CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-452

CORRESPONDENCE

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: Noemi Guma	**From:** Christy Cottrell
Fax: (609) 818-5831	**Fax:** (301) 594-0499
Phone: (609) 818-5759	**Phone:** (301) 594-5761
Pages, including cover sheet: 33	**Date:** 7-14-03

Re: NDA 20-452 for Paraplatin (carboplatin aqueous solution) Injection

Noemi,

Attached is a courtesy copy of the Approval letter that issued today, July 14, 2003, for NDA 20-452.

If you have any questions, please feel free to call me at (301) 594-5761.

Thanks,

[5]

Christy Cottrell

- in DFS

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DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

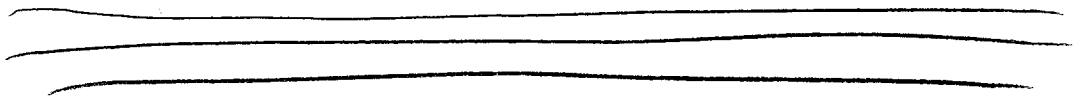
To: Noemi Guma	**From:** Christy Cottrell
Fax: (609) 818-5831	**Fax:** (301) 594-0499
Phone: (609) 818-5759	**Phone:** (301) 594-5761
Pages, including cover sheet: 2	**Date:** 7-14-03

Re: NDA 20-452 for Paraplatin (carboplatin aqueous solution) Injection

Noemi,

Please refer to your pending NDA 20-452 for Paraplatin (carboplatin aqueous solution) Injection. Included in this fax is a comment from the chemistry reviewer that explains the specifics of the photostability study that BMS has agreed to conduct. **We will need to receive your revised commitment to conduct this study as requested in this fax no later than 2:00 pm today since we would like to take an action this afternoon.**

Concerning the Photostability Study:



If you have any questions, please feel free to call me at (301) 594-5761.

Thanks,

LST

Christy Cottrell

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	1314
CONNECTION TEL	916098185831
SUBADDRESS	
CONNECTION ID	
ST. TIME	07/14 09:41
USAGE T	00'35
PGS. SENT	2
RESULT	OK

FAX

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FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: Noemi Guma	**From:** Christy Cottrell
Fax: (609) 818-5831	**Fax:** (301) 594-0499
Phone: (609) 818-5759	**Phone:** (301) 594-5761
Pages, including cover sheet: 5	**Date:** 5-8-03

Re: NDA 20-452 for Paraplatin (carboplatin aqueous solution) Injection – Telecon minutes

Noemi,

Attached are the Division's finalized minutes from the April 2, 2003, teleconference to discuss outstanding review issues for NDA 20-452.

If you have any questions, please feel free to call me at (301) 594-5761.

Thanks,

Christy Cottrell

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
5600 Fishers Lane, Rockville, MD 20857

To: Noemi Guma	**From:** Christy Cottrell
Fax: (609) 818-5831	**Fax:** (301) 594-0499
Phone: (609) 818-5759	**Phone:** (301) 594-5761
Pages, including cover sheet:	**Date:** 4-17-03

Re: NDA 20-452 for Paraplatin (carboplatin aqueous solution) Injection

Noemi,

Please refer to your pending NDA 20-452 for Paraplatin (carboplatin aqueous solution) Injection. Included in this fax are the Division's recommended labeling changes based on your proposed labeling submitted with this NDA.

1. In the **DESCRIPTION** section, the first paragraph, you proposed:

   "PARAPLATIN (carboplatin aqueous solution) Injection is supplied as a sterile, pyrogen-free, 10 mg/mL aqueous solution of carboplatin

   *Comment: The following changes are recommended for the **DESCRIPTION** section:*

   "PARAPLATIN (carboplatin aqueous solution) Injection is supplied as a sterile, pyrogen-free, 10 mg/mL aqueous solution of carboplatin. Carboplatin is a platinum coordination compound. The chemical name for carboplatin is..., and carboplatin has the following structural formula:"

2. You proposed the following for the **STABILITY** section:

"Unopened vials of PARAPLATIN (carboplatin aqueous solution) Injection are stable for the life indicated on the package when stored at [redacted]. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration."

*Comment: 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."

3. You proposed the following for the **HOW SUPPLIED** section:

"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. [redacted]
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. [redacted]
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. [redacted]

Comment: It is recommended that the descriptions be modified as follows:

"PARAPLATIN (carboplatin aqueous solution) Injection

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.

4. You proposed the following for the **STORAGE** section:

[redacted]

*Comment: 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."

Please review these proposed revisions and determine whether they are acceptable to you. You may fax your response to my attention at (301) 594-0499. If you have any questions, please feel free to call me at (301) 594-5761.

Thanks,

Christy Cottrell

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
4/17/03 04:43:22 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-452

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

Attention: Noemi Guma, Ph.D.
Manager

Dear Dr. Guma:

We acknowledge receipt on October 15, 2002 of your October 11, 2002 resubmission to your new drug application for Paraplatin-AQ (carboplatin) Injection.

We consider this a complete, class 2 response to our December 19, 1994 action letter. Therefore, the user fee goal date is April 15, 2003.

If you have any question, call Christy Wilson, Regulatory Project Manager, at (301)594-5761.

Sincerely,

/S/

{See appended electronic signature page}

Dotti Pease
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Dotti Pease
10/25/02 12:32:04 PM

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4755 Syracuse, NY 13221-4755 315 432-2000

PARAPLATIN®- ——— , INJECTION
NDA #20-452

March 31, 1994

Gregory Burke, M.D., Ph.D., Director
Division of Oncology and Pulmonary Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research (HFD 150)
Food and Drug Administration
Suite 200N - 1401 Rockville Pike
Rockville, Maryland 20852-1448

Dear Dr. Burke:

RE: NDA #20-452: PARAPLATIN® —(carboplatin) INJECTION
General Correspondence

Reference is to our NDA submission of March 8, 1994 and to a telephone communication received today from Ms. Diane Daproza, the Division's CSO. In response to a request for waiver of evidence of in vivo bioavailability/bioequivalence, Bristol-Myers Squibb heretofore states its intention to comply.

Paraplatin — is a parenteral solution intended solely for administration by injection and contains the same active ingredient as our product Paraplatin® for Injection, which is the subject of approved NDA #19-880. Paraplatin —is the ready-to-use version of the lyophile for injection minus the mannitol which is intended to ——— There are no other differences. In light of the above rationale, we believe that we meet the requirement for a waiver under 21CFR §320.22 (b) (1)(i)(ii) and request that such be granted.

Respectfully,

Michael J. Burnett, Director
Chemistry, Manufacturing and Controls
Worldwide Regulatory Affairs
Telephone: (315) 432-2799
Telefax: (315) 432-2594

cc: J. Blumenstein
D. Daproza
E. Tolgyesi

D94-042/jlo

PARAPLATIN® Presentations

Respective Components

NDA #19-880	NDA #20-452
PARAPLATIN® (carboplatin) for Injection (Lyophile)	PARAPLATIN® (carboplatin) Injection (Ready-to-Use)
Carboplatin	Carboplatin
Mannitol, USP	
	Water for Injection, USP

D t

DEC 19 1994

NDA 20-452

Bristol-Myers Squibb Company
Pharmaceutical Research
5 Research Parkway
P.O. Box 5100
Wallingford, Connecticut 06492-7660

Attention: Michael J. Burnett
Director, Worldwide Regulatory Affairs

Dear Mr. Burnett:

Please refer to your March 8, 1994 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paraplatin [redacted] (carboplatin) Injection.

We acknowledge receipt of your amendments dated March 31, April 7, 29, October 25, and November 10, 1994.

We have completed our review and find the information presented is inadequate and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

1. Comments pertaining to the manufacturing process:

   a. State the revisions to the manufacturing process which have been instituted to reduce the occurrence of particulate formation. List the specific changes and their effect on the physicochemical characteristics of the product.

   b. Submit a detailed description of the current, optimized commercial manufacturing process, including the general description and schematic diagram of the operations. Indicate for each manufacturing step the equipment used and the points of sampling. Critical control parameters, and time frames should be provided for each major step, including holding times between steps and between the final step and packaging. Describe the storage conditions. To facilitate the evaluation of the manufacturing process, submit actual (executed) batch production and control records of a representative batch of Paraplatin [redacted] Injection,

produced at the proposed production facility, using the current production process. The use of [redacted] should be explained [redacted]

c. Submit justification for the in-process controls by demonstrating that they are suitable for minimizing particulate formation, based upon your studies investigating the source and mechanism of particulate formation. Provide a full description of all in-process controls and their allowed limits.

2. State whether any reprocessing operations will be performed and provide a full description of any proposed reprocessing methods with supporting test data.

3. Comments concerning the container/closure systems:

a. It should be stated for which vial sizes would the [redacted] stoppers be used. In addition, each vial size of Paraplatin [redacted] Injection in each packaging system must be supported by appropriate primary stability data.

b. It should be clarified whether the [redacted] stoppers are [redacted] in the commercial process, or were [redacted] previously, and for which drug product batches. If [redacted] is being or has been used, a full description is needed of this step.

4. The reaction mechanism for the formation of [redacted] [redacted] suggests [redacted] Has development work been conducted to evaluate the effect of the [redacted]

5. Comments concerning the regulatory specifications and test methods for the drug product:

a. Specify the number of individual samples to be analyzed in each test and provide a brief description of the sampling plans for production batches and selection of sub-samples for analyses. The total number of samples taken per production batch, based on the batch size, should also be stated.

b. In the [redacted] test [redacted] the specifications for [redacted] are poorly defined.

[redacted]. In addition, it is not clear whether this test is able to detect and quantitate a small amount of particulate. Is this the same method which was used for the evaluation of particulate levels in aged Paraplatin [redacted] solutions, assigning [redacted] to [redacted] ratings (Procedure No. [redacted] report on "Inspection of Carboplatin [redacted] Samples", dated 12/22/93, p. 300364)?

c. As the limit for [redacted] is set at [redacted], the precision, accuracy and assay variability for the method should be evaluated at correspondingly [redacted] concentrations. In addition, specificity should be demonstrated.

d. Submit quantitative impurity profiles for several representative production-size Paraplatin [redacted] batches, produced using the current commercial manufacturing process. All impurities and decomposition products found at 0.1% or higher, based on carboplatin content, should be listed.

e. Provide the corresponding test data for representative, current commercial batches, having been stored at 25°C for 18 months.

f. The regulatory controls for Impurities should be revised, based on the impurity profile and stability data. Appropriate specifications should be established for Total Impurities and Individual Impurity limits for each related substance which may be present in the drug product during its shelf-life at 0.1% or higher level. The specifications should require that no impurities be present at levels exceeding 0.1%, except those for which individual specifications have been established.

6. The test data in the "[redacted] Stability Report" are inadequate to support the 18-month expiration dating period for the 50 mg, 150 mg and 450 mg vials of Paraplatin [redacted] Injection in the container/closure systems utilizing the [redacted] and the [redacted] stoppers.

a. The data for only [redacted] lots [redacted] can be considered **"primary stability data"** having the same drug product manufacturer and container/closure

system as that proposed for the commercial product. The rest of the data are only "supportive data". It had been noted previously, that the drug product lots of the other manufacturer (Bristol, Syracuse) had better long-term stability.

b. None of the —lots for which long term stability data are provided utilizes drug substance produced by the proposed drug product manufacturer (only — —— stability data are provided for drug product lots formulated using the proposed bulk drug manufacturer's product).

c. All of the stability lots are considerably smaller than the commercial batch sizes. Many of the lots are ' —— , only a few are ' —— lots".

d. The commercial product uses — as ——— . The use of ——— has been stated on the 1989 filling records in the NDA. It is not clear what ' ——— was used in 1985-86 in Syracuse and Mayaguez.

e. It is not clear whether the — stoppers used for packaging of the "primary stability batches" were ——— or not.

f. The appearance of a fine precipitate in some drug product batches nearing the proposed 18-month expiration dating period is of grave concern.

The ——— , stability report was already submitted under ——— and ——— and the data were judged inadequate to support the proposed expiration dating period. Additional stability data are necessary on commercial batches produced according to the proposed manufacturing process. The requirements for the Stability Section of the NDA (number of batches for each vial size and stopper type, tests to be conducted, data reporting and analysis) were discussed in detail at the December 13, 1990 BMS/FDA meeting.

7. No process development work was reported, to evaluate the effect of various manufacturing and packaging parameters on long-term product stability and reproducibility. The Agency has recommended that the manufacturing process should be revised and additional controls established, leading to longer-term product stability and improved batch-to-batch and vial-to-vial uniformity.

8. Comments concerning the Market-Life Product Stability Report:

   a. No Production Records are submitted. The container/closure systems are not identified. The storage conditions (temperature, vial position) of the samples are not stated. No test data are provided for during the 18-month shelf life. No statistical evaluation of the data is provided.

   b. Significantly higher numbers of the more current commercial batches contain particulates after storage, than seen for earlier batches produced in 1988-89. While only of the vials produced in 1988-89 contained precipitate (see p. 300320), in some of the more recent batches of the samples contain particulates rated after months storage at 21-23°C (see p. 300358). A similar trend is seen in the data. You must explain these findings, and clarify what factors are responsible for the apparent decrease in long-term stability.

   c. As a large percentage of the recent commercial batches show insoluble particulates after storage at 21-23°C, test data are needed for the earlier, time points, to demonstrate physical stability during the proposed 18-month expiration dating period.

9. Comments pertaining to the Finished Product Stability Protocol:

   a. The number of batches placed into stability testing should be a function of the total number of batches produced that year. At least batch of each dosage size should, however, be placed on stability study each year.

   b. The protocol should state the number of dosage units selected per test. In addition to calculated means, individual test data should also be submitted when several samples are analyzed.

   c. An Appearance of Solution test, which is able to detect a small amount of particulate, should be part of the regulatory tests at each time-station.

d. [redacted] testing should be performed at release and at the end of the expiration dating period.

e. The stability testing protocol should describe the statistical method used to analyze the data.

10. Submit the impurity profiles, specifying the types and levels of impurities, for the carboplatin drug substance batches used in the pre-clinical and key clinical studies.

11. Comments pertaining to the labels and cartons:

a. A statement that the drug is sterile and nonpyrogenic should appear on the labels and cartons.

b. The warnings: **"Caution: Cytotoxic Agent"** and **"Retain in Carton until Use"** should appear on the carton.

12. Comments concerning the DESCRIPTION section of the package insert:

a. It should be stated that the drug is nonpyrogenic.

b. The first sentence should be revised to provide the quantitative ingredient information (e.g., "is supplied as a sterile, pyrogen-free, 10 mg/mL aqueous solution of carboplatin"), without [redacted]

13. Comments Pertaining to the PREPARATION OF INTRAVENOUS SOLUTIONS Subsection of the package insert:

The storage conditions and length of use-time for the diluted Paraplatin [redacted] solutions should be included in this subsection, instead of the [redacted] subsection.

14. Comments Pertaining to the HOW SUPPLIED section of the package insert:

a. State that each vial size is for single-dose use.

b. Include the concentration of the fill solution.

c. Include appropriate information to facilitate the identification of the dosage form and dosage size (e.g., [redacted] packaging components, etc.).

d. Include [redacted] in this section, instead of the separate STORAGE and HANDLING AND DISPOSAL sections.

We reserve further comment on the labels and labeling until the application is otherwise approvable.

With regard to the Environmental Assessment, we have the following comments and requests for information that should be addressed:

15. Specify the locations where Paraplatin — Injection will be used, e.g., hospital, clinic, home, etc.

16. 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.

17. 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.

18. 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 25.31(a), you should list all the substances expected to be emitted (solid, liquid and gas) and state the controls exercised (including how the active ingredient will 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 the approval of the proposed action will 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.

19. A more detailed description is necessary pertaining to the "Use of Resources and Energy", as required under 21 CFR 25.31(a)(9).

20. Certification should be provided by a responsible official stating that the information presented is true, accurate and complete.

21. 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.

22. 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 [redacted] there is greater than [redacted] 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.

23. Information should be included in sections 9 and 10 for the drug substance manufacturer.

In addition, this submission was reviewed for microbiological issues concerning sterility assurance and the following issues were not completely addressed.

24. Please describe your methods of evaluating bioburden for the bulk solution and provide specifications. How are the specifications established? Please indicate the time limits for storage of bulk drug solution.

25. Please indicate whether the [redacted] resented for [redacted] validation represented [redacted] relative to the parameters for [redacted] used during manufacture. Validation parameters should be less or no greater than the minimum process specification. Please indicate the acceptance criteria for the [redacted] processes.

26. The vials used for [redacted] were not described.

27. [redacted] assays should be performed as part of the stability test program.

Although your request for a waiver of evidence of in vivo bioequivalence does not meet all of the requirements of 21 CFR 320.22(b)(1)(ii), our Division of Biopharmaceutics has determined that there is no reason to expect any change in the pharmacokinetics of the active drug, therefore, a waiver for good cause is granted under 21 CFR 320.22(e).

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of the invoice.

Should you have any questions, please contact:

Dianne Daproza
Project Manager
Oncology Drug Products
Telephone: (301) 594-5770

Sincerely yours,

/S/

Charles P. Holberg, Ph.D.
Acting Director
Division of Oncology and
Pulmonary Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20-452
HFD-150/div. file
HFA-100 (if user fee application)
HFC-130/JAllen
HFD-5/THassall (if user fee application)
HFD-80
HFD-100/Dr. Temple
HFD-150/GWilliams
HFD-150/PAndrews
HFD-150/ETolgyesi
HFD-150 (HFD-426)/LKaus
HFD-151/DDaproza/drafted: 12-2-94
R/D init by: GWilliams/12-7-94
RDeLap (for JJohnson)/12-7-94
ETolgyesi/12-12-94
JJDeGeorge/12-7-94
LKaus/12-7-94
MMehta/12-7-94
RGScully/12-13-94
F/T by: dgdaproza/12-14-94
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NOT APPROVABLE