	Must Comply with
Assay		
Related Substances	Not monitored	Not monitored
Dissolution	NLT at	NLT
Loss on Drying	NMT	NMT

The batch results from the batches listed above are within the proposed in-process specifications of IR and DR beads. The in-process specifications are acceptable for the IR and DR beads.

Q4. Reprocessing operations on page 4-78, Vol. 1.3 state that "The times, temperatures, etc., stated in the summary of production are valid for a given batch size provided in the drug product – Manufacturing Formula and using the stated equipment. In the case of minor variations in batch size or use of other equipment of the same type (while maintaining the same basic production steps), these values may vary for technical reasons to ensure that the final product fulfills the requirements and corresponds to the established specifications." The statement is unacceptable based on the Guidance for Changes to an Approved NDA or ANDA. Please commit to reporting the changes in conditions and equipment related to reprocessing appropriately in a supplement or annual report as per the Guidance for Changes to an Approved NDA or ANDA, November 1999.

A4. Novartis commits to report any changes in the drug product as recommended in the FDA Guidance for changes to an Approved NDA or ANDA. In addition, Novartis has updated the

document of Method of Preparation to remove the statement about variation in batch size and equipment.

Evaluation: Acceptable since Novartis commits to reporting any reprocessing changes as per the FDA Guidance.

Q5. The specifications for related impurities should be reflective of the release and stability data. It is recommended that the specifications are modified to: Individual Unknown Impurities: — Total Unknown Impurities: NMT — , and Total Impurities: . — ; based on sufficient data from 9 batches for 12 months.

A5. Novartis re-evaluated the related substance specifications based on the currently available data and FDA input, and proposes the following specifications.

Table 4: Proposed Specifications for Related Substances in Drug Product Ritalin LA

Test	Current specification	FDA recommended requirements	Novartis proposed specifications
— by —	NMT —	-	NMT —
Highest other individual impurity, based on the declared content of Methylphenidate; —	NMT —	NMT —	NMT —
Total other individual impurity, based on the declared content of Methylphenidate/ —	NMT —	NMT —	NMT —
Total impurities, based on the declared content of Methylphenidate — (not including the —	NMT . —	NMT —	NMT —

Evaluation: Novartis accepted the FDA recommended specifications for Total Unknown Impurities and Total Impurities. Novartis proposes a specification of NMT — for the Individual Unknown Impurity versus the FDA proposed specification of NMT — in the approvable letter dated October 1, 2001. The rationale that the specification of NMT — is based on ICH Q3B(R) *Impurities in New Drug Products* with a maximum daily dose of 10 mg to 2 g is acceptable. The total impurity specification of NMT — recommended by FDA and accepted by Novartis does not include — levels are monitored in the drug substance and it is also monitored in the stability protocol for the drug product. Stability studies from the drug product show levels of — below the detection limit of — In addition, the — is not a degradant and therefore it is acceptable not to include a specification for the — in the drug product specifications based on ICH Q6A. Novartis is requested to provide the updated drug product specifications including the related substances specifications. The finally agreed upon dissolution specifications for the drug product are pending as per biopharm review and should be incorporated as per the final biopharm review. The following comment was addressed in an IR letter to Novartis on April 3, 2002 .

FDA DEFICIENCY 2. Please provide the updated drug product specifications for Ritalin LA including the changes in the related substances specifications. The dissolution specifications for the drug product should be incorporated as per agreement with the Agency's biopharm division and Novartis.

NOVARTIS RESPONSE DATED APRIL 16, 2002 – The updated specifications for 20, 30 and 40 mg Ritalin LA capsules have been provided to include the revisions in the related substance specifications. The updated related substances specifications are reflected as:

——— – NMT —

Highest other individual impurity – NMT —

Total other individual impurity – NMT —

Total impurities (excluding ———; – NMT —

It is noted that the dissolution specifications for the drug product as per the telecon with Novartis and Biopharm staff on April 24, 2002 are as:

———

———

———

Evaluation to the response: Acceptable since Novartis has incorporated the finally agreed upon related substances specifications and agreed upon the dissolution specifications.

Q6. The analytical methods section is poorly organized. Please submit the information in an orderly manner for a complete review of your application. The analytical methods for identification by —— determination of assay and related substances, dissolution and residual solvents must include: 1) a final method code, 2) specifications, 3) sampling plan, and 4) detailed analytical method. The sampling plan must include the final parameters used such as mobile phase, sample solvent, column type, sample concentration, flow rate, detector wavelength, injection volume, run time, column temperature, wash and equilibrium conditions for an —— method.

The Q6 was finally asked as following after two memo responding to response to Q6 in the NDA Approvable letter.

Final Q6. ***We note that your fax submission dated October 30, 2001 containing the completed table of contents with page numbers which were missing from the original resubmission. As you acknowledge in the original resubmission dated October 18, 2001 that the re-presentation of the information may not completely address the FDA concern raised in the approvable letter dated October 1, 2001 and telecon dated October 11, 2001. It is also not appropriate to refer to the Agency 2000 Draft Guidance on Analytical Procedures and Methods Validation because it is a draft guidance. In addition, this guidance does not address format, which is specifically the concern in your resubmission.***

In order to satisfactorily and completely respond to Q6 of FDA approvable letter, you should explicitly provide the following:

- ***Details of each analytical method individually including specific assay method, Impurity profile by —— Dissolution method, etc.***

- ***Each individual method must be provided in a single coherent text including***

1. ***A final method code for each method,***
2. ***Specifications,***
3. ***Sampling plan,***
4. ***Detailed analytical method.***

In General: Each analytical method submitted with the NDA should provide sufficient detail about the method, conditions, and equipment used to enable a qualified analyst to reproduce the method, obtaining comparable results.

I. ***IR Beads:*** *Provide the information for the analytical method used for each IR bead specification as listed below. Please also state if the analytical method for each specification is same or different for — 20 mg strengths of IR beads.*

- *Identification by —*
  - *Method code*
  - *Specification and principle – State the specification (for example, Identification of IR beads by — and briefly describe in a statement the principle of the analytical method (for example, the identification of IR beads is performed by —*
  - *Sampling – Provide details of the sample preparation for the analytical method including the amount of the sample used. Indicate the number of samples (for example, weight of beads, number of capsules etc.) selected and how they are used.*
  - *Analytical Method – Provide detailed analytical method including a list of all equipment (for example, equipment type, detector, column type, dimensions etc.) and equipment parameters (flow rate, temperature, run time, wavelength settings) when appropriate.*

Provide similar details for all the analytical methods listed below.

- *Assay by —*
- *Impurities by —*
- *Dissolution*

II. *DR beads: Provide the information for the analytical method for each specification similar to the IR beads. Please also state if the analytical method for each specification is same or different for — 20 mg strengths of DR beads.*

- *Identification by —*
- *Assay by —*
- *Impurities by —*
- *Dissolution*

III. *Drug Product: The detailed information must be provided for the analytical methods for each specification of the drug product similar to the IR beads data. Please also*

state if the analytical method for each specification is same or different for 20, 30, 40 mg capsule strengths.

- ***Identification by*** ——
- ***Assay by*** ——
- ***Related Substances by*** ——
- ***Content Uniformity***
- ***Dissolution***
- ***Residual Solvents***

The method validation section must provide data to validate the analytical method for each specification of the IR, DR and the drug product capsules. The validation data must provide detailed information on reference standards, system suitability, sample preparations, and data on accuracy, precision, specificity, detection limit, and quantitation limits. The data must include chromatograms and dissolution data where appropriate.

The information provided above delineates the information required for the review of analytical methods and methods validation section of N21-284. The information provided is complete and final and therefore, does not need any further clarifications.

A6. The documentation is organized into three subparts: IR beads, DR beads, and Capsules (20, 30, 40 mg). The first page of each subpart is a summary of the corresponding required tests and specifications. Then for each analytical method the following documents are provided: method summary, validation summary, and copies of detailed validation reports referenced in Validation summary.

Evaluation:

The analytical methods for IR, DR and capsules are evaluated. The analytical method for identification, assay, purity, and dissolution are same for the IR, DR and the capsule and therefore these methods are evaluated together for the IR, DR, and the capsules. In addition, the method for identification, assay and related substances is identical and the content uniformity method also employs the same —— method but different sample preparation. The content uniformity section highlights the important difference.

IR beads:

The specifications provided for IR beads are as follows (page 21, Vol. 1.1, December 6, 2001 amendment).

TEST	SPECIFICATION
[redacted]	

New purity specifications for the drug product were proposed in the response to the 02-Oct-01 Approvable letter. Novartis intends to harmonize these IR bead purity specifications once an agreement has been reached with FDA.

DR beads:

The specifications provided for DR beads are as follows (page 1-2, Vol. 1.2, December 6, 2001 amendment).

TEST	SPECIFICATION

TEST		SPECIFICATION			
*Dissolution %	Level	Hour	Hour	8 Hour	22 Hour
	L1 Each 6 of 6				
	L2 Average of 12 Each 12 of 12				
	L3 Average of 24 NLT Each 24 of 24				

*Dissolution tolerance criteria, based on USP <724> extended release articles

New purity specifications for the drug product were proposed in the response to the 02-Oct-01 Approvable letter. Novartis intends to harmonize these DR bead purity specifications once an agreement has been reached with FDA.

Capsules (20, 30, 40 mg):

The specifications provided for drug product capsules are as follows (page 1-2, Vol. 1.3, December 6, 2001 amendment).

TEST	SPECIFICATION
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
Drug Release by [redacted]	
Drug Release of METHYLPHENIDATE [redacted] after [redacted]	[redacted] of the declared content according to acceptance table 1 of USP<724> (level 1 and 2 only)
Drug Release of METHYLPHENIDATE [redacted] after [redacted]	[redacted] of the declared content according to acceptance table 1 of USP<724> (level 1 and 2 only)
Drug Release of METHYLPHENIDATE [redacted] after [redacted]	[redacted] of the declared content according to acceptance table 1 of USP<724> (level 1 and 2 only)
Drug Release of METHYLPHENIDATE [redacted] after [redacted]	Not less than [redacted] of the declared content according to acceptance table 1 of USP<724> (level 1 and 2 only)
Residual Solvents by GC:	
[redacted]	NMT [redacted]
[redacted]	NMT [redacted]

The drug release specifications reflect those agreed to in the 18 October 2001 response to the FDA approvable letter.

CHEMISTRY REVIEW

Chemistry Assessment Section

1) Test:	Identification and Assay by Novartis)
2) Sampling:	
3) Specs:	
4) Method:	The same [redacted] method is employed for the identification, assay, purity (related substances) and content uniformity. Sample preparation is different for the content uniformity to address the unit sampling and is described in the content uniformity method section below. The method conditions are as:

5) Evaluation:	The method is validated for: Linearity: Linear in the range of [redacted] of 0.2 mg/mL covering [redacted] 20, 30 and 40 mg strengths. Accuracy: Range of [redacted] with observed bias of <2.0%. Precision: %RSD by each analyst was [redacted] and over two days Specificity: No interference between analyte peak and any system responses. Robustness: [redacted]
6) Deficiencies:	None

1) Test:	Purity (Related Substances) by — same as assay method)
2) Sampling:	Same as for the identification and assay method
3) Specs:	
4) Method:	The method employed for related impurities is same as the identification and assay method.
5) Evaluation:	The validation for the related substances also includes the separation between the analyte and known degradation product or related compounds in addition to the validation provided for the assay method. In addition, the validation for each related substance was as:
6) Deficiencies:	None

1) Test:	Content Uniformity b — for 20, 30, 40 mg capsules
2) Sampling:	Prepare — mg/mL samples in mobile phase (same as the assay method) containing — Analyze 10 capsules individually. If the content uniformity requirements are not met, analyze additional 20 capsules.
3) Specs:	Complies with current USP as: % labeled amount of methylphenidate HCl:
4) Method:	The content uniformity method utilizes the same — method as identification, assay and related substances method. The sample preparation is modified for unit dose method. The final methylphenidate concentrations
5) Evaluation:	The content uniformity sample concentrations are — for the 20, 30, and 40 mg capsules respectively. And are covered in the validated ranges for accuracy and linearity of the assay

	method with the nominal concentration of [redacted]. Refer to assay method for detailed validation.
6) Deficiencies:	None.

1) Test:	Residual Solvents by [redacted]
2) Sampling:	[redacted]
3) Specs:	[redacted]
4) Method:	[redacted]
5) Evaluation:	The method is validated as follows: Linearity and accuracy: Over the range of [redacted] w/w for [redacted] and [redacted] w/w for [redacted] with a significant bias of NMT Specificity: Specific for [redacted] Precision: %RSD of different analysts and days is NMT [redacted]

6) Deficiencies:	None

1) Test:	Dissolution (drug release) by
2) Sampling:	Analyze 6 samples individually and if the requirements are not met analyze additional 6 samples.
3) Specs:	The final agreed upon dissolution specifications as per biopharm review dated May 6, 2002 are :
4) Method:	The method follows USP for extended release articles. A USP Type I (rotating basket) apparatus is employed at 100 rpm for the the samples are tested by using the same chromatographic conditions as the assay and related substance method.
5) Evaluation:	The method is validated for dissolution as: Accuracy and Bias: Precision: Linearity: mg/mL in
6) Deficiencies:	None

The following comment was addressed in an IR letter dated April 3, 2002 to Novartis.

FDA DEFICIENCY 3. Please provide the updated specifications for the IR and DR beads including the revisions in the related substances specifications as per your acknowledgement dated December 6, 2001.

NOVARTIS RESPONSE DATED APRIL 16, 2002 – The updated specifications for IR and DR beads are provided to reflect the revisions in the related substance specifications. The related substance specifications for IR and DR beads are the same as in response Q6 noted above.

Evaluation to the response: Acceptable since the revisions are incorporated in the specifications of IR and DR beads.

Q7. DMF is inadequate. from . DMF are therefore, unacceptable as a for Ritalin® LA until adequate information is provided for an acceptable DMF

A7. Novartis provides a copy of the letter from regarding DMF in Attachment 3, Vol. 5.2, October 18, 2001 submission. The letter indicates that they will no longer include certain information in their drug master file (data concerning The is therefore asking

industry to provide this information in the NDA. The dimensions of the bottles was submitted in the original NDA (Vol. 1.5, pages 4-19 – 4-28). The following information is provided for the 90 and 175 cc bottles from

For 90 cc bottles:

- Certificate from [redacted] stating that for [redacted] only [redacted] will be used during the manufacture.
- Letter of authorization from [redacted] for DMF [redacted] for [redacted]
- Letter of authorization from [redacted] for DMF [redacted] for [redacted]

For 175 cc bottles:

- Certificate from [redacted] with regards to [redacted] that only [redacted] will be used during manufacture.
- Letter of authorization from [redacted] for DMF [redacted] for [redacted]
- Letter of authorization from [redacted] for DMF [redacted] for [redacted]

Evaluation:

Novartis has provided the necessary information for the DMF [redacted]. The original NDA submission contains the appropriate data for dimensions of [redacted] bottles. The DMF [redacted] for [redacted], DMF [redacted] for [redacted], and DMF [redacted] for [redacted] have been reviewed and found adequate. The details are provided in the Chemistry Review Data Sheet section of this review. The use of [redacted] bottles from [redacted] for Ritalin LA is therefore acceptable.

Q8. You have proposed an equivalency protocol to qualify new container closure suppliers (Vol. 1.5 pages 4-33 - 4-34), using USP <661> and <671> testing. Please submit acceptance criteria for this protocol that are commensurate with the expected shelf-life of the drug product.

A8. Based on October 11, 2001 conversation between the representatives from Novartis and members from the Chemistry Review Team at the Division of Neuropharmacology, the proposal to include [redacted] bottle and Container Equivalency (comparability) protocols in the application for Ritalin LA will be withdrawn. When the information that was requested by the FDA is obtained, Novartis may re-address the container equivalency issue with the FDA.

Evaluation: Acceptable since the equivalency protocol is withdrawn.

Q9. Please clarify the information regarding [redacted] on stability protocol by correlating the suppliers of materials with reference to their DMF numbers with the to be marketed [redacted] on stability. Please summarize in a tabular form which supplier's materials for [redacted] were used in the stability studies.

A9. The suppliers of [redacted] and [redacted] for the Ritalin LA capsules, 20, 30, and 40 mg for the registration stability studies are given below on page 11, Section Chemistry Response, Vol. 5.2, Amendment October 18, 2001.

Table 5: [redacted] **Configurations from Different Vendors in Stability Studies**

[redacted]	**configurations used for Registration Stability**
[redacted]	
[redacted]	
[redacted]	
[redacted]	

Evaluation: Based on the information provided, the i [redacted] DMF [redacted] and the [redacted] from [redacted] should not be used in the [redacted] since they were not placed in any stability studies. The following comment was addressed in an IR letter dated April 3, 2002 to Novartis.

FDA DEFICIENCY 4. The [redacted] from [redacted] should not be used in the [redacted] for the commercial drug product since these were never placed on any stability studies with Ritalin LA.
NOVARTIS RESPONSE DATED APRIL 16, 2002 – The [redacted] l from [redacted] is used [redacted] used for Ritalin LA [redacted] closure with [redacted] induction seal). They are specified as part of the [redacted] is received from the [redacted] suppliers, [redacted] Therefore, it is represented in the registration stability studies. We apologize that this was not clearly stated in the October 18, 2001 response in the DMF listings.

With respect to data to support the use of [redacted] for the 100 count package configuration, Novartis believes that there is sufficient drug product stability data to allow use of [redacted] Novartis states that only one [redacted] used for all [redacted], whether they are supplied by [redacted]. The material of [redacted] for the drug product is same for both [redacted] and [redacted] suppliers. The [redacted] show acceptable stability for the registration stability studies.
Novartis commits to include [redacted] configuration in future stability studies and report the data via annual report.
Evaluation to the response: Acceptable for both [redacted] from [redacted] from [redacted]. The [redacted] as noted by Novartis is part of the stability studies as it is a component of the [redacted] The [redacted] from [redacted] are also acceptable since the [redacted] used is same as in the [redacted] from [redacted] which were part of the primary stability studies.

Q10. You have provided 12 months acceptable stability data at 25 °C/60%RH for Ritalin LA. The 6 month stability data at 40 °C/75%RH shows that eight of the eighteen batch package combinations failed the dissolution test at the [redacted] time point. Expiry period of only [redacted] is acceptable for Ritalin® LA reflective of the stability data. The expiry period may be extended based on additional real-time data through a Prior Approval Supplement.

A10. Novartis provides stability data for 24 months at 25 °C/60%RH and 26 months at 30 °C/60%RH in February 28, 2002 amendment. No additional data at 40 °C/75%RH is provided beyond the 6 month data in the original submission. The registration stability data is provided on the same three batches of each strength in 30 and 100 count bottles as in the original NDA. These batches are RD099905, RD099906, RD099907 for 20 mg, RD099908, RD109901, RD109902 for 30 mg and RD109903, RD109904, RD109905 for the 40 mg strength. Novartis is requesting a 24 month expiration based on the real time data.

Evaluation:
The following table summarizes the results of the stability data submitted by Novartis.

Table 6: Summary of Stability Data Results

Specifications	Results at 25 °C/60%RH (0-24 months)	Results at 30 °C/60%RH (0-26 months)	Proposed Regulatory
Assay [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	NMT [redacted]
[redacted]	[redacted]	[redacted]	No proposed regulatory specification – monitored as part of the drug substance specifications
Maximum Unknown	[redacted]	[redacted]	NMT [redacted]

Specifications	Results at 25 °C/60%RH (0-24 months)	Results at 30 °C/60%RH (0-26 months)	Proposed Regulatory
Impurity			
Total Unknown Impurities			NMT
Total impurities (not including the			NMT
Dissolution			Final agreed upon Dissolution specifications are pending per the biopharm review.

Novartis states that the dissolution data shows an increase of about 8% from time 0 values for time points for the 30 °C/60%RH conditions at 26 months. It is noted that in the original data submitted dissolution failed for the accelerated conditions of 40 °C/75%RH at 6 months. Based on the 24 month real time stability data, a 2 year expiry is acceptable for Ritalin® LA. It is also noted that the stability specifications are the same as the regulatory specifications at release. The following comment was addressed in an IR letter dated April 3, 2002 to Novartis.

FDA DEFICIENCY 5. A 24 month expiry for Ritalin LA is acceptable based on 24 month real time data. We also acknowledge that the stability specifications are the same as the approved regulatory specifications at release as per the February 28, 2002 amendment.
NOVARTIS RESPONSE DATED APRIL 16, 2002 – Novartis concurs with the Agency's recommendation for a 24 month expiry at the time of NDA approval. Novartis concurs that the stability specifications are the same as the approved regulatory specifications at release.
Evaluation to the response: Acceptable since Novartis concurs with the expiration date and stability specifications.

Q11. The container labels include the dosage strength written in red color for 20, 30 and 40 mg of Ritalin® LA. Please change to three distinct colors to depict the dosage strength on container labels to increase clarity.

A11. Novartis agrees to change the ink on the container labels for each dosage strength to further distinguish the different drug product strengths. The label ink colors selected are as follows:

Ritalin LA 20 mg — Red
Ritalin LA 30 mg — Green
Ritalin LA 40 mg — Purple

The updated labels are provided in Attachment 8, Vol. 5.2, October 18, 2001 amendment.
Evaluation: Acceptable since the dosage strengths are distinct on the container labels.

ADDITIONAL INFORMATION

The following information is provided in the February 28, 2002 amendment:

- Updated stability data (24 months at 25 C/60% RH) – reviewed as part of response to Q 10.
- A corrected stability commitment to rectify an incorrect date for the "Stability Protocol for Post Approval Changes". The corrected statement notes that the date should be November 9, 2000 instead of November 6, 2000.
- Contract testing laboratories for excipients are provided. The contract facilities provided are as follows (page 1, Summary section, February 28, 2002 amendment):

Contract Laboratories	Type of testing
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

The contract facilities need not be inspected by FDA Compliance for this NDA since they are for analytical and microbiological testing for excipients.

LABELING

Revised draft package insert and patient labeling are provided in the October 18, 2001 amendment. The following changes were noted in the description and how supplied sections:

DESCRIPTION: Two statements are added as shown underlined and italic in the description section first paragraph as – "....with a bi-modal release profile [redacted] *Ritalin® LA uses the proprietary SODAS® (Spheroidal Oral Drug Absorption system) technology.*[1] Each bead ....".

HOW SUPPLIED: Two changes are proposed for the how supplied section as shown below in italics and underlined.

- Deletion of bottles of [redacted] and only the 100 count bottles are to be manufactured as per electronic label submitted May 3, 2002.

- Addition of the manufacturer information as –

Manufactured for :
Novartis Pharmaceutical Corp.
East Hanover, New Jersey 07936
By ELAN HOLDINGS INC.
Pharmaceutical Division
Gainesville, GA 30504

- A statement about the patent information is added as:

"*This product is covered by US patents including US 5,837,284 and 6,228,398.*"

- Addition of the following statements about trademarks as per May 3, 2002 electronic label:

"Ritalin® LA is a trademark of Novartis AG."
SODAS™ is a registered trademark of Elan Corporation, plc."

Evaluation: The medical reviewer, Dr. Andy Mosholder, has commented about the statement about [redacted]. Please refer to Dr. Mosholder review for recommendation to not include this statement.

The information in the How Supplied section about the address of the manufacturer and the patent information are acceptable.

The statement about SODAS in the description section is inappropriate since it does not address description of the drug product but refers to manufacturing technology for the beads. Novartis was requested to remove the statement from the label and also its reference in the How Supplied section. Novartis responded on May 3, 2002 requesting that the SODAS term be kept in the label as it is since other drugs such as Procardia XL, Glucotrol XL, Covera HS, Doxil, Paxil CR. Procardia, XL, Glucotrol XL, Covera HS are all drugs that use GITS technology and a detailed description about the technology is included in the section of System Components and Performance. Doxil also uses STEALTH liposomes and a detailed System Components and Performance section is included in the description section of the label. No special trademark information is included in the label for Paxil CR. The reviewer, Dr. Gurpreet Gill-Sangha does not agree with Novartis that SODAS be used in the label. However, the ONDC management disagrees and accepts the use of SODAS terminology in the label. The reviewer believes that the SODAS information is purely promotional and does not benefit the physician or the consumer. The statement about SODAS is not explaining any *in vivo* release mechanism nor does it clarify to the physician that it is a manufacturing technology. The views of the reviewer and ONDC management were conveyed to Dr. Tom Laughren, Deputy Division Director, Division of Neuropharmacology Drugs, CDER.

DRAFT DEFICIENCY LETTER

None from CMC standpoint.

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/s/

Gurpreet Gill-Sangha
5/13/02 10:04:31 AM
CHEMIST

CMC #2

Hasmukh Patel
5/13/02 10:21:06 AM
CHEMIST

Memo

To: NDA21-284 Division file

From: Gurpreet Gill-Sangha, Ph.D., Chemistry reviewer

Through: Robert H. Seevers, Ph.D., Chemistry Team Leader

CC: Robert H. Seevers, Ph.D., Chemistry Team Leader

Gurpreet Gill-Sangha, Ph.D.

Anna Marie Homonnay, Project Manager

Date: 11/16/01

Re: Response to Novartis Fax 11/7/01

This memo responds to fax dated November 7, 2001 from Novartis. The fax is requesting further guidance on presentation of analytical methods and methods validation section of N21-284. The analytical methods section submitted in the original NDA and resubmission dated 10/18/01 were poorly organized and therefore not readily reviewable. An FDA letter dated 11/1/01 for incomplete response to FDA approvable letter dated 10/1/01 was sent to Novartis clarifying the information required for review of analytical methods and methods validation section as response to FDA CMC Q6. The information presented below provides precise details on the data required for the analytical methods and methods validation section for N21-284.

In General: Each analytical method submitted with the NDA should provide sufficient detail about the method, conditions, and equipment used to enable a qualified analyst to reproduce the method, obtaining comparable results.

1. IR Beads: Provide the information for the analytical method used for each IR bead specification as listed below. Please also state if the analytical method for each specification is same or different for — 20 mg strengths of IR beads.

- Identification by —
  - Method code
  - Specification and principle – State the specification (for example, Identification of IR beads by . —) and briefly describe in a statement the principle of the analytical method (for example, the identification of IR beads is performed by
  - Sampling – Provide details of the sample preparation for the analytical method including the amount of the sample used. Indicate the number of samples (for example, weight of beads, number of capsules etc.) selected and how they are used.

- Analytical Method – Provide detailed analytical method including a list of all equipment (for example, equipment type, detector, column type, dimensions etc.) and equipment parameters (flow rate, temperature, run time, wavelength settings) when appropriate.

Provide similar details for all the analytical methods listed below.

- Assay by —
- Impurities by —
- Dissolution

II. **DR beads:** Provide the information for the analytical method for each specification similar to the IR beads. Please also state if the analytical method for each specification is same or different for 10, 15, 20 mg strengths of DR beads.

- Identification by —
- Assay by —
- Impurities by —
- Dissolution

III. **Drug Product:** The detailed information must be provided for the analytical methods for each specification of the drug product similar to the IR beads data. Please also state if the analytical method for each specification is same or different for 20, 30, 40 mg capsule strengths.

- Identification by —
- Assay by —
- Related Substances by —
- Content Uniformity
- Dissolution
- Residual Solvents

The method validation section must provide data to validate the analytical method for each specification of the IR, DR and the drug product capsules. The validation data must provide detailed information on reference standards, system suitability, sample preparations, and data on accuracy, precision, specificity, detection limit, and quantitation limits. The data must include chromatograms and dissolution data where appropriate.

The information provided above delineates the information required for the review of analytical methods and methods validation section of N21-284. The information provided is complete and final and therefore, does not need any further clarifications.

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/s/

Gurpreet Gill-Sangha
11/16/01 08:45:37 AM
CHEMIST

Response to Novartis Fax 11/7/01

Robert H. Seevers
11/16/01 08:54:32 AM
CHEMIST

Elizabeth R. McCartney
Assistant Director
Drug Regulatory Affairs - CMC

Novartis Pharmaceuticals Corporation
419/1186
One Health Plaza
East Hanover, NJ 07936

Tel (973) 781-8391
Fax (973) 781-6325
Internet: elizabeth.mccartney@pharma.novartis.com

NOVARTIS

Fax

Attention: Anna Marie Homonnay, R. Ph.
Regulatory Health Project Manager
Division of Neuropharmacological Drug Products
CDER
Food and Drug Administration

Fax no. (301) 594-2859
Number of pages 3 including cover page

Date November 7, 2001

Concerning Ritalin® LA, NDA 21-284 – Clarification of Chemistry Issues

Dear Ms. Homonnay:

Please refer to the letter from the Division Director dated 7-Nov-01, denying Novartis' request for a meeting to clarify the content and format issues that the Chemistry review team is having with the analytical documentation provided in the NDA. As per your suggestion Novartis is faxing the attached questions as an alternate means to pinpoint the specific issues of concern. Depending on the response received to these initial questions, Novartis would like to provide additional questions for further clarification.

We appreciate your willingness to continue working with Novartis to provide the requested clarification. Our goal is to address the format and content issues as acurately and quickly as possible without wasting the time of the review team, or that of Novartis, by preparing something that does not properly address the problem.

Sincerely,

E. R. McCartney

Elizabeth R. McCartney

DRA – Chemistry Manufacturing and Controls

Memo

To: NDA21-284 Division file

From: Gurpreet Gill-Sangha, Ph.D., Chemistry reviewer

CC: Robert H. Seevers, Ph.D., Chemistry Team Leader

Gurpreet Gill-Sangha, Ph.D.

Anna Marie Homonnay, Project Manager

Date: 10/31/01

Re: NDA 21-284 CMC Resubmission is Incomplete

NDA 21-284 resubmission dated October 18, 2001 is still incomplete after the submission of fax dated October 30, 2001. The fax dated October 30, 2001 from Novartis provided the completed table of contents for the two tables in response to Q6 of the FDA approvable letter dated October 1, 2001. The page numbers were missing from these table of contents in the original resubmission. Based on the careful evaluation of the information in the fax dated October 30, 2001, responses to CMC Q3 and Q6 of FDA approvable letter dated October 1, 2001 are still incomplete. The complete evaluation to the two questions are provided below:

Response Evaluation to FDA Q3: We note that in the table of contents in the faxed response to FDA Q6, the dissolution specifications for the DR beads are provided on page 68 of the resubmission dated October 18, 2001. You imply that these are the dissolution specifications for the DR beads. You had responded in the earlier resubmission dated October 18, 2001 that the DR beads specifications for the in-process controls would be provided after NDA approval, which is unacceptable. There is still no batch data for the IR or DR beads in-process specifications. In order for a complete response to the FDA approvable letter, please provide the following:

- Confirm the DR dissolution specifications provided on page 68 of the resubmission are the same as that of the in-process dissolution specifications for the DR beads.
- Provide data on 3 batches of IR and DR beads in-process specifications including the tests, acceptance criteria limits and the batch results.

Response Evaluation to FDA Q6: We note that your fax submission dated October 30, 2001 containing the completed table of contents with page numbers which were missing from the original resubmission. As you acknowledge in the original resubmission dated October 18, 2001 that the re-presentation of the information may not completely address the FDA concern raised in the approvable letter dated October 1, 2001 and telecon dated October 11, 2001. It is also not appropriate to refer to the Agency 2000 Draft Guidance on Analytical

Procedures and Methods Validation because it is a draft guidance. In addition, this guidance does not address format, which is specifically the concern in your resubmission.

In order to satisfactorily and completely respond to Q6 of FDA approvable letter, you must explicitly provide the following:

- Details of each analytical method individually including specific assay method, Impurity profile by — , Dissolution method, etc.
- Each individual method must be provided in a single ***coherent*** text including

1. A final method code for each method,
2. Specifications,
3. Sampling plan,
4. Detailed analytical method.

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/s/

Gurpreet Gill-Sangha
10/31/01 11:41:07 AM
CHEMIST

Robert H. Seevers
10/31/01 11:47:18 AM
CHEMIST

Memo

To: NDA21-284 Division file

From: Gurpreet Gill-Sangha, Ph.D., Chemistry reviewer

CC: Robert H. Seevers, Ph.D., Chemistry Team Leader

Gurpreet Gill-Sangha, Ph.D.

Anna Marie Homonnay, Project Manager

Date: 10/29/01

Re: NDA 21-284 Resubmission is Incomplete for CMC

The N21-284 re-submission dated October 18, 2001 to FDA approvable letter dated October 1, 2001 is incomplete for the CMC section. The responses to Q3 and 6 for the chemistry section are incomplete. The evaluation is as follows for each question:

Response Evaluation to FDA Q3: Novartis provides tests for the in-process controls for the IR beads but no information is provided for the acceptance criteria limits and the corresponding batch records for in-process IR beads. The resubmission does not contain any data for the in-process tests, acceptance criteria limits and batch results of DR beads. The firm states that it will provide DR beads acceptance criteria specifications and batch results on approval of the application. This is unacceptable. DR beads are not identical to the drug product which is a mixture of both the IR and DR beads. It is important to review the in-process controls for DR beads to ensure product quality. The firm needs to provide the acceptance criteria limits and batch results for both IR and DR for a complete response to the application.

Response Evaluation to FDA Q6: The analytical methods section of the application is unchanged form the original and is therefore still poorly organized. The firm proposed to provide two tables in front of the represented test methods and validation methods sections. However, the two tables are missing from each section. Currently the analytical methods and methods validation section are identical to the original submission in the NDA except the addition of a sampling plan. The sponsor has not addressed the question 6 of the FDA approvable letter. The firm needs to submit the analytical methods section of the application in an organized manner as detailed in the FDA Q6 of the approvable letter.

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/s/

Gurpreet Gill-Sangha
10/29/01 02:43:16 PM
CHEMIST

Incomplete CMC resubmission memo

Robert H. Seevers
10/29/01 03:16:40 PM
CHEMIST

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

NDA #: 21-284 **DATE REVIEWED: 17-Aug-2001** **REVIEW #: 1**

REVIEWER: Gurpreet Gill-Sangha, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	28-Nov-2000	30-Nov-2000	7-Dec-2000
N(BC) Amendment	28-Feb-2001	1-Mar-2001	9-Mar-2001

NAME & ADDRESS OF APPLICANT
Novartis Pharmaceuticals Corporation
59 Route 10, East Hanover, NJ 07936-1080

DRUG PRODUCT NAME

Proprietary:	Ritalin® LA
Established:	Methylphenidate HCl
Code Name/#:	RITI24D
Chem.Type/Ther.Class:	3S

PHARMACOL. CATEGORY/INDICATION
ADHD

DOSAGE FORM AND STRENGTHS
Modified Release Capsules – 20, 30, 40 mg

ROUTE OF ADMINISTRATION
Oral

Rx/OTC X Rx ___OTC
SPECIAL PRODUCTS: ___Yes X N

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT

CA Name: _____
USAN Name: Methylphenidate Hydrochloride
Chemical Formula: _____
Molecular Weight: 269.77
CAS registry #: 298-59-9
Structure:

_____

SUPPORTING DOCUMENTS

Type/No.	Subject	Holder/ LOA	Pg./ Vol. in NDA	Status	Review and Letter Date
N10-187	Methylphenidate Hydrochloride	Novartis		Approved on 5-Dec-1955	N/A
DMF TYPE IV			Vol. 1.3, page 4-96	Adequate	Review by Susan Zuk on Aug-4-1999
DMF TYPE III			Vol. 1.5, page 4-11	**Inadequate** Review by P. Peri on Dec-29-2000 The holder is not providing the information on the and appropriate regulations code	
DMF TYPE III			Vol. 1.5, page 4-12	Adequate	Review by Don Klein on Sep-26-2000
DMF TYPE III			Vol. 1.5, page 4-13	Adequate	Review by Don Klein on Sep-28-2000
DMF TYPE III			Vol. 1.5, page 4-14	Adequate	Review by Don Klein on Mar-23-2000
DMF TYPE III			Vol. 1.5, page 4-15	Adequate	Primary DMF is which is adequate by Don Klein for on Oct-12-2000
DMF TYPE III			Vol. 1.5, page 4-16	Adequate	Review by Sharon Kelly on Sep-26-2000
DMF TYPE III			Vol. 1.5, page 4-18	Adequate	Review by Don Klein on Oct-12-2000

RELATED DOCUMENTS

1.
2. NDA 10-187, Methylphenidate Tablets, Approved as of 5-Dec-1955.
3. NDA 18-029, Ritalin SR Tablets 20 mg, Approved as of 30-Mar-1982

OTHER REQUESTS

Establishment evaluation requests were sent out as listed below:

Site CFN#	Site Location	Site Function	Submit to OC	Status
1035761	ELAN HOLDINGS INC	Drug product manufacturer and quality control	8-Dec-00	Alert as of 22-Jan-2001
2416082	Novartis Pharmaceuticals (CIBA)	Drug product quality control, stability and packaging	8-Dec-00	Acceptable as of 2-Jan-01
2210396	Novartis Pharmaceuticals (Sandoz)	Drug product Microbiological quality control only	8-Dec-00	Acceptable as of 19-Dec-00
2530802	[redacted]	[redacted]	8-Dec-00	Acceptable as of 12-Dec-00
2210396	Novartis Pharmaceuticals (Sandoz)	Drug Substance Manufacturer	17-Jan-01	Acceptable as of 2-Feb-01

Overall Compliance Recommendation: WITHHOLD AS OF 2-Feb-2001. EES reports that the Elan site inspected in 6/00 revealed laboratory and data integrity issues and the firm is unacceptable as manufacturer/testing/packager.

REMARKS

1. N10-187 is referenced for the drug substance methylphenidate hydrochloride, USP. The drug substance section of this NDA is therefore acceptable.
2. The following CMC sections of the drug product are acceptable:
   - Specifications and Methods for Drug Product Ingredients,
   - Manufacturer,
   - Investigational Formulations,
   - Environmental Assessment, and
   - Methods Validation.
3. The following sections in the drug product section are deficient and need further clarifications (see draft letter for specifics):
   - Components and Composition,
   - Methods of Manufacturing and Packaging,
   - Regulatory Specifications and Test Methods for Drug Product,
   - Container Closure System,
   - Drug Product Stability,
   - Labeling, and
   - Establishment Inspection (Withhold recommendation from FDA Compliance).

CONCLUSIONS & RECOMMENDATIONS

NDA 21-284 is recommended **NOT APPROVABLE** based on CMC section. The **non-approval** is based on the withhold recommendation from FDA Compliance for the drug product manufacturing, testing and packaging site (Elan Holdings, GA). The withhold recommendation revealed laboratory and data integrity issues at the Elan site. It is unknown whether the integrity issues specifically affect data submitted for this NDA. The remaining NDA is approvable contingent on adequate responses from the sponsor to the questions addressed in the draft letter related to various sections of the drug product.

TABLE OF CONTENTS

LIST OF TABLES

CHEMISTS'S REVIEW NOTES

1. DRUG SUBSTANCE

(Vol. 1.3, pages 4-24 – 4-38)

On page 4-25, Vol. 1.3, NDA 10-187 is referenced for the drug substance (methylphenidate hydrochloride, USP). Ritalin HCl is manufactured by Novartis Pharmaceuticals Corporation, East Hanover, NJ (CFN # 2210396). Methylphenidate HCl is accepted by ELAN (drug product manufacturer) based on Novartis Certificate of Analysis. The Novartis quality standard document (Vol. 1.3, page 4-26 – 4-27) represents 7/14/00 edition and supersedes the 7/20/99 edition. The 7/14/00 follows the specifications consistent with USP and the approved NDA 10-187. In particular the document provides limits of the assay and chromatographic impurities as follows:

Assay

	NMT
	NMT
Other individual impurities	NMT
Total impurities (excluding	NMT

Four batches of methylphenidate hydrochloride manufactured by Novartis are used to manufacture Ritalin® LA clinical and stability batches. The four batches are 9C016, 9H001, 9H002 and 8F001. All the four batches meet the methylphenidate hydrochloride specifications (Vol. 1.5, page 4-220)

Evaluation: Acceptable since no new changes are incorporated from the USP and approved NDA 10-187 specifications and the batches manufactured by Novartis for Ritalin® LA meet all the specifications.

2. DRUG PRODUCT

2.1/2.2 Components/Composition

(Vol. 1.3, pages 4-37 – 4-42, 4-84 – 4-105)

Table 1: Components of Ritalin Modified Release Pellets

Components	*References to Standards*
Methylphenidate Hydrochloride	USP
Sugar Spheres (25/30 mesh)	NF
	NF
Methacrylic Acid copolymer	NF
Triethyl Citrate	NF
Talc	USP
Polyethylene Glycol	NF
	USP
	USP

The following non-compendial inactive ingredient (non-USP or non-NF) has been reviewed:

- (DMF has been reviewed adequate by S. Zuk on 8/4/99

Quality control specifications and testing profile for [redacted] is provided (Vol. 1.3, pages 4-86 – 4-105). [redacted] for 20 and 30 mg are respectively. 40 mg capsule is [redacted] The release specifications include [redacted] dimensions. The product specifications include product name, size, type, [redacted] composition, imprinting, packaging and storage condition information.

[redacted] (holder of DMF [redacted]) has provided a letter dated 31-Aug-200 (Vol. 1.3, page 4-104) stating that the [redacted] meets the Certificate of Suitability and USFDA September 1997 BSE Guidance for Industry.

Table 2: Composition of Ritalin modified release capsules, 20, 30 and 40 mg

Ingredient	Amount per capsule (mg)			Function	Reference to standards
Strengths	20 mg	30 mg	40 mg		
Capsule fill					
Methylphenidate hydrochloride	[redacted]			Active ingredient	USP
Sugar spheres	[redacted]			[redacted]	NF
	[redacted]			[redacted]	NF
Methacrylic acid copolymer	[redacted]			[redacted]	NF
Talc	[redacted]				USP/Ph. Eur.
Triethyl citrate	[redacted]			[redacted]	NF/Ph. Eur.
Polyethylene glycol	[redacted]				NF/Ph. Eur.
	[redacted]				USP/Ph. Eur.
	[redacted]				USP/Ph. Eur.
Capsule fill weight (theoretical)	[redacted]			—	—
[redacted] theoretical weight)	[redacted]			For encapsulation	[redacted]
Total capsule weight (theoretical)	[redacted]				—

***removed during processing

Evaluation: The specification and analytical methods for all the components are provided in Vol. 1.5, pages 4-221 – 4-232. This information is included in the section labeled Drug Product – BA/BE/Primary Stability Studies – Batch Information. It is one of the most unusual places in the application for this information.

2.2.1 Formulation Rationale

(Vol. 1.3, pages 4-37 – 4-65)

Ritalin® LA is proposed to be a modified release capsule containing beads coated in the ratio of 1:1 for immediate release: delayed release.

Table 3: Nominal IR and DR bead quantities in each capsule strength

Strength (mg)	Weight of DS* in IR beads/weight of DS* in DR beads per capsule (mg)	Theoretical fill weight of IR beads (mg/capsule)	Theoretical fill weight of DR beads (mg/capsule)
20			
30			
40			

* DS = drug substance methylphenidate hydrochloride

Elan Pharmaceutical Technologies under contract with Novartis has developed once-a-day modified release pulse formulation for methylphenidate hydrochloride based on their SODAS® (Spheroidal Oral Drug Absorption System) technology. The objective of this modified release dosage form is to deliver methylphenidate hydrochloride once-a-day for school age children. A number of development studies and prototype formulations were evaluated at Elan Pharmaceutical Technologies, Anthone, Ireland. The final formulation and the process were transferred to Elan Holdings Inc., Gainsville, GA for scale-up and commercial scale validation.

A. IR Beads Formulation

The formulation for immediate release beads requires complete release of drug substance methylphenidate in approximately . Two prototype formulations were evaluated. One used and the second contained only and released approximately

B. DR Beads Formulation

mechanisms of control were evaluated: a Formulations were assessed by in a system designed to

pH dependent mechanism:

was used to test for the The results from the data show

that [redacted]

[redacted] was used to test the [redacted] The [redacted]. Release of the drug substance occurs by [redacted] Dissolution data show that [redacted] delays the release of methylphenidate HCl but does not favor a subsequent [redacted] after the required [redacted] delay. [redacted] tested in combination with either [redacted] or [redacted] also did not exhibit the required dissolution specifications.

[redacted] was combined with [redacted] in a [redacted] ratio for this formulation. [redacted], has a [redacted] and [redacted] allowing for dissolution of the drug. [redacted] for [redacted] of methylphenidate HCl after the initial [redacted] delay.

The data shows that the [redacted] formulation allowed for a faster release of methylphenidate HCl after the initial [redacted] delay due to its pH sensitivity.

Formulations and excipients used in the manufacture of Ritalin® LA are listed below:

- Immediate Release (IR) beads are sugar spheres [redacted] methylphenidate HCl layered and coated with [redacted]
- The IR beads are coated with a mixture of [redacted] [redacted] is [redacted] and dissolves at [redacted] or above forming [redacted] in the [redacted]
- No compatibility studies were performed of the active ingredient with excipients used for formation of Ritalin LA. In particular, the most important is the interaction between the [redacted]. However, the drug product is on a stability protocol and degradation of the active material can be monitored.

Evaluation: The Ritalin® LA formulation is proposed to contain [redacted] of [redacted] Based on the values in Table 2, it is unclear how the [redacted] value is derived.

COMMENT 1: [redacted] is proposed to be [redacted] in the final Ritalin® LA formulation. For example, the 20 mg capsule contains [redacted] Please explain in detail the derivation of [redacted] value for [redacted] in each dosage strength.

2.3 Specifications & Methods for Drug Product Ingredients
(Vol. 1.3, page 4-25 – 4-41)

A. Active Ingredient

Methylphenidate HCl as the active ingredient is acceptable as per NDA 10-187 (refer to section 1 of this review for evaluation).

B. Inactive Ingredients

Compendial Excipients and Non-Compendial Excipients: Compendial excipients include [redacted] sugar spheres, triethyl citrate, talc, and PEG [redacted] The only non-compendial excipient used is the hard gelatin capsule. As per the evaluation in section 2.1/2.2 the capsules from [redacted] are acceptable.

Evaluation: Acceptable

2.4 Manufacturer
(Vol. 1.3, pages 4-46, 4-67 – 4-69)

The manufacture of drug substance (DS), manufacture, packaging and stability studies of drug product (DP) are listed at the following sites:

Site CFN#	Site Location	Site Function
1035761	ELAN HOLDINGS INC	Drug product manufacturer and quality control
2416082	Novartis Pharmaceuticals (CIBA)	Drug product quality control, stability and packaging
2210396	Novartis Pharmaceuticals (Sandoz)	Drug product Microbiological quality control only
2530802	[redacted]	Drug product packaging
2210396	Novartis Pharmaceuticals (Sandoz)	Drug Substance Manufacturer

2.5 Methods of Manufacturing and Packaging

A. Production Operations
(Vol. 1.3, page 4-81)

[redacted]

The following schemes provided by the sponsor illustrate the manufacturing process with in process controls at various steps: