Michelle W. Kloss, Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
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West Point PA 19486-0004
Tel 484 344 2905
Fax 484 344 2516

DESK COPY

July 26, 2001

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Soreth:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to the pending NDA for INVANZ™ cited above, submitted as an electronic archive on November 30, 2000. Reference is also made to a July 20, 2001 teleconference meeting between representatives of FDA and Merck Research Laboratories (MRL, a Division of Merck & Co., Inc.) and to a July 20, 2001 facsimile communication from Ms. Maureen Dillon Parker (FDA) to Dr. Michelle Kloss (MRL), in follow-up to the teleconference meeting cited above, which requested additional beta-lactamase information for several patients with Haemophilus influenzae and/or Moraxella catarrhalis infections in Protocols 018 and 020.

With this submission, we are providing the information requested by the Agency in the July 20, 2001 teleconference meeting and facsimile communication cited above. All information is in an electronic format as indicated in the Table of Contents for this submission.

This response is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories is providing one Compact Disk (CD) which contains the response. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100MB. We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 4.0, Symantec Corp., 1991-1997) and we authorized the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Anti-Infective Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Maureen Dillon Parker, Regulatory Project Manager, Division of Anti-Infective Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Please direct questions or need for additional information to Michelle W. Kloss, Ph.D. (484-344-2905) or, in my absence, Bonnie J. Goldmann, M.D. (484-344-2383).

Sincerely yours,

M C Kloss for

Michelle W. Kloss, Ph.D.
Senior Director, Regulatory Affairs

Enclosure: CD

Federal Express #1

[redacted]: [redacted] Maureen Dillon Parker, Regulatory Project Manager (cover letter), [redacted] Room 8506

Federal Express #2

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Michelle W. Kloss, Ph.D.
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July 31, 2001

DESK COPY

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Soreth:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to the pending NDA for INVANZ™ cited above submitted as an electronic archive on November 30, 2000. Reference is also made to a July 19, 2001 telephone conversation between Ms. Maureen Dillon-Parker (FDA) and Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) during which the Agency requested that MRL submit all the patient Case Report Forms (CRFs) for Protocol 029. During this conversation, per the Agency's request, it was agreed that MRL would also provide a desk copy of these Protocol 029 CRFs for use by the Medical Reviewer.

With this submission, we are providing the Protocol 029 CRFs as requested by the Agency in the July 19, 2001 telephone conversation cited above as well as the desk copy on CD for use by the Medical Reviewer. All information is in an electronic format as indicated in the Table of Contents for this submission.

This response is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs*. As an attachment to this letter, Merck Research Laboratories is providing one Compact Disk (CD) which contains the response. All documents requiring signatures for certification are included as paper for archival purposes.

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A list of reviewers from the Division of Anti-Infective Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Maureen Dillon-Parker, Regulatory Project Manager, Division of Anti-Infective Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Please direct questions or need for additional information to Michelle W. Kloss, Ph.D. (484-344-2905) or, in my absence, Bonnie J. Goldmann, M.D. (484-344-2383).

Sincerely yours,

Michelle W. Kloss

Michelle W. Kloss, Ph.D.
Senior Director, Regulatory Affairs

Enclosure: CD

Federal Express #1

Desk Copy: Ms. Maureen P. Dillon Parker, Regulatory Project Manager (cover letter + CD)
HFD-520, Room S306
Federal Express #2

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Michelle W. Kloss, Ph.D.
Senior Director
Regulatory Affairs

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August 1, 2001

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Soreth:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to the pending NDA for INVANZ™ cited above, submitted as an electronic archive on November 30, 2000. Reference is also made to a July 9, 2001 facsimile communication from Ms. Maureen Dillon-Parker (FDA) to Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) which provided Chemistry Reviewer Comments on the Chemistry Section of the NDA cited above.

With this submission, we are providing a complete response to the Agency's comments in the July 9, 2001 communication cited above. All information is in an electronic format as indicated in the Table of Contents for this submission.

This response is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories is providing one Compact Disk (CD) which contains the response. All documents requiring signatures for certification are included as paper for archival purposes.

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A list of reviewers from the Division of Anti-Infective Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Maureen Dillon-Parker, Regulatory Project Manager, Division of Anti-Infective Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Please direct questions or need for additional information to Michelle W. Kloss, Ph.D. (484-344-2905) or, in my absence, Bonnie J. Goldmann, M.D. (484-344-2383).

Sincerely yours,

Michelle W. Kloss

Michelle W. Kloss, Ph.D.
Senior Director, Regulatory Affairs

Enclosure: CD

Federal Express #1

Desk Copy: Ms. Maureen P. Dillon-Parker, Regulatory Project Manager (cover letter)
HFD-520, Room S306
Federal Express #2

Desk Copy/att: Dr. Vithal Shetty, HFD-520, Room N356
Federal Express #3

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Michelle W. Kloss, Ph.D.
Senior Director
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August 14, 2001

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Soreth:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to the pending NDA for INVANZ™ cited above, submitted as an electronic archive on November 30, 2000. Reference is also made to an August 9, 2001 telephone conversation between Ms. Maureen Dillon Parker (FDA) and Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) regarding MRL's request for Agency concurrence on the pediatric dose regimens for Protocols 036 and 038. During this telephone conversation, Ms. Dillon Parker requested that MRL provide the age and dose for patients participating in Protocol 028. Reference is also made to the August 9, 2001 facsimile communication from Dr. Kloss to Ms. Dillon Parker providing the requested information.

With this submission, MRL is following up with an official submission of the August 9, 2001 facsimile cited above. All information is in an electronic format as indicated in the Table of Contents for this submission.

This response is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs*. As an attachment to this letter, Merck Research Laboratories (MRL), a division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the response. All documents requiring signatures for certification are included as paper for archival purposes.

We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 4.0, Symantec Corp., 1991-1997) and we authorized the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Anti-Infective Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Maureen Dillon Parker, Regulatory Project Manager, Division of Anti-Infective Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this amendment should be directed to Michelle W. Kloss, Ph.D. (484-344-2905) or, in my absence, to Bonnie J. Goldmann, M.D. (484-344-2383).

Sincerely yours,

Michelle C. Kloss FOR

Michelle W. Kloss, Ph.D.
Senior Director, Regulatory Affairs

Enclosure: CD

Federal Express #1

Desk Copy: Ms. Maureen Dillon Parker, Regulatory Project Manager (cover letter)
HFD-520, Room S306
Federal Express #2

Q\maione\mk826\nda amendments\09aug01_P028

Michelle W. Kloss, Ph.D.
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August 22, 2001

DESK COPY

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Soreth:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

AMENDMENT TO PENDING NEW DRUG APPLICATION

~~Reference is made to the pending NDA for INVANZ™~~ cited above, submitted as an electronic archive on November 30, 2000. Reference is also made to an August 16, 2001 facsimile communication from Ms. Maureen Dillon Parker (FDA) to Dr. Dennis Erb for Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) which requested additional analyses regarding electrocardiographic data and mortality data and to an August 17, 2001 teleconference meeting between representatives of FDA and MRL to discuss this Agency facsimile communication. During this teleconference meeting, the Agency was informed of MRL's recent discovery of an error in the tabular reporting of deaths within the Clinical Study Reports (CSRs) of Protocols 017 and 023; this error involved Tables 60 and 51 of Protocols 017 and 023, respectively, entitled *"Clinical Adverse Experience Summary During Parenteral Therapy-Treated Population"*. It was agreed during this teleconference meeting that MRL would submit corrected, replacement tables to the Agency as soon as possible. Final reference is made to an August 20, 2001 facsimile communication submission which provided these replacement tables.

With this submission, in follow-up to the teleconference meeting cited above and to the August 20, 2001 facsimile communication submission cited above, we are providing a corrected, replacement table for Table 60 in the Protocol 017 CSR and a corrected, replacement table for Table 51 in the Protocol 023 CSR. As discussed during the teleconference meeting cited above, these replacement tables involve a correction for mortality data; the revised row is bolded within each replacement table. The reason for the correction is that the numbers within these tables in the CSR reflect actual mortality during the parenteral therapy period plus AEs that lead to death later; the replacement tables contain only mortality. We apologize for any inconvenience that this error may have caused the Agency.

This amendment is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories is providing one Compact Disk (CD) which contains the amendment. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100MB. We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 4.0, Symantec Corp., 1991-1997) and we authorized the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Anti-Infective Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Maureen Dillon Parker, Regulatory Project Manager, Division of Anti-Infective Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Please direct questions or need for additional information to Michelle W. Kloss, Ph.D. (484-344-2905) or, in my absence, Bonnie J. Goldmann, M.D. (484-344-2383).

Sincerely yours,

Cheri Sanders, MS for Michelle W. Kloss, PhD

Michelle W. Kloss, Ph.D.
Senior Director, Regulatory Affairs

Enclosure: CD

Federal Express #1

Desk Copy: Ms. Maureen P. Dillon Parker, Regulatory Project Manager (cover letter)
HFD-520, Room S306
Federal Express #2

Q:\kane\mk826\nda amendments\17Aug01 replace tables

Michelle W. Kloss, Ph.D.
Senior Director
Regulatory Affairs

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August 24, 2001

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Soreth:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to the pending NDA for INVANZ™ cited above submitted as an electronic archive on November 30, 2000. Reference is also made to an August 16, 2001 facsimile communication from Ms. Maureen Dillon Parker (FDA) to Dr. Dennis Erb for Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) which requested additional analyses regarding electrocardiographic data and mortality data and to an August 17, 2001 teleconference meeting between representatives of FDA and MRL to discuss this Agency facsimile communication.

With this submission, in follow-up to the teleconference meeting cited above, MRL is providing a response to the Agency's August 16, 2001 request for additional mortality data analyses. Please note that, as agreed to in the August 17, 2001 teleconference meeting cited above, our response to the Agency's request for additional electrocardiographic data analyses will be provided under separate cover shortly.

This response is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories is providing one Compact Disk (CD) which contains the response. All documents requiring signatures for certification are included as paper for archival purposes.

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Sincerely yours,

Michelle W. Kloss

Michelle W. Kloss, Ph.D.
Senior Director, Regulatory Affairs

Enclosure: CD

FAX/Federal Express #1

Desk Copy: Ms. Maureen P. Dillon Parker, Regulatory Project Manager (cover letter)
HFD-520, Room S306
FAX / Federal Express #2

Ms. Frances LeSane, Supervisory Regulatory Project Manager (cover letter)
HFD-520, Room N355
FAX / Federal Express #2

Dr. Jean Mulinde, Medical Reviewer (cover letter)
HFD-520, Room S342
FAX / Federal Express #2

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Michelle W. Kloss, Ph.D.
Senior Director
Regulatory Affairs

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August 24, 2001

MERCK

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Soreth:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

RESPONSE TO FDA REQUEST FOR INFORMATION

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With this submission, in follow-up to the teleconference meeting cited above, MRL is providing a response to the Agency's August 16, 2001 request for additional mortality data analyses. Please note that, as agreed to in the August 17, 2001 teleconference meeting cited above, our response to the Agency's request for additional electrocardiographic data analyses will be provided under separate cover shortly.

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Please direct questions or need for additional information to Michelle W. Kloss, Ph.D. (484-344-2905) or, in my absence, Bonnie J. Goldmann, M.D. (484-344-2383).

Sincerely yours,

Michelle W. Kloss

Michelle W. Kloss, Ph.D.
Senior Director, Regulatory Affairs

Enclosure: CD

FAX/Federal Express #1

Desk Copy: Ms. Maureen P. Dillon Parker, Regulatory Project Manager (cover letter)
HFD-520, Room S306
FAX / Federal Express #2

Ms. Frances LeSane, Supervisory Regulatory Project Manager (cover letter)
HFD-520, Room N355
FAX / Federal Express #2

Dr. Jean Mulinde, Medical Reviewer (cover letter)
HFD-520, Room S342
FAX / Federal Express #2

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Michelle W. Kloss, Ph.D.
Senior Director
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August 30, 2001

DESK COPY

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products

RECEIVED
AUG 31 2001
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c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

MERCK

Dear Dr. Soreth:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to the pending NDA for INVANZ™ cited above, submitted as an electronic archive on November 30, 2000. Reference is also made to an August 16, 2001 facsimile communication from Ms. Maureen Dillon Parker (FDA) to Dr. Dennis Erb for Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) which requested additional analyses regarding electrocardiographic data and mortality data and to an August 17, 2001 teleconference meeting between representatives of FDA and MRL to discuss this Agency facsimile communication.

With this submission, in follow-up to the teleconference meeting cited above, we are providing a response to the Agency's August 16, 2001 request for additional electrocardiographic data analyses. Please note that our response to the Agency's request for additional mortality data analyses was previously provided under separate cover via facsimile communication on August 24, 2001 and via Federal Express on August 27, 2001.

This response is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories is providing one Compact Disk (CD) which contains the response. All documents requiring signatures for certification are included as paper for archival purposes.

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We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Please direct questions or need for additional information to Michelle W. Kloss, Ph.D. (484-344-2905) or, in my absence, Bonnie J. Goldmann, M.D. (484-344-2383).

Sincerely yours,

Tamra L Goodrow for MWK
Michelle W. Kloss, Ph.D.
Senior Director, Regulatory Affairs

Enclosure: CD

Federal Express #1

Desk Copy: Ms. Maureen P. Dillon Parker, Regulatory Project Manager (cover letter)
HFD-520, Room S306
Federal Express #2

Dr. Jean Mulinde, Medical Reviewer
HFD-520, Room S342
Federal Express #2

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Michelle W. Kloss, Ph.D.
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September 4, 2001

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Soreth:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

~~RESPONSE TO FDA REQUEST FOR INFORMATION~~

Reference is made to the pending NDA for INVANZ™ cited above, submitted as an electronic archive on November 30, 2000. Reference is also made to an August 30, 2001 facsimile communication from Ms. Maureen Dillon Parker (FDA) to Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) in which the Biopharmaceutical Reviewer requested additional information regarding Protocol 015.

With this submission, we are providing the information for Protocol 015 requested by the Agency in the August 30, 2001 communication cited above.

This response is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories is providing one Compact Disk (CD) which contains the response. All documents requiring signatures for certification are included as paper for archival purposes.

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A list of reviewers from the Division of Anti-Infective Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Maureen Dillon Parker, Regulatory Project Manager, Division of Anti-Infective Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Please direct questions or need for additional information to Michelle W. Kloss, Ph.D. (484-344-2905) or, in my absence, Bonnie J. Goldmann, M.D. (484-344-2383).

Sincerely yours,

Michelle W. Kloss

Michelle W. Kloss, Ph.D.
Senior Director, Regulatory Affairs

Enclosure: CD

Federal Express #1

Desk Copy: Ms. Maureen P. Dillon Parker, Regulatory Project Manager (cover letter)
HFD-520, Room S306
FAX/Federal Express #2

Q:\maione\mk826\nda amendments\30Aug01_P015

FDA Comment:

Please submit the time that elapsed between the end of IV infusion (ertapenem 1 gram IV) and the initiation of hemodialysis for each subject (N=5) in study P015 with end-stage renal impairment during period 2. The protocol only states that subjects received a single 1 gram dose of ertapenem immediately prior the initiation of hemodialysis lasting 4 hrs.

MRL Response:

Provided below from Protocol 015 is a list of subjects by allocation number (AN), the actual start time of infusion, the actual stop time for the end of infusion, and the actual start time for hemodialysis during Period 2. The elapsed time between the end of infusion and the start of hemodialysis (Delta) is calculated by subtracting the infusion stop time from the hemodialysis start time. Study number 015001 indicates that the primary investigator for these subjects was Dr. Domenic Sica at the Medical College of Virginia, Richmond, VA. Study number 015002 indicates that the primary investigator for these subjects was Dr. Suzanne Swan at Total Renal Research in Minneapolis, MN.

Study No.	AN	Infusion Start Time (hr:min)	Infusion Stop Time (hr:min)	Hemodialysis Start Time	Delta* (min)
015001	0019	10:05	10:30	11:09	39
015001	0020	10:00	10:26	10:41	15
015001	0021	10:00	10:30	10:43	13
015002	0024	08:05	08:35	08:40	05
015002	0116	08:13	08:43	08:48	05

*Delta is the time elapsed between the end of infusion and the start of hemodialysis.

Michelle W. Kloss, Ph.D.
Senior Director
Regulatory Affairs

DESK COPY

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September 14, 2001

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products

Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Soreth:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to the pending New Drug Application (NDA) cited above for INVANZ™, submitted as an electronic archive on November 30, 2000. Reference is also made to an August 30, 2001 telephone conversation between Ms. Maureen Dillon Parker (FDA) and Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) during which the Agency requested that Merck submit updated Integrated Summary of Safety (ISS) tables to include data from the Safety Update Report (submitted to FDA on March 30, 2001) and from Protocol 029 (submitted to FDA on July 3, 2001) and to a September 4, 2001 facsimile communication from Ms. Dillon Parker to Dr. Kloss identifying the specific updated tables requested by the Agency. Additional reference is made to a September 7, 2001 telephone conversation between Ms. Dillon Parker and Dr. Kloss during which it was agreed that MRL would provide the requested revised tables on a 'roll-out' basis in two separate submissions.

With this submission, MRL is providing the first submission of the updated ISS tables as requested by the Agency in the September 4, 2001 facsimile communication cited above. In addition, as requested by the Agency during the August 30, 2001 conversation cited above, we are providing a desk copy on CD for use by the Medical Reviewer. Please note that the final submission of these revised ISS tables will be provided shortly under separate cover. All information is in an electronic format as indicated in the Table of Contents for this submission.

This response is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the response. All documents requiring signatures for certification are included as paper for archival purposes.

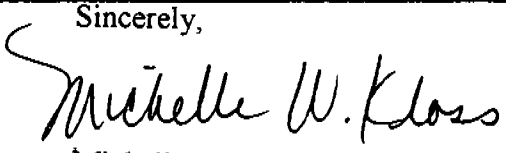
We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 4.0, Symantec Corp., 1991-1997) and we authorized the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Anti-Infective Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Maureen Dillon Parker, Regulatory Project Manager, Division of Anti-Infective Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Michelle W. Kloss, Ph.D. (484-344-2905) or, in my absence, to Bonnie J. Goldmann, M.D. (484-344-2383).

Sincerely,



Michelle W. Kloss, Ph.D.
Senior Director, Regulatory Affairs

Enclosure: CD

Hand Deliver

Desk Copy: Ms. Maureen Dillon Parker, Regulatory Project Manager (cover letter + CD)
HFD-520, Room S306
Hand Deliver

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Michelle W. Kloss, Ph.D.
Senior Director
Regulatory Affairs

DESK COPY

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2905
Fax 484 344 2516

September 17, 2001

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Soreth:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

~~RESPONSE TO FDA REQUEST FOR INFORMATION~~

Reference is made to the pending NDA for INVANZ™ cited above, submitted as an electronic archive on November 30, 2000. Reference is also made to a September 6, 2001 facsimile communication from Ms. Maureen Dillon Parker (FDA) to Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) which provided a request from the Microbiology reviewer for additional analyses.

With this submission, we are providing a response to the September 6, 2001 request cited above for additional analyses.

This response is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories is providing one Compact Disk (CD) which contains the response. All documents requiring signatures for certification are included as paper for archival purposes.

We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 4.0, Symantec Corp., 1991-1997) and we authorized the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Anti-Infective Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Maureen Dillon Parker, Regulatory Project Manager, Division of Anti-Infective Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Please direct questions or need for additional information to Michelle W. Kloss, Ph.D. (484-344-2905) or, in my absence, Bonnie J. Goldmann, M.D. (484-344-2383).

Sincerely yours,

Michelle W. Kloss

Michelle W. Kloss, Ph.D.
Senior Director, Regulatory Affairs

Enclosure: CD

Federal Express #1

Desk Copy: Ms. Maureen P. Dillon Parker, Regulatory Project Manager (cover letter)
HFD-520, Room S306
FAX/Federal Express #2

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Michelle W. Kloss, Ph.D.
Senior Director
Regulatory Affairs

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DESK COPY

September 18, 2001

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products

Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Soreth:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to the pending New Drug Application (NDA) cited above for INVANZ™, submitted as an electronic archive on November 30, 2000. Reference is also made to the July 3, 2001 submission of the Clinical Study Report (CSR) for Protocol 029, submitted in response to an Agency request for this CSR. Additional reference is made to an August 9, 2001 telephone conversation between Ms. Maureen Dillon-Parker (FDA) and Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) during which the Financial Disclosure information for Protocol 029 was discussed and it was agreed that Merck would provide this Financial Disclosure information as a single, separate submission by the third week in September 2001.

With this submission, in follow-up to the July 3, 2001 submission and the August 9, 2001 conversation cited above, MRL is providing the Financial Disclosure information for Protocol 029. All information is in an electronic format as indicated in the Table of Contents for this submission.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 4.0, Symantec Corp., 1991-1997) and we authorized the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Anti-Infective Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Maureen Dillon-Parker, Regulatory Project Manager, Division of Anti-Infective Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Michelle W. Kloss, Ph.D. (484-344-2905) or, in my absence, to Bonnie J. Goldmann, M.D. (484-344-2383).

Sincerely,

Jamia L Goodrow for MWK

Michelle W. Kloss, Ph.D.
Senior Director, Regulatory Affairs

Enclosure: CD

Hand Deliver

Desk Copy: Ms. Maureen Dillon-Parker, Regulatory Project Manager (cover letter)
HFD-520, Room S306
Hand Deliver

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Michelle W. Kloss, Ph.D.
Senior Director
Regulatory Affairs

DESK COPY

Merck & Co., Inc.
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September 21, 2001

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products

Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Soreth:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to the pending New Drug Application (NDA) cited above for INVANZ™, submitted as an electronic archive on November 30, 2000. Reference is also made to a September 13, 2001 facsimile communication from Ms. Maureen Dillon-Parker (FDA) and Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) which provided comments from the CMC-Microbiology Reviewer.

With this submission, MRL is providing a response to the September 13, 2001 facsimile communication cited above. All information is in an electronic format as indicated in the Table of Contents for this submission.

This response is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the response. All documents requiring signatures for certification are included as paper for archival purposes.

We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 4.0, Symantec Corp., 1991-1997) and we authorized the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Anti-Infective Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Maureen Dillon-Parker, Regulatory Project Manager, Division of Anti-Infective Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Michelle W. Kloss, Ph.D. (484-344-2905) or, in my absence, to Bonnie J. Goldmann, M.D. (484-344-2383).

Sincerely,

Michelle W. Kloss, Ph.D.
Senior Director, Regulatory Affairs

Enclosure: CD

Federal Express

Desk Copy: Ms. Maureen Dillon-Parker, Regulatory Project Manager (cover letter)
HFD-520, Room S306
Fax/Federal Express

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Michelle W. Kloss, Ph.D
Senior Director
Regulatory Affairs

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Tel 484 344 2905
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DESK COPY

September 21, 2001

MERCK

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Soreth:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to the pending New Drug Application (NDA) cited above for INVANZ™, submitted as an electronic archive on November 30, 2000. Reference is also made to an August 30, 2001 telephone conversation between Ms. Maureen Dillon-Parker (FDA) and Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) during which the Agency requested that MRL submit updated Integrated Summary of Safety (ISS) tables to include data from the Safety Update Report (submitted to FDA on March 30, 2001) and from Protocol 029 (submitted to FDA on July 3, 2001) and to a September 4, 2001 facsimile communication from Ms. Dillon-Parker to Dr. Kloss identifying the specific updated tables requested by the Agency. Additional reference is made to a September 7, 2001 telephone conversation between Ms. Dillon-Parker and Dr. Kloss during which it was agreed that MRL would provide the requested revised tables on a 'roll-out' basis in two separate submissions, the first of which was submitted on September 14, 2001.

With this submission, MRL is providing the final submission of the updated ISS tables as requested by the Agency in the September 4, 2001 facsimile communication cited above. In addition, as requested by the Agency during the August 30, 2001 conversation cited above, we are providing a desk copy on CD for use by the Medical Reviewer. All information is in an electronic format as indicated in the Table of Contents for this submission.

This response is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the response. All documents requiring signatures for certification are included as paper for archival purposes.

We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 4.0, Symantec Corp., 1991-1997) and we authorized the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Anti-Infective Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Maureen Dillon-Parker, Regulatory Project Manager, Division of Anti-Infective Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Michelle W. Kloss, Ph.D. (484-344-2905) or, in my absence, to Bonnie L. Goldmann, M.D. (484-344-2383).

Sincerely,

Michelle W. Kloss

Michelle W. Kloss, Ph.D.
Senior Director, Regulatory Affairs

Enclosure: CD

Hand Deliver

Desk Copy: Ms. Maureen Dillon-Parker, Regulatory Project Manager (cover letter – CD)
HFD-520, Room S306
Hand Deliver

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Michelle W. Kloss, Ph.D.
Senior Director
Regulatory Affairs

DESK COPY

Merck & Co., Inc.
BLA-20
P.O. Box 4
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Tel 484 344 2905
Fax 484 344 2516

September 26, 2001

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products

Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Soreth:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to the pending New Drug Application (NDA) cited above for INVANZ™ submitted as an electronic archive on November 30, 2000. Reference is also made to an August 24, 2001 submission containing additional information regarding mortality data for Protocol 017 in response to an August 16, 2001 Agency request and to a September 17, 2001 teleconference meeting between FDA and Merck Research Laboratories (MRL, a Division of Merck & Co., Inc.) to discuss the August 24, 2001 submission. During this teleconference meeting, the Agency requested further information about mortality rates in Protocol 017.

With this submission, MRL is providing the additional mortality information requested by the Agency in the September 17, 2001 teleconference meeting cited above. All information is in an electronic format as indicated in the Table of Contents for this submission.

This response is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the response. All documents requiring signatures for certification are included as paper for archival purposes.

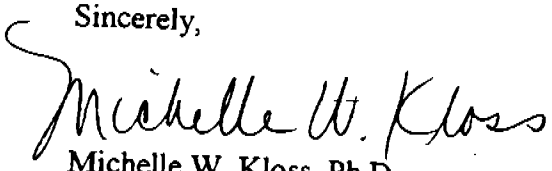
We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 4.0, Symantec Corp., 1991-1997) and we authorized the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Anti-Infective Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Maureen Dillon-Parker, Regulatory Project Manager, Division of Anti-Infective Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Michelle W. Kloss, Ph.D. (484-344-2905) or, in my absence, to Bonnie J. Goldmann, M.D. (484-344-2383).

Sincerely,



Michelle W. Kloss, Ph.D.
Senior Director, Regulatory Affairs

Enclosure: CD

Federal Express

Desk Copy: Ms. Maureen Dillon-Parker, Regulatory Project Manager (cover letter)
HFD-520, Room S306
Fax/Federal Express #2

Q:\maione\mk826\nda amendment\mortality2

Michelle W. Kloss, Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2905
Fax 484 344 2516

DESK COPY

September 27, 2001

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products

Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Soreth:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to the pending New Drug Application (NDA) cited above for INVANZ™, submitted as an electronic archive on November 30, 2000. Reference is also made to a September 26, 2001 facsimile communication from Ms. Maureen Dillon-Parker (FDA) to Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) which requested that MRL provide the list of allocation numbers (ANs) for patients with absolute neutrophil count <1000 cells/μl and with AST>5 times the upper limit of normal.

With this submission, MRL is providing the information requested in the September 26, 2001 facsimile communication cited above. All information is in an electronic format as indicated in the Table of Contents for this submission.

This response is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the response. All documents requiring signatures for certification are included as paper for archival purposes.

We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 4.0, Symantec Corp., 1991-1997) and we authorized the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Anti-Infective Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Maureen Dillon-Parker, Regulatory Project Manager, Division of Anti-Infective Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Michelle W. Kloss, Ph.D. (484-344-2905) or, in my absence, to Bonnie J. Goldmann, M.D. (484-344-2383).

Sincerely,

Verna L Godrow for MWK

Michelle W. Kloss, Ph.D.
Senior Director, Regulatory Affairs

Enclosure: CD

Federal Express

Desk Copy: Ms. Maureen Dillon-Parker, Regulatory Project Manager (cover letter)
HFD-520, Room S306
Fax/Federal Express

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Michelle W. Kloss, Ph.D.
Senior Director
Regulatory Affairs

DESK COPY

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2905
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September 28, 2001

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Soreth:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

AMENDMENT TO PENDING NEW DRUG APPLICATION

Reference is made to the pending New Drug Application (NDA) cited above for INVANZ™ submitted as an electronic archive on November 30, 2000. Reference is also made to an August 17, 1999 FDA/Merck teleconference meeting during which it was agreed that Merck would provide, in lieu of site-specific stability data, Certificates of Analyses for three validation batches of ertapenem drug substance and three validation batches of drug product three months prior to the user fee goal (PDUFA) date for NDA 21-337. Additional reference is made to April 20, 2000 and April 24, 2000 FDA/Merck teleconference meetings, held in follow-up to a proposal for Agency concurrence submitted on April 14, 2000, during which it was agreed that the Certificates of Analyses cited above would be accompanied by a memo certifying that validation of ertapenem drug substance and product had been completed successfully. Reference is also made to a May 7, 2001 submission which provided a proposal for Agency concurrence regarding a revised submission timeline for the Certificates of Analyses for the validation batches of drug product and to a May 16, 2001 teleconference meeting between FDA and Merck to discuss this revised submission timeline proposal. During this May 16, 2001 teleconference meeting, the Agency was informed that the Certificates of Analyses for three validation batches of ertapenem drug substance would be submitted by June 1, 2001 and that the Certificates of Analyses for three validation batches of drug product would be submitted on August 30, 2001. Additional reference is made to the May 21, 2001 submission of Certificates of Analyses for ertapenem drug substance. Reference is also made to June 20, 2001 and August 8, 2001, and September 17, 2001 telephone conversations between Ms. Maureen Dillon-Parker (FDA) and Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) during which the drug product validation batch manufacture was discussed and revised timelines for submission of the Certificates of Analyses for the three validation batches of drug product were discussed; during the September 17, 2001 conversation, the Agency was informed that these Certificates of Analyses, along with the memo certifying that a validation of INVANZ™ had been completed successfully, would be submitted by October 3, 2001.

In accordance with the May 16, 2001 teleconference meeting discussions and September 17, 2001 conversation cited above, with this submission and as indicated on the attached Form FDA 356h, we are providing three Certificates of Analyses containing the release data for the manufacturing process validation batches for INVANZ™ manufactured at Merck Manufacturing Division facility

been completed successfully. All information is in an electronic format as indicated in the Table of Contents for this amendment.

This amendment is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs*. As an attachment to this letter, Merck Research Laboratories (MRL), a division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the amendment. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100MB. We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 4.0, Symantec Corp., 1991-1997) and we authorized the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Anti-Infective Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Maureen Dillon-Parker, Regulatory Project Manager, Division of Anti-Infective Drug Products.

Pursuant to 21 CFR 314.50, a complete field copy of this amendment has been submitted to the FDA Philadelphia District Office.

We consider the filing of this amendment to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this amendment should be directed to Michelle W. Kloss, Ph.D. (484-344-2905) or, in my absence, to Bonnie J. Goldmann, M.D. (484-344-2383).

Sincerely yours,

Michael C. Kloss FOR

Michelle W. Kloss, Ph.D.
Senior Director
Regulatory Affairs

Q:\maione\mk826\nda amendment\drug product coas

Enclosure: CD

Federal Express #1

Desk Copies/att: Ms. Maureen Dillon-Parker, Regulatory Project Manager
HFD-520, Room S-306,
Fax / Federal Express #2

Dr. B. Vithal Shetty, HFD-520, Room N-356
Fax / Federal Express #2

Philadelphia District Office, FDA
Federal Express #3

Michelle W. Kloss, Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
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October 1, 2001

DESK COPY

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products

Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Soreth:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to the pending New Drug Application (NDA) cited above for INVANZ™, submitted as an electronic archive on November 30, 2000. Reference is also made to a September 24, 2001 teleconference meeting between FDA and MRL during which the Agency requested that MRL review the ertapenem clinical trials safety database (i.e. Phase IIa, Phase IIb, and Phase III studies) to identify patients with chronic hepatic disease and to classify the degree of hepatic insufficiency in such patients using the Child-Pugh's classification of the severity of hepatic disease. For each Child-Pugh category, FDA requested that MRL provide a clinical and a laboratory adverse experience counts table that covered the study therapy plus follow-up period. It was agreed that, if there were ≤10 patients in any particular Child-Pugh category, patients in more than one category could be combined for these tables.

With this submission, MRL is providing the information requested in the September 24, 2001 teleconference meeting cited above. In addition, we are providing a desk copy on CD for use by the Medical Reviewer. All information is in an electronic format as indicated in the Table of Contents for this submission.

This response is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the response. All documents requiring signatures for certification are included as paper for archival purposes.

We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 4.0, Symantec Corp., 1991-1997) and we authorized the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Anti-Infective Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Maureen Dillon-Parker, Regulatory Project Manager, Division of Anti-Infective Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Michelle W. Kloss, Ph.D. (484-344-2905) or, in my absence, to Bonnie J. Goldmann, M.D. (484-344-2383).

Sincerely,

Michelle W. Kloss

Michelle W. Kloss, Ph.D.
Senior Director, Regulatory Affairs

Enclosure: CD

Hand Deliver

Desk Copy: Ms. Maureen Dillon-Parker, Regulatory Project Manager (cover letter + CD)
HFD-520, Room S306
Fax/Hand Deliver

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Michelle W Kloss, Ph.D
Senior Director
Regulatory Affairs

Merck & Co., Inc
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Tel 484 344 2905
Fax 484 344 2516

October 1, 2001

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products

Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Soreth:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to the pending New Drug Application (NDA) cited above for INVANZ™, submitted as an electronic archive on November 30, 2000. Reference is also made to a September 24, 2001 teleconference meeting between FDA and MRL during which the Agency requested that MRL review the ertapenem clinical trials safety database (i.e. Phase IIa, Phase IIb, and Phase III studies) to identify patients with chronic hepatic disease and to classify the degree of hepatic insufficiency in such patients using the Child-Pugh's classification of the severity of hepatic disease. For each Child-Pugh category, FDA requested that MRL provide a clinical and a laboratory adverse experience counts table that covered the study therapy plus follow-up period. It was agreed that, if there were ≤10 patients in any particular Child-Pugh category, patients in more than one category could be combined for these tables.

With this submission, MRL is providing the information requested in the September 24, 2001 teleconference meeting cited above. In addition, we are providing a desk copy on CD for use by the Medical Reviewer. All information is in an electronic format as indicated in the Table of Contents for this submission.

This response is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the response. All documents requiring signatures for certification are included as paper for archival purposes.

We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 4.0, Symantec Corp., 1991-1997) and we authorized the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Anti-Infective Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Maureen Dillon-Parker, Regulatory Project Manager, Division of Anti-Infective Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Michelle W. Kloss, Ph.D. (484-344-2905) or, in my absence, to Bonnie J. Goldmann, M.D. (484-344-2383).

Sincerely,

Michelle W. Kloss

Michelle W. Kloss, Ph.D.
Senior Director, Regulatory Affairs

Enclosure: CD

Hand Deliver

Desk Copy: Ms. Maureen Dillon-Parker, Regulatory Project Manager (cover letter + CD)
HFD-520, Room S306
Fax/Hand Deliver

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Michelle W Kloss, Ph.D.
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October 3, 2001

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products

MERCK

Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Soreth:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to the pending New Drug Application (NDA) cited above for INVANZ™, submitted as an electronic archive on November 30, 2000. Reference is also made to a September 27, 2001 facsimile communication from Ms. Maureen Dillon-Parker (FDA) to Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) which requested that MRL identify the location within the INVANZ™ NDA of narratives of selected patients from Protocol 018 and 020. Further reference is made to a September 27, 2001 facsimile communication to Ms. Dillon-Parker from Dr. Tamra Goodrow (MRL), on behalf of Dr. Kloss, which provided the requested information.

With this submission, MRL is providing an official copy of the information sent via facsimile on September 27, 2001 cited above. The requested narratives for allocation number 6413 and 6417 in Protocol 018 and allocation number 3878 in Protocol 020 are located in the following sections of the INVANZ™ NDA.

Integrated Summary of Safety (ISS):
(1) Protocol 018--6413: Page E-396 of ISS
(2) Protocol 018--6417: Page E-397 of ISS
(3) Protocol 020--3878: Page E-395 of ISS

All information is in an electronic format as indicated in the Table of Contents for this submission.

This response is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the response. All documents requiring signatures for certification are included as paper for archival purposes.

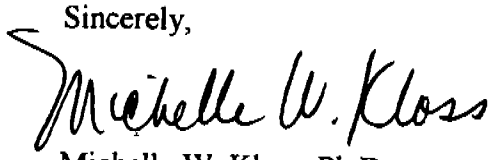
We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 4.0, Symantec Corp., 1991-1997) and we authorized the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Anti-Infective Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Maureen Dillon-Parker, Regulatory Project Manager, Division of Anti-Infective Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Michelle W. Kloss, Ph.D. (484-344-2905) or, in my absence, to Bonnie J. Goldmann, M.D. (484-344-2383).

Sincerely,



Michelle W. Kloss, Ph.D.
Senior Director, Regulatory Affairs

Enclosure: CD

Federal Express

Desk Copy: Ms. Maureen Dillon-Parker, Regulatory Project Manager (cover letter)
HFD-520, Room S306
Federal Express #2

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Michelle W. Kloss, Ph.D.
Senior Director
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DESK COPY

November 7, 2001

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Soreth:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

AMENDMENT TO PENDING NEW DRUG APPLICATION

Reference is made to the pending NDA for INVANZ™ cited above (submitted as an electronic archive on November 30, 2000) and to the October 26, 2001 and October 29, 2001 facsimile communications from Ms. Maureen Dillon-Parker (FDA) to Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) providing FDA comments on the INVANZ™ package circular. Reference is also made to the October 31, 2001 facsimile communication from Dr. Kloss to Ms. Dillon-Parker which provided proposed package circular revisions in response to these Agency comments. Further reference is made to the November 1, 2001 FDA/MRL teleconference meeting held to discuss package circular labeling for this NDA. Additional reference is made to the November 2, 2001 facsimile communication from Dr. Kloss to Ms. Dillon-Parker providing proposed revisions to the ADVERSE REACTIONS section and to the November 2, 2001 facsimile communication from Ms. Dillon-Parker to Dr. Kloss providing additional Agency comments regarding the CLINICAL STUDIES section of the package circular; these facsimile communications were in follow-up to the discussions at the November 1, 2001 teleconference meeting cited above. Final reference is made to the November 5, 2001 MRL/FDA teleconference meeting during which verbal agreement with the Division was reached on the INVANZ™ package circular labeling.

In follow up to the November 5, 2001 teleconference meeting cited above, we are providing an amendment to the NDA cited above; as indicated on the attached Form FDA 356h, this amendment provides for changes in the *Labeling Section* of the pending New Drug Application for INVANZ™. With this submission, we are providing proposed package circular labeling as agreed to in the teleconference meetings cited above. In addition to the agreed upon text, please note that the following editorial revisions have also been made for consistency throughout the proposed circular:

- Under **CLINICAL PHARMACOLOGY**, **Susceptibility Tests**, *Diffusion Techniques*, the ATCC number "49247" in footnote "m" has been revised to read "49766" for consistency with "*Haemophilus influenzae*" to which the footnote refers in the quality control table for diffusion techniques.
- Under **PRECAUTIONS**, *Nursing Mothers*, the third statement has been revised for clarity from "It should be administered..." to "INVANZ should be administered...".

- Under **DOSAGE AND ADMINISTRATION**, Table 5 text regarding "Complicated skin and skin structure infections, including diabetic lower extremity infections" has been revised to read "Complicated skin and skin structure infections" for consistency with the **INDICATIONS** section (i.e., the text "...including diabetic lower extremity infections..." has been deleted).
- The tables have been renumbered due to the deletion of tables under the **CLINICAL PHARMACOLOGY**, **Susceptibility Tests** section per the Agency's request.

All information is in an electronic format as indicated in the Table of Contents for this amendment. The Microsoft WORD version of the proposed labeling text is also provided on a separate diskette.

This amendment is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories is providing one Compact Disk (CD) which contains the response. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100MB. We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 4.0, Symantec Corp., 1991-1997) and we authorized the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Anti-Infective Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Maureen Dillon-Parker, Regulatory Project Manager, Division of Anti-Infective Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

We thank the Agency for its input during the November 1, 2001 and November 5, 2001 teleconference meetings cited above and trust that the proposed revised labeling within this submission meets with the Agency's approval. Please direct questions or need for additional information to Michelle W. Kloss, Ph.D. (484-344-2905) or, in my absence, to Bonnie J. Goldmann, M.D. (484-344-2383).

Sincerely yours,

Michelle W. Kloss

Michelle W. Kloss, Ph.D.
Senior Director, Regulatory Affairs

Enclosure: CD
Hand Deliver

Desk Copy: Ms. Maureen P. Dillon-Parker, Regulatory Project Manager (cover letter + diskette)
HFD-520, Room S306
Hand Deliver

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Michelle W. Kloss, Ph.D.
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November 19, 2001

DESK COPY

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Soreth:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to the pending NDA for INVANZ™ cited above submitted as an electronic archive on November 30, 2000. Reference is also made to a November 5, 2001 teleconference meeting between FDA and MRL during which Phase IV commitments were discussed and to a November 6, 2001 facsimile communication from Ms. Maureen Dillon Parker (FDA) to Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) which provided an Agency request for Phase IV commitments for INVANZ™.

With this submission, in follow-up to the Agency's facsimile communication cited above, MRL states its commitments to the following Phase IV activities in support of ertapenem sodium:

1. MRL commits to submitting the final study report for Protocol 035 entitled *"A Randomized, Double-Blind, Parallel-Panel, Placebo-Controlled Study to Investigate the Effects of Maximum Plasma Concentrations of MK-0826 on QTc Interval Following Single IV Dose Administration in Healthy Subjects"* by May 30, 2002.

2. MRL commits to revising Protocol 037 entitled "A Prospective, Multicenter, Double Blind with In-House Blinding, Randomized, Comparative Study to Evaluate the Efficacy, Safety, and Tolerability of Ertapenem Sodium versus Piperacillin/Tazobactam in the Treatment of Complicated Intra-Abdominal Infections in Hospitalized Adults" to incorporate a review of mortality at the end of parenteral therapy, 14 days post study therapy, and at 4-6 weeks post therapy and to revise inclusion and exclusion criteria such that they will be similar to those used in Protocol 017. MRL commits to submitting the final study report for Protocol 037 by May 31, 2004.

All of the information is contained on one CD and is not more than 100MB. We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 4.0, Symantec Corp., 1991-1997) and we authorized the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Anti-Infective Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Maureen Dillon Parker, Regulatory Project Manager, Division of Anti-Infective Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Michelle W. Kloss, Ph.D. (484-344-2905) or, in my absence, Bonnie J. Goldmann, M.D. (484-344-2383).

Sincerely yours,

Michelle W. Kloss

Michelle W. Kloss, Ph.D.
Senior Director
Regulatory Affairs

Enclosure: CD

HAND DELIVER

Desk Copy: Ms. Maureen P. Dillon Parker, Regulatory Project Manager (cover letter)
HFD-520, Room S306
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Michelle W. Kloss, Ph.D.
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September 21, 2001

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products

Central Document Room
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Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Soreth:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to the pending New Drug Application (NDA) cited above for INVANZ™, submitted as an electronic archive on November 30, 2000. Reference is also made to a September 13, 2001 facsimile communication from Ms. Maureen Dillon-Parker (FDA) and Dr Michelle Kloss (MRL, a Division of Merck & Co., Inc.) which provided comments from the CMC-Microbiology Reviewer.

With this submission, MRL is providing a response to the September 13, 2001 facsimile communication cited above. All information is in an electronic format as indicated in the Table of Contents for this submission.

This response is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the response. All documents requiring signatures for certification are included as paper for archival purposes.

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Michelle W. Kloss, Ph.D.
Senior Director, Regulatory Affairs

Enclosure: CD

Federal Express

Desk Copy: Ms. Maureen Dillon-Parker, Regulatory Project Manager (cover letter)
HFD-520, Room S306
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Michelle W Kloss Ph D
Senior Director
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July 6, 2001

MERCK

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Soreth:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to the pending NDA for INVANZ™ cited above, submitted as an electronic archive on November 30, 2000. Reference is also made to a June 22, 2001 facsimile communication from Ms. Maureen Dillon-Parker (FDA) to Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) providing Pharmacology/Toxicology reviewer comments on the NDA. Further reference is made to a July 2, 2001 teleconference meeting between representatives of FDA and MRL held at MRL's request in order to obtain further clarification from the Agency regarding Comments #2, #3 and #4 of the facsimile communication. During this teleconference meeting discussion, Dr. Ken Seethaler (Pharmacology/Toxicology Reviewer) indicated that he would consult his supervisor further regarding these comments and it was agreed that MRL would provide its responses to these specific comments in writing to facilitate Dr. Seethaler's consultation.

With this submission, MRL is providing a summary of its responses to Comments #2, #3, and #4 as agreed during the July 2, 2001 teleconference cited above. All information is in an electronic format as indicated in the Table of Contents for this submission.

This response is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs*. As an attachment to this letter, Merck Research Laboratories (MRL), a division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the response. All documents requiring signatures for certification are included as paper for archival purposes.

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Sincerely yours,

Michelle W. Kloss

Michelle W. Kloss, Ph.D
Senior Director, Regulatory Affairs

Enclosure. CD

Federal Express #1

Desk Copy: Ms. Frances LeSane, Supervisory Regulatory Project Manager (cover letter)
HFD-520, Room N355
Fax/Federal Express #2

Ms Maureen Dillon-Parker, Regulatory Project Manager (cover letter)
HFD-520, Room S306
Fax/Federal Express #2

Dr Ken Seethaler (cover letter)
HFD-520, Room N357
Fax/Federal Express #2