CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-317

CORRESPONDENCE

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P O Box 1910
Morristown, NJ 07962-1910
Phone 973 254-5000

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

December 15, 2000

SUBJECT: Original New Drug Application #21-317
Extra Strength Bayer Migraine
500 mg buffered aspirin OTC

Dear Sir/Madam:

Pursuant to section 505(b)(1) of the Act and 21 CFR 314.50, Bayer Corporation, Consumer Care Division (Bayer) is submitting the New Drug Application (NDA) for EXTRA STRENGTH BAYER MIGRAINE (500 mg buffered aspirin). We also refer you to our IND [redacted] for all investigational activities and communications related to the subject product, and to the pre-NDA meeting (9/21/00) between representatives of the Agency and Bayer. As requested in the meeting, Bayer is also providing the Final Study Reports, Tables and Data Listings on a CD-ROM with bookmarks to assist in the review.

This product is intended for OTC use as a migraine treatment. It is a bilayer caplet which combines aspirin and calcium carbonate in an immediate release formulation. This product has been marketed, in accordance with the Internal Analgesic Monograph, for nearly ten years.

A significant body of information exists for buffered aspirin in the OTC monograph cited, as well as, in this application. The drug is well characterized and well documented from a technical perspective.

The safety and efficacy for EXTRA STRENGTH BAYER MIGRAINE are supported by the adequate and well controlled trials conducted in subjects suffering from migraine. The primary efficacy variable designated in the clinical trials was the percent responders, defined as those subjects who experienced a change in pain intensity from a baseline evaluation of moderate to severe, to mild or none at 2 hours post-dose. Secondary efficacy variables included reduction of symptoms of nausea, photophobia and phonophobia.

Our clinical program also included a bioequivalence trial to compare the plain aspirin utilized in the clinical program to the proposed buffered aspirin. Bioequivalence was established.

The proposed labeling for Extra Strength Bayer Migraine follows Drug Facts Format. In addition to Bayer labeling, also enclosed, please find labeling for the identical formulation [redacted] The labeling incorporates statements approved under the Internal Analgesic Tentative Final Monograph, as well as, comments provided by FDA during the pre-NDA meeting.

Provided, under separate cover, to the FDA Philadelphia District Office is a field copy of the technical sections of this application, the application form and the technical summary. Bayer certifies that the field copy is a true copy of the technical section contained in the archival and review copies of this submission.

The drug review process for this NDA is covered by the Prescription Drug User Fee Act (PDUFA II). Bayer certifies that the entire full application fee is being provided to FDA, under separate cover. The assigned User Fee number for this application is #4029.

This application and all communications or materials submitted to the Agency in connection with this matter, now or in the future, constitute privileged and confidential commercial information and/or trade secrets that may not be disclosed to any third party without express prior written consent from Bayer.

We look forward to maintaining an open and collaborative dialogue to facilitate the overall review process. Please contact the undersigned at 973-408-8181 should you have any questions or requests.

Sincerely,

Bayer Corporation
Bayer Consumer Care Divison

Judy Doyle

Judy Doyle
Associate Director,
Regulatory Affairs

Submitted in duplicate

cc: Debra Pagano
PAI Manager
FDA Philadelphia District Office

Bayer

Consumer Care Division

Bayer Corporation
Columbia Road
Box 1910
stown, NJ 07962-1910
973 254-5000

Mr. Rao Puttagunta
Chemistry Reviewer
Food and Drug Administration
Center for Drug Evaluation and Research
Attention: Document Control Room
12229 Wilkins Avenue
Rockville, MD 20852

January 30, 2001
(Via facsimile)

SUBJECT: NDA #21-317
General Correspondence: Drug Substance Inquiry

Dear Mr. Puttagunta:

Reference is made to the original New Drug Application for 500 mg aspirin for the treatment of migraine submitted December 15, 2000. In the Chemistry, Manufacturing and Controls section of this submission, reference is made in Volume 2, page 3 to four drug substance facilities as follows:

The drug product, Extra Strength Bayer (ESB) Migraine, contains Aspirin USP, which is the active principle, and Calcium Carbonate USP, which acts as a buffering agent.

Aspirin USP will be manufactured, tested and released by:[1]

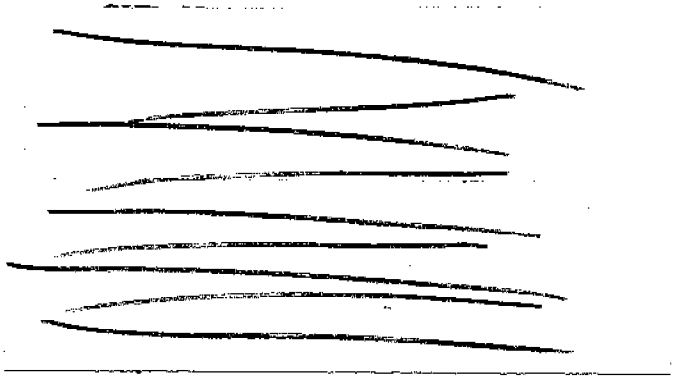
[redacted]

[1] Aspirin USP and 90:10 Calcium Carbonate USP/Pregelatinized Starch NF may be accepted from a vendor certificate of analysis, with a confirmatory USP identification test for aspirin and calcium carbonate performed at a minimum upon receipt of the respective ingredient by Bayer Corp., Myerstown, PA (the drug product manufacturer).

[2] Quimica Farmacéutica Bayer, S.A.Bayer is under the ownership of Bayer.

[3] This material may be referred to in the cited DMFs as 90:10 or 91:9 Calcium Carbonate USP/Pregelatinized Starch NF. For consistency, the 90:10 designation will be used throughout the NDA CMC section.

ORIGINAL



The four drug substance facilities listed above are prepared for pre-approval inspections in conjunction with NDA 21-317.

Sincerely,

Bayer Corporation
Bayer Consumer Care Divison

Judy Doyle

Judy Doyle
Associate Director,
Regulatory Affairs

Bayer Corporation
Bayer Consumer Care Division

facsimile transmittal

To:	Rosemary Cook	Fax:	301-827-2315
From:	Judy Doyle Joanne Robinett	Date:	02/08/01
Re:	NDA 21-317	Pages:	3

☐ Urgent ☐ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

Please see the attached correspondence which is a follow up to our discussion 2/6. A hard copy will be submitted via overnight delivery to the document control room.

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

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

February 7, 2001

SUBJECT: **NDA 21-317**
Extra Strength Bayer Migraine
500 mg buffered aspirin OTC
General Correspondence: ISS

Dear Sir/Madam:

This correspondence provides clarification, as requested, for the paper copy of the Integrated Summary of Safety (ISS) section of the NDA originally submitted December 15, 2000. The pagination on the ISS (located at the top of each page) is numbered from 1 to 64. Pages 51 to 64 were inadvertently omitted from the ISS due to an administrative error. These pages, 51 to 64, are included in the Safety Update section of the NDA.

In the electronic PDF file *ISEISS/ISEV6*, pages 1 to 64 of the Integrated Summary of Safety are correctly included in one section. There is no electronic file provided for the Safety Update section of the NDA.

For your reference, please refer to the following table that lists all information included on the CD-ROM previously provided. Hyperlinks were inserted throughout the reports. Any place in the text where a table is referenced with a **bracket and page number**, clicking on the page number will pull up the table.

Clinical Reports – Table of Contents	
Controlled Study Reports	Folder\File name
S98-072 – A multicenter, prospective, randomized, double-blind, parallel group, single dose, placebo controlled study of the efficacy of Extra Strength Bayer® Aspirin (1000 mg) in subjects with acute migraine attacks	[redacted]
Annex	[redacted]

Clinical Reports – Table of Contents	
S98-073 - A multicenter, prospective, randomized, double-blind, parallel group, single dose, placebo controlled study of the efficacy of Extra Strength Bayer® Aspirin (1000 mg) in subjects with acute migraine attacks Annex	[redacted]
S98-074 - A multicenter, prospective, randomized, double-blind, parallel group, single dose, placebo controlled study of the efficacy of Extra Strength Bayer® Aspirin (1000 mg) in subjects with acute migraine attacks Annex	[redacted]
Pharmacokinetic Study Reports	
S99-102 – Comparative, randomized, 2-way crossover bioavailability study of commercial Extra Strength Bayer® Plus Buffered Aspirin and commercial Extra Strength Bayer® Aspirin Caplets in healthy adults under fasting conditions following administration of a single oral dose.	[redacted]
Integrated Summary of Efficacy	[redacted]
Integrated Summary of Safety	[redacted]

If there are any further questions that arise during the review of NDA 21-317, please contact the undersigned at (973) 408-8181.

Sincerely,

Bayer Corporation
Bayer Consumer Care Divison

Judy Doyle
Associate Director,
Regulatory Affairs

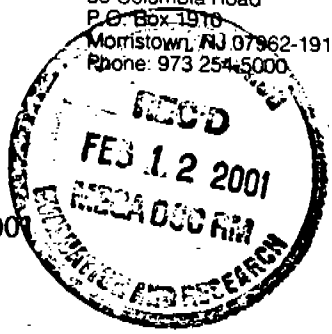
cc: facsimile to R. Cook, W. Ellenberg

NEW CORRESP
NC

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000



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

February 7, 2001

SUBJECT: **NDA 21-317**
Extra Strength Bayer Migraine
500 mg buffered aspirin OTC
General Correspondence: ISS

Dear Sir/Madam:

This correspondence provides clarification, as requested, for the paper copy of the Integrated Summary of Safety (ISS) section of the NDA originally submitted December 15, 2000. The pagination on the ISS (located at the top of each page) is numbered from 1 to 64. Pages 51 to 64 were inadvertently omitted from the ISS due to an administrative error. These pages, 51 to 64, are included in the Safety Update section of the NDA.

In the electronic PDF file *ISEISS/ISEV6*, pages 1 to 64 of the Integrated Summary of Safety are correctly included in one section. There is no electronic file provided for the Safety Update section of the NDA.

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Clinical Reports – Table of Contents	
Controlled Study Reports	Folder\File name
S98-072 – A multicenter, prospective, randomized, double-blind, parallel group, single dose, placebo controlled study of the efficacy of Extra Strength Bayer® Aspirin (1000 mg) in subjects with acute migraine attacks	[redacted]
Annex	[redacted]

ORIGINAL

Bayer Corporation
Bayer Consumer Care Divison

facsimile transmittal

To:	Walt Ellenberg	Fax:	301-827-2316
From:	Judy Doyle	Date:	03/21/01
Re:	NDA 21-317	Pages:	4

☐ Urgent ☐ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

Walt Ellenberg:

Attached please find a response by Bayer to Dr. Lewin in Clinical Investigations regarding NDA 21-317.

Judy Doyle
Bayer Consumer Care
973-408-8181

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910
Phone: 973 254-5000

NDA #21-317
Extra Strength Bayer Migraine
(500 mg buffered aspirin) OTC

March 15, 2001

Constance Lewin, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Scientific Investigations
GCP Branch 2
7520 Standish Place
Room 119
Rockville, MD 20855

SUBJECT: General Correspondence: Clinical Study Site Data Per FDA Request

Dear Dr. Lewin:

As requested in your telephone contact March 7, 2001, this correspondence provides a summary of clinical study site information for S98-072 and S98-074. The attached table describes the names and addresses of Principal Investigators participating in the Bayer aspirin migraine trials, total number of subjects enrolled in each treatment arm, study drop outs by subject number, and all serious events by subject number. In addition, enclosed please find two desk copies of the original protocol and amendments submitted to the IND.

Please contact the undersigned at 973-408-8181 should you have any questions or requests.

Sincerely,

Bayer Corporation
Bayer Consumer Care Divison

Judy Doyle
Associate Director,
Regulatory Affairs

cc: letter only W. Ellenberg (OTC), L. Chen (Neuropharm)

Protocol Investigator	Number of Subjects by Treatment Arm (Intent to Treat)	Serious Adverse Events	Study Drop Outs
S98-072 Albert Yataco, M.D. Innovative Medical Research 1001 Cromwell Bridge Road Suite 302 Towson, Maryland 21286	Placebo N=119 2 x 500 mg Aspirin N=113	• Subject 178 (randomized to placebo) experienced perforated appendix two weeks after study medication dosing.	Subjects 161, 171, 178 were all lost to follow up.
S98-072 Jeffrey Baggish, M.D. Innovative Medical Research 4 West Rolling Crossroads Suite 1 Catonsville, Maryland 21228	Placebo N=85 2 x 500 mg Aspirin N=92	N/A	None
S98-074 Site 1 Roger Cady, M.D. Headache Care Center 1230 E. Kingsley Springfield, Missouri 65804	Placebo N=37 2 x 500 mg Aspirin N=38	N/A	None

Protocol/ Investigator	Number of Subjects by Treatment Arm (Intent to Treat)	Description of Events	
S98-074 Site 2 Marek Gawel. M.D. Sunnybrook Health Science Center 2075 Bayview Avenue E425 Toronto, Ontario M4N3M5 Canada	Placebo N=47 2 x 500 mg Aspirin N=45	• Subject 441 (randomized to 2 x 500 mg aspirin) experienced a GI bleed and had surgery approximately 6 weeks after enrollment. Subject did not dose with study drug.	None
S98-074 Site 3 Jerome Goldstein, M.D. San Francisco Headache Clinic 909 Hyde Street, Suite 230 San Francisco, California 94109	Placebo N=82 2 x 500 mg Aspirin N=68	• Subject 281 (randomized to 2 x 500 mg aspirin) was diagnosed with a brain tumor two weeks after enrollment. Subject did not dose with study drug.	Subjects 142, 279, 295, 403 were all lost to follow up.
S98-074 Site 4 Egilius L.H. Spierings, M.D., Ph.D. 25 Walnut Street, Suite 401 Wellesley Hills, Massachusetts 02481	Placebo N=42 2 x 500 mg Aspirin N=41	N/A	None

Bayer Corporation
Bayer Consumer Care Division

facsimile transmittal

To:	Walt Ellenberg	Fax:	301-827-2316
From:	Judy Doyle	Date:	03/22/01
Re:	NDA 21-317	Pages:	1

☐ Urgent ☐ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

Walt:
Thank you for taking the time this afternoon to discuss the 3/16/01 Information Request (IR) regarding NDA 21-317. To summarize our issues discussed, please note the items below . Since it is our intention to provide adequate responses to the IR in a timely manner, we are seeking concurrence on the items noted.

- The case report data sets will be provided to FDA in SAS transport files with accompanying code lists and derivation formulas. There will be no linking to previously submitted NDA text or files.

- An ITT Analysis will be provided for the 1180 subjects which includes a comparison of headache response at 2 hours and the proportion of patients with secondary migraine symptoms at 2 hours. Bayer is not intending to reanalyze other groups unless requested.

- Bayer will provide a description of the literature search method used to provide the worldwide safety report.

Bayer intends to provide a complete response to the IR no later than April 4th, 2001.

Judy Doyle
973-408-8181

Bayer Corporation
Bayer Consumer Care Division

facsimile transmittal

To:	Dr. Walt Ellenberg	**Fax:**	301-827-2316
From:	Judy Doyle	**Date:**	05/31/01
Re:	NDA 21-317	**Pages:**	7
CC:	Lana Chen, Project Manager, Neuropharm		

☐ Urgent ☐ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

Walt:

Attached please find your desk copy of the Bayer response to FDA's statistical inquiries of May 18. I am submitting the hard copy to the docket per the usual overnight delivery.

Judy Doyle

973-408-8181

Bayer

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, N.J. 07962-1910
Phone: 201 254-5000

NDA #21-317
Extra Strength Bayer Migraine
(500 mg buffered aspirin) OTC

May 31, 2001

N 000/82
NDA ORIG AMENDMENT

Charles Ganley, M.D., Director
Division of Over-the-Counter Drug Products
HFD-560
Food and Drug Administration
Center for Drug Evaluation and Research
Attention: Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850-3202

General Correspondence: Response to Information Request

Dear Dr. Ganley:

This correspondence provides the information requested by FDA May 18, 2001 regarding NDA 21-317. These issues relate to variable definitions, extrapolation, and re-analysis of protocols S98-072 and S98-074. For ease of reference, the FDA Reviewer inquiry item appears bolded, followed in standard type, by the Bayer response.

Question:

1. Please clarify and define the variables "Time1, Time2, Time3, etc" located in Study S98-072.

Response:

TIME1 is the time at which the 30-minute evaluation was made by the subject. TIME2, TIME3, TIME4, TIME5, TIME6, and TIME7 are the times at which the 1-hour, 2-hour, 3-hour, 4-hour, 5-hour, and 6-hour post-dosing evaluations were made, respectively.

To assist in understanding the database structure, it may be useful to note that these times were converted to military time using an additional variable (AP1-AP7) which specifies if the observation was recorded in the a.m. or p.m. The variables LTIME1 through LTIME7 represent the equivalent military time at which the post-dosing evaluations were made.

ORIGINAL

The analysis of the data relies on determining the length of time between dosing and the post-dosing evaluations. The variables DIFF1-DIFF7 contain the elapsed times between the post-dosing evaluation and the time at which the subject dosed with study medication. The elapsed time between dosing and the 2-hour evaluation is calculated by the formula: DIFF3 = LTIME3 – LMEDTIME where LMEDTIME is the military time of dosing with the study medication.

To summarize, the variables TIME1 to TIME7 record the post-dosing evaluation times which need to be processed with the am/pm flags and the time of dosing to yield the elapsed time between dosing and post-dosing evaluations.

Question:

2. Please provide the formula used to determine the extrapolated results of Headache Severity at 2 hours (i.e. LSEV3).

Response:

For reference, the following is Section 11.4.2.2 from the S98-072 report that outlines the methods used in the extrapolation/interpolation of data. These methods were used consistently across all studies.

Section 11.4.2.2 HANDLING OF DROPOUTS OR MISSING DATA

a. If a subject remedicated with rescue medication before the end of the 6-hour study, the subsequent efficacy variable scores (pain intensity scores, nausea, photophobia, phonophobia, and ability to function) were set equal to either the baseline score or the score recorded immediately prior to remedication, whichever score was more severe.

b. Efficacy variable scores for the 6-hour study period, excluding baseline, which remained missing after the application of (a) above were replaced by carrying forward the preceding non-missing score.

c. Any missing efficacy variable score for a subject who medicated to treat a recurrence was set equal to either the baseline score or the most recent non-missing score recorded prior to medication, whichever score was more severe.

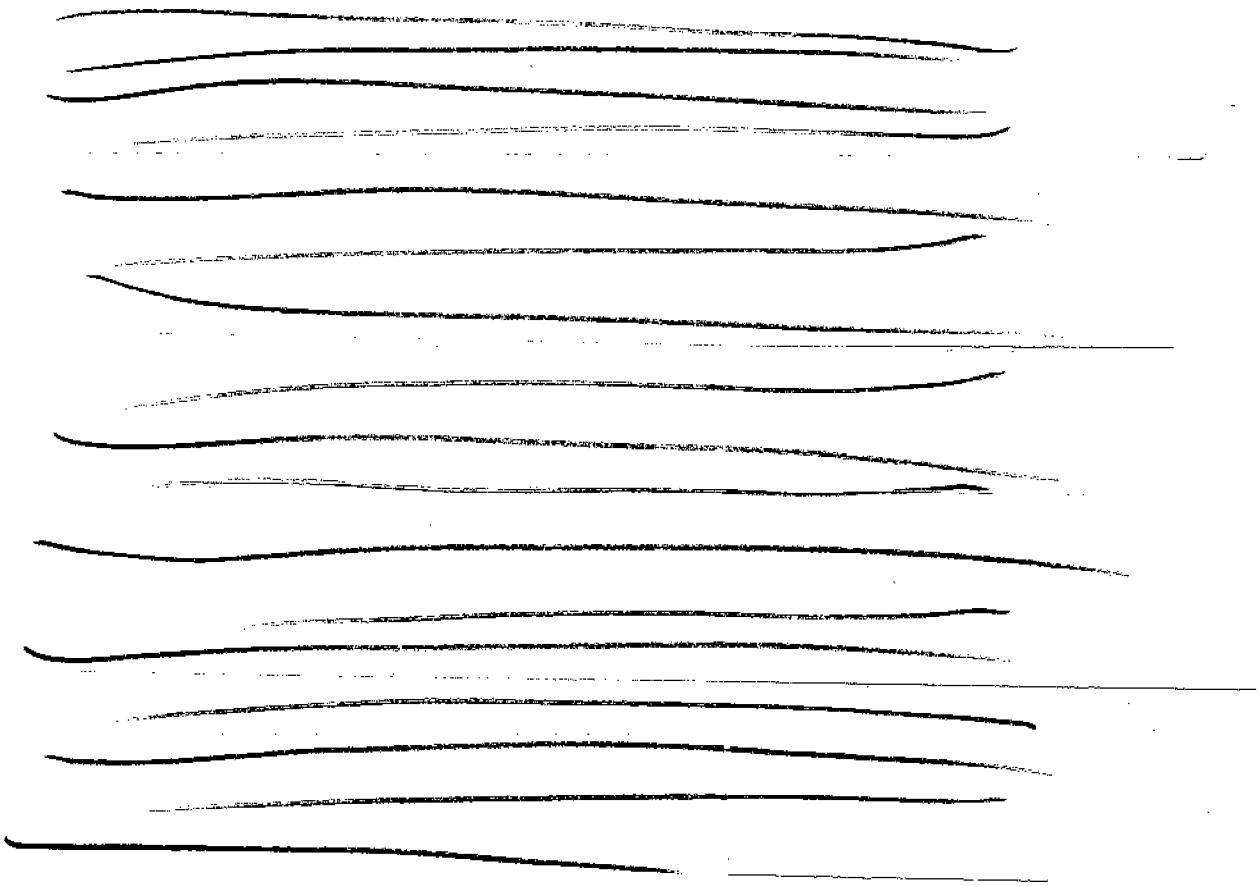
d. The 2-hour reading was interpolated in the event that the 2-hour evaluation was off-schedule by more than 15 minutes. Linear interpolation was used if there was observed data that preceded and followed the 2-hour clock time. The last observation was carried forward if the data subsequent to the 2-hour value was missing.

As mentioned in (d), the 2-hour reading was interpolated in the event that the 2-hour evaluation was off-schedule by more than 15 minutes. Linear interpolation was used if there was observed data that preceded and followed the 2-hour clock time. The last observation was carried forward if the data subsequent to the 2-hour value was missing.

Formulas for extrapolation/interpolation are as follows:

If an evaluation was missing, the previous non-missing evaluation was carried forward.

or



Question:

3. It does not appear that the actual 2-hour efficacy results were used in the calculation. Please explain.

Example: Patient 18 (Study S98-072) had at "TIME3" (the 2 hour timepoint) a headache severity of 2 (SEV3), i.e., a non-responder. "TIME3" for this subject actually corresponded to 3 hours and 30 minutes (TIME3 minus BASETM). "TIME1" (the ½ hour timepoint) actually occurred 2 hours after "BASETIM" and had a severity of 1 (SEV1) which would have made this subject a responder.

Response:

All calculations that determine time from dosing with study medication should use the variable LMEDTIME which is the time that the subject dosed with study medication, not the time the migraine began (BASETM). Although subject 18's migraine began at 3:30 pm, this subject did not dose with study medication unitl 5:00 pm. All subsequent evaluations were made according to protocol at 30 minutes, 1-, 2-, 3-, 4-, 5-, and 6-hours post-dose.

Question:

4. Please re-analyze the statistical calculations for all three studies using those timepoints closest to the actual 2-hour assessment as opposed to "TIME3". We request a LOCF algorithm for missing data. Those subjects with their first post-treatment efficacy assessment ≥3 hours should not be included in the 2-hour analyses.

Response:

In a telephone contact between Dr. Walt Ellenberg and Bayer's Joanne Robinett 5/22/01, Bayer was advised not to re-analyze the data since addressing the variable definitions and extrapolation criteria would be adequate from the Agency's standpoint. However, upon further review of the data, 3 subjects in the S98-072 study made the 2-hour evaluation ≥3 hours subsequent to dosing and 4 subjects in the S98-074 study recorded their 2-hour evaluation at ≥3 hours post-dose. All subjects of S98-073 provided the 2-hour evaluation at less than 3 hours. The evaluation times and severity scores for those subjects whose 2-hour evaluation was ≥3 hours from the time of dosing are provided below. Review of these data reveal that using the actual assessment closest to the 2-hour assessment would not alter the classification as a responder for the subjects with their 2-hour evaluation greater or equal to 3 hours. Additionally, the algorithm used in the event that the post-treatment efficacy assessment was missing and not concurrent with remedication was a LOCF (See extrapolation rule (b) above).

Please note that "Baseline" refers to the time at which the subject dosed with study medication.

S98-072

	Baseline	30-Min	1-HR	2-HR	3-HR	4-HR	5-HR	6-HR	Respond
PTID: 135									
Time	11:00 am	11:30 am	12:30 pm	2:30 pm	3:30 pm	4:30 pm	5:30 pm	6:30 pm	yes
Severity	3	1	0	0	0	0	0	0	
PTID: 154									
Time	4:30 am	5:00 am	6:00 am	8:00 am	9:00 am	10:00 am			no
Severity	2	2	2	3	3	3	3	3	
PTID: 439									
Time	1:20 pm	1:50 pm	2:50 pm	4:50 pm	6:50 pm	10:50 pm			yes
Severity	2	1	0	0	0	0	0	0	

S98-074

	Baseline	30-Min	1-HR	2-HR	3-HR	4-HR	5-HR	6-HR	Respond
PTID: 49									
Time	6:30 pm	7:00 pm	8:00 pm	10:00 pm	1:00 am	5:00 am	10:00 am	4:00 pm	no
Severity	2	2	2	2	2	2	2	2	

	Baseline	30-Min	1-HR	2-HR	3-HR	4-HR	5-HR	6-HR	Respond
PTID: 164									
Time	7:30 am	8:00 am	9:30 am	10:30 am	11:30 am	12:30 pm	1:30 pm	2:30 pm	no
Severity	2	2	2	2	3	3	3	2	

	Baseline	30-Min	1-HR	2-HR	3-HR	4-HR	5-HR	6-HR	Respond
PTID: 215									
Time	9:45 am	10:17 am	11:45 am	12:45 pm	1:45 pm	2:45 pm	3:45 pm	4:45 pm	no
Severity	2	3	3	3	2	1	1	0	

	Baseline	30-Min	1-HR	2-HR	3-HR	4-HR	5-HR	6-HR	Respond
PTID: 288									
Time	11:33 am	12:03 pm	1:05 pm	2:38 pm	3:15 pm	4:30 pm	5:30 pm	6:30 pm	no
Severity	3	3	3	3	2	2	2	2	

Please contact the undersigned at 973-408-8181 with questions.

Sincerely,

Bayer Corporation
Bayer Consumer Care Divison

Judy Doyle
Associate Director
Regulatory Affairs

cc: desk copies faxed to Project Managers W. Ellenberg and L. Chen

Bayer Corporation
Bayer Consumer Care Divison

faesimile transmital

To:	Dr. Walt Ellenberg	Fax:	301-827-2315
From:	Judy Doyle	Date:	10/05/01
Re:	10/5 teleconference	Pages:	1

☐ Urgent ☐ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

The Bayer attendees during our teleconference were as follows:

Judy Doyle, Associate Director Regulatory Affairs

Joanne Robinett, Director Regulatory Affairs

Dr. Randy Koslo, Director Medical and Clinical Affairs

Dr. Laureen MacEachern, Senior Associate Director Clinical Affairs

Diana Plaza, Manager Clinical Affairs

Bayer Corporation
Bayer Consumer Care Divison

facsimile transmittal

To:	Dr. Walt Ellenberg	**Fax:**	301-827-2315
From:	Judy Doyle	**Date:**	10/10/01
Re:	Migraine labeling	**Pages:**	1

☐ Urgent ☐ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

This correspondence responds to your request for clarification on the use of the extra strength descriptor with the aspirin migraine product. The proposed label submitted in the original application stated *"Bayer Extra Strength Migraine"*.

It is our intention, based on the 10/5 teleconference, to relocate the descriptor away from migraine and use it in conjunction only with the Bayer aspirin name on the principle display panel.

Extra Strength Bayer Migraine Pain

Please contact me if there are any further issues for discussion.

Judy Doyle

Bayer

NDA #21-317
Extra Strength Bayer Migraine
(500 mg buffered aspirin) OTC

Consumer Care Division

Bayer Corporation
36 Columbia Road
P.O. Box 1910
Morristown, N.J. 07962-1910
Phone: 201 254-5000

October 9, 2001

Walter Ellenberg, Project Manager
Division of Over-the-Counter Drug Products
HFD-560
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Blvd.
Rockville, MD 20850-3202

General Correspondence: Response to Labeling Comments

Dear Dr. Ellenberg:

Reference is made to the October 2, 2001 correspondence and the October 5, 2001 teleconference, both of which addressed the proposed labeling for the 500 mg aspirin data in support of migraine.

In order of appearance in your written correspondence, the following labeling issues are addressed:

1. The Bayer aspirin migraine product will be labeled for the treatment of mild to moderate migraine pain as supported by clinical data.
2. The PDP will represent the statement of identity as "buffered aspirin tablets 500 mg" followed by "pain reliever" and will appear prominently with the trade name.
3. "Extra Strength" will be used in connection to the trade name, and not to the indication.
4. The statement "Plus Helps Protect Against Stomach Upset" will not be used in product labeling. Other statements, such as "contains buffering ingredients" may be used.
5. The statement "Ask Your Doctor About Other Benefits of Bayer Aspirin" will not appear in the product labeling.
6. The labeling will comply fully with 21 CFR 201.66 format and content requirements for OTC drug products.
7. The Drug Facts prototype provided by FDA will be used for the Bayer Migraine product. One statement will be modified as agreed to state, "Ask a doctor or pharmacist before use if you are taking any other drug *on a regular basis*".

We thank you for your prompt attention to the review of NDA 21-317. Please contact the undersigned at 973-408-8181 with questions.

Sincerely,

Bayer Corporation
Bayer Consumer Care Divison

Judy Doyle

Judy Doyle
Associate Director,
Regulatory Affairs

CONVERSATION RECORD

DATE 10-17-01	TIME
CENTER REPRESENTATIVE	WJE
SPONSOR REPRESENTATIVE	Joanne Robinette
SPONSOR TELEPHONE NUMBER	973- 408- 8093
SPONSOR NAME	Bayer
SUBJECT	21 317

TEXT

Judy Doyle - out of the office -

I asked Joanne to fax a commitment to the withdrawal of the [redacted]

This issue was agreed to on 10-11-01 during a T-con w/ D. Hopkins & W. Ellenberg, J Doyle (Bayer)

The fax will arrive on 10-17-01

CONVERSATION RECORD

DATE 10-17-01	TIME
CENTER REPRESENTATIVE	WJL
SPONSOR REPRESENTATIVE	Joann Robinette
SPONSOR TELEPHONE NUMBER	~~908-4~~ 973-408-8093
SPONSOR NAME	Bayer
SUBJECT	21-317

TEXT

Left message - Please provide the final Name for your product.

Please send a fax which identifies this information ASAP.

CONVERSATION RECORD

DATE 10-17-01	TIME
CENTER REPRESENTATIVE	WJL Charley Caley
SPONSOR REPRESENTATIVE	Joanne Robinette
SPONSOR TELEPHONE NUMBER	~~900~~ 973 408-8093
SPONSOR NAME	Bayer
SUBJECT	21-317

TEXT

Joanne called back to clarify the 2nd bullet of the PDP.

She indicated that two bullets would be added.

After discussing the options it was determined that the following could appear on the PDP.

- Clinically proven to treat migraine pain
- Caffeine free

CONVERSATION RECORD

DATE 10-11-01	TIME
CENTER REPRESENTATIVE	WJE + D Lumpkins
SPONSOR REPRESENTATIVE	Judy Doyle
SPONSOR TELEPHONE NUMBER	973-408-8181
SPONSOR NAME Bayer	
SUBJECT 21-317 T-con -	

TEXT

Two items to discuss:

① The Agency finds the use of the name "EXTRA STRENGTH BAYER MIGRAINE" for provided in the Oct. 10, Fax.

I Requested that they provide a visual layout/ description for the product

We suggested (using current extra strength Bayer Product labels) that they:

↓ Size of EXTRA STRENGTH

↑ Aspirin size and add 500 mg Tablets on yellow field - Separate for the Bayer Logo add → "Migraine Pain"

They agreed and will do so ASAP.

CONVERSATION RECORD

DATE 10-10-01	TIME
CENTER REPRESENTATIVE	WJE & DL
SPONSOR REPRESENTATIVE	Judy Doyle
SPONSOR TELEPHONE NUMBER	973-408-8181
SPONSOR NAME	Bayer
SUBJECT 21-317	

TEXT

Please Note the following.

We received the fax explaining the Name "Extra Strength Bayer Migraine Pain" (Extra Strength) This is not going to be acceptable as it still modifies the migraine pain.

→ Potentially - we want something regarding

Extra Strength Bayer Aspirin for Migraine Pain } Name not given to Bayer.

- a Quick mockup - showing the labeling would be good.

→ The agency needs an official request.

CONVERSATION RECORD

DATE 10-10-01	TIME
CENTER REPRESENTATIVE	WJE
SPONSOR REPRESENTATIVE	Judy Doyle
SPONSOR TELEPHONE NUMBER	973-408-3181
SPONSOR NAME	Bayer
SUBJECT 21 317	

TEXT

Based on your fax -

please provide info/information regarding (ITEM 3)

Specifically. What is the actual name?.

How will it be presented on the PDP

We will evaluate it based on what is provided in the Fax.

She will send the Fax ASAP.

CONVERSATION RECORD

DATE 10-9-01	TIME
CENTER REPRESENTATIVE WJL	
SPONSOR REPRESENTATIVE Judy Doyle	
SPONSOR TELEPHONE NUMBER 973-408-8181	
SPONSOR NAME Bayer	
SUBJECT 21-317	

TEXT

I received the fax

Text of labels would be possible but they cannot provide actual labels as the label graphics are outsourced.

Aluminum to be addressed in the letter.

CONVERSATION RECORD

DATE 10-9-01	TIME
CENTER REPRESENTATIVE WJE	
SPONSOR REPRESENTATIVE Judy Doyle	
SPONSOR TELEPHONE NUMBER 973-408-8181	
SPONSOR NAME Bayer	
SUBJECT 21-317	

TEXT

Please respond to the fax sent last week. If we do not receive any info from you by today - (as stated in the fax) we will generate a approvable letter.

CONVERSATION RECORD

DATE 10-5-01	TIME
CENTER REPRESENTATIVE	WJE
SPONSOR REPRESENTATIVE	Judy Doyle
SPONSOR TELEPHONE NUMBER	973-408-8181
SPONSOR NAME	Bayer
SUBJECT 21317	

TEXT

Please send a list of attendees that took part in Bobby's F-con.

She said she would fax the information

CONVERSATION RECORD

DATE 10-4-01	TIME
CENTER REPRESENTATIVE	WJE
SPONSOR REPRESENTATIVE	Judy Doyle
SPONSOR TELEPHONE NUMBER	973-408-8181
SPONSOR NAME	Bayer
SUBJECT	21-317

TEXT

T-con call in # [redacted]

- They will have 3 clinical + 2 regulatory people attending.

They will address 3 Clinical Questions in response to The Fax of 10-2-01

① Bayer plans to discuss ITEM #1
Symptoms v. Pain

② Bayer questions the Name Issue

[redacted]

Label Questions: (Typo/Format Questions)

① Does Arthritis need to be aligned - is the position correct.

② Do not take if
Taking any other drug (on a regular basis)"?

③ Questions Comments
- Days/Times should be with the Phone #
not the website.

CONVERSATION RECORD

DATE 10-4-01	TIME
CENTER REPRESENTATIVE	WIE
SPONSOR REPRESENTATIVE	July Dunfy
SPONSOR TELEPHONE NUMBER	973-408-8181
SPONSOR NAME	Bayer
SUBJECT 21-317	

TEXT

Answers to Judy's / Bayer's Questions

① We agree - the bullet for arthritis should be aligned under the 5th bullet. (Ask a Doctor Section) or pharm.

② We agree - (Ask a Doctor or pharm Section) bullet. Taking any other drug should be followed by "on a regular basis"

③ Question + Comments Section - it is voluntary. they can put the days + times after the phone #

CONVERSATION RECORD

DATE 10-3-01	TIME .
CENTER REPRESENTATIVE WJE	
SPONSOR REPRESENTATIVE Judy Doyle	
SPONSOR TELEPHONE NUMBER 973-408-8181	
SPONSOR NAME Bayer	
SUBJECT Confirming Receipt of Fax sent 10-2-01	

TEXT

Will find a conference Room -

↳ She will call us a.m. for Friday

She confirmed that she received the docum + that they would participate in the T-con Fri. A.M.

CONVERSATION RECORD

DATE 9-20-01	TIME
CENTER REPRESENTATIVE	Ellenberg
SPONSOR REPRESENTATIVE	Judy Doyle
SPONSOR TELEPHONE NUMBER	973- 407-8181
SPONSOR NAME	Bayer
SUBJECT 21 317	

TEXT

I received her message regarding the labeling however, we have no comments to make at this time - as it is under review.

CONVERSATION RECORD

DATE 8-29-01	TIME 1545
CENTER REPRESENTATIVE	ELLENBERG
SPONSOR REPRESENTATIVE	JUDY DOYLE
SPONSOR TELEPHONE NUMBER	973-408-8181
SPONSOR NAME	BAYER
SUBJECT	21-317

TEXT

Follow-up to Call of 8-28-01

additional Request - Please provide the # of units sold in Germany.

Message to Drug Safety

↳ most people on vacation

Weeks 9-5-01 or Thurs the 6th, 01 **

Distribution Data for Germany.

CONVERSATION RECORD

DATE 8-29-01	TIME 1510
CENTER REPRESENTATIVE	ELLENBERG
SPONSOR REPRESENTATIVE	JUDY DOYLE
SPONSOR TELEPHONE NUMBER	973-408-8181
SPONSOR NAME	Bayer
SUBJECT	21-317

TEXT

REQUEST FOR DATES

- Called & left a detailed voice mail regarding the following:

① According to what they submitted, the world wide literature search started in the mid-1960's but no stop date was provided. Please provide this stop date.

② Bayer has been marketed in Germany since July 2000. They performed their own database for adverse events associated w/ any/all aspirin containing products used to treat migraine. Only 15 case reports were found. Please provide the time period queried, the amt of 500 mg strength tablets sold during this period, and the total number of adverse events reported in association with these products.

- Please return my call for clarification - please call 8-29-01 for more information.

CONVERSATION RECORD

DATE 7-18-01 | TIME 430

CENTER REPRESENTATIVE ELLENBERG

SPONSOR REPRESENTATIVE Judy Doyle

SPONSOR TELEPHONE NUMBER 973-408-8181

SPONSOR NAME Bayer

SUBJECT 21-317

TEXT

Please send copies to my attention then when the remaining papers are translated you can send the full package to the document room in the same way that you would submit the NDA.

Also- do you have a date for the AERS Data Summary.

Please call w/ the info.

CONVERSATION RECORD

DATE 7-16-01	TIME
CENTER REPRESENTATIVE ELLENBERG	
SPONSOR REPRESENTATIVE Judy Doyle	
SPONSOR TELEPHONE NUMBER 973-404-8181	
SPONSOR NAME Bayer	
SUBJECT 21-317	

TEXT

Received a voicemail - the 23 papers were sent to me on June 26th.

- She indicated that the others were submitted to the ~~docket room~~ "Docket"

~~- However - She~~.

She should know the Date of the Data search soon.

CONVERSATION RECORD

DATE 7-16-01	TIME 1550
CENTER REPRESENTATIVE	ELLENBERG
SPONSOR REPRESENTATIVE	Judy Doyle
SPONSOR TELEPHONE NUMBER	973-408-8181
SPONSOR NAME	Bayer Consumer Care
SUBJECT	21-[redacted]317

TEXT

Called to follow-up w/ Time Frame

① 27 Papers ?

② AERS DATA Summary Adverse Events

Called - left voice - requesting info on the above items

CONVERSATION RECORD

DATE 7-12-01	TIME 4:40
CENTER REPRESENTATIVE Elmbay	
SPONSOR REPRESENTATIVE Judy Doyle	
SPONSOR TELEPHONE NUMBER 973-408-8181	
SPONSOR NAME Beyer	
SUBJECT Status of Requested INFO 21-[redacted]317	

TEXT

Called. Left message -

What is the status of the info request?

CONVERSATION RECORD

DATE 6/26/01 TIME 8:30

CENTER REPRESENTATIVE Walt Filenberg

SPONSOR REPRESENTATIVE Judy Doyle

SPONSOR TELEPHONE NUMBER 973-408-8181

SPONSOR NAME Bayer

SUBJECT 21317

TEXT

I rec. a call from Judy Doyle - we discussed the following -

(1) all papers are in But one -
I told her to scan them and go ahead and send all papers that she currently has. Then forward the others when they arrive.

(2) They have submitted a request w/ FOI for the AERS database - However, they do not know the time frame - I told her to follow-up w/ the rep. frequently to get a estimate of the time to completion.

Investigation: Judy told by her medical person (director) that FDA is investigating one of the clinical sites. They had been contacted by the CRO regarding this matter - I told her that I was uncertain as to the potential or status of such inspection and that it not a matter that I ~~dealt~~ normally handle.

CONVERSATION RECORD

DATE 6-18-01	TIME 400 P.M.
CENTER REPRESENTATIVE	ELLENBERG
SPONSOR REPRESENTATIVE	Judy Doyle
SPONSOR TELEPHONE NUMBER	973- 408- 8181
SPONSOR NAME	Bayer
SUBJECT	21317

TEXT

Time frame: ? they don't know → may take a while

AERS - Asylum + Migraine Adverse events

FOI General case Report + Summary -

Top Line: May not be much info w/ migraine

Time: will call w/ more info as they have it.

Papers by weekend:

CONVERSATION RECORD

DATE 6-12-01	TIME 1139
CENTER REPRESENTATIVE	Ellenberg
SPONSOR REPRESENTATIVE	Judy Doyle
SPONSOR TELEPHONE NUMBER	973-408-8181
SPONSOR NAME	Bayer Consumer Care
SUBJECT	NDA 21-317

TEXT

called back to make sure that she is aware that she needs to check Bayer's own AER. Database - in the global search as well.

Needs to also provide a time for completing the request.

CONVERSATION RECORD

DATE 6-12-01 | TIME 0950

CENTER REPRESENTATIVE ELLENBERG

SPONSOR REPRESENTATIVE Judy Doyle

SPONSOR TELEPHONE NUMBER Bayer 973-408-8181

SPONSOR NAME

SUBJECT Bayer Consumer Care NDA 21217 - Bayer extra strength migraine

TEXT

Please provide the following information:

① All 26 articles → 19 old articles (submitted w/ orig. NDA)
7 new safety

ASAP ② Send / fax to me.

③ Send / fax to Document Room as amendment to NDA.

② Re. Why did they fail to provide AERS Data base for their drug.

You were informed of the requirement to do so in letters dated ~~9-15-01~~ 9-21-01 & 3-16-01

Resp: - misunderstanding - was focused unfamiliar w/ AERS.

I requested - per Rosemarie Nunn, that the sponsor provide 10 yrs - (aspirin only) no combination products -

- NDH faxed EG of call.

He wants the time frame, may need to write a letter

CONVERSATION RECORD

DATE 5-22-01	TIME 1445
CENTER REPRESENTATIVE Ellenberg	
SPONSOR REPRESENTATIVE Joanne Robinette	
SPONSOR TELEPHONE NUMBER 973-409-8191	
SPONSOR NAME Bayer	
SUBJECT N. 21-317	

TEXT

J Joanne Called - to provide a time frame for answering the questions. Estimated June 5.

I informed her that the M.O. re-reviewed the data and feels that he is now able to interpret the data. However, therefore, the need for re-running the data is removed.

However, the agency still requests that Bayer/CRO should answer the questions presented.

→ Defined terms, presentation of the formula were inadequate.

CONVERSATION RECORD

DATE 5-18-01 | TIME 908

CENTER REPRESENTATIVE Ellenberg

SPONSOR REPRESENTATIVE Judy Doyle

SPONSOR TELEPHONE NUMBER 973- 408- 7181

SPONSOR NAME Bayer

SUBJECT Statistical Concerns NDA21-317

TEXT

Called. Left a voice mail -

will call Joanne Robinette 973- 408- 8093

Called Joanne Robinette - left a voice mail -

Detailing each room - & enumerated each concern.

will Call Judy Doyle back and give them the same info mation.

Judy Doyle -

CONVERSATION RECORD

DATE 5-18-01	TIME 10:00
CENTER REPRESENTATIVE Ellenberg	
SPONSOR REPRESENTATIVE Joanne Robinette. (Judy Doyle)	
SPONSOR TELEPHONE NUMBER 973-408-7181	
SPONSOR NAME Bayer	
SUBJECT NDA 21-317	

Bayer Extra Strength Mcetaene TEXT

I spoke to Joanne Robinette at 10:00 (incoming call)

- She acknowledged receipt of her voice mail and indicated that she and Judy Doyle had discussed the issue.

- They will contact the CRO to resolve the issue and get a response from Joanne together.

I thanked her for her immediate attention to this matter -

CONVERSATION RECORD

DATE 4-26-01 | TIME 10:30

CENTER REPRESENTATIVE W. Ellenberg

SPONSOR REPRESENTATIVE Judy Doyle

SPONSOR TELEPHONE NUMBER Bayer 973-487-8181

SPONSOR NAME Bayer

SUBJECT : Biopharm Info.

TEXT

I called Judy to clarify the question regarding information that the Biopharm reviewers had requested.

She claimed that all of the Biopharm info was submitted in the ER Pckage - 3 weeks ago -

Some of the infor mation was provided in Paper and the clinical data was provided in the electronic format.

I told her that we would follow-up if anything was missing.

CONVERSATION RECORD

DATE 2-7-01	**TIME** 2:00
CENTER REPRESENTATIVE Walt Ellenberg	
SPONSOR REPRESENTATIVE Judy Doyle	
SPONSOR TELEPHONE NUMBER 973-408-8181	
SPONSOR NAME Bayer Consumer Care	
SUBJECT	

TEXT

Judy informed me that she feels that the NDA has been sorted out. Most appears to be a pagination issue w/ the CRO - Their pagination does not match that of the CRO. She acknowledged the discrepancy and is addressing the differences.

I informed her that she needs to clearly state the reasons/explanation about ~~the~~ for the differences - send it to me ASAP.

~~Also~~ These differences can be a bioability issue.

In addition, I informed her that we are putting together a list of additional information that is requested for this NDA. The letter "IR" would be sent shortly. She needs to address these issues ~~prop~~ ~~prompt~~ promptly.

She agreed - conversation concluded well.

CONVERSATION RECORD

DATE 1-26-01	**TIME** 3:17 P.M.
CENTER REPRESENTATIVE	W. Ellenberg
SPONSOR REPRESENTATIVE	Bayer Consumer Care
SPONSOR TELEPHONE NUMBER	973-254-5000
SPONSOR NAME	Judy Doyle
SUBJECT	Questions / Concerns

TEXT

Called to ask two items:

① Please provide 8 additional Desk copies
- she will

② upon Review (K. Prohaska)
it was noted that the hard copy pST → The Global Safety Report of the IDS was NOT ENCLUDED. Please explain why the hard copy was different from the electronic version →

③ Finally, please provide the study protocols and Amend. of Annual → they were originally referenced w/ END

→ She also commented that she was contacted by Rose Hagerton regarding a 1 page abstract that the drug facilities are await for inspection

CONVERSATION RECORD

DATE 1-18-01	TIME 7— 800
CENTER REPRESENTATIVE	
SPONSOR REPRESENTATIVE	Judy Doyle
SPONSOR TELEPHONE NUMBER	973-408-8181
SPONSOR NAME	Bayer
SUBJECT	NDA 21 317

TEXT

Requested the Disk of files (CD Rom)

Also

Status of vers. 1.1 Desk copies -