

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201277Orig1s000

CHEMISTRY REVIEW(S)

NDA 201-277

Gadavist®

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Bayer Healthcare, Inc.

Applicant: Bayer Healthcare
PO Box 5225,
Princeton, NJ 06134

Background: This is a new molecular entity B1 type NDA. GADAVIST is approved in more than 50 countries, including the European Union (EU), Canada, Australia, South Africa, Mexico, New Zealand, Turkey and several of the Asian countries. It was first approved in Switzerland in 1998.

Indication: Magnetic Resonance Imaging Contrast Agent: (b) (4)

Presentation: Sterile solution for injection, presented in 7.5, 10, and 15mL, three prefilled syringes with 7.5, 10, and 15mL, and as Pharmacy Bulk Packs of 30 and 65 mL. Gadavist will be administered as an IV bolus prior to performing MRI scanning of the patient.

Establishments Evaluation Report (EER) Status: Acceptable

Consults:	EA -	Acceptable
	Statistics -	N/A
	Methods Validation -	Acceptable
	Biopharm-	N/A
	Microbiology -	Acceptable
	Pharm Toxicology -	Acceptable

Supporting DMFs All Acceptable

Original Submission: May 14, 2010
Re-submissions: N/A
Post-Approval CMC Agreements: None at this time.

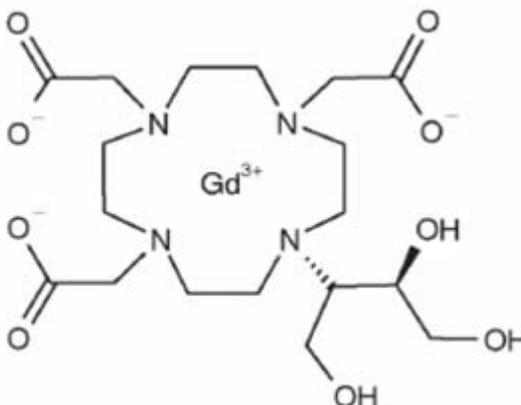
Drug Substance

The active ingredient of GADAVIST is “gadobutrol” (USAN) a racemic metal coordination complex of the rare earth element gadolinium (Gd^{3+}) which has strong paramagnetic properties which serves as the basis for contrast enhancement.

The octadentate ligand (butrol) of gadobutrol is a derivative of tetrazacyclododecane substituted at nitrogens with three acetate groups and one 2,3-dihydroxy-1-hydroxymethyl sidechain. (b) (4)

Gadobutrol is a white to off-white substance having a chemical formula of $C_{18}H_{31}GdN_4O_9$ and a molecular weight of 604.72. The racemic mixture contains two asymmetric centers in the trihydroxybutyl side chain.

Chemical structure, Molecular formula and Molecular weight:



Chemical Name(s):

10-[(1*SR*,2*RS*)-2,3-dihydroxy-1-hydroxymethylpropyl]-1,4,7,10-tetraazacyclododecane- 1,4,7-triacetic acid, gadolinium complex

IUPAC name: {10-[(1RS,2SR)-2,3-Dihydroxy-1-(hydroxymethyl)propyl]-1,4,7,10-tetraazacyclododecan- 1,4,7- triacetato}gadolinium(III)

Molecular Formula: C₁₈H₃₁GdN₄O₉ (anhydrous)

Molecular Weight: 604.72

The Drug substance information has been referenced to Bayer DMF 13061. A subset of DMF information is provided in the NDA. GDAVIST has a (b) (4) room temperature retest date. The DMF was reviewed and was found acceptable.

Drug substance is satisfactory

Drug product

GDAVIST is a non-ionic macrocyclic gadolinium contrast agent for magnetic resonance imaging (MRI). It is a sterile, pyrogen-free aqueous solution for intravenous injection containing 1.0 M gadobutrol (604.720 mg/mL). Its composition per each milliliter also includes (b) (4) of calcium sodium butrol, (b) (4) of trimetamol, (b) (4) of hydrochloric acid (1N) and (b) (4) of water for injection (WFI). It is packaged in single use, USP Type I glass vials (7.5 mL, 10 mL and 15 mL), pre-filled glass syringes (7.5 mL, 10 mL and 15 mL) and a pharmacy bulk package (30 mL and 65 mL). Following intravenous injection, GDAVIST distributes exclusively within the extracellular fluid, and is subject to fast elimination via the renal system. Exiry is 60 months.

Drug product is satisfactory

Labeling

Note that original proposed trade name “Gadovist” has been changed to Gadavist at the request of DMEPA.

Proposed label and labeling are acceptable except for the inclusion of a (b) (4)

The Division will request (b) (4) .

Overall Conclusion: From CMC point of view, the NDA is recommended for approval.

Eric Duffy, Ph.D.
Director, Division III
ONDQA/CDER/FDA

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/s/

ERIC P DUFFY
03/14/2011

NDA 201-277

Gadavist®

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Bayer Healthcare, Inc.

Applicant: Bayer Healthcare
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Princeton, NJ 06134

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	Statistics -	N/A
	Methods Validation -	Acceptable
	Biopharm-	N/A
	Microbiology -	Acceptable
	Pharm Toxicology -	Acceptable

Supporting DMFs All Acceptable

Original Submission: May 14, 2010
Re-submissions: N/A
Post-Approval CMC Agreements: None at this time.

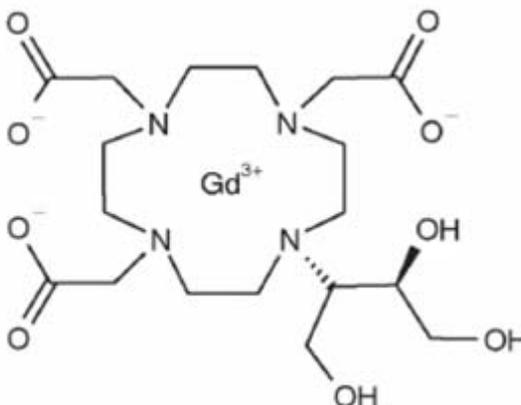
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Chemical structure, Molecular formula and Molecular weight:



Chemical Name(s):

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IUPAC name: {10-[(1RS,2SR)-2,3-Dihydroxy-1-(hydroxymethyl)propyl]-1,4,7,10-tetraazacyclododecan- 1,4,7- triacetato}gadolinium(III)

Molecular Formula: C₁₈H₃₁GdN₄O₉ (anhydrous)

Molecular Weight: 604.72

The Drug substance information has been referenced to Bayer DMF 13061. A subset of DMF information is provided in the NDA. GADAVIST has a (b) (4) room temperature retest date. The DMF was reviewed and was found acceptable.

Drug substance is satisfactory

Drug product

GADAVIST is a non-ionic macrocyclic gadolinium contrast agent for magnetic resonance imaging (MRI). It is a sterile, pyrogen-free aqueous solution for intravenous injection containing 1.0 M gadobutrol (604.720 mg/mL). Its composition per each milliliter also includes (b) (4) of calcium sodium butrol, (b) (4) of trimetamol, (b) (4) of hydrochloric acid (1N) and (b) (4) of water for injection (WFI). It is packaged in single use, USP Type I glass vials (7.5 mL, 10 mL and 15 mL), pre-filled glass syringes (7.5 mL, 10 mL and 15 mL) and a pharmacy bulk package (30 mL and 65 mL). Following intravenous injection, GADAVIST distributes exclusively within the extracellular fluid, and is subject to fast elimination via the renal system. Expiry is 60 months.

Drug product is satisfactory

Overall Conclusion: From CMC point of view, the NDA is recommended for approval.

Eric Duffy, Ph.D.
Director, Division III
ONDQA/CDER/FDA

Labeling

Proposed label and labeling are acceptable except for the tradename for the drug product: note that original proposed trade name "Gadovist" has been changed to Gadavist at the request of DMEPA. Updated FPL is awaited.

(b) (4)

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/s/

ERIC P DUFFY
03/11/2011

Review of Chemistry, Manufacturing, and Controls

NDA 201–277

Gadavist[®]

Bayer Healthcare, Inc.

by

Chemistry Reviewer: David A. Place, PhD

Division of New Drug Quality Assessment III Division IX

for

Clinical Review Division: HFD-160

Division of Medical Imaging Products

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Chemistry Review Data Sheet

1. NDA 201-277

2. REVIEW # 1

3. REVIEW DATE: 24-FEB-2011

4. REVIEWER: David A. Place, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents

N/A

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Document Date

14-MAY-2010

7. NAME & ADDRESS OF APPLICANT:

Name: Bayer Healthcare
Address: PO Box 1000, Montville, NJ 07045-1000
Representative: Philip Johnson, Deputy Director, Global Regulatory Affairs
Telephone: (973) 487-2181

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Gadavist®
b) Non-Proprietary Name: Gadobutrol (INN)
c) Code Name/# (ONDC only): BAY 86-4875
d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Not Applicable to NDAs

10. PHARMACOLOGICAL CATEGORY/INDICATION: Magnetic Resonance Imaging Contrast Agent: ^{(b) (4)}

11. DOSAGE FORM: Sterile solution for injection, presented in 7.5, 10, and 15mL, three prefilled syringes with 7.5, 10, and 15mL, and as Pharmacy Bulk Packs of 30 and 65 mL.

12. STRENGTH/POTENCY: 1.0 M, equiv. to 604.72 mg gadobutrol/mL

13. ROUTE OF ADMINISTRATION: IV

14. OTC DISPENSED: X OTC

15. SPOTS (Special Products On-Line Tracking System)

_____ SPOTS product – Form Completed

 X Not a SPOTS product**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

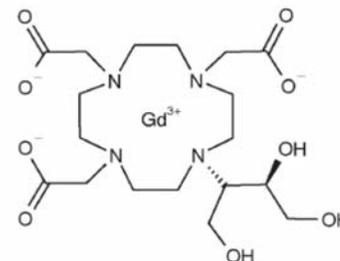
Chemical Name(s): 10-[(1*SR*,2*RS*)-2,3-dihydroxy-1-hydroxymethylpropyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, gadolinium complex

IUPAC name: { 10-[(1*RS*,2*SR*)-2,3-Dihydroxy-1-(hydroxymethyl)propyl]-1,4,7,10-tetraazacyclododecan-1,4,7-triacetato }gadolinium(III)

CAS Registry No. 138071-82-6

Molecular Formula: C₁₈H₃₁GdN₄O₉ (anhydrous)

Molecular Weight: 604.72

**17. RELATED/SUPPORTING DOCUMENTS:****A. DMFs:**

DMF #	Type	Holder	Item Referenced	Code ^a	Status ^b	Date Review Completed	Comments
13061	II	Bayer	Gadobutrol	1	Adequate	24-FEB-2011	N/A
13063	II	Bayer	Calcobutrol	1	Adequate	24-FEB-2011	N/A

a Action codes for DMF Table:

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")

b Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

Patent: US patent No. 5,980,864, issued 11/9/199, expires 11/9/2016

Exclusivity: Five years requested.

18. STATUS:

ONDC:

CONSULTS/ CMC Related Reviews	RECOMMENDATION	DATE	REVIEWER
Biometrics		N/A	
EES	Acceptable		2/24/2011
Pharm/Tox	Acceptable	2/15/2011	Olayinka A. Dina
Biopharm		N/A	
LNC	USAN Approved	N/A	
Methods Validation	Acceptable		
OPDRA	Acceptable		
EA	Categorical Exclusion Satisfactory		David Place
Microbiology	Acceptable	1/13/2011	Jessica Cole

OGD:

CONSULTS/ CMC Related Reviews	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	N/A		
Methods Validation	N/A		
Labeling	N/A		
Bioequivalence	N/A		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW (OGD Only): *Not Applicable*

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes
 ____ No If no, explain reason(s) below:

Chemistry Review for NDA 201–277

Executive Summary

I. Recommendations

- A. Recommendation and Conclusion on Approvability
NDA 201–277 is recommended for approval.
- B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
None identified.

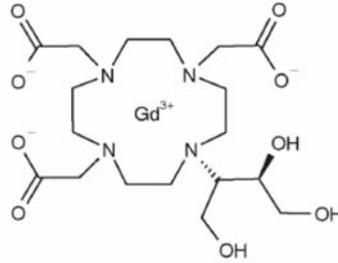
II. Summary of Chemistry Assessments

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

GADAVIST is a non-ionic macrocyclic gadolinium contrast drug for magnetic resonance imaging (MRI). It is a sterile, pyrogen-free aqueous solution for intravenous injection containing 1.0 M gadobutrol (604.720 mg/mL). Its composition per each milliliter also includes (b) (4) of calcium sodium butrol, (b) (4) of trimetamol, (b) (4) of hydrochloric acid (1N) and (b) (4) of water for injection (WFI). It is packaged in single use, USP Type I glass vials (7.5 mL, 10 mL and 15 mL), pre-filled glass syringes (7.5 mL, 10 mL and 15 mL) and a pharmacy bulk package (30 mL and 65 mL). Following intravenous injection, GADAVIST distributes exclusively within the extracellular fluid, and is subject to fast elimination via the renal system. The active ingredient of GADAVIST is “gadobutrol” (USAN) a racemic metal coordination complex of the rare earth element gadolinium (Gd^{3+}) which has strong paramagnetic properties which serves as the basis for contrast enhancement. GADAVIST is approved in more than 50 countries, including the European Union (EU), Canada, Australia, South Africa, Mexico, New Zealand, Turkey and several of the Asian countries. It was first approved in Switzerland in 1998.

The octadentate ligand (butrol) of gadobutrol is a derivative of tetrazacyclodecane substituted at nitrogens with three acetate groups and one 2,3-dihydroxyl-1-hydroxymethyl sidechain. (b) (4)

Gadobutrol is a white to off-white substance having a chemical formula of $C_{18}H_{31}GdN_4O_9$ and a molecular weight of 604.72. The racemic mixture contains two asymmetric centers in the trihydroxybutyl side chain. It is electrically neutral and has the following chemical structure:



The two extra OH groups on the trihydroxybutyl side chain enhances its aqueous solubility. It has a thermodynamic stability constant $\log K_{GdL}$ of 21.75 ± 0.3 . GADAVIST has an expiration date of 60 months at room temperature. Calcium sodium butrol (or calcobutrol), the calcium complex of the ligand functions as (b) (4)

All manufacturing sites have received an acceptable CGMP inspection (02/24/2011).

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

Single-dose vials of Gadavist containing 1.0 M gadobutrol will be administered as an IV bolus prior to performing MRI scanning of the patient.

C. Basis for Approvability or Not-Approval Recommendation

The submission contains comprehensive and complete information on the drug substance and drug product manufacturing, controls, and stability. There are no pending CMC issues. All manufacturing sites have been found to be acceptable by the Office of Compliance.

III. Administrative

A. Reviewer's Signature

David A. Place

Chemist David A. Place, PhD _____ Date: 24-FEB-2011

B. Endorsement Block Same date as draft review

Chemistry Lead Eldon Leutzinger, PhD _____ Date: _____

Branch Chief Ali Al Hakim, PhD _____ Date: _____

Project Manager James Moore, MPH _____ Date: _____

C.

cc: Orig. NDA 201-277
HFD-160/Division File
HFD-
HFD-160/MO/
HFD-160/Pharm/
HFD-160/DivDir/

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/s/

DAVID A PLACE
02/25/2011

ALI H AL HAKIM
02/25/2011

Initial Quality Assessment (IQA) Branch VII

Division of New Drug Quality Assessment-III Office of New Drug Quality Assessment

OND Division: Division of Medical Imaging Products

NDA: **201277**

Applicant: Bayer HealthCare Pharmaceuticals Inc., P.O. Box 1000, Monville, NJ 07045-1000

Stamp Date: 14-May-2010

PDUFA Date:

Trademark: Gadovist (Proposed)

Established Name: Gadobutrol Injection

Laboratory Code: ZK 00135079

Dosage Form: Injection solution

Route of Administration: Intravenous Injection

Strength: 1 mmol/mL

Indication: Gadovist is indicated for intravenous use in diagnostic MRI in adults and children (2 years of age and older) to detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system.

CMC Reviewer: Ravindra K. Kasliwal, Ph.D.

	YES	NO
ONDQA Fileability:	X	
Comments for 74-Day Letter	X	

Summary and Critical Issues:

A. Summary

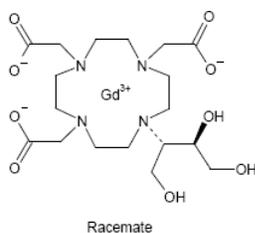
Background Summary

GADOVIST is a non-ionic macrocyclic gadolinium-based extracellular contrast agent for magnetic resonance imaging (MRI) that, after intravenous injection, distributes exclusively within the extracellular fluid, and is subject to fast elimination via the renal system, without metabolism. The active ingredient is Gadobutrol, a racemic complex of the rare earth element gadolinium (Gd³⁺) that has strong paramagnetic properties. The paramagnetic properties are the basis for contrast enhancement in MRI.

GADOVIST was first approved in Switzerland in 1998. Gadobutrol has since been approved in more than 50 countries, including all of the European Union (EU) countries, Canada, Australia, South Africa, Mexico, New Zealand, Turkey, and several Eastern European and Asian countries.

Drug Substance Summary:

Gadobutrol, a white to off-white substance having the molecular formula C₁₈H₃₁GdN₄O₉ and a molecular weight of 604.72, and contains two asymmetric centers in the trihydroxybutyl side chain. The active pharmaceutical ingredient (API) Gadobutrol (I.N.N.) is an electrically neutral gadolinium complex, formed by complexation reaction of gadolinium ions (Gd³⁺) and the ligand Butrol. Butrol is a heterocyclic compound substituted with three molecules acetic acid and a trihydroxybutyl side chain.



The drug substance is manufactured (synthesis, purification and release control) by:

Bayer Schering Pharma AG,
Bergkamen plant
Ernst-Schering-Straße 14,
D-59179 Bergkamen, Germany

The Drug substance information has been referenced to Bayer DMF 13061. A subset of DMF information is provided in the NDA. A Letter of Authorization (dated 30-Sep-2009) from is provided in Module 1 of the NDA.

The DMF contains the manufacturing process information. Company indicates that in the course of development the Gadobutrol synthesis was (b) (4)

The NDA and DMF contain detailed impurity characterization data, which should be reviewed for safety and conformance to ICH requirements.

A retest period of (b) (4) has been proposed. The stability data / studies should be evaluated to determine suitability of proposed retest period.

Drug Product Summary:

The drug product has following composition:

No.	Name of Ingredient	Unit	Function	Refer to Standards
Active substances:				
1.	Gadobutrol	604.720 mg	Active ingredient	(b) (4)
Excipients:				
1.	Calcium sodium butrol (Calcobutrol sodium)	(b) (4)		(b) (4)
2.	Trometamol	(b) (4)		USP
3.	Hydrochloric acid, (b) (4)	(b) (4)		USP
4.	Water for injection	(b) (4)		USP

GADOVIST solution for injection will be marketed in following configuration:

- Single dose vials in sizes of 7.5, 10, and 15 mL.
- Single dose pre-filled glass syringes of 7.5, 10 and 15 mL.
- Pharmacy bulk pack of 30 mL in a glass vial and 65 mL (b) (4)

All sizes of GADOVIST will also be available with a Radio Frequency Identification (RFID) tag incorporated into the vial/syringe label.

The excipient **Calcobutrol sodium** in GADOVIST functions as (b) (4)

Calcium sodium butrol (Calcobutrol) is described as excipient in the DMF (see USDMF No. 13063). A Letter of Authorization (dated 30-Sep-2009) from Bayer is provided in Module 1 of the NDA. Calcobutrol is considered a novel excipient and its safety should be evaluated by the Pharmtox reviewer.

GADOVIST is manufactured by Bayer Schering Pharma AG at Wedding Plant in Müllerstr. 170 - 178, D-13353 Berlin, Germany.

The manufacturing process consists of the manufacture of the bulk solution. (b) (4)

The controls for the manufacturing process and finished product are proposed which should be evaluated for adequacy.

The company has proposed an expiration dating period of 60 months at controlled room temperature storage. The stability data are provided that should be evaluated for adequacy to support the 60 month expiration dating period in different configurations.

The following facilities are involved in drug product manufacture and testing:

Name and Address	Contact Person at Site	Telephone Number / Fax Number	E-mail Address	Registration Number	Stage of Manufacturing	Ready for Inspection
Bayer Schering Pharma AG Ernst-Schering Str. 14 D-59179 Bergkamen, Germany	(b) (6)			(b) (6)	Facility for synthesis, purification, testing, release and stability testing of drug substance	Yes
Bayer Schering Pharma AG Wedding Plant Müllerstr. 170 - 178 D-13353 Berlin, Germany					Manufacturing, filling, sterilization, labeling and packaging of drug product. Release and stability testing.	Yes
Bayer Healthcare LLC Animal Health 12809 Shawnee Mission Parkway Shawnee, KS 66216, USA					Secondary Packaging	Yes
(b) (4)				(b) (4)	Secondary Packaging	Yes
Bayer HealthCare Pharmaceuticals 6 West Belt Wayne, NJ 07470, USA	(b) (6)			2243252	Administrative (paper) Release for distribution	Yes

B. Critical Issues for Review

Following are preliminary CMC aspects that have been noted and the primary reviewer should review the NDA in detail for CMC acceptability. The following steps are critical steps and particular attention should be paid to these during the review.

- The controls for the input materials in the drug product are adequate.
- Sufficient information exists to support stability of drug substance.
- Controls for drug substance and drug product are adequate.
- Critical process parameters and product specifications should be evaluated.
- Product's stability as well as in-use stability should be evaluated.
- Sufficient data exists to support use of pharmacy bulk pack.
- Sterility assurance is adequate.
- Container closure system that maintains product sterility.

C. Comments for 74-Day Letter

Provide DMF references for the vial, syringes and pharmacy bulk pack bottles that are used for Gadovist product.

Fileability Summary

	PARAMETER	YES	NO	COMMENTS
1.	Is the CMC section sufficiently complete to permit substantive review to begin?	X		
2.	Is the CMC section indexed, paginated and organized in a manner to allow substantive review to begin?	X		
3.	Is the CMC section legible so that substantive review can begin?	X		
4.	Are all of the facilities (manufacturing, packaging, testing, sterilization, etc.) appropriately delineated with full addresses?	X		
5.	Is a statement provided that all the facilities are ready for cGMP / PAI inspection?	X		
6.	Has the applicant developed an environmental impact assessment or claimed categorical exclusion under the applicable regulations?	X		
7.	Does the section contain controls for drug substance?	X		
8.	Does the section contain controls for drug product?	X		
9.	Has the stability data and analysis been provided to support the proposed expiry?	X		
10.	Has all the information requested during the IND phase, and the pre-NDA meetings been included?	X		
11.	Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional labeling policies, and the design of the development package?	X		
12.	Has an investigational formulations section been provided?	X		

13.	Has the applicant provided a method validation package?	X		
14.	Is a separate microbiological section included?		X	Microbiology information is provided in module 3 of the NDA.

Drug Master Files Referenced					
DMF Number	Holder	Item Referenced	LOA Included		Comments
			Yes	No	
13061	Bayer HealthCare Pharmaceuticals Inc. Box 1000, Montville NJ 07045-1000 USA	Gadobuterol	X		Type II; LOA is located in M1, Section 1.4.1.
13063	Bayer HealthCare Pharmaceuticals Inc. Box 1000, Montville NJ 07045-1000 USA	Calcobuterol sodium	X		Type IV; LOA is located in M1, Section 1.4.1.

Consults To Be Initiated:	
Item	Consult To
1. Trademark: Gadovist 1.0	DMEPA
2. Microbiology	OPS Microbiology Staff

IQA Performed By: Ravindra K. Kasliwal, Ph.D.
CMC Reviewer

Date: 24-June-2010

Branch Chief: Ali Al-Hakim, Branch Chief

Date: 24-Jun-2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201277	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	GADOBUTROL INJECTION

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/s/

RAVINDRA K KASLIWAL
06/24/2010

ALI H AL HAKIM
06/24/2010