CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-337

CORRESPONDENCE

2-16-01

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-337

Merck & Co., Inc.
Attention: Michelle W. Kloss, Ph.D.
Senior Director, Regulatory Affairs
P.O. Box 4
Sumneytown, Pike, BLA-20
West Point, PA 19486-0004

Dear Dr. Kloss:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: INVANZ™ ~~(ertapenem sodium) I.V/I.M.~~

Review Priority Classification: Standard (S)

Date of Application: November 30, 2000

Date of Receipt: November 30, 2000

Our Reference Number: NDA 21-337

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 30, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be September 30, 2001 and the secondary user fee goal date will be November 30, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the

application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products , HFD-520
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products , HFD-520
Attention: Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call Maureen Dillon-Parker, Project Manager, at (301) 827-2125.

Sincerely,

{See appended electronic signature page}

Frances V. LeSane
Chief, Project Management Staff
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

NDA 21-337

Merck & Co., Inc.
Attention: Michelle W. Kloss, Ph.D.
Senior Director, Regulatory Affairs
P.O. Box 4
Sumneytown Pike, BLA-10
West Point, PA 19486-0004

Dear Dr. Kloss:

We acknowledge receipt on July 3, 2001, of your July 3, 2001, amendment to your new drug application for INVANZ™ (ertapenem sodium).

We consider this a major amendment received by the agency within three months of the user fee due date of September 30, 2001 [10-month clock]. Therefore, as agreed to in the telephone conversation between yourself and Ms. Maureen Dillon-Parker of this Division, the user fee clock is extended two months. The new due date is November 30, 2001.

If you have any questions, please contact Ms. Maureen Dillon-Parker, Project Manager, at (301) 827-2125.

Sincerely yours,

Janice Soreth, M.D.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 610 397 2905
Fax 610 397 2516

DESK COPY

December 19, 2000

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

NDA 21-337: INVANZ™ (Ertapenem Sodium)

Response to FDA Request for Additional Paper Review Copies

Reference is made to the pending NDA cited above for INVANZ™ submitted as electronic archive on November 30, 2000. Reference is also made to a telephone conversation between Ms. Maureen Dillon Parker (FDA) and Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) on December 15, 2000, during which Ms. Dillon Parker requested 6 additional paper review copies of Volume 1 of the original NDA submitted on November 30, 2000.

With this submission, we are providing 6 paper review copies as requested by the Agency in the conversation cited above.

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. (610/397-2905) or, in my absence, Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely yours,

Michelle W. Kloss

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

Enclosure: CD (letter only)
Federal Express #1

Desk Copies/att (6): Ms. Maureen Dillon Parker, Regulatory Project Manager
HFD-520, Rm. S306
Federal Express #2

Q:\maione\mk826\reviewcopies.doc

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

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 610 397 2905
Fax 610 397 2516

DESK COPY

January 10, 2001

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

MERCK

NDA 21-337: INVANZ™ (Ertapenem Sodium)

Response to FDA Request for Information

Reference is made to the Original NDA for INVANZ™ cited above, submitted as an electronic archive on November 30, 2000. Reference is also made to a December 15, 2000 telephone conversation between Dr. Jean Mulinde, Dr. George Rochester and Ms. Maureen Dillon Parker (FDA) and Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) during which the FDA requested the submission of the following additional information as review aids to facilitate its review of this NDA:

1) Case Report Forms (CRFs) in electronic format (.pdf) for specific patients
2) Sample, annotated Case Report Forms in electronic format (.pdf) for each Phase IIb/III protocol in this NDA
3) A single SAS Transport File (STF) containing all efficacy data from the Phase IIb/III clinical trials (.xpt)
4) A single STF containing the safety data from all Phase I, II, and III clinical trials (.xpt)
5) Text file including all narratives in this NDA (.doc)

Further reference is made to a December 15, 2000 FDA facsimile communication from Ms. Parker to Dr. Kloss which provided, in follow-up to the December 15, 2000 conversation cited above, the list of patients for which electronic CRFs were requested and also provided instructions regarding the preparation of the text file narratives. Additional reference is made to a series of telephone conversations held on December 18 and 19, 2000 between representatives of FDA and MRL to further discuss the Agency's December 15, 2000 request for STFs. During the December 19, 2000 telephone conversation, it was agreed that, in place of providing a single STF containing the efficacy data from the Phase IIb/III clinical trials, MRL would submit two efficacy STFs integrated across the pivotal (Phase IIb/III) studies that were a concatenation of the statistical review aids previously provided with the November 30, 2000 NDA submission: one efficacy STF on a per patient basis and one efficacy STF on a per

pathogen basis. During this same conversation, it was agreed that MRL would provide the requested safety STFs as follows: five STFs for laboratory values (one each for chemistry, hematology, urine, serology and other) integrated across the Phase I, II and III studies, a single adverse experience STF integrated across the Phase I, II, and III studies, and four STFs integrated across the Phase IIb/III studies (one each for demographics, medical history, drug exposure and prior/concomitant medications parameters).

With this submission, MRL is providing the following information in response to the Agency's December 15, 2000 request and in accordance with the agreements reached during the December 19, 2000 conversation cited above:

1) Sample, annotated Case Report Forms in electronic format (.pdf) for each Phase IIb/III protocol in this NDA
2) Two STFs containing efficacy data from the Phase IIb/III clinical trials (.xpt)
3) Six STFs containing the clinical and laboratory safety data from all Phase I, II, and III clinical trials (.xpt)
4) Four STFs containing patient demographic data (demographics, medical history, drug exposure, prior/concomitant medications) from Phase IIb/III clinical trials (.xpt)
5) Text file including all narratives in this NDA (.doc)

The narratives provided in this submission are verbatim to those found in the NDA and are ordered by Protocol by allocation number. Except for the allocation numbers noted below, there is only one narrative per patient in the NDA. Please note that there are two narratives per patient in the NDA for the following eight patients: allocation numbers 018 004 006794, 018 015 006413, 018 015 006417, 018 015 006485, 018 026 007079, 018 038 006199, 018 052 006272, and 018 059 007055. In general, these paired narratives contain different information; e.g., for allocation number 018 004 006794, one narrative reports a clinical adverse experience of seizure and the other narrative reports a clinical adverse experience of cervical malignancy. For one patient, allocation number 018 026 007079, there is a typographic error in one of the paired narratives; the patient's age should be 75 years but is incorrectly reported as 74 years.

We trust that the information provided in this submission adequately addresses the Agency's requests and that it will facilitate the Agency's review of the application. Please note that, as discussed during the December 19, 2000 conversation cited above, the requested Case Report Forms in electronic format (.pdf) will be provided shortly under separate cover.

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 two Compact Disks (CDs) which contains this response. All documents requiring signatures for certification are included as paper for archival purposes.

All electronic archival information is contained on two CDs and is not more than 640MB. The word version of the AE narratives are provided on a separate diskette. We have taken precautions to ensure that the contents of the CDs and diskette 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. MRL will follow-up with Ms. Dillon Parker to ensure that the appropriate reviewers have been given access to this electronic submission.

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. (610-397-2905) or, in my absence, Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely yours,

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

Enclosure: CD
Q:\malone\mk826\ndaresponses\15dec00_nda
Federal Express #1

Desk Copy: Ms. Maureen P. Dillon Parker, Regulatory Project Manager (cover letter and diskette containing the WORD version of the narratives)
HFD-520, Room S306
Federal Express #2

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

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 610 397 2905
Fax 610 397 2516

January 18, 2001

DESK COPY

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

MERCK

NDA 21-337: INVANZ™ (Ertapenem Sodium)

Response to FDA Request for Information

Reference is made to the Original NDA for INVANZ™ cited above, submitted as an electronic archive on November 30, 2000. Reference is also made to a December 15, 2000 telephone conversation between Dr. Jean Mulinde, Dr. George Rochester and Ms. Maureen Dillon Parker (FDA) and Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) during which the FDA requested additional SAS Transport File (STF) and Case Report Form information to facilitate its review of the NDA and to a January 9, 2001 telephone conversation between Ms. Dillon Parker and Dr. Kloss during which it was discussed that MRL's response would be separated into two submissions: the submission of the SAS Transport File information followed by the submission of the requested Case Report Forms. Further reference is made to a January 10, 2001 submission of the STF information.

With this submission, MRL is providing the requested Case Report Forms in electronic format (.pdf) as agreed to in the January 9, 2001 conversation cited above. We trust that the information provided in this submission adequately addresses the Agency's requests and that it will facilitate the Agency's review of the application.

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 two Compact Disks (CDs) which contain this response. All documents requiring signatures for certification are included as paper for archival purposes.

All electronic archival information is contained on two CDs. We have taken precautions to ensure that the contents of the CDs 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. MRL will follow-up with Ms. Dillon Parker to ensure that the appropriate reviewers have been given access to this electronic submission.

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. (610-397-2905) or, in my absence, Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely yours,

Michelle W. Kloss

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

Enclosure: Two CDs

Q:\maione\mk826\ndaresponses\15dec00p2_nda

Federal Express #1

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

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

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 610 397 2905
Fax 610 397 2516

January 24, 2001

MERCK

Gary K. Chikami, M.D., Acting Director
Division of Anti-Infective Drug Products
HFD-520, Room N348
Office of Drug Evaluation IV (CDER)
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Dear Dr. Chikami:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

Response to FDA Request for Information

Reference is made to the Original NDA for INVANZ™ cited above submitted as an electronic archive on November 30, 2000. Reference is also made to a January 23, 2000 telephone conversation between Dr. B. Vithal Shetty (FDA) and Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc) during which Dr. Shetty requested 3 additional hard copies of the Methods Validation Package for INVANZ™. During this conversation, it was agreed that the location of the drug product assay information would be identified/flagged within these copies of the Methods Validation Package.

With this submission, we are providing 3 additional hard copies of the Methods Validation Package as requested in the January 23, 2001 telephone conversation cited above. The location of the drug product assay entitled: '______________________________

____

______ is found in Section E.4.2 *Drug Product* following page C-21;. the first page of this assay method is indicated by a red flag on the attached hard copies.

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 this submission. 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 100 MB. 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 authorize the use of anti-virus software, as appropriate.

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. (610-397-2905) or, in my absence, Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely yours,

Michelle W. Kloss

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

Enclosure

Federal Express #1

Desk copy: Dr. B. Vithal Shetty (3 copies of the Methods Validation Package), HFD-520, Room N356, Federal Express #2

[redacted]

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

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 610 397 2905
Fax 610 397 2516

DESK COPY

January 29, 2001

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

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 a January 25, 2001 telephone call to the office of Ms. Maureen Dillon Parker (FDA) by Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) and to a January 29, 2001 telephone conversation between Ms. Dillon Parker and Dr. Kloss during which Dr. Kloss informed the Agency of an inadvertent omission of one component of the administrative documentation within the electronic NDA for INVANZ™.

As noted in the telephone call cited above, MRL recently identified that the Regulatory Background Information component of the administrative documentation within the INVANZ™ NDA was inadvertently omitted from the November 30, 2000 electronic submission. This Regulatory Background Information documentation summarizes the understandings and agreements reached between FDA and MRL during the development process of ertapenem sodium. (Although it was not present within the electronic NDA, this Regulatory Background Information documentation was contained within Volume 1 of the NDA review copies which were provided in hard copy at the time of the November 30, 2000 submission.) With this submission, we are providing the Regulatory Background Information component electronically as an amendment to this pending application.

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 has an approximate size of 100MB. We have taken precautions to insure that any software on the CD is 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 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.

We sincerely apologize for any inconvenience that this inadvertent error may have caused the Agency. Questions concerning this amendment should be directed to Michelle W. Kloss, Ph.D. (610/397-2905) or, in my absence, to Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely,

Michelle W. Kloss

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\regbackinf.doc

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

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel. 215 397 2905
Fax 215 397 2516

MERCK

February 9, 2001

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

NDA 21-337: INVANZ™ (Ertapenem Sodium)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to the pending NDA cited above for INVANZ™ submitted as electronic archive on November 30, 2000 and to a January 5, 2001 telephone conversation between Dr. Mathew Thomas (DSI, FDA) and Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) during which the Agency requested that MRL submit additional site-specific patient information from several United States clinical trial sites. Reference is also made to a January 16, 2001 submission providing this site-specific patient information to Dr. Thomas in response to this January 5, 2001 request. Further reference is made to a February 1, 2001 telephone conversation between Dr. Thomas and Dr. Kloss during which Dr. Thomas requested that MRL provide information similar to that contained within the January 16, 2001 submission for the following two additional clinical trial sites outside of the United States: Dr. Nora Quintero Perez (016-034) and Dr. Alvaro Fernandez (017-060). During this same conversation, Dr. Thomas also requested that MRL provide, in electronic format (.pdf), the information for Dr. Robert Brooks Gainer (014-002) that had been included as hard copy within the January 16, 2001 submission.

In accordance with the Agency's request of February 1, 2001 cited above, with this submission, MRL is providing an electronic version of the following site-specific patient information for the ex-U.S. clinical trial sites of Dr. Nora Quintero Perez (016-034) and Dr. Alvaro Fernandez (017-060):

1) Copy of the protocol
2) All amendments to the protocol
3) Sample case report forms
4) Data listings specific for each site on a per patient basis for the following information:
    a) Clinical efficacy
    b) Microbiology efficacy
    c) Adverse Events
    d) Laboratory Abnormalities
    e) Concomitant treatment/medications

Please note that, since the ex-U.S. case report forms were electronically printed from data keyed utilizing worksheets completed by the investigator, blank case report forms do not exist. In lieu of a blank case report form, we have provided sample case report forms which contain either dummy or individual patient data in all fields, so that all fields in the case report form will appear.

ORIGINA

To facilitate the Agency's preparation for inspection of these clinical sites, the Data Handling Guidelines for Protocols 016 and 017 are also provided in this submission. This submission also includes, per the Agency's request of February 1, 2001, an electronic version of the patient information for the site of Dr. Robert Brooks Gainer (014-002), which was previously submitted in hard copy to the Agency on January 16, 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 (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.

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 authorize 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. (610-397-2905) or, in my absence, Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely,

Michelle W. Kloss

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

Q:\maione\mk826\DrThomas\exussites_cl

Enclosure: CD

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

Dr. Mathew T. Thomas [hard copy of site specific patient information for Dr. Perez and Dr. Fernandez. 1 CD for each site: Dr. Perez (016-034), Dr. Fernandez (017-060) and Dr. Gainer (014-002)], HFD-45, Room 125
Federal Express #3

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

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 610 397 2905
Fax 610 397 2516

February 13, 2001

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

NDA 21-337: INVANZ™ (ertapenem sodium)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to the pending Original New Drug Application cited above for INVANZ™ submitted as an electronic archive on November 30, 2000. Reference is also made to a facsimile communication dated January 24, 2001 from Ms. Maureen Dillon Parker (FDA) to Dr. Michelle Kloss (MRL, a division of Merck & Co., Inc.) which provided two comments regarding this NDA from the biopharmaceutical reviewer.

With this submission, on Compact Disk (CD), Merck is providing responses to the Agency's comments outlined in the January 24, 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. This response 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.

All of the information is contained on one CD and is not more than 100MB. We have taken precautions to insure that any software on the CD is 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 filing of this information 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. (610/397-2905) or, in my absence, to Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely,

Tamra L Goodrow for MWK

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:graz/chris/invanz/response

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

DESK COPY

Merck & Co., Inc
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West Point PA 19486-0004
Tel 610 397 2905
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February 22, 2001

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

NDA 21-337: INVANZ™ (Ertapenem Sodium)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to the pending New Drug Application cited above for INVANZ™ submitted as an electronic archive on November 30, 2000. Reference is also made to a January 29, 2001 teleconference between representatives from FDA and Merck Research Laboratories (MRL, a Division of Merck & Co., Inc.) during which the Agency requested that MRL submit additional worksheet source documentation for specific patients at ex-U.S. clinical trial sites and to a January 29, 2001 facsimile communication from Ms. Maureen Dillon Parker (FDA) to Dr. Michelle Kloss (MRL) which provided the list of specific patients for which this worksheet source documentation was requested. Further reference is made to a follow-up teleconference on February 2, 2001 between FDA and MRL during which MRL agreed, as requested by the Agency, to provide copies of the source workbooks for the requested foreign clinical site patients and it was also agreed that this source documentation would be submitted to the Agency on a "roll-out" basis over the next several weeks.

As indicated on the attached Form FDA 356h and as agreed to in the February 2, 2001 teleconference meeting cited above, we are submitting certified copies of the source workbooks for a portion of the foreign clinical site patients requested by the Agency; the table of contents for Item 12 lists the patients included in this submission. As agreed to in the February 2, 2001 teleconference cited above, this submission represents the first of several "roll-out" submissions in fulfillment of this Agency request. To facilitate the Agency's review of the workbook documentation provided in this submission, a brief summary of Merck's data entry and coding guidelines is provided below.

All phase IIb and phase III pivotal and supportive studies (i.e. protocols 014, 016, 017, 018, 020, 021, and 023) enrolled patients both within the U.S. (domestic patients) and outside of the U.S (international patients). The general data flow to capture patient information was identical for domestic and international patients. Study data were recorded in writing at each site, were source-verified at each site against source documents, and were entered via uniform data entry screens into an electronic database (i.e. Merck's WCDS database) following protocol-specific data entry/handling guidelines. Eventually the data in the WCDS database, except for comments and large text-based data fields (e.g., operative summaries and case narratives), were reformatted and consolidated into analytic databases (i.e. Merck's CDMS databases).

The official case report forms (CRFs) for domestic and for international patients in the INVANZ™ program are different. For domestic patients, the official CRFs are the hand-written forms completed at the site and are signed by the investigator. For international patients, the handwritten forms (worksheets) may be in the native language; therefore the official CRFs are printed from the data entered into the WCDS database in English and are signed by the investigator. Except for a limited number of forms, all written data including additional comments provided by the investigator were entered into the WCDS database. As the international CRFs reflect the data that was entered into the WCDS database, they do not contain some elements from the hand-written worksheets completed at the site. Data that were not entered into the WCDS database include the following:

- For randomized patients in all protocols, individual responses to each inclusion or exclusion criteria were not captured electronically; overall responses indicating that the patient met the inclusion and exclusion criteria were captured electronically. The reason(s) that a patient did not meet the inclusion/exclusion criteria, however, was entered into the WCDS database as a comment on the inclusion/exclusion form and is present as a comment on the international CRF.
- The culture result forms (general and blood) were modified during the course of the studies to act as a shipping log when specimens were sent to the central microbiology laboratory; none of the shipping information was captured electronically.
- In the community acquired pneumonia studies (Protocols 018 and 020), the individual components used to determine the Pneumonia Severity Index (PSI) were not captured electronically; the PSI risk group was captured electronically.
- In the community acquired pneumonia studies, serology specimens, if collected, were processed by a central laboratory and the results were electronically transferred directly into the CDMS database; these data were not collected on a CRF or worksheet.
- In the intra-abdominal study (Protocol 017), the individual components used to determine the Glasgow Coma Score and the APACHE II score were not captured electronically; the total Glasgow Coma score and the APACHE II score were captured electronically.
- For those studies in which optional plasma samples were obtained (i.e. Protocols 017, 018, and 020), the plasma collection information was not captured electronically.

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.

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 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. (610/397-2905) or, in my absence, Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely yours,

Jamia L. Goodson for MWK

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

Enclosure: CD

Federal Express

Q:\maione\mk826\workbookrequest2

Desk Copies: Ms. Maureen Dillon Parker, Regulatory Project Manager (cover letter)
HFD-520, Room S 306
Federal Express #2

Stability update

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

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February 27, 2001

MERCK

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12229 Wilkins Avenue
Rockville, MD 20852

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 a July 13, 1998 meeting and a March 12, 1999 teleconference meeting between Merck Research Laboratories (MRL, a Division of Merck & Co., Inc.) and the FDA to discuss MRL's planned stability program for INVANZ™; MRL's summaries of these meetings were submitted to IND [redacted] on August 3, 1998 (Serial No. 098) and May 14, 1999 (Serial No. 167), respectively. During these meetings, the Agency agreed with MRL's proposal to submit additional stability data within 3 months of the NDA submission. Additional reference is made to a January 10, 2001 telephone conversation between Ms. Maureen Dillon Parker (FDA) and Dr. Michelle Kloss during which the timeline for submission of this additional stability data was discussed.

As indicated on the attached Form FDA 356h, per the agreements reached at the FDA/MRL meetings cited above, we are submitting an amendment to the pending NDA cited above. This amendment provides for changes in the Chemistry Section of the pending NDA for INVANZ™. All information is in an electronic format as indicated in the Table of Contents for this amendment. This amendment provides additional stability data (up to 18 months) to support the stability of the primary Market Container Stability Study (MCSS) batches as well as updated data for the additional stability batches included in the original application. Based on the statistical analysis of the available stability data, 18-month expiry dating is requested for the drug product. Additionally, this amendment also provides an update to Section B.1.4.2.1 Typical Process Related Impurities, an update to Reference C-3: Drug Product [redacted] Method, and DMF authorization letters for a key raw material used in the synthesis of the drug substance.

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 Product 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.

Please direct questions or need for additional information to Michelle W. Kloss, Ph.D. (610-397-2905) or, in my absence, Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely yours,

Dennis M. Erb for,
Michelle W. Kloss, Ph.D.
Senior Director, Regulatory Affairs

Enclosure: CD

Q:\maione\mk826\stabilitydata.doc

Hand Deliver

Desk Copy: Ms. Maureen Dillon Parker, Regulatory Project Manager (cover letter), HFD-520, Room S306
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Desk Copy/att: Dr. B. Vithal Shetty, HFD-520, Room N356
Hand Deliver

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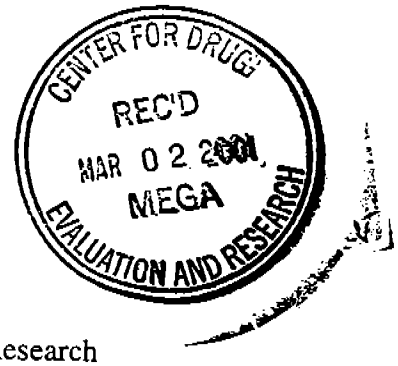

MERCK

February 28, 2001

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

NDA ORIG AMENDMENT

NDA 21-337: INVANZ™ (Ertapenem Sodium)

Bm

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to the pending New Drug Application cited above for INVANZ™ submitted as an electronic archive on November 30, 2000. Reference is also made to a January 29, 2001 teleconference between representatives from FDA and Merck Research Laboratories (MRL, a Division of Merck & Co., Inc.) during which the Agency requested that MRL submit additional worksheet source documentation for specific patients at ex-U.S. clinical trial sites and to a January 29, 2001 facsimile communication from Ms. Maureen Dillon Parker (FDA) to Dr. Michelle Kloss (MRL) which provided the list of specific patients for which this worksheet source documentation was requested. Further reference is made to a follow-up teleconference on February 2, 2001 between FDA and MRL during which MRL agreed, as requested by the Agency, to provide copies of the source workbooks for the requested foreign clinical site patients and it was also agreed that this source documentation would be submitted to the Agency on a "roll-out" basis over the next several weeks. Final reference is made to the first submission of source documentation dated February 22, 2001.

As indicated on the attached Form FDA 356h and as agreed to in the February 2, 2001 teleconference meeting cited above, we are submitting certified copies of the source workbooks for a portion of the foreign clinical site patients requested by the Agency; the table of contents for Item 12 lists the patients included in this submission. As agreed to in the February 2, 2001 teleconference cited above, this submission represents the second of several "roll-out" submissions in fulfillment of this Agency request. To facilitate the Agency's review of the workbook documentation provided in this submission, a brief summary of Merck's data entry and coding guidelines is provided below.

ORIGINAL

All phase IIb and phase III pivotal and supportive studies (i.e. protocols 014, 016, 017, 018, 020, 021, and 023) enrolled patients both within the U.S. (domestic patients) and outside of the U.S (international patients). The general data flow to capture patient information was identical for domestic and international patients. Study data were recorded in writing at each site, were source-verified at each site against source documents, and were entered via uniform data entry screens into an electronic database (i.e. Merck's WCDS database) following protocol-specific data entry/handling guidelines. Eventually the data in the WCDS database, except for comments and large text-based data fields (e.g., operative summaries and case narratives), were reformatted and consolidated into analytic databases (i.e. Merck's CDMS databases).

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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 filing of 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. (610/397-2905) or, in my absence, Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely yours,

Charles H. Landes, MS for Michelle W. Kloss,

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

Enclosure: CD

Federal Express

Q:\maione\mk826\workbookrequest_rel2

Desk Copies: Ms. Maureen Dillon Parker, Regulatory Project Manager (cover letter)
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Michelle W. Kloss, Ph.D.
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March 7, 2001

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Rockville, MD 20852

MERCK

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.

With this submission, we are providing an amendment to the pending NDA cited above. As indicated on the attached Form FDA 356h, this amendment provides for changes in the *Labeling* Section of the pending NDA for INVANZ™. This submission provides revised proposed carton and container labeling that more closely reflects the branding logo that has been adopted for INVANZ™; these revisions include a stylized typeface for the brand name and a different typeface for the generic name. In addition, the tray labels were slightly revised to provide an area to the far right of the label where no printing should appear. Beyond these revisions, the carton and container labeling included in this submission is identical to that included within the original application submitted on November 30, 2000. All information is in an electronic format as indicated in the Table of Contents for this amendment.

With this submission, MRL is providing the following proposed labeling:

- Carton Label
  a. Trade 2x5 tray label
  b. Trade 5x5 tray label
  c. Complimentary 2x5 tray label
  d. Complimentary Carton
- Container Labels
  a. Trade vial labels (2x5 tray)
  b. Trade vial labels (5x5 tray)
  c. Complimentary vial label for 2x5 tray
  d. Complimentary vial label for carton

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 Product 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 Product.

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. (610-397-2905) or, in my absence, to Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely,

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

Enclosure: CD

Federal Express #1

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

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Michelle W. Kloss, Ph.D.
Senior Director
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March 13, 2001

DESK COPY

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12229 Wilkins Avenue
Rockville, MD 20852

MERCK

NDA 21-337: INVANZ™ (Ertapenem Sodium)

PROPOSAL FOR FDA CONCURRENCE IN FOLLOW-UP TO 3/12/01 TELECONFERENCE MEETING

Reference is made to the NDA for INVANZ cited above submitted as an electronic archive on November 30, 2000. Additional reference is made to a March 8, 2001 facsimile communication from Ms. Maureen Dillon-Parker (FDA) to Dr. Michelle Kloss (MRL, a division of Merck & Co., Inc.) which provided a request for additional MITT statistical analyses and to a teleconference meeting held on March 12, 2001 between FDA and MRL to discuss this Agency request. With this submission, per the Agency's request, we are providing information in follow-up to the teleconference meeting cited above.

According to the discussions held at the teleconference cited above, per the Agency's March 8, 2001 facsimile communication request, MRL will perform new clinical and microbiological MITT analyses to parallel each of the MITT analyses presented in the Clinical Study Reports of protocols 014, 016, 017, 018, 020, 021, and 023; these analyses are in addition to those which were prespecified in the DAPs for each study that were discussed with the Agency at December 21, 1999 and January 28, 2000 teleconference meetings and that were provided in NDA 21-337. As discussed and agreed upon between MRL and the Agency at this March 12, 2001 teleconference meeting, a summary of these new MITT analyses is described below. As discussed during the teleconference meeting, it is anticipated that these analyses will be available to the Agency by the first week of April 2001.

For the new clinical MITT analyses, the MITT outcome will be determined at the test-of-cure visit (TOC). As discussed and agreed upon at the March 12, 2001 FDA/MRL teleconference meeting, the following rules will be applied in the clinical MITT population.

- The MITT outcome will be based on the investigator-reported TOC outcome except for patients withdrawn from study therapy because of a drug-related adverse experience and who receive further therapy with a non-study parenteral antibiotic; in this event the patient's MITT outcome will be unfavorable. The same convention with respect to drug-related adverse experiences was used for the MITT analyses submitted in the NDA.
- All unfavorable outcomes prior to TOC will be carried forward as unfavorable outcomes to the TOC visit. The MITT analyses submitted in the NDA also used this rule.
- Patients who do not have a favorable TOC outcome will have an unfavorable outcome; i.e. unfavorable, missing, or indeterminate clinical outcomes at TOC will be unfavorable.

- A favorable TOC outcome will be determined using the same rules as those applied to the per protocol population; i.e. a cure reported late outside of the TOC window will be carried back as a favorable MITT outcome.

For the new microbiologic MITT analyses, the overall MITT outcome will be determined at the TOC. As discussed and agreed upon at the March 12, 2001 FDA/MRL teleconference meeting, the following rules will be applied in the microbiologic MITT population.

- The MITT outcome will be based on the overall TOC microbiologic outcome.
- All unfavorable overall outcomes prior to TOC will be carried forward as unfavorable outcomes to the TOC visit. The MITT analyses submitted in the NDA also used this rule.
- Patients who do not have a favorable overall TOC outcome will have an unfavorable outcome; i.e. unfavorable, missing, or indeterminate microbiologic TOC outcomes will be unfavorable.
- An overall favorable TOC outcome will be determined using the same rules as those applied to the per protocol population.

During the March 12, 2001 teleconference meeting, the Agency also requested that MRL provide new per pathogen MITT analyses that are in addition to those which were prespecified in the DAPs for each study cited above. There was some additional discussion regarding this additional verbal request and, in the interest of time, it was agreed that MRL would provide a written proposal regarding this request for FDA concurrence. This per pathogen MITT analysis proposal is summarized below. These MITT per pathogen analyses would be conducted using the overall MITT outcomes as outlined above for each baseline pathogen identified in microbiological MITT patients for each protocol in the NDA. For the individual protocols such analyses are proposed to be conducted as follows:

- For protocols 016, 017, 018, 020, and 023 (in which the primary endpoint is clinical response) , the analysis presented will be the clinical MITT outcome according to the conventions above applied per pathogen in the microbiologic MITT population for each study, in a format similar to that used in the NDA.

- For the UTI studies, protocols 014 and 021 (in which the primary endpoint is microbiologic response), the analysis presented will be the overall microbiologic MITT outcome according to the conventions above applied per pathogen in the microbiologic MITT population in each study, in a format similar to that used in the NDA.

MRL anticipates that these new MITT per pathogen analyses can be available to the Agency by the week of April 9, 2001 and we are committed to providing the requested analyses as expeditiously as possible. MRL notes that the interpretation of these new MITT per pathogen analyses has certain limitations: as these analyses were not prespecified in the DAPs, they represent post-hoc analyses and they will not be directly comparable with the per pathogen outcomes for protocol evaluable populations in the NDA because of changes in both the population and in outcomes conventions; e.g., 1) the population is now microbiologic MITT rather than microbiologic protocol evaluable and 2) new outcomes conventions will now apply.

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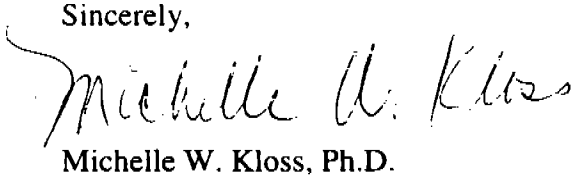
A list of reviewers from the Division of Anti-Infective Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Maureen Dillon Parker, Regulatory Project Manager, Division of Anti-Infective Drug Products.

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 believe that the proposed MITT per pathogen analysis described above meets the Agency's request as discussed in the March 12, 2001 teleconference meeting and we respectfully request Agency concurrence with this proposal. If needed, we would be happy to discuss this proposal further with the Agency. Please direct questions concerning this submission to Michelle W. Kloss, Ph.D. (610/397-2905) or, in my absence, to Bonnie J. Goldmann, M.D. (610/397-2383).

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

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

March 15, 2001

MERCK

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Rockville, MD 20852

NDA 21-337: INVANZ™ (ertapenem sodium)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to the pending New Drug Application cited above for INVANZ™ submitted as an electronic archive on November 30, 2000. Reference is also made to a January 29, 2001 teleconference between representatives from FDA and Merck Research Laboratories (MRL, a Division of Merck & Co., Inc.) during which the Agency requested that MRL submit additional worksheet source documentation for specific patients at ex-U.S. clinical trial sites and to a January 29, 2001 facsimile communication from Ms. Maureen Dillon Parker (FDA) to Dr. Michelle Kloss (MRL) which provided the list of specific patients for which this worksheet source documentation was requested. Further reference is made to a follow-up teleconference on February 2, 2001 between FDA and MRL during which MRL agreed, as requested by the Agency, to provide copies of the source workbooks for the requested foreign clinical site patients and it was also agreed that this source documentation would be submitted to the Agency on a "roll-out" basis over the next several weeks. Final reference is made to the first, second, and third submissions of source documentation dated February 22, 2001, February 28, 2001, and March 7, 2001 respectively.

As indicated on the attached Form FDA 356h and as agreed to in the February 2, 2001 teleconference meeting cited above, we are submitting certified copies of the source workbooks for a portion of the foreign clinical site patients requested by the Agency; the table of contents for Item 12 lists the patients included in this submission. As agreed to in the February 2, 2001 teleconference cited above, this submission represents the fourth and final of several "roll-out" submissions in fulfillment of this Agency request.

To facilitate the Agency's review of the workbook documentation provided in this submission, a brief summary of Merck's data entry and coding guidelines is provided below.

All phase IIb and phase III pivotal and supportive studies (i.e. protocols 014, 016, 017, 018, 020, 021, and 023) enrolled patients both within the U.S. (domestic patients) and outside of the U.S (international patients).

The general data flow to capture patient information was identical for domestic and international patients. Study data were recorded in writing at each site, were source-verified at each site against source documents, and were entered via uniform data entry screens into an electronic database (i.e. Merck's WCDS database) following protocol-specific data entry/handling guidelines. Eventually the data in the WCDS database, except for comments and large text-based data fields (e.g., operative summaries and case narratives), were reformatted and consolidated into analytic databases (i.e. Merck's CDMS databases).

The official case report forms (CRFs) for domestic and for international patients in the INVANZ™ program are different. For domestic patients, the official CRFs are the hand-written forms completed at the site and are signed by the investigator. For international patients, the handwritten forms (worksheets) may be in the native language; therefore the official CRFs are printed from the data entered into the WCDS database in English and are signed by the investigator. Except for a limited number of forms, all written data including additional comments provided by the investigator were entered into the WCDS database. As the international CRFs reflect the data that was entered into the WCDS database, they do not contain some elements from the hand-written worksheets completed at the site. Data that were not entered into the WCDS database include the following:

- For randomized patients in all protocols, individual responses to each inclusion or exclusion criteria were not captured electronically; overall responses indicating that the patient met the inclusion and exclusion criteria were captured electronically. The reason(s) that a patient did not meet the inclusion/exclusion criteria, however, was entered into the WCDS database as a comment on the inclusion/exclusion form and is present as a comment on the international CRF.
- The culture result forms (general and blood) were modified during the course of the studies to act as a shipping log when specimens were sent to the central microbiology laboratory; none of the shipping information was captured electronically.
- In the community acquired pneumonia studies (Protocols 018 and 020), the individual components used to determine the Pneumonia Severity Index (PSI) were not captured electronically; the PSI risk group was captured electronically.
- In the community acquired pneumonia studies, serology specimens, if collected, were processed by a central laboratory and the results were electronically transferred directly into the CDMS database; these data were not collected on a CRF or worksheet.
- In the intra-abdominal study (Protocol 017), the individual components used to determine the Glasgow Coma Score and the APACHE II score were not captured electronically; the total Glasgow Coma score and the APACHE II score were captured electronically.
- For those studies in which optional plasma samples were obtained (i.e. Protocols 017, 018, and 020), the plasma collection information was not captured electronically.

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 filing of 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. (610-397-2905) or, in my absence, Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely yours,

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

Enclosure: CD

Federal Express #1

Desk Copies: Ms. Maureen Dillon Parker
Regulatory Project Manager (cover letter)
HFD-520, Room S 306
Federal Express #2

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

Merck & Co., Inc.
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March 22, 2001

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

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 February 28, 2001 facsimile communication from Ms. Maureen Dillon Parker (FDA) to Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) requesting further information and analyses regarding the pending NDA, including a request for results of Protocol 029 (IM clinical study) and a request for safety analyses by gender, race, and age for the all treated populations (parenteral and oral therapy through follow-up).

With this submission, MRL is providing a complete response to the Agency's February 28, 2001 facsimile communication cited above. We trust that the responses provided in this submission will adequately address the Agency's comments and requests. 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.

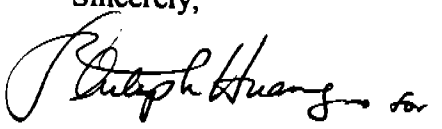
All of the information is contained on one CD and is not more than 100MB. We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 4.0, Symantec Corp., 1991-1997) and we authorized the use of anti-virus software, as appropriate.

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. (610/397-2905) or, in my absence, to Bonnie J. Goldmann, M.D. (610/397-2383).

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

Q:domingo\invanz\Feb28Response (Invanz)

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

Merck & Co., Inc.
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P.O. Box 4
West Point PA 19486-0004
Tel 610 397 2905
Fax 610 397 2516

March 30, 2001

Gary K. Chikami, M.D., Acting Director
Division of Anti-Infective Drug Products
ODE IV

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

Dear Dr. Chikami:

NDA 21-337: INVANZ™ (Ertapenem Sodium)

SAFETY UPDATE REPORT

Reference is made to the New Drug Application (NDA) cited above for INVANZ™ submitted as an electronic archive on November 30, 2000.

With this submission, MRL is providing a Safety Update Report (SUR) to NDA 21-337. This SUR provides updated safety information on ertapenem that has been received since the time of the reporting cutoff dates established in the original marketing application through the SUR in-house cutoff dates of November 19, 2000 for Case Report Form (CRF) data and December 15, 2000 for Merck Worldwide Adverse Experience System (WAES) data. No new clinical studies with ertapenem have been completed and no new patients have been unblinded since the original marketing application; therefore, no new patients were added to the database since the reporting cutoff date of the original marketing. Thus, the data changes presented in this SUR represent only those changes that were required as a result of data clarification that were pending at the time of the reporting cutoff date for the original marketing application and which were received in-house between that date and the reporting cutoff date for the SUR; these changes were generally minor. Information presented in this SUR does not change the original safety assessment and conclusions regarding the product as outlined in the original marketing application.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations. This Safety Update Report 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 Safety Update Report. All documents requiring signatures for certification

are included as paper for archival purposes. All information in this submission is in an electronic format as indicated in the Table of Contents.

All of the information is contained on one CD and has an approximate size of 100 MB. We have taken precautions to insure that any software on the CD is free of computer viruses (Norton Anti-Virus 4.0, Symantec Corp., 1991-1997) and we authorize 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 filing of this information 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 supplemental application should be directed to Michelle W. Kloss, Ph.D. (610/397-2905) or, in my absence, to Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely,

Michelle W. Kloss

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

Enclosure: CD

Q:\maione\mk826\sur

Federal Express #1

Desk Copy: Ms. Maureen Dillon Parker, Regulatory Project Manager (cover letter)
HFD-520, Room S-306
Federal Express #2

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

DEC[illegible]Y

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April 4, 2001

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation V (CDER)

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 Original NDA for INVANZ™ cited above, submitted as an electronic archive on November 30, 2000. Reference is also made to a March 7, 2001 facsimile communication from Ms. Maureen Dillon Parker (FDA) to Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) which provided Agency requests for additional analyses and information and to a March 12, 2001 teleconference between representatives of FDA and MRL to discuss this March 7, 2001 facsimile communication. Additional reference is made to a March 13, 2001 communication which provided a summary of the agreements reached at the March 12, 2001 teleconference meeting.

With this submission, MRL is providing the additional analyses and information in response to the Agency's March 7, 2001 request; the information provided herein is in accordance with the agreements reached during the March 12, 2001 teleconference meeting and summarized in the March 13, 2001 communication cited above.

We trust that the information provided in this submission adequately addresses the Agency's requests and that the information will facilitate the Agency's review of the application.

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 two Compact Disks (CDs) which contain this response. All documents requiring signatures for certification are included as paper for archival purposes.

All electronic archival information is contained on one CD. We have taken precautions to ensure that the contents of the CDs and diskette 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. (610-397-2905) or, in my absence, Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely yours,

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

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

These copies are
OFFICIAL FDA Copies
not desk copies.

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April 9, 2001

MERCK

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Product
Office of Drug Evaluation IV (CDER)

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 Original NDA for INVANZ™ cited above, submitted as an electronic archive on November 30, 2000 and to a March 7, 2001 facsimile communication from Ms. Maureen Dillon Parker (FDA) to Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) which provided Agency requests for additional analyses and information. Reference is also made to a March 12, 2001 teleconference between representatives of FDA and MRL to discuss this March 7, 2001 facsimile communication during which the Agency requested that MRL also provide a new per pathogen MITT analysis. Additional reference is made to a March 13, 2001 facsimile communication from Dr. Kloss to Ms. Dillon Parker which provided a summary of the agreements reached at the March 12, 2001 teleconference meeting as well as a content/timeline proposal for Agency concurrence regarding this requested per pathogen MITT analysis. Final reference is made to a March 30, 2001 telephone conversation between Ms. Dillon Parker and Dr. Kloss during which the March 13, 2001 proposal was discussed.

With this submission, MRL is providing the per pathogen MITT analyses as requested by the Agency in the March 12, 2001 teleconference meeting cited above; these analyses are in accordance with the summary provided in the March 13, 2001 communication cited above. We trust that the information provided in this submission adequately addresses the Agency's requests and that the information will facilitate the Agency's review of the application.

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 two Compact Disks (CDs) which contain this response. All documents requiring signatures for certification are included as paper for archival purposes.

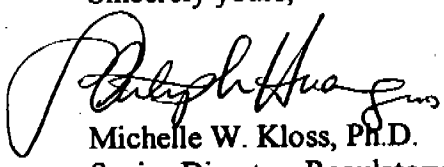
All electronic archival information is contained on one CD. We have taken precautions to ensure that the contents of the CDs and diskette are free of computer viruses (Norton Anti-Virus 4.0, Symantec Corp., 1991-1997) and we authorized the use of anti-virus software, as appropriate.

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. (610-397-2905) or, in my absence, Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely yours,



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

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

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DESK COPY

May 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)

AMENDMENT TO A 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, 2001. Reference is also made to a March 7, 2001 amendment providing for proposed carton and container labeling that more closely reflects the branding logo that has been adopted for INVANZ™.

With this submission, we are providing an amendment to the pending 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™. This submission revises the proposed vial labels to remove the peel-off section of the label. The peel-off section of the label, which contained duplicate text from the main section of the vial label, is being removed for conformity with other Merck vial labels for injectable products. In addition, "1 g" has been deleted from the colored bar on the main section of the vial label and "Rx only" has been relocated to the top left corner of the main section of the vial label. All information is in an electronic format as indicated in the Table of Contents for this amendment.

With this submission, MRL is providing the following proposed labeling:

- Container Labels
  a. Vial labels (2x5 tray)
  b. Vial labels (5x5 tray)
  c. Complimentary vial label (2x5 tray)
  d. Complimentary vial label (carton)

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.

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.

Please direct questions or need for additional information to Michelle W. Kloss, Ph.D. (610-397-2905) or, in my absence, to Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely,

M.C. Eli 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

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

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Fax 610 397 2516

DESK COPY

May 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

ap. 25 - CRF + Source Post-17

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 April 25, 2001 facsimile communication from Ms. Maureen Dillon Parker (FDA) to Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) which requested the submission of additional Case Report Forms (CRFs) and workbook source documentation for Protocols 017 and 023. Additional reference is made to a May 4, 2001 telephone conversation between Ms. Dillon Parker and Dr. Kloss to discuss this Agency request and the timelines for submission of the requested documentation. During this conversation, the Agency was also informed of an inadvertent omission of the SCON page attachment in the previously submitted CRFs for domestic patients in this NDA (i.e., those submitted on November 30, 2000 and January 18, 2001) and timelines for submission of replacement CRFs with the SCON page attachment were discussed. It was agreed during this conversation that, per the Agency's request, MRL would provide written documentation that summarized the anticipated submission timelines for this outstanding CRF and workbook source documentation.

With this letter, in response to the May 4, 2001 FDA request cited above and in accordance with the May 4, 2001 conversation cited above, MRL is providing the requested written documentation that summarizes the anticipated submission timelines for the outstanding CRF and workbook source documentation. All domestic CRFs requested in the April 25, 2001 FDA facsimile communication cited above are planned for submission during the week of May 14, 2001; all international CRFs and workbook source documentation requested in the April 25, 2001 facsimile communication will be submitted during the week of June 4, 2001. In addition, MRL will provide replacement CRFs that include the SCON page attachments for all previously submitted domestic CRFs during the week of May 28, 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 (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.

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 filing of this request 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. (610-397-2905) or, in my absence, Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely yours,

Michelle W. Kloss

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

Enclosure: CD

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Federal Express

Desk Copy: Ms. Maureen Dillon Parker, Regulatory Project Manager
HFD-520, Room S306
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Michelle W. Kloss, Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
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May 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)

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 April 25, 2001 facsimile communication from Ms. Maureen Dillon Parker (FDA) to Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) which requested the submission of additional Case Report Forms (CRFs) and workbook source documentation for Protocols 017 and 023. Additional reference is made to a May 4, 2001 telephone conversation between Ms. Dillon Parker and Dr. Kloss to discuss this Agency request and the timelines for submission of the requested documentation. During this conversation, the Agency was also informed of an inadvertent omission of the SCON page attachment in the previously submitted CRFs for domestic patients in this NDA (i.e., those submitted on November 30, 2000 and January 18, 2001) and timelines for submission of replacement CRFs with the SCON page attachment were discussed. It was agreed during this conversation that, per the Agency's request, MRL would provide written documentation that summarized the anticipated submission timelines for this outstanding CRF and workbook source documentation.

With this letter, in response to the May 4, 2001 FDA request cited above and in accordance with the May 4, 2001 conversation cited above, MRL is providing the requested written documentation that summarizes the anticipated submission timelines for the outstanding CRF and workbook source documentation. All domestic CRFs requested in the April 25, 2001 FDA facsimile communication cited above are planned for submission during the week of May 14, 2001; all international CRFs and workbook source documentation requested in the April 25, 2001 facsimile communication will be submitted during the week of June 4, 2001. In addition, MRL will provide replacement CRFs that include the SCON page attachments for all previously submitted domestic CRFs during the week of May 28, 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 (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.

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 filing of this request 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. (610-397-2905) or, in my absence, Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely yours,

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

Enclosure: CD

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Federal Express

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

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

Merck & Co., Inc.
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May 7, 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)

CMC Proposal for FDA Concurrence and Request for Teleconference Meeting

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 13, 1998 (End of Phase II meeting) and March 12, 1999 meetings between representatives from FDA and Merck to discuss the acceptability of Merck's planned stability program for INVANZ™, including content and timing of providing stability data to FDA. Further reference is 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 Analysis 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 a May 7, 2001 telephone conversation between Ms. Frances LeSane (FDA) and Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) during which the Agency was informed of a delay in the manufacture of the validation batches of the INVANZ™ drug product. During this conversation, a revised timeline for submission of the Certificates of Analysis of the drug product validation batches was proposed for Agency concurrence and a teleconference meeting with the Agency was requested to discuss this issue.

With this submission, in follow-up to the telephone conversation cited above, Merck is requesting a teleconference meeting with the Agency to provide an update regarding the status of manufacture of the validation batches for the NDA cited above and to discuss a revised timeline proposal for Agency concurrence regarding submission of the drug product validation documentation to this NDA. A background document which provides details of our proposal is included in this submission to facilitate discussion at the teleconference meeting. This background document also provides notification of our intent to file a CMC amendment to the NDA cited above to update Reference C-2 of the CMC information

The Merck attendees for the upcoming teleconference meeting will include representatives from Regulatory Affairs and Regulatory Analytical Sciences, CMC; a list of attendees will be provided to the Agency once a date for this teleconference meeting has been scheduled. I will contact the Agency shortly to discuss the status of its review of this proposal and to schedule the date for the requested teleconference meeting to discuss and reach consensus on this issue.

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 request 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 trust that the proposal provided in this submission meets with the Agency's approval and concurrence and look forward to discussing this issue at a teleconference meeting at the Agency's earliest convenience. Please direct questions or need for additional information to Michelle W. Kloss, Ph.D. (610-397-2905) or, in my absence, Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely yours,

Michelle W. Kloss

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

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Enclosure: CD

Federal Express

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