

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-277

CHEMISTRY REVIEW(S)

**Initial Quality Assessment
Branch V
Pre-Marketing Assessment Division III
Office of New Drug Quality Assessment**

OND Division: Division of Drug Oncology Products
NDA: 22-277
Applicant: Schering Corporation.
Letter Date: 23 January, 2008
Stamp Date: 24 January, 2008
PDUFA Goal Date: 24 November, 2008 (standard)
Tradename: Temodar
Established Name: Temozolamide
Dosage Form: Powder for Injection -- 100 mg/vial
Route of Administration: IV
Indication: Newly Diagnosed GBM and Refractory Anaplastic Astrocytoma.

Regulatory Filing For 505 (b) (2)
Related IND IND 68,395

Assessed by: Haripada Sarker

Yes No

ONDQA Fileability: x

Comments for 74-Day Letter: x

Background Summary

The application introduces the drug product, Temodar ^{(b) (4)} for Injection. Temodar® is supplied as a lyophilized powder to be reconstituted with Sterile Water for Injection at the time of use. The IV formulation is intended for use in patients with swallowing difficulties as well as those where nausea and vomiting related to the use of the oral formulation prevent them from making use of temozolomide. Temodar® (oral) capsules (5 mg, 20 mg, 25mg, 100 mg, 14mg, 180mg and 250 mg) is currently approved in the United States under Schering's NDA 21-029. Temodar® (also known as the trade name Temodal® is approved internationally in similar indications in over 80 countries as temozolomide capsules, 5 mg, 20 mg, 100 mg, and 250 mg.

Applicant referred to approved NDA 21-029 for drug substance CMC information. The CMC section of the submission mostly includes drug product related information. No pre-NDA meeting with CMC issue is indicated as per DARRTS document search. However, applicant has made several communications to the Agency to demonstrate the bioequivalence between two formulations (capsule vs injection solution). The CMC information of the NDA is submitted as per CTDQ format.

Drug Substance (DS)

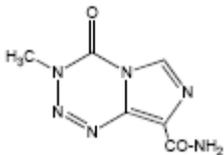
Applicant referred to approved NDA 21-029 for all drug substance CMC information. Only differences are Bacterial Endotoxins and Microbial limit tests have been added to the specifications of the parenteral grade temozolomide drug substance. Request has been made to office of compliance to provide inspection report for the DS related sites listed in the submission. The DS is identified with following attributes.

Chemical Name: 3,4-Dihydro-3-methyl-4-oxoimidazo-[5,1-d]-1,2,3,5-tetrazin-8-carboxamide

Formulas: $C_5H_6N_5O_2$

Molecular Weight: 194.15

Structural Formula:



DS Critical Issues

- Updated information on Bacterial Endotoxins and Microbial limit tests have been added to the DS specifications, which is needed to be consulted with microbial reviewer.
- EER information for DS needs to be re-examined for accuracy.
- The cross-referred NDA 21-029 for DS information should be evaluated to support the NDA. Specifically, any change in DS manufacturing site, specification or stability in reference NDA 21-029.

Drug Product (DP)

Temozolomide ^{(b) (4)} for Injection is formulated as a sterile lyophilized powder. The powder is filled into a vial (100 mg/vial), which is intended to reconstitute with WFI (2.5mg/mL) prior to administration. The powder formulation contains the API and the following compendial (USP/NF) excipients: Mannitol, L-threonine, Polysorbate 80, Sodium Citrate Dihydrate, Hydrochloric Acid, and Water for Injection q.s. Temozolomide Powder is manufactured by ^{(b) (4)}

^{(b) (4)} The analytical test results are provided from the ^{(b) (4)} batches representative of commercial process of Temozolomide ^{(b) (4)} for Injection. The filled vials ^{(b) (4)} are tested for: Description, Reconstituted Solution Color (UV), Assay and Degradation (HPLC), Identification (IR), pH, Moisture (KF), Uniformity of Dosage Units <USP 905>, Particulate Matter <USP 788>, Bacterial Endotoxins <USP 85>, Sterility <USP 71>. DP is presented in 100 mL-20 mm ^{(b) (4)} glass vials sealed with 20 mm rubber stopper and capped with 20 mm aluminium flip-off seals.

The filled vials are tested for description, particulate matter, extractable volume, assay (HPLC), identification (HPLC and TLC), chromatographic purity (HPLC), ethanol content (GC), sterility (USP <71>), and bacterial endotoxins (USP <85>). Temozolomide ^{(b) (4)} for Injection is packaged into Type I clear glass vials fitted with gray ^{(b) (4)} rubber stoppers and flip-off aluminum seals.

Compatibility studies of Temozolomide Powder in container/closure system as well as compatibility of DP reconstituted WFI in infusion system are conducted during drug development studies. The proposed manufacturing site is listed below:

Manufacturing and Testing:

(b) (4)

The Applicant provides long term (5°C, 24 months; 25°C/60% RH, 24 months; 30°C/65% RH, 24 months) and accelerated (40°C/75% RH, 6 months) stability data for (b) (4) registration batches of DP stored in 100 mL vial. Stability of DP infusion solution at 25°C/60% RH is provided to support 24 hours stability.

The Applicant proposes a 36-month expiration dating period for the Temozolomide (b) (4) for Injection, when stored under refrigerated condition (5°C).

Drug Product Critical Issues

- New degradants in DP powder (finished dosage form) and infusion solution, when compared with DS specification.
- Check EES of DP sites for accuracy.
- DP showed decomposition on (b) (4) sterilization, thus (b) (4) sterilization was chosen. Microbial consult for sterilization methods and specification are required for evaluation.
- DMFs for container/closure system need to be reviewed for adequacy of the NDA.
- Two different acceptance criteria for DP impurity, (b) (4) is proposed for release and for stability specification. Enough justification should be provided to qualify the level.
- Justification of 36-months expiration based on 24-months stability data and whether ICH Q1E can be applied for this extrapolation.
- The DP labeling, which is submitted in PRL format, need to be evaluated for its relevant CMC sections.

Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		

8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		Tentatively.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		Not applicable. No CMC issue in pre-NDA meeting.
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		
16	Have all consults been identified and initiated? (bolded items to be handled by ONDQA PM)	√ √ √		Microbiology Pharm/Tox Biopharm Statistics (stability) OCP/CDRH/CB ER LNC DMETS/ODS EER

Have all DMF References been identified? Yes (√) No ()

DMF Number	Holder	Description	LOA Included
8533 (Type III)	Schering-Plough Corp., NJ	Temozolamide DP Container (b) (4) glass	Yes
(b) (4) (Type III)	(b) (4)	(b) (4)	Yes

Comments and Recommendations

The application is fileable and no 74-Day Letter issue has been identified at this point. Facilities have been entered into EES for inspection. A single reviewer is recommended for this NDA, since the manufacturing process is not particularly complex.

Haripada Sarker
Pharmaceutical Assessment Lead (PAL)

March 18, 2008
Date

Ravi Harapanhalli, Ph.D.
Branch Chief

March 18, 2008
Date

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/s/

Haripada Sarker
3/18/2008 03:54:19 PM
CHEMIST

Ravi Harapanhalli
3/19/2008 09:50:49 AM
CHEMIST

Memorandum

To: NDA 22-277
Through: Sarah C. Pope, Ph.D.
From: Debasis Ghosh, Ph.D.
Date: 18-FEB-2009
Re: Final CMC Recommendation for NDA 22-277

NDA 22-277 (Temodar[®] for injection) was initially submitted on 23-JAN-2008 and was granted a standard review by the Agency. Resolution of all CMC deficiencies is captured in Chemistry Review #1 (dated 12-NOV-2008), with the exception of a final acceptable recommendation from the Office of Compliance. Due to this deficiency, a Complete Response letter was issued by the Agency on 24-NOV-2008. The Applicant subsequently responded in an amendment (#0014) dated 22-DEC-2008.

The Office of Compliance issued an overall acceptable recommendation (dated 08-JAN-2009) for this application. Therefore, there are currently no outstanding CMC deficiencies for this application.

From a CMC perspective, approval of NDA 22-277 is recommended.

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/s/

Debasis Ghosh
2/23/2009 02:17:07 PM
CHEMIST

Sarah Pope
2/23/2009 02:33:03 PM
CHEMIST

Memorandum

To: NDA 22-277
CC: Jila Boal, Ph.D.; Haripada Sarker, Ph.D.
From: Sarah C. Pope, Ph.D.
Through: Rik Lostritto, Ph.D.
Date: 11/24/2008
Re: Final CMC recommendation for NDA 22-277

NDA 22-277 was initially submitted on 24-JAN-2008 and was granted a standard review by the Agency. Resolution of all CMC deficiencies is captured in Chemistry Review #1 (dated 13-NOV-2008) with the exception of a final recommendation from the Office of Compliance.

This memo serves to update that determination. The Office of Compliance issued an overall withhold recommendation for this application on 20-NOV-2008. Accordingly, from a CMC perspective, approval of NDA 22-277 cannot be recommended until any related deficiencies are resolved.

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/s/

Sarah Pope
11/24/2008 11:16:56 AM
CHEMIST

Richard Lostritto
11/24/2008 01:11:48 PM
CHEMIST

Chemistry Assessment Section

NDA 22-277

**Temodar® (temozolomide) for Injection
100 mg/Vial**

Schering Corporation

Jila H. Boal, Ph. D.

**Office of New Drug Quality Assessment
Division of Pre-marketing Assessment and Manufacturing Science**

**Chemistry, Manufacturing, and Controls (CMC)
Review of Original NDA
For the Division of Drug Oncology Products
(HFD-150)**

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Chemistry Review Data Sheet

1. NDA # 22-277

2. REVIEW #: 1

3. REVIEW DATE: November 12, 2008

4. REVIEWER: Jila H. Boal, Ph. D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA 21-029	12-Aug-1998

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
CMC Review # 1 of NDA 21-029	31-Nov-1998
Supplements for NDA 21-029	All CMC supplements submitted since the approval of the NDA
Annual Reports of NDA 21-029	All ARs since the approval of the NDA.
Original NDA 22-277	23-January-2008
Amendment 0001, BC (drug substance specifications and stability data)	16-May-2008
Amendment 0003, BC (drug product specification and post-approval stability)	22-August-2008
Amendment 0004, BC, (microbiology)	24-September-2008
Amendment 0005, BC (drug substance polymorphic form in the lyophilized powder and the solubility of the drug product lyophilized powder)	2-October-2008
Amendment 0007, Labeling including the corrections	17-October-2008
Amendment 0008, Draft Container / Closure Labels including the corrections	04-November-2008



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

E-mail containing the final corrections to the PI, PPI and Container / Closure Labels	12-Nov-2008
---	-------------

7. NAME & ADDRESS OF APPLICANT:

Name: Schering Corporation
Address: 2000 Galloping Hill Road
Kenilworth, NJ 07033
Representative: Lucine Karjian, Associate Director
Global Regulatory Affairs - CMC
Telephone: 908-740-5100

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: Temodar
Non-Proprietary Name (USAN): Temozolomide
Code Name/# (ONDQA only): SCH 52365
Chem. Type/Submission Priority (ONDQA only): 2S
Chem. Type: 3 (New Dosage Form), Standard Review, substantially equivalent
Submission Priority: No

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

10. PHARMACOL. CATEGORY: Antineoplastic

11. DOSAGE FORM: Lyophilized Powder for Injection

12. STRENGTH/POTENCY: 100 mg/vial, 2.5 mg/ml upon reconstitution in ^(b)₍₄₎ ml of Sterile Water For Injection (SWFI)

13. ROUTE OF ADMINISTRATION: Intravenous infusion

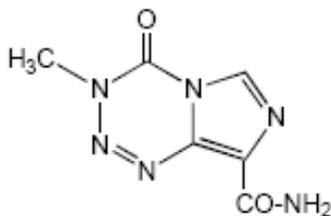
14. Rx/OTC DISPENSED: Rx OTC

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

Not a SPOTS product

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

Chemistry Assessment Section



CAS Name: 3,4-Dihydro-3-methyl-4-oxoimidazo[5,1-d]-as-tetrazine-8-carboxamide

The (CAS) Registry Number: 85622-93-1

Molecular weight for the drug substance: 194.15

Molecular Formula: C₆H₆N₆O₂

17. RELATED/SUPPORTING DOCUMENTS: None.

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COD E ¹	STATUS ²	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	August 2, 2007	3 and 4	Adequate for use in lyophilized powder for injection drugs	Reviewed in 1998 by Ravi Harapanhalli, Ph.D. for NDA 20-975, in 1999 and 2000 by chemists at the OGD.
(b) (4)	III	(b) (4)	(b) (4)	May 9, 2007	3	Adequate for use in lyophilized powder for infusion drugs	Reviewed on October 10, 2002 by Elisabeth Chikhale, Ph.D. for NDA 21-223.

¹ 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")

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

Other Documents: None

Chemistry Assessment Section

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDQA:

CONSULTS / CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not consulted. Real time stability data provided.	NA	NA
EES	Pending	Submitted on Feb 15, 2008	Shawnte Adams
Pharm / Tox	<p>Pharm-Tox was consulted regarding the qualification of the drug substance process impurity (b) (4) exceeding ICH Q3A threshold of 0.15% and qualification of (b) (4) degradation product, NMT (b) (4) in the drug product exceeding the ICH Q3B threshold of 0.2%. It was determined that the submitted qualification toxicity studies for these (b) (4) impurities were not adequate. De novo studies will be conducted as a phase IV commitment.</p> <p>The adequacy of the safety assessment on the total amount of bromine leaching from the stopper was consulted to the Pharm-Tox discipline and was determined to be acceptable.</p>	Communicated through an e-mail dated October 20, 2008.	Hans Rosenfeldt, Ph.D.
Biopharm	N/A		
LNC	N/A, conventional dosage form.		
Methods Validation	N/A, according to the current ONDQA policy.		
DDMAC	To review the proposed	Submitted on Feb	Stephanie Victor,

Chemistry Assessment Section

	product labeling and any relevant advertising for this NDA.	15, 2008 Review Completion date: October 15, 2008	PharmD, Regulatory Review Officer There was one comment on the labeling regarding the likely side effects of Temodar. Please see this comment in the DDMAC review in DFS.
DMETS / DSRCS*	To review Package insert labeling and patient labeling contained in the NDA submission. To review the proprietary Name	Submitted date Feb 15, 2008	Tara P. Turner, Pharm. D. Division of Medication Error Prevention and Analysis. Office of Surveillance and Epidemiology
EA	Categorical exclusion granted (see CMC Review Notes, below)	October 24, 2008	Jila H. Boal
Microbiology	Recommend Approval for evaluation of test methods and specification related to the DS and the DP sterility, and any other related microbial validation during drug product manufacturing. Validation of the (b) (4) filling and the Sterilization process.	Submitted on March 19, 2008 Review Completion date: Sept 25, 2008	Bryan S. Riley, Ph.D.

*DMETS has recently been changed to DMEPA (Division of Medication Error Prevention and Analysis) due to the reorganization.

The Chemistry Review for NDA # 22-277

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the perspective of chemistry, manufacturing, and controls, this NDA is recommended for approval, pending an overall acceptable recommendation from the Office of Compliance.

The CMC reviewer's revisions of the package insert, patient information, and SPL Drug Listing Data Element, are included. These revisions were accepted by the applicant. Amendment 0007, October 17, 2008 contained the suggested corrections to the label. The corrections to the carton label and the vial label were conveyed to the applicant on October 30, 2008. The applicant's response to the CMC reviewer's and the DMEPA reviewer's final corrections is satisfactory. The responses were received as e-mail on November 12, 2008.

The CMC reviewer found that the acceptance criteria of NMT (b) (4) for (b) (4) impurity in the drug substance and (b) (4) of NMT (b) (4) in the drug product exceeds the recommended ICH Q3A and ICH Q3B qualification thresholds. During the NDA review, it was determined by the Pharmacology-Toxicology reviewer (Dr. H. Rosenfeldt) that the (b) (4) impurities (b) (4) were not adequately qualified. The Pharmacology-Toxicology discipline did not find the submitted toxicity studies adequate to qualify these (b) (4) impurities. The (b) (4) impurities needed to be qualified, according to the toxicity studies recommended by the Division of Drug Oncology Pharmacology-Toxicology review team. The qualification of these (b) (4) impurities was deferred as a Pharmacology-Toxicology Phase IV commitment. Please refer to the Pharmacology-Toxicology review for further information.

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 and Drug Substance

(1) Drug Substance:

The pro-drug temozolomide is a cytotoxic alkylation agent related to a series of imidazotetrazinones. At neutral and alkaline pH, temozolomide is rapidly hydrolyzed to the active 5-(3-methyltriazene-1-yl) imidazole-4-carboxamide (MTIC). Temozolomide hydrolysis

Chemistry Assessment Section

takes place even faster at alkaline pH. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA at the O6 and N7 positions of guanine.

Schering cross referenced their NDA 21-029 for all CMC information related to the drug substance. NDA 21-029 was submitted for an oral capsule formulation of temozolomide and was approved in 1999. There have not been any major changes in the temozolomide manufacturing process, and since the approval of the NDA 21-029, the drug substance manufacturing site has remained the same.

The drug substance batches that will be used for this parenteral formulation will be tested for microbial limit and bacterial endotoxins. Stability data for three batches of the drug substance showed that the drug substance remained sterile and endotoxin free for up to 24 months. The drug substance long term stability storage condition is $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$.

Note that the chemical stability of the drug substance is based on a retest date of $(b)(4)$ months when stored at 5°C (approved in NDA 21-029). Although data on the drug substance sterility and endotoxins are available for up to 24 months, since the drug product remains sterile and endotoxin free for up to 24 months when kept at 5°C long term, and $25^{\circ}\text{C}/60\%\text{RH}$ and $30^{\circ}\text{C}/65\%\text{RH}$ accelerated storage conditions, the retest date of $(b)(4)$ months for the drug substance batches manufactured for use in the parenteral formulation of temozolomide, is considered valid.

The levels of drug related impurities and degradation products, except for the process impurity $(b)(4)$ of NMT $(b)(4)$ in the drug substance are based on the ICH Q3A recommendations. The $(b)(4)$ impurity exceeded the qualification threshold and was consulted to the Pharmacology-Toxicology reviewer for assessment of qualification. The previous qualification toxicity study performed on this impurity was through oral dosing in rats. The Pharm-Tox discipline recommended that the applicant qualify this impurity according to the intravenous (IV) route of administration for this product. The toxicity qualification was deferred as a Pharmacology-Toxicology Phase 4 commitment to the applicant.

There is no structural alert genotoxic impurity in the drug substance.

The drug substance shipped from the U.S. manufacturing site to Schering's Cork Ireland facility is accepted based on the Certificate of Analysis (COA). The drug substance is then shipped to the drug product manufacturing site at $(b)(4)$.

The drug substance specifications are the same as in the approved NDA 21-029 with additional tests for sterility and bacterial endotoxins.

Based on the acceptable stability data provided for temozolomide drug substance, a retest date of $(b)(4)$ months for temozolomide, when kept at the long term storage temperature of $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$, is justified.

Chemistry Assessment Section

(2) Drug Product:***Description of the Drug Product***

Temozolomide for Injection (100 mg/vial) is for IV administration. The IV formulation has been developed as a bioequivalent dosage form to the approved capsules.

The drug product is formulated as a lyophilized powder and contains temozolomide (100 mg), Mannitol, USP (600 mg), L-threonine, USP (160 mg), Polysorbate 80, NF (120mg), Sodium Citrate Dihydrate, USP (235.2 mg) and Hydrochloric acid, NF (160.0 mg). Prior to administration, the lyophilized powder is to be reconstituted with (b) (4) ml of Sterile Water for Injection, USP to achieve a label strength of 2.5 mg/mL. Stability studies on the reconstituted product showed that it should be used within 14 hours, including the infusion time, with the provision that the increase of up to (b) (4) for the level of the degradation product (b) (4) be qualified. The reconstituted solution should be clear and essentially free of visible particles.

This formulation contains conventional excipients that have already been used in approved drug products for injection. The specifications for the excipients of the formulation included tests for Bacterial Endotoxins and Microbial Limits.

Formulation Development

- Temozolomide is slightly soluble in water (~3.1 mg/mL), methanol (~4.4 mg/mL) and ethanol (~0.6 mg/mL). Optimizing the solubility of temozolomide was an essential part of the pre-formulation development studies. Studies were conducted to identify excipients capable of enhancing the solubility and stability of temozolomide for an IV formulation.
- Temozolomide is susceptible to hydrolysis at alkaline pH. Therefore, the lyophilized formulation needs to be protected from moisture and contained at a stable pH.

The poor solubility and pH stability proved that a lyophilized powder formulation of temozolomide, which also limits the hydrolytic degradation of temozolomide to (b) (4) was a better formulation strategy.

Various lyophilized powder formulations were developed and were evaluated for moisture content, dissolution time, and pH. L-threonine and polysorbate 80 were selected as (b) (4) for the final formulation. Mannitol was added as a (b) (4), and (b) (4) using hydrochloric acid and sodium citrate dihydrate. The final amino-acid based formulation was selected because it met the targets set at the time of study execution.

- The pH range of 3 to 4.5 was identified to be optimal for stability of temozolomide in the formulation.
- The specification of (b) (4) for residual moisture in the lyophilized powder was found to be adequate in order to limit the degradation of temozolomide to (b) (4)

The solid state properties of Temozolomide for Injection placebo and the drug product were investigated through a physical-chemical characterization study using x-ray diffraction (b) (4), infrared spectroscopy (b) (4) and differential scanning calorimetry (b) (4)

Chemistry Assessment Section

(b) (4)



Thus existence of the (b) (4) forms of temozolomide in the lyophilized drug product by virtue of its rapid solubility in water does not adversely impact the product quality and safety.

Manufacturing Process

(b) (4) sterilization was not considered for Temozolomide for Injection due to the sensitivity of temozolomide to (b) (4). The bulk solution of Temozolomide for Injection is sterilized by (b) (4). No (b) (4) was used in the manufacturing process.

Manufacturing process parameters were determined through characterization studies that included: Compatibility with materials of construction, Compounding, Temperature, pH, Sterilization, Vial filling and Lyophilization.

Key product batches that were manufactured throughout the drug development are listed:

- A Bioavailability batch 79229-058 was manufactured a (b) (4) scale at (b) (4)
- The Bioequivalency / Primary Stability batches are 5D004, 5D005, and 5E006. These batches were manufactured at scale of (b) (4) at (b) (4).
- Process Characterization batches are 6C007, 6C010, 6D009 and 6D008. These batches were manufactured at (b) (4) scale at the (b) (4). The intention was to demonstrate the robustness and reproducibility of the process under potentially worst-case processing conditions, at the limits of the in-process parameters.

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- A Technology Transfer batch 6G011 was manufactured at a (b) (4) scale at (b) (4). The technology transfer batch study results confirmed the ranges of mixing parameters, dissolution time, total process time, fill speeds, and lyophilization cycle identified in the process characterization batches.
- A maximum hold time of 14 hours during manufacture of Temozolomide for Injection was justified through stability studies on the bulk solution.
- These studies showed that the manufacturing process for temozolomide IV powder for injection does not have any Critical Process Parameters (CPPs). However, process parameters will be monitored during the manufacturing process. These process parameters (PP's) and in-process controls (IPC's) for the Temozolomide for Injection manufacturing process steps are the parameters and controls that are maintained within predetermined criteria to ensure a consistent product.
- Based on the release test results of all four batches and the stability results of batches 6D009 and 6D008 meeting all of the specifications, the target values for the process parameters used in the process characterization batch study will be used in future batch manufacture.

During solution manufacture and filling operations, the drug product solution comes in contact with various manufacturing parts. The manufacturing parts consists of, (b) (4)

(b) (4)

The drug product solution for lyophilization is compatible with (b) (4). Solutions in contact with (b) (4) at ambient temperature conditions were similar to the control sample, with respect to color and were free of any visible particles after 24 hours of storage. The temozolomide assay values and pH met the acceptance criteria for samples exposed to (b) (4). The impurities/degradation products results met the acceptance criteria at all levels.

Filter qualification studies, included:

- compatibility,
- bubble-point testing
- bacterial retention
- filter extractables: (b) (4)

- suitability of the filter for the (b) (4) filtration process: (b) (4)

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Results demonstrate compatibility of the (b) (4) filter in a single-use application with Temozolomide for Injection at $23 \pm 2^\circ\text{C}$ for a minimum of 21 hours and 38 minutes, which exceeds the maximum manufacturing processing time of 14 hours with no significant adsorption throughout the total filtration test.

Moisture profile studies on the lyophilized vials of Temozolomide for Injection established the robustness of the lyophilization process with regard to the selected parameters.

Drug Product Specifications

The specifications were proposed according to the ICH Q6 A for a parenteral drug formulation. Impurities reported with temozolomide IV are (b) (4) (not more than (b) (4) in specifications of the drug product) and (b) (4) (not more than (b) (4) in specifications of the drug product). AIC is a metabolite of temozolomide via MTIC and is an intrinsic compound associated with purine biosynthesis. A one-cycle oral toxicity study in rats and genotoxicity studies (bacterial mutagenicity and chromosome aberration study) were conducted using temozolomide drug substance to which the impurities (b) (4) and (b) (4) were added. Toxicity findings similar to those observed with temozolomide without added impurities were observed (see the Pharmacology-Toxicology review). These impurities are considered qualified for the oral route of administration since the amount of each impurity administered to rats was 1.8-times and 1.1-times the maximum daily human intake in mg for (b) (4).

No genotoxicity was observed.

The lyophilized drug product is for intravenous administration, consequently (b) (4) are required to be qualified for the intravenous route. The Pharmacology-Toxicology review team was alerted to the proposed specifications for (b) (4) and the applicant made a Phase IV (Pharmacology-Toxicology) commitment to perform additional qualification studies on these (b) (4) impurities.

Primary Container-Closure System

The proposed commercial product presentation consists of 100 mL-20mm (b) (4) glass vial, 20mm (b) (4) stopper, and 20 mm (b) (4) seal providing 100 mg/vial of temozolomide.

The container/closure system of vials used for Temozolomide for Injection, 100 mg/vial was physically and microbiologically evaluated through dye leak test, dye exclusion test, and microbial challenge test. No ingress of dye was detected in any of the samples tested. The sterility was conserved as was determined on samples on stability. With respect to the adequacy of the test methods and results please refer to the microbiology review of this application by Bryan S. Riley dated September 25, 2008 in DFS.

Container / Closure Extractables and Leachables

The lyophilized drug product for toxicology studies was packaged in a smaller size 20 ml vials, providing 25mg/vial of temozolomide. The components and composition of this vial were the

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same as the commercial container closures. Thus the toxicology study samples represent a more stringent condition for extractables and leachables.

Extractables and leachables were assessed during the evaluation of the suitability of the (b) (4) 20 mm (b) (4) rubber stoppers. Since Temozolomide for Injection is a lyophilized product, there is little likelihood of interactions between the powder and the container closure system. Thus extractable and leachable testing was only conducted for volatile organic extractables and anionic extractables.

(b) (4)

| | | | |

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studies. Therefore, protection from light is not necessary and a clear vial is appropriate.

Stability

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Stability data for up to 24 months for the three registered stability batches that were manufactured at commercial scale of (b) (4) were provided.

Samples were placed on ICH stability conditions of $5^{\circ} \pm 3^{\circ}\text{C}$, $25^{\circ} \pm 2^{\circ}\text{C}/60 \pm 5\% \text{RH}$, $30^{\circ} \pm 2^{\circ}\text{C}/65 \pm 5\% \text{RH}$, and $40^{\circ} \pm 2^{\circ}\text{C}/75 \pm 5\% \text{RH}$. Samples stored at $25^{\circ}\text{C}/60\% \text{RH}$, $30^{\circ}\text{C}/65\% \text{RH}$, and $40^{\circ}\text{C}/75\% \text{RH}$ developed a light pink color. The level of the impurity (b) (4) product was not quantifiable in samples that were stressed under ICH conditions i.e., it was below the detection level as was determined by the HPLC analysis with PDA detector and UV visible studies.

The Sponsor requests 36 months shelf-life for the drug product when stored refrigerated at $2^{\circ}\text{C}-8^{\circ}\text{C}$ ($36^{\circ}\text{F}-46^{\circ}\text{F}$). Although the refrigerated samples were not tested prior to 24 months, all of the data from the ICH stability conditions of $25^{\circ}\text{C}/60\% \text{RH}$ (1 through 24 months), $30^{\circ}\text{C}/65\% \text{RH}$ (3 through 24 months) and $40^{\circ}\text{C}/75\% \text{RH}$ (1 through 6 months) met the proposed registration specifications for all tests except color. The ICH stability data for $25^{\circ}\text{C}/60\% \text{RH}$ and $30^{\circ}\text{C}/65\% \text{RH}$ can be considered as accelerated stability data. Therefore, the requested 36 months shelf life at refrigerated conditions of $2^{\circ}\text{C}-8^{\circ}\text{C}$ ($36^{\circ}\text{F}-46^{\circ}\text{F}$) is acceptable.

Freeze-thaw Cycles Studied

The Freeze thaw cycle studies demonstrated stability of Temozolomide for Injection 100 mg/Vial, following exposure to the three temperature cycles of (48 hours each at -21°C and 40°C).

The reconstituted Temozolomide for Injection in the IV bag and associated IV infusion set is stable for 14 hours at $25^{\circ}\text{C}/60\% \text{RH}$. The level of the degradation product (b) (4) of NMT (b) (4) needs be qualified. The applicant has agreed to perform the qualification study as a Phase IV commitment.

The stability protocol for the post approval commercial batches includes the tests for Reconstitution Time at 0 time point, Bacterial Endotoxins and Microbial limits tests performed at the time points of 24, and 36 months on ICH long term stability condition of $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$. This was found to be adequate sampling interval as approved by the microbiology discipline.

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

Temodar (temozolomide) is available as 100 mg/vial powder for injection. Each vial of Temodar for Injection contains sterile, pyrogen-free temozolomide lyophilized powder.

How is Temodar for Injection prepared?

1. Temodar for Injection vials should be stored refrigerated at $2^{\circ}\text{C}-8^{\circ}\text{C}$ ($36^{\circ}\text{F}-46^{\circ}\text{F}$).
2. Bring the vial to room temperature prior to reconstitution in Sterile Water for Injection.
3. Using aseptic technique, reconstitute each vial with 41 mL Sterile Water for Injection. The resulting solution will contain 2.5 mg/mL temozolomide.
4. Vial should be gently swirled and not shaken. Inspect vials, and any vial containing visible particulate matter should not be used. Reconstituted product must be used within 14 hours, including infusion time.

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5. Using aseptic technique, withdraw up to 40 mL from each vial to make up the total dose and transfer into an empty 250 mL PVC infusion bag. Studies with non-PVC bags have not been conducted.
6. (b) (4)

How is Temodar for Injection administered?

Temodar for Injection is administered as an intravenous infusion over 90 minutes. Bioequivalence has been established only when Temodar for Injection was given over 90 minutes. Temodar for Injection should be administered only by intravenous infusion.

Because no data are available on the compatibility of Temodar for Injection with other intravenous substances or additives, other medications should not be infused simultaneously through the same intravenous line.

The daily dose of Temodar for a given patient is calculated by the physician, based on the patient's body surface area (BSA). The resulting dose is then rounded off to the nearest 5 mg. An example of the dosing may be as follows: the initial daily dose of Temodar in milligrams is the BSA multiplied by mg/m²/day, (a patient with a BSA of 1.84 is 1.84 x 75 mg = 138, or 140 mg/day). The dose for subsequent cycles may be adjusted according to nadir neutrophil and platelet counts in the previous cycle and at the time of initiating the next cycle.

Daily Dose Calculations by Body Surface Area (BSA)

Total BSA (m ²)	75 mg/m ² (mg daily)	150 mg/m ² (mg daily)	200 mg/m ² (mg daily)
1.0	75	150	200
1.1	82.5	165	220
1.2	90	180	240
1.3	97.5	195	260
1.4	105	210	280
1.5	112.5	225	300
1.6	120	240	320
1.7	127.5	255	340
1.8	135	270	360
1.9	142.5	285	380
2.0	150	300	400
2.1	157.5	315	420
2.2	165	330	440
2.3	172.5	345	460
2.4	180	360	480

(b) (4)

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C. Basis for Approvability or Not-Approval Recommendation

The drug substance temozolomide has already been approved in an oral capsule formulation. Adequate safety data are available with respect to control of impurities and degradation products in the drug substance and the drug product.

During the NDA review, the CMC reviewer found that the impurities (b) (4) in the drug substance and (b) (4) in the drug product exceeded the ICH Q3A and ICHQ 3B qualification thresholds. The Pharmacology-Toxicology team determined that the impurities (b) (4) in the drug substance and (b) (4) in the drug product were not adequately qualified (see Pharmacology-Toxicology review by Dr. H. Rosenfeldt). In order to resolve this issue, the applicant committed to perform the toxicity qualification studies as Phase IV (Pharmacology-Toxicology) commitment. The excipients of the formulation are conventional and have been used in parenteral formulations.

The manufacturing process for the drug substance is already approved. The manufacturing of the parenteral formulation is straight forward. Adequate justification was provided to ensure a robust process. Sterility and endotoxin tests were reviewed by the Office of Microbiology and were deemed adequate. Please see the microbiology review of this NDA by Dr. Bryan S. Riley in DFS.

Sufficient stability data was provided to justify an expiration dating of 36 months for the drug product at the long term storage condition of 2°C-8°C (36°F-46°F).

All of the CMC review deficiencies were resolved. This application is recommended for approval from a CMC perspective, pending an overall acceptable recommendation from the Office of Compliance.

III. Administrative**A. Reviewer's Signature: (electronic)**

(See appended electronic signature page)

Jila H. Boal, Ph. D. CMC Reviewer, ONDQA

B. Endorsement Block

(See appended electronic signature page)

Sarah C. Pope, Ph.D., Acting Branch Chief, DPAlII, ONDQA

CC Block: entered electronically in DFS

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**This is a representation of an electronic record that was signed electronically and
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/s/

Jila Boal
11/13/2008 04:59:56 PM
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Sarah Pope
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