

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20-452**

**ADMINISTRATIVE DOCUMENTS**

Bristol-Myers Squibb  
Pharmaceutical Research Institute

P.O. Box 5400 Princeton, NJ 08545-5400 609 818-5000

NDA Amendment: Patent Submission

X P

NDA 20-452

PARAPLATIN® (carboplatin aqueous solution) Injection

March 27, 2003

Richard Pazdur, M.D., Director  
Division of Oncologic Drug Products, (HFD 150)  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research  
Food and Drug Administration  
1451 Rockville Pike  
Rockville, MD 20852-1448

RECEIVED  
MAR 28 2003  
HFD-150 / CDER

Dear Dr. Pazdur:

Reference is made to our pending New Drug Application for Paraplatin® (carboplatin aqueous solution) Injection, 10 mg/mL, NDA 20-452.

Patent information on Paraplatin® (carboplatin aqueous solution) Injection is provided on the following page and a copy of this information will also be mailed to the U.S. FDA, CDER, Office of Generic Drugs, Orange Book Staff, 7500 Standish Place, Metro Park North II, Rockville, MD 20855-2773.

If any question arises, please contact me at (609) 818-5759, or Elizabeth Yamashita, Group Director, Global Regulatory Science-CMC, at (609) 818-4768.

Sincerely,

*Noemi C. Guma*  
Noemi C. Guma, Ph.D.  
Manager  
Global Regulatory Science, CMC



A Bristol-Myers Squibb Company

TIME SENSITIVE PATENT INFORMATION

pursuant to 21 C.F.R. 314.53

for

NDA # 20-452

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: Paraplatin<sup>®</sup> (carboplatin aqueous solution) Injection
- Active Ingredient: carboplatin
- Strengths: 50 mg/vial, 150 mg/vial and 450 mg/vial
- Dosage Form: Injectable
- Approval Date: pending

**A. Patent Information**

U.S. Patent No.: 4,657,927

Expiration Date: April 14, 2004

Type of Patent:

1. Drug Substance (Active Ingredient)    \_\_\_ Y   x   N
2. Drug Product (Composition/Formulation)      x   Y \_\_\_ N
3. Method of Use      x   Y \_\_\_ N

- a. Approved method of use for which approval is being sought: Method of treating malignant tumors

**B. Formulation and Method of Use Claim**

The undersigned declares that the above stated United States Patent Number 4,657,927 covers the formulation and/or method of use of Paraplatin<sup>®</sup>(carboplatin aqueous solution) Injection. This product is the subject of this application for which approval is being sought.

Signed: Suzanne DeLajko

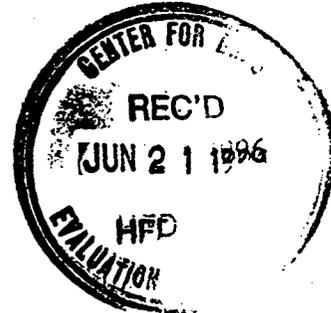
Date: March 27, 2003

copy: AG. PCG  
S. Browne well/HF  
6-25-96  
das

# Bristol-Myers Squibb Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000  
609 252-5761 Fax: 609 252-6000  
Internet: Joseph\_A\_Linkewich@ccmail.bms.com

Joseph A. Linkewich, Pharm.D.  
Director  
U.S. Regulatory Liaison  
Worldwide Regulatory Affairs



**NDA 20-452**  
**Paraplatin® — (carboplatin) Injection**

June 12, 1996

(X2)

Robert DeLap, M.D.  
Director  
Division of Oncologic Drug Products, HFD-150  
Food and Drug Administration  
Center for Drug Evaluation and Research  
5600 Fishers Lane  
Rockville, Maryland 20857

Dear Dr. DeLap:

Reference is made to our pending New Drug Application for Paraplatin® — (carboplatin), NDA 20-452, dated March 8, 1994. This application provides for a solution ready-for-use. Please find patent information enclosed.

Should there be any questions regarding this notification, kindly contact the undersigned.

Sincerely,

Joseph A. Linkewich, Pharm.D.  
Director, U.S. Regulatory Liaison  
Worldwide Regulatory Affairs  
(609) 252-5761

JAL/MP/pak  
Desk copy: Ms. Dianne Spillman, HFD-150



A Bristol-Myers Squibb Company

## PATENT AND EXCLUSIVITY DATA

Bristol-Myers Squibb Company  
P.O. Box 4000  
Princeton, New Jersey 08543

- |   |   |
|---|---|
| 1) Active Ingredient  | Carboplatin   |
| 2) Strengths  | 50, 150 and 450 mg carboplatin  |
| 3) Trade name   | PARAPLATIN —  |
| 4) Dosage Form<br>Route of Administration   | Solution Ready-for-use<br>Intravenous   |
| 5) Applicant Firm Name  | Bristol-Myers Squibb Company  |
| 6) NDA Number   | 20-452  |
| 7) Approval Date  | Pending   |
| 8) Exclusivity Under Section<br>505(j)(4)(D)(iii) of the<br>Federal Food, Drug and<br>Cosmetics Act | 3 years   |
| 9) Applicable Patent Numbers<br>and Expiration Dates  | <p>U.S. Patent No. 4,140,707 expiring August 24, 1998 covers the compound "carboplatin" known as PARAPLATIN. See claims 1,5,6 and 7. Claim 7 covers carboplatin specifically.</p> <p>U.S. Patent No. 4,657,927 expiring April 14, 2004 covers the "method of treating malignant tumors" (Claim 1) and a composition therefor (Claim 3).</p> |

PATENT INFORMATION CERTIFICATION

The undersigned declares that U. S. Patent No. 4,657,927 expiring April 14, 2004 covers the formulation and the uses of Paraplatin (aqueous carboplatin) for the first-line treatment of advanced ovarian carcinoma. This product is the subject of this application for which approval is being sought:

*Initial treatment of advanced ovarian carcinoma.*

  
Frank P. Hoffman  
Associate Patent Counsel  
Bristol-Myers Squibb Company  
345 Park Avenue  
New York, NY 10154-0037

Dated: June 6, 1996

EXCLUSIVITY SUMMARY for NDA # 20-452 SUPPL #

Trade Name Paraplatin Generic Name carboplatin aqueous solution

Applicant Name Bristol-Myers Squibb Company HFD- 150

Approval Date July 14, 2003

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/X/ NO /\_\_\_/

b) Is it an effectiveness supplement? YES /\_\_\_/ NO /X/

If yes, what type(SE1, SE2, etc.)?

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /\_\_\_/ NO /X/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /\_\_\_/ NO /\_x\_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /\_\_\_/ NO /\_x\_/

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /\_\_\_/ NO /\_X\_/

If yes, NDA # \_\_\_\_\_ Drug Name

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

3. Is this drug product or indication a DESI upgrade?

YES /\_\_\_/ NO /\_X\_/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).**

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /x/ NO /\_\_\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-880 Paraplatin (carboplatin) for  
Injection

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /\_\_\_/ NO /\_\_\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /\_\_\_/ NO /\_X\_/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /\_\_\_/ NO /\_\_\_/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /\_\_\_/ NO /\_\_\_/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /\_\_\_/ NO /\_\_\_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/ NO /\_\_\_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /\_\_\_/ NO /\_\_\_/

Investigation #2 YES /\_\_\_/ NO /\_\_\_/

Investigation #3 YES /\_\_\_/ NO /\_\_\_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1                      YES /\_\_\_/                      NO /\_\_\_/

Investigation #2                      YES /\_\_\_/                      NO /\_\_\_/

Investigation #3                      YES /\_\_\_/                      NO /\_\_\_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # \_\_\_\_\_ Study #

NDA # \_\_\_\_\_ Study #

NDA # \_\_\_\_\_ Study #

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #\_\_, Study #

Investigation #\_\_, Study #

Investigation #\_\_, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	!		
	!		
IND # _____	!	YES /___/	NO /___/ Explain:
	!		
	!		
	!		
	!		
Investigation #2	!		
	!		
IND # _____	!	YES /___/	NO /___/ Explain:
	!		
	!		
	!		
	!		

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!		
	!		
YES /___/ Explain _____	!	NO /___/ Explain _____	
_____	!	_____	
_____	!	_____	
	!		
Investigation #2	!		
	!		
YES /___/ Explain _____	!	NO /___/ Explain _____	
_____	!	_____	
_____	!	_____	
	!		

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /\_\_\_/          NO /\_\_\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_  
Signature of Preparer  
Christy Cottrell  
Title: Consumer Safety Officer

Date

Signature of Division Director  
Richard Pazdur, M.D.

Date

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

/s/

-----  
Christy Cottrell  
7/14/03 04:26:48 PM

Richard Pazdur  
7/17/03 11:55:27 AM

**PEDIATRIC PAGE**

*(Complete for all APPROVED original applications and efficacy supplements)*

NDA/BLA #: 20-452 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

Stamp Date: October 15, 2002 (Resubmission) Action Date: July 14, 2003

HFD -150 Trade and generic names/dosage form: Paraplatin (carboplatin aqueous solution) Injection

Applicant: Bristol-Myers Squibb Therapeutic Class: 5010100

Indication(s) previously approved: Initial treatment of advanced ovarian carcinoma in established combination with other approved chemotherapeutic agents, and for the palliative treatment of patients with ovarian carcinoma recurrent after prior chemotherapy.

**Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.**

Number of indications for this application(s): 2

Indication #1: Initial treatment of advanced ovarian carcinoma in established combination with other approved chemotherapeutic agents.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval

Formulation needed

Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Christy Cottrell  
Consumer Safety Officer

cc: NDA  
HFD-950/ Terrie Crescenzi  
HFD-960/ Grace Carmouze  
(revised 9-24-02)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960  
301-594-7337**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: For the palliative treatment of patients with ovarian carcinoma recurrent after prior chemotherapy.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: \_\_\_ Partial Waiver \_\_\_ Deferred \_\_\_ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Christy Cottrell  
Consumer Safety Officer

cc: NDA  
HFD-960/ Terrie Crescenzi  
(revised 1-18-02)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960  
301-594-7337**

NDA ##-###

Page 5

**APPEARS THIS WAY  
ON ORIGINAL**



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

/s/

-----  
Christy Cottrell  
7/17/03 04:13:36 PM

Dotti Pease  
7/18/03 06:54:54 AM

CERTIFICATION REGARDING DEBARRED PERSONS

This certifies that Bristol-Myers Squibb did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [Section 306(a) or (b)], in connection with this application.

DATE: March 8, 1994.

Authorized Representative: Michael J. Burnett  
Michael J. Burnett, Director  
Worldwide Regulatory Affairs

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 20-452	Efficacy Supplement Type	Supplement Number
Drug: Paraplatin (carboplatin aqueous solution) Injection		Applicant: Bristol-Myers Squibb Company
RPM: Christy Cottrell		HFD- 150      Phone # (301) 594-5761
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		RS
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		July 15, 2003
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input checked="" type="checkbox"/> Other Resubmission
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		N/A
• OC clearance for approval		N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified   N/A
❖ Exclusivity Summary (approvals only)		Included
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)		N/A

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	Not Approvable-December 19, 1994
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	Included
• Most recent applicant-proposed labeling	Included – April 30, 2003
• Original applicant-proposed labeling	Included
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings ( <i>indicate dates of reviews and meetings</i> )	Included DDMAC review – March 5, 2003 CSO review- July 14, 2003 Biopharm- February 12, 2003
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	Included
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Included
❖ Memoranda and Telecons	Included
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

<b>Clinical and Biopharmaceutical Information</b>	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	N/A
❖ Clinical review(s) (indicate date for each review)	N/A
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Included
❖ Statistical review(s) (indicate date for each review)	N/A
❖ Biopharmaceutical review(s) (indicate date for each review)	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
<b>CMC Information</b>	
❖ CMC review(s) (indicate date for each review)	Included Review dated 7-11-03
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	See CMC review
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	Included Review dated March 27, 2003
❖ Facilities inspection (provide EER report)	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ Methods validation	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested
<b>Nonclinical Pharmacology Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

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

/s/

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Christy Cottrell  
7/14/03 04:25:38 PM



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297  
Expiration Date: November 30, 1996.

USER FEE COVER SHEET

The reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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Hubert H. Humphrey Building, Room 721-A  
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Washington, DC 20201  
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and to:

Office of Management and Budget  
Paperwork Reduction Project (0910-0297)  
Washington, DC 20503

Please DO NOT RETURN this form to either of these addresses.

See Instructions on Reverse Before Completing This Form.

<p>1. APPLICANT'S NAME AND ADDRESS BRISTOL-MYERS SQUIBB CO. Pharmaceutical Research Institute 5 Research Parkway, PO Box 5100 Wallingford CT 06492-7660</p>	<p>2. USER FEE BILLING NAME, ADDRESS, AND CONTACT BRISTOL-MYERS SQUIBB CO. PO Box 4000 Princeton, NJ 08543  ATTN: Mr. Edward J. Joyce Worldwide Regulatory Affairs</p>
<p>3. TELEPHONE NUMBER (Include Area Code) 203 - 284-7730</p>	
<p>4. PRODUCT NAME Paraplatin® (carboplatin) Injection</p>	

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA?  YES  NO  
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

<p>USER FEE I.D. NUMBER #2511</p>	<p>7. LICENSE NUMBER/ANDA NUMBER No. 20452</p>
---------------------------------------	--

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 3/1/82	<input type="checkbox"/> THE APPLICATION IS SUBMITTED UNDER 505(b)(2) (See reverse before checking box.)
<input type="checkbox"/> AN INSULIN PRODUCT SUBMITTED UNDER 506	
FOR BIOLOGICAL PRODUCTS ONLY	
<input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION	<input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT
<input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 3/1/82	<input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 381 OF THE PHS ACT

9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION?  YES  NO  
(See reverse if answered YES)

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?  YES  NO  
(See reverse if answered YES)

This completed form must be signed and accompany each new drug or biologic product, original or supplement.

<p>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE Carl E. Fuller Edward J. Joyce</p>	<p>TITLE Sr. Regulatory Affairs Assoc. Executive Director.</p>	<p>DATE 3/8/94</p>
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**DIVISION OF ONCOLOGY DRUG PRODUCTS  
CSO LABELING REVIEW**

**NDA:** NDA 20-452  
**DRUG:** Paraplatin® (carboplatin aqueous solution) Injection  
**SPONSOR:** Bristol-Myers Squibb Company

**DATES OF SUBMISSIONS:**

<u>Submission</u>	<u>Letter Date</u>	<u>Receipt Date</u>
N(000) AC	October 11, 2002	October 15, 2002
N(000) BL	February 14, 2003	February 19, 2003

**BACKGROUND:**

NDA 20-452 was originally submitted on March 8, 1994 and received a Not Approvable letter on December 19, 1994. On October 11, 2002, BMS submitted a complete response to the Not Approvable letter as a major amendment to the NDA that restarted the review clock.

On February 14, 2003, BMS submitted a minor labeling amendment to the pending NDA that incorporated some editorial changes to the labeling and changed the proposed tradename from Paraplatin®-, Injection to Paraplatin® (carboplatin aqueous solution) Injection.

The PDUFA due date for this application is April 15, 2003.

I compared the proposed labeling to the currently approved labeling for the lyophilized product, Paraplatin® (carboplatin for injection). All changes and/or discrepancies are outlined below.

**DISCUSSION:**

1. Throughout the package insert, the name PARAPLATIN® (carboplatin for injection) has been changed to PARAPLATIN® (carboplatin aqueous solution) Injection.

*Comment: The tradename is currently under review by DMETS. Acceptability of these changes will depend on the recommendation of DMETS.*

2. In the DESCRIPTION section, the first paragraph has been changed as follows:

“PARAPLATIN® (carboplatin for injection) is supplied as a sterile, lyophilized white powder available in single dose vials containing 50 mg, 150 mg, and 450 mg of carboplatin for administration by intravenous infusion. Each vial contains equal parts by weight of carboplatin and mannitol.”

has been changed to

*Comment: This change was reviewed by the Chemist and was found to be acceptable.*

4. The **STABILITY** section has been revised as follows:

“Unopened vials of PARAPLATIN are stable for the life indicated on the package when stored at 25° C (77° F) [excursions permitted to 15°- 30° C (59°- 86° F), see USP Controlled Room Temperature] and protected from light.

When prepared as directed, PARAPLATIN solutions are stable for 8 hours at room temperature (25° C). Since no antibacterial preservative is contained in the formulation, it is recommended that PARAPLATIN be discarded 8 hours after dilution.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.”

has been changed to

“Unopened vials of PARAPLATIN (carboplatin aqueous solution) Injection are stable for the life indicated on the package when stored at \_\_\_\_\_

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.”

*Comment: This change was reviewed by the Chemist. It is recommended that the STORAGE and STABILITY sections be combined into one section titled STORAGE. The new STORAGE section should read as follows:*

*“Unopened vials of PARAPLATIN (carboplatin aqueous solution) Injection are stable for the life indicated on the package when stored at 25° C (77° F); excursions permitted from 15°- 30° C (59°-86° F)[see USP Controlled Room Temperature]. Protect from light.*

*Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Solutions for infusion should be discarded 8 hours after preparation.”*

*These revisions were faxed to the sponsor on April 17, 2003. The sponsor agreed to the changes and revised labeling was submitted on April 30, 2003.*

5. The **HOW SUPPLIED** section has been revised as follows:

“PARAPLATIN® (carboplatin for injection)

NDC 0015-3213-30	50 mg vials, individually cartoned, shelf packs of 10 cartons, 10 shelf packs per case. (Yellow flip-off seals)
NDC 0015-3214-30	150 mg vials, individually cartoned, shelf packs of 10 cartons, 10 shelf packs per case. (Violet flip-off seals)
NDC 0015-3215-30	450 mg vials, individually cartoned, shelf packs of 10 cartons,

10 shelf packs per case. (Blue flip-off seals)”

has been changed to

“PARAPLATIN® (carboplatin aqueous solution) Injection

NDC 0015-3210-30 50 mg/5 mL aqueous solution in single-dose vials, individually cartoned, shelf packs of 10 cartons, 10 shelf packs per case.

NDC 0015-3211-30 150 mg/15 mL aqueous solution in single-dose vials, individually cartoned, shelf packs of 10 cartons, 10 shelf packs per case.

NDC 0015-3212-35 450 mg/45 mL aqueous solution in single-dose vials, individually cartoned, shelf packs of 10 cartons, 10 shelf packs per case.

*Comment: This change was reviewed by the Chemist. It is recommended that the descriptions be modified as follows:*

NDC 0015-3210-30 50 mg/5 mL aqueous solution in single-dose vials (with white flip-off seals), individually cartoned, shelf packs of 10 cartons, 10 shelf packs per case.

NDC 0015-3211-30 150 mg/15 mL aqueous solution in single-dose vials (with white flip-off seals), individually cartoned, shelf packs of 10 cartons, 10 shelf packs per case.

NDC 0015-3212-35 450 mg/45 mL aqueous solution in single-dose vials (with white flip-off seals), individually cartoned, shelf packs of 10 cartons, 10 shelf packs per case.

*These revisions were faxed to the sponsor on April 17, 2003. The sponsor agreed to the changes and revised labeling was submitted on April 30, 2003.*

6. In the STORAGE section, the first sentence has been revised as follows:

“Store the unopened vials at 25° C (77° F); excursions permitted to 15°- 30° C (59°- 86° F)[see USP Controlled Room Temperature].”

has been changed to

---

*Comment: This change was reviewed by the Chemist. It is recommended that the STORAGE and STABILITY sections be combined into one section titled STORAGE. The new STORAGE section should read as follows:*

*“Unopened vials of PARAPLATIN (carboplatin aqueous solution) Injection are stable for the life indicated on the package when stored at 25° C (77° F); excursions permitted from*

*15°-30°C (59°-86°F)[see USP Controlled Room Temperature]. Protect from light.*

*Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Solutions for infusion should be discarded 8 hours after preparation."*

*These revisions were faxed to the sponsor on April 17, 2003. The sponsor agreed to the changes and revised labeling was submitted on April 30, 2003.*

7. Minor editorial changes have been made throughout the labeling.

*Comment: The editorial changes are acceptable.*

**RECOMMENDATIONS:**

Acceptability of these changes is indicated by the concurrences below. With these concurrences, this labeling will accompany the APPROVAL letter for NDA 20-452.

\_\_\_\_\_  
Christy Cottrell  
Consumer Safety Officer

concurrence: /DWP/ 7-14-03 \_\_\_\_\_  
Dotti Pease  
Chief, Project Management Staff

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

/s/

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Christy Cottrell  
7/14/03 04:28:02 PM  
CSO

Dotti Pease  
7/15/03 07:51:45 AM  
CSO

**CONSULTATION RESPONSE**

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT  
OFFICE OF DRUG SAFETY  
(DMETS; HFD-420)**

**DATE RECEIVED:** January 29, 2003

**DUE DATE:** April 1, 2003

**ODS CONSULT #:** 03-0023  
03-0088

**TO:** Richard Pazdur, M.D.  
Director, Division of Oncology Drug Products  
HFD-150

**THROUGH:** Christy Cottrell  
Project Manager  
HFD-150

**PRODUCT NAME:**  
Paraplatin  
(Carboplatin Injection)  
50 mg/5 mL, 150 mg/15 mL, and 450 mg/45 mL

**NDA SPONSOR:**  
Bristol-Myers Squibb Company

**NDA:** 20-452

**SAFETY EVALUATOR:** Denise P. Toyer, Pharm.D.

**SUMMARY:** In response to a consult from the Division of Oncology Drug Products (HFD-150), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Paraplatin" to determine the potential for confusion with approved proprietary and established names as well as pending names.

**RECOMMENDATIONS:**

- A. DMETS has no objection to the use of the proprietary name Paraplatin. However, DMETS is concerned with the introduction of this new dosage form into the market. We believe it will increase the risk of name confusion between Carboplatin and Cisplatin. We recommend the sponsor develop a risk management plan to address the confusion. We would like to meet with the Division to discuss this further.
- B. DMETS recommends implementation of the labeling revisions outlined in Section III of this review.
- C. DDMAC finds the proprietary name Paraplatin acceptable from a promotional perspective.

/s/

/s/

Carol Holquist, RPh  
Deputy Director,  
Division of Medication Errors and Technical Support  
Office of Drug Safety  
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, RPh  
Associate Director  
Office of Drug Safety  
Center for Drug Evaluation and Research  
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)

Office of Drug Safety

HFD-420; Parklawn Rm. 6-34

Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: March 31, 2003  
NDA # 20-452  
NAME OF DRUG: Paraplatin  
(Carboplatin Injection)  
NDA HOLDER: Bristol Myers Squibb Company

I. INTRODUCTION:

This consult was written in response to a request from the Division of Oncology Drug Products, to review the proprietary name Paraplatin, regarding potential name confusion with other proprietary and established drug names. Paraplatin (Carboplatin for Injection) was approved on March 3, 1989. The product is currently available as a lyophilized powder in 50 mg, 150 mg, and 450 mg vials. Bristol Myers Squibb Company (BMS) submitted a new drug application (NDA) for Paraplatin Injection, which is an aqueous solution available in 50 mg/5 mL, 150 mg/15 mL, and 450 mg/45 mL vials. BMS would like to use the proprietary name Paraplatin for both the lyophilized powder and aqueous solution products. The draft container labels, carton and package insert labeling were reviewed for possible interventions to minimize medication errors.

PRODUCT INFORMATION

The sponsor originally submitted the proprietary name Paraplatin — for the aqueous solution. However, the sponsor withdrew Paraplatin — and submitted the proprietary name Paraplatin. Paraplatin (carboplatin) Injection is a sterile aqueous solution of carboplatin 10 mg/mL. Paraplatin is indicated for initial treatment of advanced ovarian carcinoma or as secondary treatment of advanced ovarian carcinoma. Paraplatin Injection may be used as a single agent or in combination with Cyclophosphamide. The dosage as a single agent is 360 mg/m<sup>2</sup> intravenously on day one every four weeks. In previously untreated patients the combination of Paraplatin Injection 300 mg/m<sup>2</sup> and Cyclophosphamide 600 mg/m<sup>2</sup> intravenously every four weeks for six cycles may be used. Alternatively, formula dosing may also be used which is based on a patient's pre-existing renal function or renal function and desired platelet nadir. Both Carboplatin Injection and Carboplatin for Injection have the same dosing regimens and indications of use. Carboplatin Injection will be available in 50 mg/5 mL, 150 mg/15 mL, and 450 mg/45 mL vials.

## II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>1</sup> as well as several FDA databases<sup>2</sup> for existing drug names which sound-alike or look-alike to "Paraplatin" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted.<sup>3</sup> The Saegis<sup>4</sup> Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

### A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Paraplatin." Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. The members of this panel include DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel did not identify any names as having the potential for confusion with Paraplatin. However, the panel questioned whether there were differences between Paraplatin Injection and Paraplatin for Injection that may potentially cause medication errors.
2. DDMAC did not have concerns about the name Paraplatin with regard to promotional claims.
3. Through independent review, DMETS identified Pravastatin and Cisplatin as having the potential for confusion with Paraplatin.

APPEARS THIS WAY  
ON ORIGINAL

<sup>1</sup> Facts and Comparisons, 2003, Facts and Comparisons, St. Louis, Mo. <http://www.efactsweb.com/index.asp>  
MICROMEDEX Integrated Index, 003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2003).

<sup>2</sup> The Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

<sup>3</sup> WWW location <http://www.uspto.gov/main/trademarks.htm>

<sup>4</sup> Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com)

Product Name	Dosage form(s) & established name(s)	Usual adult dose	Other
Paraplatin	Carboplatin Solution for Injection 50 mg, 150 mg, and 450 mg Vials	Initially, 360 mg/m <sup>2</sup> IV on day 1 when used as single agent therapy or 300 mg/m <sup>2</sup> IV on day 1 when used in combination with cyclophosphamide. The dosage is repeated every 4 weeks, with dosage adjustments made according to the lowest post-treatment platelet or neutrophil value as assessed by weekly blood counts.	N/A
Paraplatin	Carboplatin Lyophilized Powder for Injection 50 mg, 150 mg, and 450 mg Vials	Initially, 360 mg/m <sup>2</sup> IV on day 1 when used as single agent therapy or 300 mg/m <sup>2</sup> IV on day 1 when used in combination with cyclophosphamide. The dosage is repeated every 4 weeks, with dosage adjustments made according to the lowest post-treatment platelet or neutrophil value as assessed by weekly blood counts.	LA/SA
Platinol AQ	Cisplatin	20–75 mg/m <sup>2</sup> IV a single dose, the regimen may be repeated every 5 to 21 days (dose and dosing interval is dependent upon indication)	LA/SA
Pravachol	Pravastatin 10 mg, 20 mg, 40 mg, and 80 mg Tablets	20 mg to 40 mg per day with increases up to 80 mg per day	LA/SA
* Frequently used, not all-inclusive. ** L/A (look-alike), S/A (sound-alike)			

## B. PRESCRIPTION ANALYSIS STUDIES

### 1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Paraplatin with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 107 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Paraplatin (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

**BEST POSSIBLE COPY**

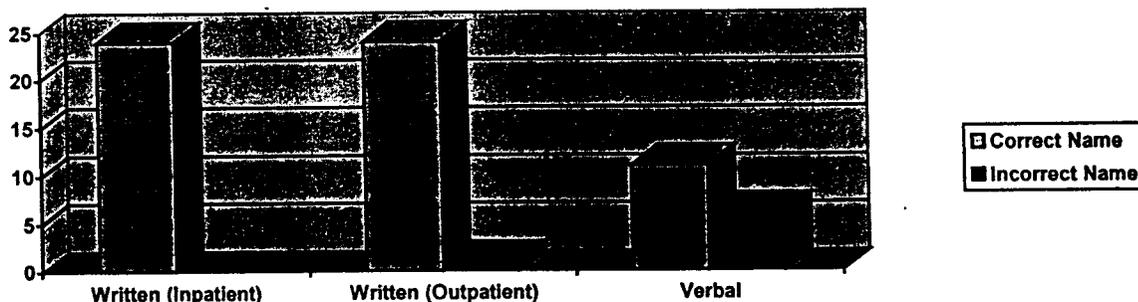
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><u>Outpatient RX:</u></p> <p>Paraplatin 450mg/45ml 450mg IV to be given today in clinic #1</p>	<p>The second is Paraplatin 450 mg per 45 mL. Sig: 450 mg IV to be given today in the clinic. Dispense #1.</p>
<p><u>Inpatient RX:</u></p> <p><del>Paraplatin 450mg IV X 1 today</del></p>	

2. Results:

The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	40	24 (60%)	24 (100%)	0 (0%)
Written Outpatient	35	25 (71%)	24 (96%)	1 (4%)
Verbal	32	17 (53%)	11 (65%)	6 (35%)
Total	107	66 (62%)	59 (24%)	7 (76%)



In the verbal study 11 of 17 (65%) participants interpreted Paraplatin correctly. The majority of the incorrect name interpretations were phonetic variations of "Paraplatin." These include Periplitin (3), Pariplitin (2), and Pereiplatin (1). The incorrect misinterpretations were phonetic versions of Paraplatin.

In the two written prescription studies, the majority of the participants interpreted Paraplatin correctly. All (100%) of the 24 participants in the inpatient studies interpreted the proprietary name Paraplatin correctly. In the outpatient study 23 (95%) of the 24 participants interpreted Paraplatin correctly. The single misinterpretation was Paraplastin, which is similar in spelling to the currently marketed product Paraplatin.

None of the misinterpreted names in either study were similar to an approved product.

### 3. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Paraplatin, the Expert Panel's concerns were related to potential confusion between the proposed Paraplatin Injection and the currently marketed Paraplatin for Injection. The Expert Panel noted that potential medication errors could occur if there are differences between Paraplatin Injection and Paraplatin for Injection and practitioners substitute the products without being aware of those differences. DMETS conducted a comparison of the proposed labeling for Paraplatin Injection with the labeling for Paraplatin for Injection. Although there are minor additions to the proposed Paraplatin Injection labeling that do not appear in the current labeling of Paraplatin for Injection, the major sections (e.g., indications of use, adverse events, dosage and administration, etc) are identical. Thus, the major difference between the two products is the dosage form (lyophilized powder for reconstitution vs. aqueous solution). Additionally, through independent review Pravastatin and Cisplatin were also identified as potential look and sound-alike names.

DMETS conducted prescription studies to simulate the prescription ordering process. There was no confirmation that Paraplatin could be confused with Cisplatin or Pravastatin. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to small sample size. The majority of the interpretations from the verbal and written prescription studies were phonetic misinterpretations or spelling variations of the drug name Paraplatin.

Pravastatin and Paraplatin have sound and look alike similarities. The beginning letters (Prava and Para) of each name may look and sound alike depending upon how they are scripted or pronounced. The endings (atin) of both names are identical which increases the look and sound-alike similarities. Both names have four syllables. However, when the second and third syllable of each name are pronounced together (vastat vs. raplat) they are phonetically different. Additionally when written, Paraplatin has a downstroke whereas Pravastatin does not have any downstroke letters. There are also product differences between Pravastatin and Paraplatin that include: dosage form (tablet vs. solution), route of administration (oral vs. intravenously), and dosing intervals (daily vs. one time). The latter would help practitioners differentiate the two prescriptions. Pravastatin is a drug for a chronic indication and would probably not be prescribed in a single dose (i.e., x1, times one, one time). It is also unlikely that more than one dose of Paraplatin will be prescribed at a specific time since the next dose would be based on the patient's neutrophil and platelet counts. Moreover, Paraplatin may be infused over a 15 minute to one hour timeframe or by continuous infusion over 24 hours. Thus prescriptions for Paraplatin will usually require that an infusion rate be noted. Since Paraplatin is dosed on body surface area, there is a possibility that the dose could overlap. However, as noted above, an infusion rate (e.g., over 15 minutes) would usually be required. Additionally, since Pravastatin and Paraplatin are currently marketed, the Adverse Event Reporting System (AERS) was searched using the product names Pravastatin (Prava%) and Paraplatin (Parapla% and Carbop%) and the MEDDRA Preferred Terms (PT) "Medication Error" and "Overdose." The search did not identify any reports associated with name confusion between Pravastatin and Paraplatin. Thus, at this time DMETS has not identified in AERS any potential postmarketing reports associated with potential name confusion between Pravastatin and Paraplatin. Based on

the dosing intervals, conditions of use, and negative number of postmarketing reports the potential for name confusion between Pravastatin and Paraplatin is minimal.

Cisplatin (the established name for Platinol AQ) has look and sound-alike similarities to Carboplatin (the established name for Paraplatin). Both Carboplatin and Cisplatin begin with the letter (C) and end with the letters (platin), which increases the potential for name confusion. Although both products are chemotherapeutic agents and are administered intravenously, the  $\text{mg}/\text{m}^2$  dose of Carboplatin is substantially higher than the dose of Cisplatin ( $360 \text{ mg}/\text{m}^2$  vs.  $20\text{-}75 \text{ mg}/\text{m}^2$  respectively). Thus medication errors due to name confusion between Carboplatin and Cisplatin have resulted in significant overdoses of Cisplatin (e.g., when a Carboplatin order is filled with Cisplatin). Additionally, depending upon the type of cancer being treated the treatment protocol could involve carboplatin or cisplatin. For example, in the treatment of stage II ovarian epithelial cancer, post surgery, the following regimens may be used:

- paclitaxel (Taxol) + cisplatin or carboplatin
- cyclophosphamide + cisplatin
- cyclophosphamide + carboplatin

These similarities are well documented in postmarketing reports of confusion between these two established names resulting in overdose and fatalities. Subsequent to these reports of Cisplatin overdoses and dosing errors between Carboplatin and Cisplatin, the sponsor Bristol Myers Squibb revised the labels and labeling for Cisplatin. See Figure 1 for a picture of the revised Platinol-AQ carton labeling. In addition to revisions of the container and carton, the sponsor put a warning on the ferrule of the vial that states "Call MD if dose is greater than  $100 \text{ mg}/\text{m}^2$ ." Changes to the Cisplatin labeling appears to have decreased the number of reported medication error cases related to name confusion. As of December 1995, the sponsor received eight cases of name confusion between Cisplatin and Carboplatin. BMS submitted a Changes Being Effected labeling supplement in August 1996 that contained the aforementioned label and labeling changes. A BMS submission dated June 1998 indicated that BMS had received one report of name confusion between the two products after the labeling change. DMETS concurs that changes to the labeling appear to have decreased reports, since a recent review of AERS and Drug Quality Reporting System (DQRS) reports did not identify any reports of name confusion between the two products. Although no reports were identified and name confusion between the existing products may be minimal, the introduction of the new dosage form may increase the potential for name confusion between Cisplatin Injection and Carboplatin Injection.

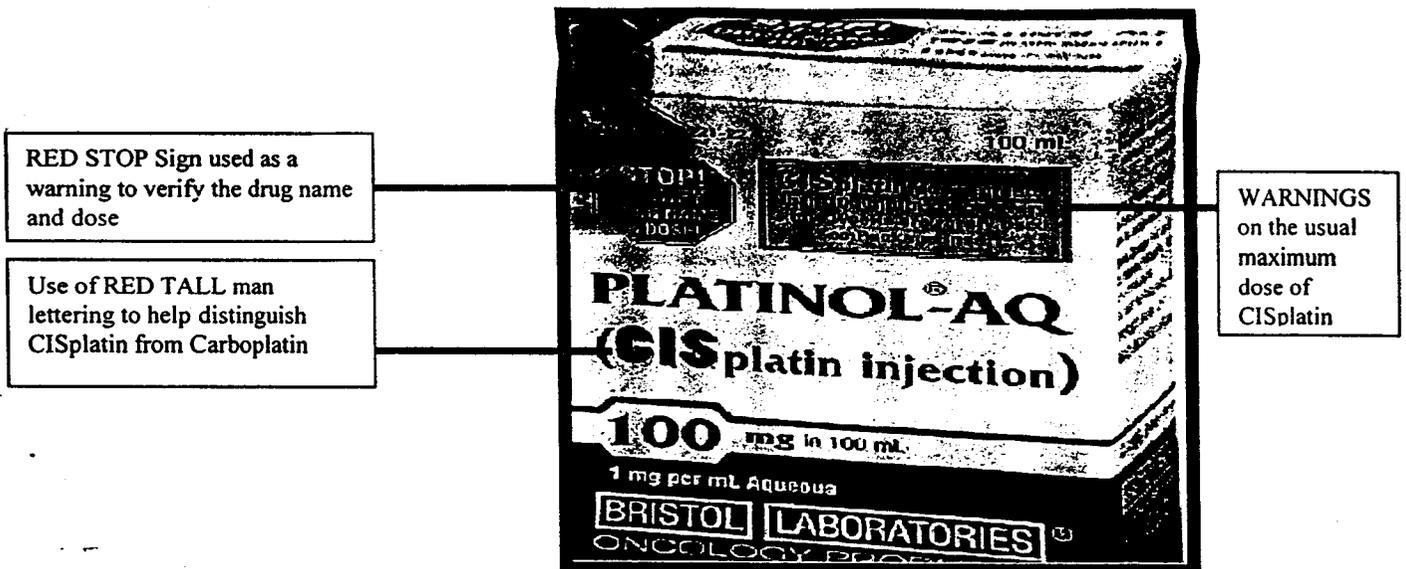


Figure 1

In addition to the labeling revisions mentioned above, the manufacturer discontinued marketing Cisplatin lyophilized powder to further differentiate and decrease the chances of confusion. Thus Cisplatin is only marketed in a solution for injection (Platinol AQ) whereas Carboplatin is marketed as a lyophilized powder. Although the potential for confusion was decreased by the Platinol AQ label and labeling revisions, the introduction of the proposed solution of Carboplatin Injection into the marketplace may initiate a recurrence of confusion between Carboplatin Injection and Cisplatin Injection especially since Carboplatin and Cisplatin can be used to treat the same cancers and are part of similar treatment protocols.

Carboplatin Injection and Cisplatin Injection will both be available in the same dosage form, thus eliminating one of the differing characteristics between the two products. Although, the Cisplatin labeling has extensive warnings, this may not help in the case of selection errors where a practitioner selects Carboplatin Injection instead of Cisplatin Injection. Previously, the different dosage forms (solution vs. lyophilized powder) would serve as an additional trigger for a practitioner to realize that the wrong medication was selected. With both products being manufactured in the same dosage form, and from the same manufacturer, this differing characteristic can no longer help to prevent errors. Thus the known similarity in established names in combination with the commonality of the dosage forms increases the potential for name confusion.

Therefore, it is important that the labels and labeling of Carboplatin Injection and Cisplatin Injection are substantially different. The Carboplatin Injection labels and labeling should not contain the warnings, etc found on the Cisplatin labels and labeling. The current labels and labeling for Cisplatin are very distinct (see Figure 1) and are familiar to healthcare practitioners. They contain warnings that help to minimize potential name confusion. In contrast the Carboplatin for Injection labeling does not contain similar warnings. Providing similar warnings on the Carboplatin Injection labels and labeling may confuse practitioners. If the Carboplatin Injection labels and labeling are similar in color and design to the existing Carboplatin for Injection labels and labeling practitioners may be less likely to confuse Carboplatin Injection for Cisplatin.

Practitioners are familiar with the existing Carboplatin for Injection labels and labeling. *Therefore similarity between the Carboplatin for Injection and Carboplatin Injection labels and labeling may help to reduce the potential for confusion of these products with Cisplatin Injection.*

Therefore, Bristol Myers Squibb should develop a risk management plan that will address the risk of introducing this dosage form into the marketplace. With the introduction of the new dosage form, it is extremely important that healthcare practitioners are educated on the availability of the new dosage form of Carboplatin and on the potential for name confusion between Cisplatin Injection and Carboplatin Injection. This information should also include the potential outcome of confusing Cisplatin for Carboplatin and vice versa. The education campaign should begin before the launch of Carboplatin Injection and should continue after the launch. Bristol Myers Squibb should propose a timeframe as to when the education campaign should end.

### III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

The Paraplatin labels and labeling were submitted in draft format, which did not allow for a comprehensive evaluation of the color, format, etc. However, DMETS has attempted to focus on safety issues relating to possible medication errors and identified the following areas of possible improvement, which might minimize potential user error.

#### A. GENERAL COMMENTS

1. The labels and labeling of Paraplatin Injection must be differentiated to minimize potential confusion between Paraplatin Injection and Cisplatin Injection.

2

3. We recommend relocating the secondary expression of strength (mg/mL) so that it is in close proximity to the concentration. For example:

Paraplatin  
(Carboplatin Injection)  
150 mg per 15 mL  
(10 mg/mL)

4. We suggest relocating the net quantity to the lower section of the label so that it will not be confused with the product concentration.
5. Revise the statement 'Each vial contains 150 mg Carboplatin.' to '\_\_\_\_\_'

#### IV. RECOMMENDATIONS:

- A. *DMETS has no objection to the use of the proprietary name Paraplatin. However, DMETS is concerned with the introduction of this new dosage form into the market. We believe it will increase the risk of confusion between Carboplatin and Cisplatin. We recommend the sponsor develop a risk management plan to address the name confusion. We would like to meet with the Division to discuss this further.*
- B. *DMETS recommends implementation of the labeling revision outlined in Section III of this review.*
- C. *DDMAC finds the proprietary name acceptable from a promotional perspective.*

*DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.*

---

Denise P. Toyer, Pharm.D.  
Safety Evaluator/Team Leader  
Division of Medication Errors and Technical Support

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this page is the manifestation of the electronic signature.**

/s/

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Denise Toyer  
5/29/03 11:39:49 AM  
PHARMACIST

Carol Holquist  
5/30/03 07:34:23 AM  
PHARMACIST

2 Page(s) Withheld

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6 Draft Labeling Page(s) Withheld

## MEMORANDUM OF TELECON

**DATE:** April 2, 2003

**APPLICATION NUMBER:** NDA 20-452  
Paraplatin (carboplatin aqueous solution) Injection

**BETWEEN:**

Noemi Guma, Ph.D., Manager, Global Regulatory Science-CMC  
Charles LaPree, R.A.C., Director, Global Regulatory Science-CMC  
Li-Chun Wang, Ph.D., Associate Director-Global Pharm Tech & Development TL for  
Carboplatin

Barry Scheer, Ph.D., Associate Director, Analytical R&D  
Michael Kril, Ph.D., Senior Research Investigator II, Analytical R&D  
Daniel Kim, M.S., Senior Manager, Global Pharm Tech  
Marianne Kammer, Site Director, Global Labeling-CNS/Oncology  
Susan Martindale, Senior Labeling Associate, Global Labeling-Marketed Products

Representing: Bristol-Myers Squibb Company

**AND**

Christy Cottrell, Consumer Safety Officer  
William Timmer, Ph.D., Chemistry Reviewer  
Rebecca Wood, Ph.D., Chemistry Team Leader  
Hasmukh Patel, Ph.D., Deputy Director, DNDC1

Representing: Division of Oncology Drug Products, HFD-150

**SUBJECT:** Outstanding CMC issues from NDA review

**DISCUSSION:**

The numbered agenda items were faxed to the sponsor prior to the meeting. All discussion points are noted in *italics* immediately following the coinciding agenda item.

1. The testing specification for Carboplatin Injection (Item 4, Vol 5, Page 005) indicates that there are five pages (Page 1 of 5). Only three pages are included. The sponsor is requested to supply the remaining two pages; same for the 150 and 450 mg/vial presentations.

*Comment: The sponsor indicated that the missing pages were blank pages and were intentionally left out of the submission. The sponsor agreed to either submit the pages or submit a statement that the missing pages contain no information for review.*

2. In the carboplatin assay, please explain:

- a. the very broad peak \_\_\_\_\_ in the HPLC tracing, and
- b. the rationale for not using the USP method for the carboplatin assay.

*Comment: The sponsor clarified that the broad peak was related to a gradient shift. The sponsor explained that the USP method did not show carboplatin-related impurities, so they developed a new method that shows potency and impurity.*

3. The stability test methods are numbered as \_\_\_\_\_, etc., while the test methods for the carboplatin drug product begin with the prefix \_\_\_\_\_xxxxx.
  - a. Please explain the difference or similarities between the assays (carboplatin, \_\_\_\_\_, \_\_\_\_\_), for the marketed product and the methods used to acquire the \_\_\_\_\_ batch] stability data, and
  - b. Is the formulation of the foreign-marketed drug product the same as the formulation of the drug product that is to-be-marketed in the US?

*Comment: The sponsor explained that there were two methods; the old method (for the \_\_\_\_\_ series) was stability-indicating but did not show impurities, while the new method (for the \_\_\_\_\_ series) shows carboplatin-related impurities. The sponsor noted that the \_\_\_\_\_ batches of stability data were acquired with the \_\_\_\_\_ series, and the \_\_\_\_\_ series are the new batches that they will be using. The sponsor further explained that they have comparability data between the \_\_\_\_\_ series and some non-sequential stability samples from the \_\_\_\_\_ series. The Division asked whether the sponsor had methods validation data for the old method and the sponsor stated that they did, but it was not up to 2003 standards since it was done in 1985. The Division asked the sponsor to submit the comparability data for the old method versus the new method along with any stability data they may have for the new method. Although previously submitted with the original NDA in 1994, the Division asked the sponsor to resubmit the methods validation data for the old method. Regarding the foreign-marketed formulation, the sponsor noted that it is the same as the product that is to-be-marketed in the United States. The sponsor agreed to submit documentation that the formulations are the same.*

4. We request BMS to commit to either an ICH photostability study or a conditions-of-use photostability study.

*Comment: The sponsor stated that there was some photostability data submitted with the original NDA in 1994 and for ease of review, they will resubmit that data. The sponsor agreed to conduct a conditions-of-use photostability study and will submit the commitment along with the information requested under item #3.*

5. We request your concurrence with the following storage statement:

Store at 20°-25° C (68°-77° F)

Excursions permitted from 15°-30° C (59°-86° F)

[see USP Controlled Room Temperature]

*Comment: The sponsor agreed with this labeling change. The Division stated that there were additional changes not noted above and that the labeling would be sent to the sponsor shortly for concurrence.*

The sponsor asked to discuss issues that were identified during the inspection of the facilities in Puerto Rico. The Division stated that the findings by the inspector could not be considered finalized until the review went through the District Office and the Office of Compliance. The Division explained that discussion of these findings would be deferred until the review is completed.

The sponsor was informed that the tradename review was also still pending.

**ACTION ITEMS:**

- Sponsor to submit the following no later than Monday, April 7, 2003:
  - Comparability data for the old method versus new method for the stability test method assays
  - Stability data for the new method
  - Commitment to conduct a conditions-of-use photostability study
  - Resubmit the methods validation data for the old method that was submitted in the original NDA
  - Resubmit photostability data that was submitted in the original NDA
- Division to send labeling changes to the sponsor for review and concurrence

/S/

\_\_\_\_\_  
Christy Cottrell  
Consumer Safety Officer

/S/

Concurrence: \_\_\_\_\_

William Timmer, Ph.D.  
Chemistry Reviewer

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/s/

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Christy Cottrell

4/17/03 11:24:28 AM

Draft minutes initialed by Wtimmer on 4-9-03; RWood on  
4-10-03; HPatel on 4-17-03.

William Timmer

4/17/03 11:58:21 AM

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/s/

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Christy Cottrell  
5/8/03 10:54:38 AM  
CSO

## MEMORANDUM OF TELECON

**DATE:** April 9, 2003

**APPLICATION NUMBER:** NDA 20-452  
Paraplatin (carboplatin aqueous solution) Injection

**BETWEEN:**

Noemi Guma, Manager, Global Regulatory Science, CMC  
Elizabeth Yamashita, Group Director, Global Regulatory Science, CMC

**Representing:** Bristol-Myers Squibb Company

**AND**

Christy Cottrell, Consumer Safety Officer  
Richard Pazdur, M.D., Division Director  
William Timmer, Ph.D., Chemist

**Representing:** Division of Oncology Drug Products, HFD-150

**SUBJECT:** Extension of PDUFA due date for pending NDA

The Division explained to BMS that the Division will be extending the PDUFA due date for this NDA. The Division stated that the additional CMC information submitted on April 4, 2003, will be considered a major amendment received within 3 months of the PDUFA due date. The Division noted that this extension will allow adequate time to review the data contained in the amendment and will also give BMS an opportunity to address the issues identified during the inspection of their manufacturing facility.

The Division asked that BMS contact the Division when the manufacturing issues have been addressed so a new inspection can be requested, if needed. The Division stated that labeling negotiations would still take place in the interim.

/s/

---

Christy Cottrell  
Consumer Safety Officer

/s/

Concurrence:

---

William Timmer, Ph.D.  
Chemistry Reviewer

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/s/

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Christy Cottrell

4/16/03 01:43:16 PM

Draft minutes initialed by Wtimmer on 4-11-03.

William Timmer

4/17/03 11:55:03 AM

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Christy Cottrell  
5/8/03 11:38:49 AM  
CSO

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Summary of Preliminary Review of NDA 20-452 (Paraplatin) Stability Study

This is a summary of my preliminary review of the stability data of NDA 20-452 submitted by the sponsor.

I. Insufficient numbers of lots/batches for each package type.

Since only six lots (S86F026, S87L003, S86F027, S86F028, S86F029, and S87L004) made by Bristol Caribbeau Inc. in Mayaguez P. R. are selected by the reviewing chemist Dr. Eva Tolgyesi, there are not enough lots for each package type to conduct a proper stability analysis.

According to the FDA guideline, the sponsor should at least include three lots (or batches) per package type in the stability study. However, based on the six lots, both package types A and G used two lots each (lots S86F026 and S87L003 for package type A; lots S86F028 and S86F029 for package type G) and both package types C and H used only one lot each (lot S86F027 for package type C; lot S87L004 for package type H).

Moreover, lots S87L003 and S87L004 only have data at each temperature.

II. Exact values missing for test variables and

Besides Assay HPLC, Dr. Tolgyesi is also interested in analyzing and . However, instead of giving the true values for both and the sponsor only provided the upper bound information.

III. Final Remark.

In order to conduct a proper stability analysis, the sponsor is requested to provide more data (on diskette, especially, at temperature 25°C) for the FDA statistician to perform independent analyses.

The variables in the data diskette should include

Drug product manufacture, Package type, Lot number, Temperature, Strength (Mg per Vial), Storage position (upright or inverted), Stoper number, Pottency (HPLC),  and

Please leave at least one space between two adjacent variables.

LS/

Wen-Jen Chen, Ph.D.,  
Mathematical Statistician

LS/

Concur: Karl K. Lin, Ph.D.,  
Group Leader, SARB

Cc: HFD-150/Dr. Burke  
HFD-150/Dr. Poochikian  
HFD-150/Dr. Tolgyesi  
HFD-715/Dr. K. Lin  
HFD-715/Dr. Chen  
HFD-715/SARB Chron  
HFD-715/DRU 2.1.1 NDA 20-452 (Paraplatin).

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NDA #: 20-452

Submission Date: March 9, 1994

Drug Name: Paraplatin — (carboplatin) Injection

Sponsor: Bristol-Myers Squibb

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PHARMACOLOGY REVIEWER COMMENTS:

1. Supplementing Dr. Tolgyesi's concern regarding the analysis, I would be particularly interested in the detailed methodology for the HPLC assay of           . This is a very            compound that exist as a mixture of           . The            change dramatically from carboplatin as well. This assay may thus be very complicated, inaccurate, and imprecise. I will mention this to Eva.
2. The            form of the drug is known to be quite toxic. The aquated species as a group are suspected of being the causal agents in the nephrotoxicity of cisplatin. Since carboplatin aquates quite slowly ( $t_{1/2} \sim 18$  hr?) the amount of aquated impurities present in the aqueous formulation may be much higher than in a fresh solution made from a lyophilized formulation. The sponsor thus needs to provide not only details of how the aquated impurities are assayed, but how these levels compare to those normally present in the approved formulation of carboplatin. Data on the levels of the aquated species that may normally form in plasma after carboplatin administration would also be useful for assessing the potential toxicity of the new aqueous formulation.

MICROBIOLOGY CONSULT:

Dr. Cooney received the NDA (Bob Scully delivered it twice) and concluded that sufficient information is present to perform a substantive review from the standpoint of sterility assurance. He will inform us of the identity of the reviewer and an estimated completion date ASAP.

# CARBOPLATIN

Paraplatin Injection

NDA 20-452

Bristol-Myers Squibb, Syracuse, NY

Submission Date: March 8 and 31, 1994

October 25, 1994

Reviewer: Lydia C. Kaus, M.S., PhD.

Type of Submission: waiver request.

## Background:

Paraplatin<sup>TM</sup> injection was

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

A meeting was held in December 13, 1990 subsequent to which the firm submitted NDA 20-452 to the Agency. This recent submission is the subject of this review.

## Proposed Changes:

The firm is removing mannitol from the formulation and proposing to have an aqueous solution of carboplatin rather than the present lyophilized product (see attached tabulated comparison from Chemist's Review). The final product will be a sterile 10 mg/mL aqueous solution of carboplatin in three different sized vials ( \_\_\_\_\_ in volume) to provide 50, 150 and 450 mg of carboplatin respectively. These are the same strengths as in the lyophilized product. The firm want to provide a ready-to-use product with advantages over the present lyophilized product that requires re-constitution prior to use.

## Comments:

Both products have the same final concentration of 10 mg/mL carboplatin as an aqueous solution. The pH range of the two is the same (pH 5-7). The information on the osmolarity of the products however is still pending. (The reviewer asked the firm to provide this information). The firm has sent osmolality data which is quite different between the two products (see Appendix to this review).

In § 320.22 (b) (1) (i) (ii) of the 21CFR the following is stated as criteria for waiver of evidence of *in vivo* bioavailability:

For certain drug products, the *in vivo* bioavailability or bioequivalence of the drug product may be self-evident. FDA shall waive the requirement for the submission of evidence obtained *in vivo* demonstrating the bioavailability or bioequivalence of these drug products. A drug product's *in vivo* bioavailability or bioequivalence may be considered self-evident based on other data in the application if the product meets one of the following criteria:

(1) The drug product:

- (i) Is a parenteral solution intended for administration by injection, or an ophthalmic or otic solution; and
- (ii) Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application.

The submission does not fully meet the criteria set out in § 320.22 (b) (1) (ii) in that the inactive ingredients are different by the removal of mannitol.

If removal of mannitol has altered the osmolarity of the product, there may be altered tonicity. The effect of tonicity is primarily on the rbc resulting in possible physical changes if the osmolarity of a solution infused into the veins is not isotonic.

**Recommendation:**

The Biopharmaceutics Division has reviewed the formulation and waiver request submitted by the firm and has the following comment:

The criteria of the waiver as per § 320.22 (b) (1) (ii) of the 21CFR has not been met. The pharmacokinetics of the active ingredient should be unaltered by the formulation change and provided the Chemist Reviewer is satisfied with the stability and general quality assurance of the product, the Division of Biopharmaceutics waives the requirement for evidence of *in vivo* bioequivalence. However, the firm needs to show that there will be no adverse local effects due to the change in formulation compared to the old formulation. The Reviewing Medical Officer needs to concur with this recommendation.

LS

Lydia C. Kaus, MS, Ph.D.  
Pharmacokinetics Evaluation Branch

FT \_\_\_\_\_ LS  
Mehul Mehta, Ph.D., Section Head

cc

HFD 150: NDA 20-452

HFD-150: Div. File

HFD-150: Tolgyesi

HFD-426: Biopharm/Mehta

HFD-426: Biopharm/ Drug File

HFD-426: Biopharm/Fleischer

HFD-426: Biopharm/Chen

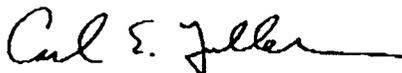
**APPENDIX**

**Osmolality Data for Each Formulation**

Osmolality (mOsm/kg)				
Product	Ready-to-Use		Lyophile	
Lot No.	S87L003	S87L004	S87L000	S87L002
<b>Average</b>	<b>29.4</b>	<b>29.4</b>	<b>81.2</b>	<b>82.4</b>

If further questions should arise regarding this or additional issues in connection with this NDA, please feel free to contact Mr. Michael Burnett at (315) 432-2799.

Sincerely,



Carl E. Fuller  
Sr. Regulatory Affairs Associate  
Chemistry, Manufacturing and Controls Group  
Worldwide Regulatory Affairs  
Telephone: 315-432-2564  
Telefax: 315-432-2594

TABLE  
PRODUCT COMPOSITIONS

Page 4  
NDA 19-880

INGREDIENTS	<u>PARAPLATIN<sup>(R)</sup> for injection</u>			<u>PARAPLATIN<sup>(R)</sup> injection, 10 mg/mL</u>		
	<u>IN3213</u>	<u>IN3214</u>	<u>IN3215</u>	<u>IN3210</u>	<u>IN3211</u>	<u>IN3212</u>
	50 mg vial	150 mg vial	450 mg vial	50 mg vial	150 mg vial	450 mg vial
CARBOPLATIN — .a)	50 mg	150 mg	450 mg	50 mg	150 mg	450 mg
MANNITOL, USP	50 mg	150 mg	450 mg	-	-	-
WATER FOR INJECTION, (b) USP, QS to	_____			to 5 mL	to 15 mL	to 45 mL

INGREDIENTS	<u>TYPICAL BATCH</u>			<u>TYPICAL BATCH (d)</u>		
	_____	_____	_____	_____	_____	_____
CARBOPLATIN — , (a)	_____	_____	_____	_____	_____	_____
WATER FOR INJECTION, (b) USP, QS to	_____			_____	_____	_____
Fill per vial	_____			5 mL	15 mL	45 mL

(a) This represents 100% label claim at 100% purity  
 (b) \_\_\_\_\_  
 (c) \_\_\_\_\_  
 (d) Any size vial may be filled

**\*\*\*SENSITIVE\*\*\***

**REVIEW**

**OF**

**ENVIRONMENTAL ASSESSMENT**

**FOR**

**NDA 20-452**

**PARAPLATIN<sup>®</sup> AQ**

**(Carboplatin Injection)**

**REVIEW DIVISION: HFD-150**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**HFD-102**

**DATE COMPLETED: November 23, 1994**

ENVIRONMENTAL ASSESSMENT

1. Date:

EA dated: 11/19/1993  
NDA Submitted: 03/08/1994  
EA review HFD-150: not given  
Consult to HFD-102 11/16/1994  
Assigned: 11/17/1994

CSO: Diane Daproza

2. Name of applicant/petitioner:

Bristol-Myers Squibb Company

3. Address:

P.O. Box 4755  
Syracuse, NY 13221-4755

Eva Tolgyesi of HFD-150 reviewed parts 1-6 and 12-15. See Attachment 3. A consult was sent requesting review of section 7-11.

7. Fate of emitted substances in the environment:

Parent Compound: Carboplatin  
Excreted metabolites: Majority (~70%) is excreted unchanged  
Species of Interest: Platinum

Platinum is the species of interest in the environment whether in the form of a metal complex or in its elemental state. Platinum has a half life of millions of years and is naturally occurring in the earth's crust at about 0.01 ppm (information from Merck Index). Based on the data summarized in Appendix 1, the compound should amass in the aquatic environment.

8. Environmental effects of released substances:

The data provided indicates that there should be no significant impact to the environment as the MEEC is much lower than the concentrations toxic to the test organisms. See Attachment 2.

The non-confidential section is not readable/understandable due to the manner in which information was deleted. DEFICIENT. We remind you that this document is made available for public inspection after approval of the application. You should summarize the confidential information to the extent possible. For example when relating the toxicity information to the MEEC it could be stated that the MEEC is much less than 1% of the EC<sub>50</sub>, there is greater than 3 (4, 5,...) orders of magnitude safety factor between the two or other such general statements. Reference to the confidential section for the exact information should be made.

9. Use of resources and energy:

BMS:

a. Production:

There will be no discernable increase in use of energy or water. Adequate.

b. Effect on Endangered/Threatened Species:

None. Adequate.

c. Effect on Properties Listed/Eligible for National Register of Historic Places:

None. Adequate.

No information is provided for the drug substance manufacturer. DEFICIENT.

10. Mitigation measures:

BMS will control environmental release as described in Section 6. They have site-specific emergency plans, secondary containment controls waste minimization procedures and employee protection recommendations. Adequate.

No information is provided for the drug substance manufacturer. DEFICIENT.

11. Alternatives to the proposed action:

"No action". Adequate.

DRAFT DEFICIENCY LETTER

Note to HFD-150:

- Deficiency #8 regarding fate & effects should be deleted from the Chemist's list of deficiencies.
- Deficiencies # 2, 3, 4: I haven't been asking applicants to provide a description of the environments present at or adjacent to disposal facilities that are permitted/licensed (which they always are) because this is evaluated by or under the control of the EPA or appropriate State Agency which issues the permit. It is a legitimate question based on the CFR, but it would be acceptable to the EA reviewer if this part of the deficiency was deleted.
- The limited information provided under section 9 for drug product is acceptable to the EA reviewer.

Add the following deficiencies to the Chemist's list of deficiencies:

1. The non-confidential information provided for section 8 is not readable/understandable due to the manner in which information was deleted. We remind you that this document is made available for public inspection after approval of the application. You should summarize the confidential information to the extent possible. For example when relating the toxicity information to the MEEC it could be stated that the MEEC is much less than 1% of the  $EC_{50}$ , there is greater than 3 (4, 5, ...) orders of magnitude safety factor between the two or other such general statements. Reference to the confidential section for the specific information should be made.
2. Information should be included in sections 9 and 10 for the drug substance manufacturer.

ATTACHMENT 1				
TIER 0 - Carboplatin				
Attribute	Test Method	Compliance w/ Protocol (Y/N)	Result	Comments
Water Solubility	—	Y	—	—
Hydrolytic Stability (Kh)				Not needed. Environmental species of interest is platinum which does not degrade for many years.
Dissociation Constant	—	Y	—	—
Octanol/Water (Log P)	—	Y	—	—
Vapor Pressure or Henry's Law Constant				Due to the nature of the compound, this was not determined as agreed to by P. Vincent.
Other (specify) Sorption Desorption Properties	—	Y	—	Compound is —
REVIEW CONCLUSIONS	The compound is expected to amass in the aquatic environment. Bioaccumulation is not indicated.			

ATTACHMENT 2				
TIER 1 (Aquatic Compartment) - Carboplatin				
Attribute	Test Method	Compliance w/ Protocol (Y/N)	Result	Comments
Aerobic Biodegradation $t_x$				Not needed. Environmental species of interest is Platinum which does not degrade for many years.
Anaerobic Biodegrad. $t_x$				
Microbial Inhibition Testing	_____	Y	_____	
Acute Aquatic Toxicity <i>Daphnia magna</i>	_____	Y	_____	
V/Visible Spectrum				Not needed. See Biodegradation.
Photolytic $t_x$				
Expected Environmental Concentration	Standard calculation	Y	_____	Based on annual production of _____
Other (specify)				None
REVIEW CONCLUSIONS	Material is nontoxic based on the toxicity definition in the CFR.			

**DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS**

**REVIEW OF ENVIRONMENTAL ASSESSMENT**

**FOR**

**NDA 20-452 PARAPLATIN (carboplatin) INJECTION**

A.3  
p 6b

1. DATE OF DOCUMENT:

March 8, 1994

2. NAME OF APPLICANT:

Bristol-Myers Squibb Company  
Pharmaceutical Research Institute

3. ADDRESS:

P.O. Box 4755  
Syracuse, NY 13221-4755

4. DESCRIPTION OF PROPOSED ACTION:

a. Describe the requested approval

Bristol-Myers Squibb is requesting approval to manufacture and market PARAPLATIN (carboplatin) Injection, a platinum compound, for the treatment of ovarian cancer. PARAPLATIN Injection is a sterile aqueous solution with a 10 mg/mL carboplatin concentration and is supplied in 50 mg, 150 mg and 450 mg single-use vials.

Estimated Patient Use: Estimated production volume of carboplatin drug substance in five years is \_\_\_\_\_, for PARAPLATIN Injection \_\_\_\_\_ for both PARAPLATIN Injection and PARAPLATIN for Injection.

b. Describe the need for action

PARAPLATIN Injection is indicated for the therapy of ovarian cancer.

c. Describe locations where the products are to be

(1) Produced:

The drug substance carboplatin is manufactured by \_\_\_\_\_

The drug product, PARAPLATIN (carboplatin) Injection, will be manufactured, filled, packaged and controlled at Bristol Caribbean, Inc., a wholly owned and operated facility of Bristol-Myers Squibb Co. Bristol Caribbean, Inc. is located in the Mayaguez Foreign Trade Zone, on State Road No. 114, Mayaguez, Puerto Rico, 00708. This facility is located next to the Guanajibo Industrial Park, 2 miles from the city of Mayaguez, 3 1/2 miles from the Port of Mayaguez.

A.3  
p6c

(2) Use:

PARAPLATIN (carboplatin) Injection will be used worldwide for treatment of ovarian cancer. It is anticipated that its distribution will be primarily to the United States, \_\_\_\_\_

DEFICIENT. The Applicant should specify where the drug product will be used, e.g., hospital, clinic, home, etc.

(3) Disposal:

a. Drug Substance

Will be returned to the source facility ( \_\_\_\_\_ )  
\_\_\_\_\_ for rework and recycling, if possible.

DEFICIENT. The mode and site of disposal of drug substance that can not be recycled by \_\_\_\_\_ should be specified. The type of environment at and adjacent to that location should be also described.

b. Drug Product

In Puerto Rico all returned drug product is sent to the warehouse of Bristol-Myers Squibb (BMS) in Catano, then transferred to the BMS manufacturing facility in Mayaguez, PR. There the returned PARAPLATIN Injection vial contents will enter the site's oncological wastewater system for deactivation. The empty vials will be shipped to an approved incinerator for final disposal.

The BMS Distribution Center in Mt. Vernon, Indiana is the processing center for returned drugs from domestic sites. The returned products are checked and may be sent to a processing site for further evaluation or directed for disposal. PARAPLATIN Injection vials slated for disposal are transported to a permitted incineration facility, by an approved carrier.

DEFICIENT. For drug product disposal in Puerto Rico provide the mode of deactivation of the drug product before it enters the local sewer system and for the drug vial disposal the name and location of the approved incinerating facility. Additionally, describe the environments present at and adjacent to those locations.

Pertaining to the disposal of PARAPLATIN from the Mt. Vernon, IN center, provide the name and address of the incinerating facility that will be used, and describe its environment.

A.3  
p 6d

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT OF THE PROPOSED ACTION

The Applicant listed the physicochemical properties of carboplatin and PLATINOL-AQ in the Material Safety Sheets in Appendix A .

DEFICIENT. The identity and level of impurities and degradation products in the bulk drug and drug product should be provided.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

a. Drug Substance Production Site

No information provided.

DEFICIENT. No information was provided pertaining to the manufacturing site of the drug substance, listing the substances to be emitted, the controls exercised, compliance with applicable emission requirements at the production site, type and quantities of substances to enter the environment.

b. Drug Product Manufacturing Site

(Bristol Caribbean, Inc., Mayaguez, Puerto Rico)

The Applicant certifies compliance with applicable environmental, occupational health and safety standards and national, federal, state and local emission regulations. A brief description is provided in the submission of the emissions to air and wastewater as well as treatment of solid waste.

DEFICIENT. A more detailed description is needed pertaining to the introduction of substances into the environment at the Bristol Caribbean, Inc., Mayaguez site. As required under 21 CFR 25.31a, you should list all the substances expected to be emitted (solid, liquid and gas) and state the controls exercised (including how will the active ingredient be degraded before entering the sewer system and what are the reaction products, what solid wastes will be incinerated, which will be disposed of in a landfill and provide the name and address of the landfill facility). Discuss what effect will have the approval of the proposed action upon compliance with current emission requirements and estimate the quantities and concentrations of substances expected to enter the environment as a result of use and/or disposal of products affected by the action.

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6.e

The Applicant states that an amendment will be submitted to this Environmental Assessment when the on-going studies pertaining to Sections 7 and 8 (Fate of Emitted Substances in the Environment and Environmental Effects of Released Substances) have been completed.

12. LIST OF PREPARERS:

The list of the persons who prepared the Environmental Assessment document, as well as their qualifications are provided.

ADEQUATE.

13. CERTIFICATION:

DEFICIENT. No certifications is provided by a responsible official stating that the information presented is true, accurate and complete.

14. REFERENCES:

No references are listed.

DEFICIENT. Complete citations should be listed for all referenced material. Copies of referenced articles not generally available should be attached.

15. APPENDICES

Material Safety Sheets, description of the drug product and a diagram of the manufacturing process for PARAPLATIN-AQ Injection are included into the appendices.

ADEQUATE.

Reviewed by:

Eva Tolgyesi, Ph.D.

- cc:
- HFD-150 Div. File for NDA 20-452
- HFD-150/ETolgyesi
- HFD-150/JBlumenstein
- HFD-151/DDaproza
- File: C:\WPFILES\N20452EA.000

LIST OF DEFICIENCIES:

1. Specify the locations where PARAPLATIN — Injection will be used, e.g., hospital, clinic, home, etc.
2. Provide a detailed description of the method and site of disposal for returned drug substance that will not be recycled by \_\_\_\_\_ The type of environment present at and adjacent to that location should be also described.
3. Describe how will returned PARAPLATIN ← Injection be deactivated in Mayaguez, Puerto Rico, before it enters the local sewer system and provide the name and address of the approved incinerating facility that will be used for the disposal of the vials. In addition, describe the environments present at and adjacent to those locations.
4. Provide the name and address and describe the environment for the incinerating facility that will be responsible for the disposal of PARAPLATIN — Injection returned to the Mt. Vernon, Indiana Distribution Center of the Bristol-Myers Squibb Co.
5. Additional information is needed pertaining to the identification of chemical substances that are subject of the proposed action. List the impurities and decomposition products and state their levels in the bulk drug and in the drug product.
6. Information should be submitted concerning the introduction of substances into the environment from the production site of the drug substance. List the substances to be emitted; state the controls exercised; include a citation of, and statement of compliance with, applicable emission requirements at the Federal, State and local level; and discuss the effect the approval of the proposed action will have upon compliance with current emission requirements at this production site. Through use of calculations and/or direct measures, estimate to the extent possible the quantities and concentrations of substances expected to enter the environment as a result of use and/or disposal of products affected by the action.

7. More detailed information is needed pertaining to the introduction of substances into the environment at the Bristol Caribbean, Inc., Mayaguez, P.R. site. As required under 21 CFR 25.31a, you should list all the substances expected to be emitted (solid, liquid and gas) and state the controls exercised (including how will the active ingredient be degraded before entering the sewer system and what are the reaction products, what solid wastes will be incinerated, which will be disposed of in a landfill and provide the name and address of the incinerator and landfill facilities). Discuss what effect will the approval of the proposed action have upon compliance with current emission requirements and estimate the quantities and concentrations of substances expected to enter the environment as a result of use and/or disposal of products affected by the action.
8. Submit the required information and calculations concerning the "Fate of Emitted Substances in the Environment" and "Environmental Effects of Released Substances".
9. A more detailed description is necessary pertaining to the "Use of Resources and Energy", as required under 21 CFR 25.31(a)9.
10. Certification should be provided by a responsible official stating that the information presented is true, accurate and complete.
11. The Environmental Assessment document should be supported by appropriate citations from the literature and/or other documents. Provide a list of all referenced material and attach copies of referenced articles which are not generally available.

Endorsements:

HFD-102/NBSager

HFD-102/PGVincent

CC: Original NDA 20-452/DDaproza copy to NDA/HFD-150  
EA File 20452.REV  
CGood/HFD-102

File: 20452E1a.RNS

F/T by NBS/11/23/1994

## IV. ENVIRONMENTAL IMPACT ANALYSIS REPORT

Environmental Assessment

1. Date: December 1987
2. Name of Applicant:  
Bristol-Myers Company  
Industrial Division  
Mayaguez Operations
3. Address of Applicant:  
Foreign Trade Zone No. 7  
P.R. Road No. 114  
Mayaguez, PR 00708
4. Description of Proposed Action:

Bristol-Myers Co., Industrial Division, plans to add carboplatin to the manufacturing process at its Mayaguez Plant. The plant is located in the Mayaguez Foreign Trade Zone (FTZ) next to the Guanajibo Industrial Park on State Road No. 114, 2 miles from the city of Mayaguez and 3 1/2 miles from the Port of Mayaguez. The FTZ was authorized pursuant to a grant issued on June 27, 1960 by the Foreign Trade Zone's Board, Washington, D.C. . This area has been developed by the Puerto Rico Industrial Company for the light, "dry" type industry.

Total area for the main manufacturing building is → square feet. No additional building, parking space, or landscaping will be required for the proposed operation, thus the building structure will remain the same.

The new product is to be known as Paraplatin<sup>(R)</sup> (carboplatin) for injection, a lyophilized composition, and Paraplatin<sup>(R)</sup> (carboplatin) injection, a ready-to-use solution.

This new operation will be conducted in addition to the manufacture of \_\_\_\_\_,

The products will be manufactured \_\_\_\_\_

Approximately \_\_\_\_\_ of carboplatin will be consumed during the first year of manufacturing. The drug is intended for human use in the U.S.A. and Puerto Rico.

5. Identification of Chemical Substances that are the Subject of the Proposed Action:

Three components will be used in the manufacture of Paraplatin. The chemical substances are described in Attachment No. 1.

6. Introduction of Substances Into the Environment:

The finished dosage forms contain carboplatin as the only active ingredient. Its introduction into the environment at the intended product strengths as a result of manufacture or use is expected to be negligible.

a) Introduction Into the Workplace

There will be no impact on land from the proposed operation. The operation for the manufacture of Paraplatin<sup>(R)</sup> involves no construction, thus there will be no impact on land use, water quality, or other natural resources from construction activities.

Personnel in the workplace are properly and adequately protected, principally with a

b) Introduction in Chemotherapy

Carboplatin has shown activity against a variety of cancerous tumors. The drug is administered to patients as an infusion by the intravenous route. Carboplatin is excreted primarily in the urine with recovery of approximately 70% of the administered platinum within 24 hours. Most of the drug is excreted in the first 6 hours.

## c) Quantities Discharged at the Place of Use

Based on current projections for the first three years of production, the amount of carboplatin expected to be filled into vials is as follows:

Number of Kilograms Per Year

Year 1      Year 2      Year 3

The quantities above which indicate the projected amount of drug to be consumed over the first three years reflect the maximum amount that could possibly be discharged to the environment at the place of use. At maximum projected use, the product would still account for only a small percentage of the total antineoplastic drug market.

Since lyophilized formulation also contains an equal amount of mannitol, preparation of this drug product will yield an equivalent quantity of material to the environment. Mannitol, however, is a straight chain hexahydric sugar alcohol already available from natural sources and not expected to adversely affect the environment.

## 7. Fate of Emitted Substances in the Environment:

It should be recognized that once the product has entered the distribution channels, Bristol-Myers Co. has only nominal control over

the use and disposal of the drug. Nonetheless, the following is an analysis of the environmental factors likely to be affected by the action.

The nature, amount and concentrations of discharges resulting from the production of this antineoplastic drug are such that no observable effects are expected on receptors. Further, it is expected that these discharges will not add to any existing burden.

a) Air Emissions

Air emissions are negligible because the process is by its nature carefully —  
— controlled, and because production volume is not large with respect to other drugs and chemicals.

The impact on air quality from this plant is limited to the generation of about tons per year of sulfur dioxide from the burning of fuel. The proposed action will not add additional emissions of sulfur dioxide. Vents from the process tanks are already permitted by the Puerto Rico Environmental Quality Board (EQB). These sources are authorized to operate under EQB operation permit number PFE-50-1287-0735-I-II-0. The permit was issued last December 1987, and it will expire in February, 1990. The air quality of the region will not be affected. The facility is in compliance with all the applicable air emission requirements.

## b) Water

No effluent is generated in the manufacturing process other than that resulting from \_\_\_\_\_

Wastewater discharges are limited in actual operations, and will increase moderately as a result of the proposed operations. The liquid wastes generated by this process, consisting mainly of \_\_\_\_\_

\_\_\_\_\_ are very dilute and will be pretreated via \_\_\_\_\_

\_\_\_\_\_ to ensure that no contamination will be discharged to the municipal wastewater treatment plant. Although the quantities for these waste streams have not been determined, it is estimated that they are very small amounts.

Urinary excretions from patients are likely to be collected and disposed of in appropriately sized and designed hospital systems or in the patient's private home throughout a variety of geographic locations. Thus the issue of large concentrations in the effluent due to large concentrated populations is unlikely. The urinary content to be discharged at any one time at any one location by any one patient relative to a dose of 400 mg/m<sup>2</sup>, is likely to suffer from such large dilutions as a result of repeated flushings as to be negligible or non-detectable in the effluent.

c) Terrestrial Ecosystems

Since product volume is small, generation of solid wastes from this process will be limited, consisting basically of \_\_\_\_\_

\_\_\_\_\_ and other protective material used by the personnel. The material will be collected in metal containers and disposed of in an approved and licensed landfill and in accordance with all federal, state and local regulations. The proposed action will not result in the generation of hazardous wastes.

8. Environmental Effects of Released Substances

The environmental effects of released substances are expected to be negligible because of the small annual volume of carboplatin relative to other drugs and chemical substances. Material that may escape actions such as \_\_\_\_\_ and \_\_\_\_\_ is likely to be so dilute as to be non-detectable.

Overall, it is expected that there will be no adverse impact on the environment from any of the released substances.

9. Use of Resources and Money

The proposed action will not affect any geological, historical, paleontological, architectural, archaeological or cultural sites

and values. It will not require the use of nonrenewable energy sources in apparently excessive or disproportionate amounts. The action will not result in destruction of vegetation, wildlife or marine life, or alter the pattern of behavior of wildlife, nor will it affect other forms of life or ecosystems of which they are a part. The nature and amount of materials being used in the proposed action are such that long term productivity of the environment will not be affected.

10. Mitigation Measured

Since all processes used to produce the product are properly controlled, and since production volumes are modest, mitigation measures beyond those described above are not necessary.

11. Alternatives to the Proposed Action

Since the proposed action will not have a negative environmental effect, alternative actions to this proposal are not advisable.

Furthermore, no reasonable or feasible alternative to the proposed action can be considered since this action involves the manufacturing of antineoplastic drugs subject to new drug approvals.

## 12. List of Preparers

This assessment has been prepared by Mr. E. Olan and Dr. R. G. Daoust.

Excel Olan, P.E., is a Professional Engineer registered in the Commonwealth of Puerto Rico. He received his B.S. degree in Mechanical Engineering from the University of Puerto Rico in 1973 and obtained a M.S. degree in Industrial Hygiene and Safety Engineering from Texas A&M University in 1981.

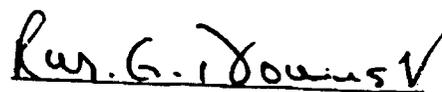
Dr. Raymond G. Daoust is an industrial pharmacy graduate from Purdue University. For over 20 years, he has served the company in the areas of product development, process development/scale-up, manufacturing and regulatory affairs in a domestic and international environment.

## 13. Certification

The undersigned officials certify that the information presented is true, accurate and complete to the best of our knowledge.



Excel Olan, P.E.  
Environmental Health &  
Safety Manager



Raymond G. Daoust, Ph.D.  
Associate Director  
Regulatory Affairs

## 14. References

- a. The Merck Index, 10th Edition, 1983
- b. Registry of Toxic Effects of Chemical Substances, NIOSM Pub. No. 81-116, February 1982
- c. Dangerous Properties of Industrial Materials, by N. Irving Sax, 5th Edition, 1979
- d. U.S. Pharmacopeia/The National Formulary, 1985

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## PARAPLATIN(R)

TABLE I: IDENTIFICATION OF CHEMICAL SUBSTANCES

<u>Chemical Substance</u>	<u>CAS Reg. No.</u>	<u>Molecular Weight</u>	<u>Structural Formula</u>	<u>Physical Description</u>
Carboplatin	41575-94-4	371.3	$C_6H_{12}N_2O_4Pt$	White Crystalline Powder
Mannitol, USP	69-65-8	182.17	$C_6H_{14}O_6$	Light White Powder
Water for Injection, USP	7732-18-5	18.02	$H_2O$	Colorless Liquid

48 Draft Labeling Page(s) Withheld