CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20757 AND 20758

CHEMISTRY REVIEW(S)

AUG 6 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Control

NDA #: 20-757 **CHEM.REVIEW #:** 3 **REVIEW DATE:** 05-AUG-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT (BC)	16-JUN-97	18-JUN-97	24-JUN-97
AMENDMENT (BC)	18-JUL-97	21-JUL-97	22-JUL-97
AMENDMENT (BC)	28-JUL-97	29-JUL-97	30-JUL-97
AMENDMENT (BC)	31-JUL-97	01-AUG-97	05-AUG-97

NAME & ADDRESS OF SPONSOR

Sanofi Winthorp, Inc.
90 Park Avenue
New York, NY 10016

USER FEE BILLING, NAME, ADDRESS AND CONTACT

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

DRUG PRODUCT NAME

Established Name:	Irbesartan
Proprietary:	AVAPRO (proposed)
Nonproprietary/USAN:	Irbesartan
Code Name/#:	SR 47,436, BMS-186295, BMS-186295-01
Chem.Type/Ther.Class:	1/S

AND Suitability Petition/DESI/Patent Status:

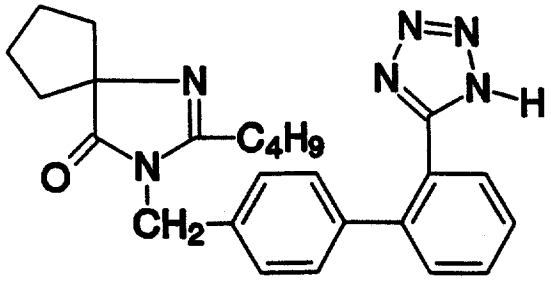
The U.S. Patent 5,270,317 held by Elf Sanofi was issued for irbesartan and is due to expire on March 2011.

PHARMACOL.CATEGORY/INDICATION: Angiotensin II Receptor Antagonist/Hypertension
DOSAGE FORM: TABLETS
STRENGTH 75 mg, 150 mg and 300 mg.
ROUTE OF ADMINISTRATION: ORAL
DISPENSED: Rx

CHEMICAL NAME 2-Butyl-3-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,3-diazaspiro[4.4]non-1-en-4-one.

CAS # 138402-11-6 **MOLECULAR FORMULA** $C_{25}H_{28}N_6O$ **MOLECULAR WEIGHT** 428.5

STRUCTURAL FORMULA



SUPPORTING DOCUMENTS:

Covered in Review # 1

RELATED DOCUMENTS (if applicable): NDA 20-758 Irbesartan/Hydrochlorothiazide

CONSULTS: None at present.

REMARKS/COMMENTS:

Reply to EA is being reviewed by HFD-357.

facility has not been reviewed yet.
The remaining establishments have been found acceptable.

CONCLUSIONS & RECOMMENDATIONS:

The applicant requested an expiration date of 2 years. The review of the data provided by applicant supports the requested expiry date of 2 years. The application is approvable after the acceptable status of facility, the manufacturer of drug substance.

APPEARS THIS WAY
ON ORIGINAL

cc:
HFD-110/Division File
HFD-110/Ram Mittal/date
HFD-110/CSO
HFD-810/C. Hoiberg
R/D Init by: RWolters/

Ramsharan D. Mittal Ph.D., Review Chemist
filename: C:\NDA\20757\20757.003

8/6/97

APPEARS THIS WAY
ON ORIGINAL

DRUG: IRBESARTAN

JUN 20 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCT
Review of Chemistry, Manufacturing, and Control

NDA #: 20-757 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 20-JUN-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT (BC)	14-APR-97	15-APR-97	19-APR-97
AMENDMENT (BL)	23-APR-97	24-APR-97	01-MAY-97

NAME & ADDRESS OF SPONSOR

Sanofi Winthorp, Inc.
90 Park Avenue
New York, NY 10016

USER FEE BILLING, NAME, ADDRESS AND CONTACT

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

DRUG PRODUCT NAME

Established Name:	Irbesartan
Proprietary:	AVAPRO (proposed)
Nonproprietary/USAN:	Irbesartan
Code Name/#:	SR 47,436, BMS-186295, BMS-186295-01
Chem.Type/Ther.Class:	1/S

AND Suitability Petition/DESI/Patent Status:

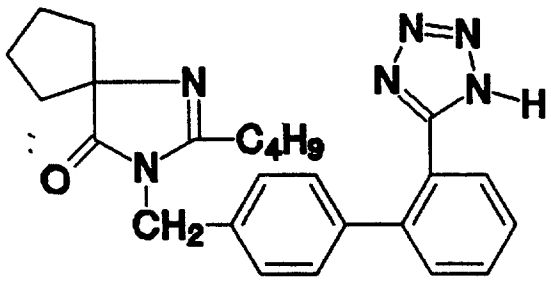
The U.S. Patent 5,270,317 held by Elf Sanofi was issued for irbesartan and is due to expire on March 2011.

PHARMACOL.CATEGORY/INDICATION: Angiotensin II Receptor Antagonist/Hypertension
DOSAGE FORM: TABLETS
STRENGTH 75 mg, 150 mg and 300 mg.
ROUTE OF ADMINISTRATION: ORAL
DISPENSED: Rx

CHEMICAL NAME 2-Butyl-3-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,3-diazaspiro[4.4]non-1-en-4-one.

CAS # 138402-11-6 **MOLECULAR FORMULA** $C_{25}H_{28}N_6O$ **MOLECULAR WEIGHT** 428.5

STRUCTURAL FORMULA



SUPPORTING DOCUMENTS:

Covered in Review # 1

RELATED DOCUMENTS (if applicable): NDA 20-758 Irbesartan/Hydrochlorothiazide

CONSULTS: None at present.

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:

The manufacturing and controls information provided in this notice is deficient in some areas, the deficiencies are not very serious.

The applicant requested an expiration date of 2 years. Based on the data provided by applicant the 2 years expiry date is recommended after successful review of the stability data (as committed by the applicant) from the manufacturing facility.

APPEARS THIS WAY
ON ORIGINAL

cc:
HFD-110/Division File
HFD-110/Ram Mittal/date
HFD-110/CSO
HFD-810/C. Hoiberg
R/D Init by: RWolters/

R D Mittal

Ramsharan D. Mittal Ph.D., Review Chemist
filename: C:\NDA\20757\20757.002

6/20/97

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

K-15 on original

FEB 7 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCT
Review of Chemistry, Manufacturing, and Control

NDA #: 20-757 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 07-FEB-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	26-SEP-96	27-SEP-96	30-SEP-96
AMENDMENT [BZ]	27-SEP-96	30-SEP-96	02-OCT-96
[NC]	14-OCT-96	15-OCT-96	25-NOV-96
[BC]	26-NOV-96	29-NOV-96	03-DEC-96
[BC]	20-DEC-96	23-DEC-96	23-DEC-96
[NC]	02-JAN-97	06-JAN-97	06-JAN-97

NAME & ADDRESS OF SPONSOR

Sanofi Winthorp, Inc.
90 Park Avenue
New York, NY 10016

USER FEE BILLING, NAME, ADDRESS AND CONTACT

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

DRUG PRODUCT NAME

Established Name:	Irbesartan
Proprietary:	AVAPRO (proposed)
Nonproprietary/USAN:	Irbesartan
Code Name/#:	SR 47,436, BMS-186295, BMS-186295-01
Chem.Type/Ther.Class:	1/8

AND Suitability Petition/DESI/Patent Status:

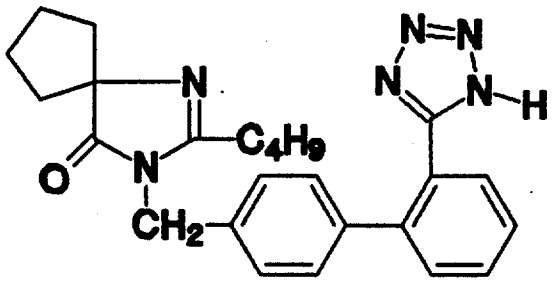
The U.S. Patent 5,270,317 held by Elf Sanofi was issued for Irbesartan and is due to expire on March 2011.

PHARMACOL.CATEGORY/INDICATION: Angiotensin II Receptor Antagonist/ Hypertension
DOSAGE FORM: TABLETS
STRENGTH 75 mg, 150 mg and 300 mg.
ROUTE OF ADMINISTRATION: ORAL
DISPENSED: Rx

CHEMICAL NAME 2-Butyl-3-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,3-diazaspiro[4.4]non-1-en-4-one.

CAS # 138402-11-6 **MOLECULAR FORMULA** $C_{25}H_{28}N_6O$ **MOLECULAR WEIGHT** 428.5

STRUCTURAL FORMULA



SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable): NDA 20-758 Irbesartan/Hydrochlorothiazide

CONSULTS: None at present.

REMARKS/COMMENTS:

Irbesartan tablets are not marketed in any country at this time.

September 27, 1996 amendment included electronic submission, which contains information of the studies performed for the clinical trials, SAS data sets, etc.

October 14, 1996 amendment notified the Agency of a proposed trade name, APROVEL for irbesartan tablets. Name was rejected.

November 26, 1996 amendment included EA for Irbesartan tablets.

December 20, 1996 amendment included additional manufacturing facility for the bulk drug substance.

January 2, 1997 amendment proposed a list of four trade names for irbesartan tablets instead of APROVEL. Names sent to the L & N committee.

The review of the DMF # is under progress.

CONCLUSIONS & RECOMMENDATIONS:

The manufacturing and controls information provided in this notice is deficient in some areas, the deficiencies are not very serious

The applicant requested an expiration date of 2 years. Since we do not have any data on the NDS or drug product manufacturer with NDS from the new facility, a date can not be set.

cc:
HFD-110/Division File
HFD-110/Ram Mittal/date
HFD-110/CSO
HFD-810/C. Hoiberg
R/D Init by: RWolters/

RD Mittal

Ramsharan D. Mittal Ph.D., Review Chemist
filename: C:\NDA\20757\20757.001

RWolters 1/7/97

AUG 15 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-758 **CHEM.REVIEW #:** 5 **REVIEW DATE:** 15-Aug-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	26-Sep-96	27-Sep-96	30-Sep-96
AMENDMENT [BC]	31-Jul-97	01-Aug-97	05-Aug-97
[BC]	08-Aug-97	11-Aug-97	14-Aug-97

NAME & ADDRESS OF APPLICANT:

Sanofi Winthrop, Inc.
90 Park Avenue
New York, NY 10016

Agent:

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

Douglas B. Hay, Ph.D., Director

LofA from Sanofi Winthrop dated August 30, 1996 is included.

DRUG PRODUCT NAME

Proprietary: Not yet determined Tablets
Nonproprietary/USAN: Irbesartan/Hydrochlorothiazide
Code Name/#: SR 47436 (Irbesartan, Sanofi)
BMS-186295 (Irbesartan. BMS)
BMS-186295-01 (Irbesartan, BMS)
CAS: 138402-11-6 (irbesartan)
CAS: 58-93-5 (Hydrochlorothiazide)

Chem.Type/Ther.Class: 4 S

ANDA Suitability Petition/DESI/Patent Status:

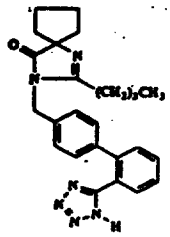
Patent Information for Irbesartan: The U.S. Patent 5,270,317 held by Elf Sanofi was issued for Irbesartan and is due to expire on March 20, 2011.

PHARMACOL.CATEGORY/INDICATION: Treatment of hypertension. Irbesartan is a specific, insurmountable, long-acting antagonist of the angiotensin II (AII) receptor with high selectivity for the AT_1 subtype.

DOSAGE FORM: Tablets
STRENGTHS: 75/12.5 mg and 150/12.5 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: ___X___ Rx _____ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Irbesartan



DMFs except for DMF referenced on previous reviews. DMF will be reviewed by Ram Mittal.

RELATED DOCUMENTS (if applicable):

CONSULTS: None.

REMARKS/COMMENTS:

Irbesartan and irbesartan/hydrochlorothiazide are not marketed in any country at this time.

EER requested on 10/1/96. Updated (added) on 12/30/96.

July 31, 1997 amendment - response to EA items, review not completed.

August 8, 1997 amendment - response regarding the ranges of excipients in the drug product.

CONCLUSIONS & RECOMMENDATIONS:

Except for trade name, the responses to deficiencies were satisfactory. EER acceptable 8/14/97.

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig. NDA 20-758
HFD-110/Division File
HFD-110/CunninghamD/8/15/97
HFD-100/CSO
HFD-810/Hoiberg
District

R/D Init by: SUPERVISOR

Danute G. Cunningham, Review Chemist
filename: 20758R05.NDA

8/15/97

APPEARS THIS WAY
ON ORIGINAL

JUN 20 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-758 **CHEM.REVIEW #:** 4 **REVIEW DATE:** 18-Jun-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	26-Sep-96	27-Sep-96	30-Sep-96
AMENDMENT [BC]	27-May-97	28-May-97	30-May-97

NAME & ADDRESS OF APPLICANT:

Sanofi Winthrop, Inc.
90 Park Avenue
New York, NY 10016

Agent:

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

Douglas B. Hay, Ph.D., Director

LofA from Sanofi Winthrop dated August 30, 1996 is included.

DRUG PRODUCT NAME

Proprietary: Not yet determined Tablets
Nonproprietary/USAN: Irbesartan/Hydrochlorothiazide
Code Name/#: SR 47436 (Irbesartan, Sanofi)
BMS-186295 (Irbesartan. BMS)
BMS-186295-01 (Irbesartan, BMS)
CAS: 138402-11-6 (irbesartan)
CAS: 58-93-5 (Hydrochlorothiazide)

Chem.Type/Ther.Class: 4 S

ANDA Suitability Petition/DESI/Patent Status:

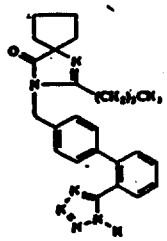
Patent Information for Irbesartan: The U.S. Patent 5,270,317 held by Elf Sanofi was issued for Irbesartan and is due to expire on March 20, 2011.

PHARMACOL.CATEGORY/INDICATION: Treatment of hypertension. Irbesartan is a specific, insurmountable, long-acting antagonist of the angiotensin II (AII) receptor with high selectivity for the AT_1 subtype.

DOSAGE FORM: Tablets
STRENGTHS: 75/12.5 mg and 150/12.5 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx _____ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Irbesartan



DMFs except for DMF referenced on previous reviews. DMF will be reviewed by Ram Mittal.

RELATED DOCUMENTS (if applicable):

CONSULTS: None.

REMARKS/COMMENTS:

Irbesartan and irbesartan/hydrochlorothiazide are not marketed in any country at this time.

EER requested on 10/1/96. Updated (added) on 12/30/96.

May 27, 1997 amendment - updated stability data included.

CONCLUSIONS & RECOMMENDATIONS:

Except for trade name, the responses to deficiencies were satisfactory.

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig. NDA 20-758
HFD-110/Division File
HFD-110/CunninghamD/
HFD-100/CSO
HFD-810/Hoiberg
District

R/D Init by: SUPERVISOR

Danute G. Cunningham, Review Chemist
filename: 20758R04.NDA

6/20/97

APPEARS THIS WAY
ON ORIGINAL

MAY 22 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-758 **CHEM.REVIEW #:** 3 **REVIEW DATE:** 21-May-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	26-Sep-96	27-Sep-96	30-Sep-96
AMENDMENT	15-May-97	16-May-97	20-May-97

NAME & ADDRESS OF APPLICANT:

Sanofi Winthrop, Inc.
90 Park Avenue
New York, NY 10016

Agent:

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

Douglas B. Hay, Ph.D., Director

LofA from Sanofi Winthrop dated August 30, 1996 is included.

DRUG PRODUCT NAME

Proprietary: Not yet determined Tablets
Nonproprietary/USAN: Irbesartan/Hydrochlorothiazide
Code Name/#: SR 47436 (Irbesartan, Sanofi)
BMS-186295 (Irbesartan. BMS)
BMS-186295-01 (Irbesartan, BMS)
CAS: 138402-11-6 (irbesartan)
CAS: 58-93-5 (Hydrochlorothiazide)

Chem.Type/Ther.Class: 4 S

ANDA Suitability Petition/DESI/Patent Status:

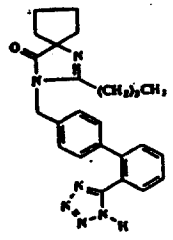
Patent Information for Irbesartan: The U.S. Patent 5,270,317 held by Elf Sanofi was issued for Irbesartan and is due to expire on March 20, 2011.

PHARMACOL.CATEGORY/INDICATION: Treatment of hypertension. Irbesartan is a specific, insurmountable, long-acting antagonist of the angiotensin II (AII) receptor with high selectivity for the AT_1 subtype.

DOSAGE FORM: Tablets
STRENGTHS: 75/12.5 mg and 150/12.5 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: ___X___ Rx _____ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Irbesartan



DMFs except for DMF . referenced on previous reviews. DMF will be reviewed by Ram Mittal.

RELATED DOCUMENTS (if applicable):

CONSULTS: None.

REMARKS/COMMENTS:

Irbesartan and irbesartan/hydrochlorothiazide are not marketed in any country at this time.

EER requested on 10/1/96. Updated (added) on 12/30/96.

May 15, 1997 amendment - response to deficiency letter.

CONCLUSIONS & RECOMMENDATIONS:

Except for trade name, the responses to deficiencies were satisfactory.

cc:
Orig. NDA 20-758
HFD-110/Division File
HFD-110/CunninghamD/5/21/97
HFD-100/CSO
HFD-810/Hoiberg
District

R/D Init by: SUPERVISOR

Danute G. Cunningham, Review Chemist
filename: 20758R03.NDA

5/22/97

APPEARS THIS WAY
ON ORIGINAL

MAY 6 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-758 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 05-May-97

SUBMISSION TYPE		DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL		26-Sep-96	27-Sep-96	30-Sep-96
AMENDMENT	[BL]	23-Apr-97	24-Apr-97	01-Apr-97

NAME & ADDRESS OF APPLICANT:

Sanofi Winthrop, Inc.
90 Park Avenue
New York, NY 10016

Agent:

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

Douglas B. Hay, Ph.D., Director

LofA from Sanofi Winthrop dated August 30, 1996 is included.

DRUG PRODUCT NAME

Proprietary: Not yet determined Tablets
Nonproprietary/USAN: Irbesartan/Hydrochlorothiazide
Code Name/#: SR 47436 (Irbesartan, Sanofi)
BMS-186295 (Irbesartan. BMS)
BMS-186295-01 (Irbesartan, BMS)
CAS: 138402-11-6 (irbesartan)
CAS: 58-93-5 (Hydrochlorothiazide)
Other names:

Chem.Type/Ther.Class: 4 S

ANDA Suitability Petition/DESI/Patent Status:

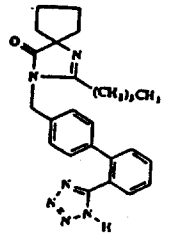
Patent Information for Irbesartan: The U.S. Patent 5,270,317 held by Elf Sanofi was issued for Irbesartan and is due to expire on March 20, 2011.

PHARMACOL.CATEGORY/INDICATION: Treatment of hypertension. Irbesartan is a specific, insurmountable, long-acting antagonist of the angiotensin II (AII) receptor with high selectivity for the AT_1 subtype.

DOSAGE FORM: Tablets
STRENGTHS: 75/12.5 mg and 150/12.5 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: ___X___ Rx _____ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Irbesartan



DMFs except for DMF referenced on previous reviews. DMF will be reviewed by Ram Mittal.

RELATED DOCUMENTS (if applicable):

CONSULTS: None.

REMARKS/COMMENTS:

Irbesartan and irbesartan/hydrochlorothiazide are not marketed in any country at this time.

April 23, 1997 amendment - proposed labeling insert.

CONCLUSIONS & RECOMMENDATIONS:

Once a trade name is established, proposed insert is satisfactory for DESCRIPTION and HOW SUPPLIED sections.

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig. NDA 20-758
HFD-110/Division File
HFD-110/CunninghamD/5/5/97
HFD-100/CSO
HFD-810/Hoiberg
District

R/D Init by: Team Leader

Danute G. Cunningham, Review Chemist
filename: 20758R02.NDA

5/6/97

APPEARS THIS WAY
ON ORIGINAL

Lofa

FEB 10 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-758 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 08-Jan-97
03-Feb-97

SUBMISSION TYPE		DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL		26-Sep-96	27-Sep-96	30-Sep-96
AMENDMENT	[BZ]	27-Sep-96	30-Sep-96	02-Oct-96
	[NC]	22-Nov-96	25-Nov-96	25-Nov-96
	[BC]	26-Nov-96	29-Nov-96	03-Dec-96
	[BC]	20-Dec-96	23-Dec-96	30-Dec-96

NAME & ADDRESS OF APPLICANT:

Sanofi Winthrop, Inc.
90 Park Avenue
New York, NY 10016

Agent:

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

Douglas B. Hay, Ph.D., Director

LofA from Sanofi Winthrop dated August 30, 1996 is included.

DRUG PRODUCT NAME

Proprietary: Not yet determined Tablets
Nonproprietary/USAN: Irbesartan/Hydrochlorothiazide
Code Name/#: SR 47436 (Irbesartan, Sanofi)
BMS-186295 (Irbesartan. BMS)
BMS-186295-01 (Irbesartan, BMS)
CAS: 138402-11-6 (irbesartan)
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Chem.Type/Ther.Class: 4 S

ANDA Suitability Petition/DESI/Patent Status:

Patent Information for Irbesartan: The U.S. Patent 5,270,317 held by Elf Sanofi was issued for Irbesartan and is due to expire on March 20, 2011.

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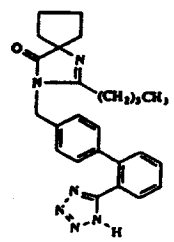
DOSAGE FORM: Tablets
STRENGTHS: 75/12.5 mg and 150/12.5 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: ___X___ Rx _____ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Irbesartan



DMFs except for DMF referenced on previous reviews. DMF will be reviewed by Ram Mittal.

RELATED DOCUMENTS (if applicable):

CONSULTS: None.

REMARKS/COMMENTS:

Irbesartan and irbesartan/hydrochlorothiazide are not marketed in any country at this time.

September 27, 1996 amendment included electronic submission, which contains information of the studies performed for the clinical trials, SAS data sets, etc.

November 22, 1996 amendment notified the Agency that the pharmacological activity of irbesartan is now being incorporated into the recalculation of the Expected Introduction Concentration (EIC). Revised EA will be submitted.

November 26, 1996 amendment included EA for Irbesartan/Hydrochlorothiazide Tablets in full.

December 20, 1996 amendment notified the Agency that will be added as a manufacturer of irbesartan. will manufacture the irbesartan in the drug substance utilizint the exact process as outline by Sanofi Chimie

CONCLUSIONS & RECOMMENDATIONS:

It is well written NDA, Minor deficiencies are found. Defficiency letter will be written.

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig. NDA 20-758
HFD-110/Division File
HFD-110/CunninghamD/1/8/97
HF[redacted]
HFD-810/Hoiberg
District

R/D Init by: SUPERVISOR

Danute G. Cunningham, Review Chemist
filename: 20758R01.NDA

2/7/97

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20757 AND 20758

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

AUG 21 1997

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Avapro™
(Irbesartan)
Tablet
20-757

Sanofi Pharmaceuticals, Inc.

U. S. FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Cardio-Renal Drug Products
(HFD-110)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-757

Avapro™

(Irbesartan)

Tablet

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that it will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Avapro™, Sanofi Pharmaceuticals, Inc., has prepared an environmental assessment (attached) in accordance with *21 CFR 25.31a(a)*, which evaluates the potential environmental impact of the manufacture, use and disposal of the product. The maximum expected environmental concentration is at a level that normally relieves the applicant from completing format items 7, 8, 9, 10, 11, and 15 in accordance with the Tier 0 approach specified in the *Guidance for Industry for the submission of an Environmental Assessment in Human Drug Applications and Supplements.*

Irbesartan is a chemically synthesized drug which is administered as a tablet in the treatment of hypertension. The drug substance will be manufactured by Sanofi Chimie, Aramon, France and a contract manufacturer. The drug product will be manufactured by Bristol-Myers Squibb, U.S. Pharmaceutical Group, Evansville, Indiana. The finished drug product will be used in hospitals, clinics and by patients in their homes.

Irbesartan may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of at a

licensed landfill. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

August 19, 1997
Date

PREPARED BY
Carl J. Berninger, Ph.D.
Environmental Scientist
Environmental Assessment Team
Center for Drug Evaluation and Research

8/21/97
Date

CONCURRED
Nancy B. Sager
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment (FOI copy)
Material Safety Data Sheet (drug substance)

Copies:

HFD-110

Kathleen Bongiovanni, PM
Original to NDA 20-757, through Kathleen Bongiovanni, PM
Division File for NDA 20-757

HFD-205

FOI Copy

HFD-357

EA File
Docket File
C. Berninger

file name: c:\fonsi\20757e01.fcb

TELEPHONE CONFERENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE:	August 21, 1997
FROM:	Carl J. Berninger, Ph.D. (HFD 110) CJB
NDA NUMBER:	20-757 and 20-758
NAME OF FIRM:	Sanofi Pharmaceuticals, Inc. (Bristol-Myers Squibb)
SUBJECT:	Correction of page numbers in Section 13, Certification
NAME OF PERSON:	Ms. Debbie McCloskey

Ms. Debbie McCloskey certified that in Irbesartan, NDA 20-757, Environmental Assessment, FOI version, the certification, Section 13 should refer to pages 004-032 rather than the given 004-037 as releasable.

In addition, she certified that in Irbesartan/Hydrochlorothiazide, NDA 20-758, Environmental Assessment, FOI version, the certification, Section 13 should refer to pages 004-037 rather than the given 004-032 as releasable.

She will follow this Telephone conversation with an official submission to the same effect as soon as possible.

ENVIRONMENTAL ASSESSMENT (FOI)

AMENDED

Irbesartan Tablets NDA #20-757

ENVIRONMENTAL ASSESSMENT
Irbesartan Tablets NDA #20-757

TABLE OF CONTENTS

ENVIRONMENTAL ASSESSMENT
Irbesartan Tablets NDA #20-757

1. **DATE** July 24, 1997

2. **NAME** Sanofi Pharmaceuticals, Inc.

3. **MAILING ADDRESS** 90 Park Avenue
New York, New York 10016

4. **DESCRIPTION OF PROPOSED ACTION**

A. Requested Approval

Sanofi Pharmaceuticals, Inc. has filed a NDA pursuant to Section 505(b) of the Federal Food, Drug and Cosmetic Act for Irbesartan Tablets, 75 mg, 150 mg and 300 mg tablets. An Environmental Assessment is being submitted pursuant to 21 CFR § 25.31 a(a) for Irbesartan Tablets.

B. Need for Action

Irbesartan Tablets are indicated for the treatment of hypertension.

C. Production Locations

1. New Drug Substance

Irbesartan, the active ingredient in the final product, which is the subject of the proposed action, is manufactured by Sanofi Chimie, Route d'Avignon, 30390 Aramon, France, DMF number 10,310 and Contract Manufacturer #1 (refer to the Confidential Appendix B7 for the name, locations and DMF number).

A detailed presentation of the synthesis and in-process controls of irbesartan is given in Sanofi Chimie's type II DMF. Only the manufacturing process from the final intermediate to irbesartan was summarized in NDA 20-757. The proprietary intermediates listed in the NDA are manufactured at Sanofi Chimie, Aramon, France and Contract Manufacturer #1. Refer to the Confidential Appendix B6 for the manufacturing scheme from the final intermediate to the drug substance, irbesartan. The information included in the Confidential Appendix B6 is taken directly from NDA 20-757.

The plant of Sanofi Chimie, Aramon, France is located about 2 miles (3 kilometers) north of Aramon, a town of about 3,000 inhabitants in the Provence region of southern France between Arles and Avignon. The facility is located on the Rhone River in a hilly area with a dry, warm climate.

The manufacturing site consists of approximately 50 acres with about 30 buildings housing manufacturing operations, quality control, warehouses, maintenance, process development laboratories and administrative and management offices. The facility is zoned industrial.

The operations at the facility include manufacturing and warehousing of bulk intermediates and fine pharmaceutical chemicals. The Prefectoral Order No. 89-006N of January 30, 1989 authorizes Sanofi Chimie Aramon to handle chemical and pharmaceutical substances in the Aramon facility where Irbesartan will be manufactured.

Waste management, minimization and spill prevention programs, policies and procedures have been instituted to ensure proper compliance with all site regulations. A waste water treatment facility receives all waste water from the plant. After treatment, the water is discharged to the Rhone River in accordance with established permit limitations.

2. New Drug Product

Irbesartan Tablets, the market presentation, will be formulated and packaged at the Bristol-Myers Squibb, U.S. Pharmaceutical Group; 2400 W. Lloyd Expressway, Evansville, Indiana, 47721.

The Evansville plant is located on a 60-acre site adjacent to the Ohio River, within the city of Evansville in Vanderburgh County. The immediate neighborhood includes a school and residential areas, as well as other industrial and commercial businesses. The upper soil is silty clay.

There are no known rare or endangered species inhabiting the area surrounding the facility; there are also no nature preserves or protected areas nearby. The site is within the 100-year flood plain of the Ohio River.

D. **Locations of Use**

Irbesartan Tablets, will be used worldwide for the treatment of hypertension. Irbesartan Tablets will be used by trained professionals in hospitals and clinics, as well as patients in their homes. It is anticipated that its distribution will be primarily to well-developed countries, particularly in the United States, Canada, and Europe.

E. **Disposal Sites**

1. -- New Drug Substance

Rejected new drug substance received in Evansville, Indiana will be disposed of as non-hazardous solid waste at an approved and permitted landfill in accordance with all federal, state and local regulations. Refer to the Confidential Appendix B2 for information on the approved landfill.

2. Drug Product

The Bristol-Myers Squibb (BMS), Distribution Center located in Mt. Vernon, Indiana, is the designated pharmaceutical finished product goods processing center for other BMS distribution centers located in the United States and its territories. North America Technical Operations Logistics has contracted with a third party processor of returned goods, The Ballantine Group, Franklin, NJ, to process the returns of finished pharmaceuticals from direct and indirect customers. Finished product that is expired, damaged, unwanted or unsalable is returned to the Mt. Vernon facility from other BMS Distribution Centers, or The Ballantine Group from customers where it is checked and inventoried pending QC disposition. In accordance with Company approved standard operating procedure, returned goods may be placed back into inventory subject to certain conditions, sent back to a processing site for further evaluation, or directed for disposal. All returns awaiting final disposition are held in a security zone within the facility in quarantine status.

Irbesartan Tablets slated for disposal are segregated at the facility as a non-hazardous off-specification pharmaceutical. Non-hazardous off-specification pharmaceuticals are packed by facility personnel and loaded for transport to a Company approved, permitted incineration facility. Transportation is provided by an approved carrier. The shipping papers (manifests) are prepared by facility personnel and accompany the waste shipment to the disposal facility. The disposal facility acknowledges receipt by signing and returning copies of the manifest to the originating facility (Mt. Vernon facility or The Ballantine Group).

As an additional security feature, destruction events may be witnessed by a firm independent from the disposal company. A written report is produced which confirms the identity and condition of the truck seal upon arrival at the disposal facility, net weight, time required for disposal and the names and signatures of the witnessing persons (when applicable). In addition all disposal facilities confirm in writing to Logistics management, the date(s) on which the actual destruction of said materials occurred. Refer to Confidential Appendix, Section B2 for a listing of the potential disposal sites.

For Irbesartan Tablets used at U.S. hospitals, pharmacies or clinics, empty or partially empty packages will be disposed of according to in-house procedures. Empty or partially empty Irbesartan Tablets containers used in the home will typically be disposed of by a community's solid waste management system which includes landfills, incineration and recycling, although minimal quantities of unused drug may be disposed of in the sewer system.

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

A. Nomenclature

i. Established Name: Irbesartan
ii. Brand/Proprietary Name: Not Approved
iii. Chemical Names

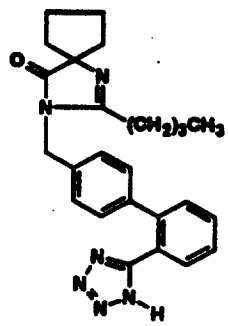
1. Chemical Abstract Name: 1,3-Diazaspiro[4.4]non-1-en-4-one,2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl methyl]-(9CI)
2. Systematic Chemical Name: 2-Butyl-3-[p-(-o-1H-tetrazol-5-ylphenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one

B. Chemical Abstract Service Number: 138402-11-6

C. Molecular Formula: $C_{25}H_{28}N_6O$

D. Molecular Weight: 428.54

E. Structure



F. Physical Description - White to off-white crystalline powder.

G. Additives

Refer to Section 6.A of this document for a listing of additives expected to be emitted into the environment during the manufacture of Irbesartan Tablets.

H. Impurities

There are no impurities in the new drug substance at levels greater than one percent (1%).

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

Irbesartan may be introduced into the environment from: 1) the manufacture of irbesartan new drug substance, 2) the manufacture of the final products, 3) the site of patient use and 4) the disposal of the drug product.

The new drug substance, irbesartan and the proprietary intermediates listed in the Confidential Appendix B6 are manufactured at a foreign facility by Sanofi Chimie and Contract Manufacturer #1. A letter certifying the following statements for the manufacturing facilities are attached in the Non-Confidential Appendix A2 for Sanofi Chimie and Confidential Appendix B7 for Contract Manufacturer #1; 1) that it is in compliance with all local and national environmental laws; 2) that it is in compliance with, or are on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and 3) that approval and the subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws.

The following is a description of the introduction of substances into the environment from the final product manufacturing site, the site of patient use, and disposal of the drug product.

A. Substances Expected to be Emitted

Refer to the Confidential Appendix B3 for substances expected to be emitted from the final product manufacturing facility.

B. Controls Exercised

1. Air Emissions

Air emissions of particulates at the Bristol-Myers Squibb Evansville site from Irbesartan Tablets processes are controlled through the use of dust-control equipment, principally wet scrubbers, that are registered by the city of Evansville Environmental Protection Agency (EPA).

2. Liquid Waste

Wastewater from the Evansville manufacturing site is discharged into a Publicly Owned Treatment Works (POTW), specifically the city of Evansville's Westside Wastewater Treatment Plant.

3. Solid Waste

Irbesartan Tablets are not listed hazardous waste as defined by 40 CFR Section 261. All non-hazardous solid waste generated from the manufacture of Irbesartan Tablets is collected in appropriate containers and disposed of at an approved and permitted landfill in accordance with all federal, state and local regulations.

4. Drug Product

Irbesartan, drug product waste may be generated as losses in manufacturing equipment, dust removed from HVAC filters and minor sources. Disposal of irbesartan material is scheduled for an approved landfill listed in the Confidential Appendix B2.

Disposal of rejected, returned, and off-specification drug product is previously described in Section 4.E.2 of this document.

C. **Citation of and Statement of Compliance with Applicable Emission Requirements**

After due inquiry and discussion with personnel charged with responsibility for such matters, applicant certifies that all necessary actions have been or will be taken so that emissions, discharges and wastes from the production of Irbesartan Tablets will be in compliance with applicable environmental, occupational health and safety standards and national, federal, state and local emission regulations and permits or with applicable consent orders and administrative orders and directives for its facility in Evansville, Indiana.

The Material Safety Data Sheet for irbesartan drug substance is included in the Non-Confidential Appendix A1.

The Evansville facility is under the jurisdiction of the city of Evansville's local Environmental Protection Agency (EPA). The city of Evansville EPA is governed by the Indiana Department of Environmental Management who is under the jurisdiction of the United States Environmental Protection Agency, Region 5.

1. Citations of Applicable Federal, State and Local Regulations

Listed below are citations of applicable Federal, State and local emission requirements and laws:

ENVIRONMENTAL ASSESSMENT
Irbesartan Tablets NDA #20-757

I. **Federal - United States**

Major environmental statutes with regulations promulgated by the United States Environmental Protection Agency that may impact pharmaceutical manufacturing include:

Air Quality: Clean Air Act of 1977 as amended 1990; 42 United States Code (U.S.C.) §§ 7401-7671q; 40 Code of Federal Regulations (C.F.R.) Parts 50-88

Waste: Resource Conservation and Recovery Act 1976 as amended by the Hazardous and Solid Waste Act Amendments 1984; 42 U.S.C. §§ 6901-6992; 40 C.F.R. Parts 240-281

Remediation: "Superfund," Comprehensive Environmental Response, Compensation and Liability Act of 1980; 42 U.S.C. §§ 9601-9675; 40 C.F.R. Parts 300-311

Water: Clean Water Act of 1972; 33 U.S.C. §§ 1251-1387; 33 C.F.R. Parts 320-330, 335-338; 40 C.F.R. Parts 104-140, 230-233, 401-477

Chemicals: Emergency Planning and Community Right-to-Know Act of 1986 (Superfund Amendments and Reauthorization Act Title III, SARA Title III) 42 U.S.C. §§ 11001-11050; 40 C.F.R. Parts 350, 355, 370, 372; Pollution Prevention Act of 1990; 42 U.S.C. §§ 13101-13209

Energy: Atomic Energy Act of 1954; 42 U.S.C. §§ 2011-2297g-2; 10 C.F.R. Parts 0-171, 760-766, 810-962; Energy Reorganization Act of 1974; 42 U.S.C. §§ 5801-5891; 10 C.F.R. Parts 88, 40.7, 50.7, 70.7, 708; Low-Level Radioactive Waste Policy Act of 1980; 42 U.S.C. §§ 10 C.F.R. Parts 61-62; Regulations implemented by the Atomic Energy Commission

Occupational Safety & Health: Occupational Safety and Health Act of 1970; 29 U.S.C. §§ 651-78; 29 C.F.R. Parts 1900-1910

ii. **State - Indiana**

Solid Waste Management Rules
329 IAC Article 2

Solid Waste Management Air Pollution Control Rules
326 IAC Article 2

Permit Review Rules
326 IAC Article 3

Monitoring Requirements Water Pollution Control Rules
327 IAC Article 5

Industrial Wastewater Pretreatment Programs (NPDES)
327 IAC 13-10-3, Sewer Use Ordinance

Indiana Occupational Safety & Health Act (IOSHA)
Title 22, Article 8, Chapter 1.1

iii. **Local - Evansville, Indiana**

Evansville Ordinance 5.53, Wastewater Discharge Regulations (local sewer ordinance).

2. Emission Permits

Listed in the following section are the emission permits and/or registrations, according to air, liquid and solid waste streams. Confidential information on permit numbers, authorizing agency and expiration dates are contained in the Confidential Appendix B4 for the manufacture of Irbesartan Tablets.

I. Air Emissions

Dust control equipment used at the BMS Evansville site for Irbesartan Tablets processes is registered by the city of Evansville EPA. An annual fee for operation is required by Evansville EPA under ID #015. The city of Evansville EPA inspects the site at least annually and is responsible for issuing the permits and registrations.

ii. Liquid Waste

The wastewater from the Evansville manufacturing site discharges into a Publicly Owned Treatment Works (POTW), specifically the city of Evansville's Westside Wastewater Treatment Plant (NPDES permit number IN0032956). The Evansville plant's industrial pretreatment permit from the city of Evansville is registered under Mead Johnson & Company.

iii. Solid Waste

The non-hazardous solid waste generated in the Irbesartan Tablets manufacture is sent to an approved and permitted landfill. Refer to the Confidential Appendix B2 for a listing of the applicable disposal site(s).

D. Discussion of the Effect of Approval on Compliance with Current Emission Requirements

The proposed action involved no new construction at the Bristol-Myers Squibb production facility in Evansville, Indiana. Hence, there was no impact on land use, water quality or other natural resources from construction activities.

The estimated fifth year production volume in the United States is listed in the Confidential Appendix B1.

Considering the estimated fifth year production volume, the manufacturing of Irbesartan Tablets should not have an adverse impact on the environment nor on compliance with current emission permits or registrations at the final product manufacturing site.

E. Expected Introduction Concentration

Irbesartan Tablets are administered to patients orally and will enter the environment primarily through the sanitary wastewater systems, at the location where the product is administered.

The estimated fifth year production volume of irbesartan drug substance for all dosage forms, estimated from projected total sales volumes of Irbesartan Tablets and the companion filing Irbesartan/Hydrochlorothiazide Tablets (NDA #20-758) in the United States, is listed in the Confidential Appendix B1.

i. Expected Introduction Concentration From Use

The expected introduction concentration is calculated using the fifth year volume for the new drug substance, irbesartan.

The Expected Introduction Concentration (EIC) entering the aquatic environment from patient use is determined as follows:

EIC-Aquatic (ppm) = A x B x C x D x E

Where

A = kg/year production
B = 1/liter per day entering POTWs*
C = year/365 days
D = 10^6 mg/kg
E = pharmacologic activity of irbesartan and its metabolites excreted in the urine and feces relative to pharmacologic activity of administered dose.**

* 1.115 X 10^{11} liters per day entering Publicly Owned Treatment Works (POTWs), source: 1992 Needs Survey, Report to Congress, September 1993, EPA 832-R-93-002.

** Refer to Confidential Appendix B1 for description of the pharmacologic activity of irbesartan and its metabolites.

EIC-Aquatic (ppm) = Refer to the Confidential Appendix B1 for the EIC value.

The EIC for irbesartan relates to the estimated concentration in waters discharged from POTWs which service domestic residences, hospitals and clinics. This concentration is expected to undergo further dilution by surface flow (average factor of 10), which would result in an Expected Environmental Concentration (EEC) an order of magnitude less than the EIC. Therefore, the Maximum Expected Environmental Concentration (MEEC) is the Expected Introduction Concentration as calculated in Confidential Appendix B1.

The MEEC (EIC) value is less than 1 part per billion and this EA qualifies for tier 0, as defined in Section III.D.7.c in the FDA CDER's guidance for industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements that was issued November 1995.

ii. Expected Introduction Concentration from Disposal

An expected introduction concentration for disposal was not calculated because as previously described in Section 4.E.2, irbesartan drug product wastes will be disposed of in approved and permitted landfills. Refer to Section 4.E.2 of this environmental assessment for further information on disposal practices.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

As determined in Section 6.E.i, this EA qualifies for tier 0 and the information for EA format items 7, 8, 9, 10, 11 and 15 are not necessary. However, Section 15 is included in this EA to report confidential information from Sections 1 - 6 and 12 - 13.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

As determined in Section 6.E.i, this EA qualifies for tier 0 and the information for EA format items 7, 8, 9, 10, 11 and 15 are not necessary. However, Section 15 is included in this EA to report confidential information from Sections 1 - 6 and 12 - 13.

ENVIRONMENTAL ASSESSMENT
Irbesartan Tablets NDA #20-757

9. USE OF RESOURCES AND ENERGY

As determined in Section 6.E.i, this EA qualifies for tier 0 and the information for EA format items 7, 8, 9, 10, 11, and 15 are not necessary. However, Section 15 is included in this EA to report confidential information from Sections 1 - 6 and 12 - 13.

10. MITIGATION MEASURES

As determined in Section 6.E.i, this EA qualifies for tier 0 and the information for EA format items 7, 8, 9, 10, 11 and 15 are not necessary. However, Section 15 is included in this EA to report confidential information from Sections 1 - 6 and 12 - 13.

11. ALTERNATIVES TO THE PROPOSED ACTION

As determined in Section 6.E.i, this EA qualifies for tier 0 and the information for EA format items 7, 8, 9, 10, 11 and 15 are not necessary. However, Section 15 is included in this EA to report confidential information from Sections 1 - 6 and 12 - 13.

12. LIST OF PREPARERS

Eileen P. Hayes, Sc.D., DABT, B.S., Pharmacy, Northeastern University; Sc.D., Toxicology, Harvard School of Public Health; post-doctoral training, Department of Pathology, Brigham & Women's Hospital/Harvard Medical School; served on the faculties of the Toxicology Programs at Northeastern University and UMDNJ - Robert Wood John Medical School/Rutgers University; Diplomate of the American Board of Toxicology, practicing professional since 1979 with experience in occupational and environmental toxicology and chemical metabolism.

James Kearney, MS, Environmental Health, University of Cincinnati; BA, Biology, University of Buffalo; Certified Industrial Hygienist; Certified Safety Professional; practicing professional since 1980 with experience in industrial hygiene, safety and environmental protection.

Beth L. Bidstrup, MHS, Industrial Hygiene and Safety, The Johns Hopkins University; BS, Industrial Hygiene and Environmental Toxicology, Clarkson University; Certified Industrial Hygienist, practicing professional since 1986 with experience in industrial hygiene, safety and product stewardship.

ENVIRONMENTAL ASSESSMENT
Irbesartan Tablets NDA #20-757

13. **CERTIFICATION**

The undersigned official certifies that the information presented is true, accurate and complete to the best of the knowledge of Sanofi Pharmaceuticals, Inc. and Bristol-Myers Squibb Company.

The undersigned officials certifies that the environmental assessment summary document (pages 004 - 037) contains non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR §1506.6.

SEE TELECON 8/21/97 CSB

Signature L Powles Date 11/08/1997

Sanofi Pharmaceuticals, Inc.

Signature Robert Simon Date 14/8/97

Robert Simon, Executive Director
Worldwide Regulatory Affairs
Bristol-Myers Squibb Company

ENVIRONMENTAL ASSESSMENT
Irbesartan Tablets NDA #20-757

14. REFERENCES

1. Guidance for Industry "For the Submission of an Environmental Assessment in Human Drug Applications and Supplements," Food and Drug Administration Center for Drug Evaluation and Research (CDER), November 1995, CMC 6, pages 1-E1.

2. "Disposition and Bioavailability of Irbesartan in Healthy Male Subjects after Intravenous and Oral Administration of [^{14}C]Irbesartan in Solution, and Oral Administration of Irbesartan Capsule," N.N. Vachharajani, Report Accession Number 910054507, February 12, 1996.

3. "Investigator Brochure - Irbesartan and Irbesartan/Hydrochlorothiazide," Bristol-Myers Squibb Pharmaceutical Research Institute, September 28, 1995.

*4. "Biotransformation of [^{14}C]BMS 186295 in Human Subjects," T. J. Chando, Report Accession Number 910054075, March 12, 1996.

5. "Mass-Balance and Absolute Bioavailability of Irbesartan in Healthy Male Subjects After 50 mg Intravenous and 150 mg Oral Administration of [14C] Irbesartan Solution," N.N. Vachharajani, Report Accession Number 910056233, April 17, 1996.

6. "Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA." Pharmaceutical Manufacturers Association, version 7, July 1991.

7. "Technical Assistant Document," FDA Environmental Assessment Technical Assistance Handbook NTIS PB 87-175345-, March, 1987.

8. National Environmental Policy Act (NEPA), 42 USC 4332, (1969) 83 Stat. 853.

9. FDA Final Rule for Compliance with National Policy Act: Policy and Procedure, Federal Register 50 FR 16636, 21 CFR 25, April 16, 1985.

*10. "Inhibitory Effects of SR 47436 Metabolites of [125I] AII Binding to Human Aortic Smooth Muscle Membranes," J.C. Breliere and J. Gougat, Report Number RS0038960806/01, August 6, 1996.

**11. M.B. Cohen, "Recovery in Radiolabel Studies", I.O.M. to D.W. Everett, May 3, 1995.

* Reports are from other sections of the NDA #20-757 and are included in the Confidential Appendix B5 as supplementary reference documents for the discussion of the pharmacologic activity of Irbesartan and its metabolites.

** Report was not included in NDA 20-757 but is included in Confidential Appendix B5.

ENVIRONMENTAL ASSESSMENT
Irbesartan Tablets NDA #20-757

15. APPENDICES

Appendices Index

A. Non-Confidential

1. Material Safety Data Sheet (MSDS) for Irbesartan
2. Environment Certification Statement - Sanofi Chimie, Aramon, France

B. Confidential

1. Manufacturing 5th Year Volume and Expected Introduction Concentration
2. Disposal Facilities
3. Substances Expected to be Emitted
4. Facility Permit and/or Registration Information
5. Reference Documents Supporting the Pharmacologic Activity of Irbesartan and Its Metabolites
6. Synthesis Scheme for the Manufacture of Irbesartan from the Final Intermediate
7. Contract Manufacturer #1 and Environmental Certification Statement

NON-CONFIDENTIAL APPENDIX

SECTION A1

Material Safety Data Sheet (MSDS) for Irbesartan

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

BRISTOL-MYERS SQUIBB
PHARMACEUTICAL GROUP
P.O. BOX 191
NEW BRUNSWICK, NJ 08903
908-519-3843.

Product Identification: Irbesartan.

Chemical Name: 2-n-Butyl-3-((2'-(1H-tetrazol-5-yl) biphenyl-4-yl)methyl)-1,3-diazaspiro(4,4)non-1-en-4-one.
Synonym: SR 47436, BMS 186295-01
How Supplied: Bulk dry powder in fiber drums.
Product Use: Treatment of hypertension.
Chemical Family: Tetrazole, diazaspironone.

Molecular Formula: $C_{25}H_{29}N_5O$ ***CAS #***: 138402-11-6

EMERGENCY CONTACTS

Health: 908-519-3843 (Monday through Friday, daytime) at other times contact Chemtrec or the local poison control center.

Transportation: CHEMTREC (800)424-9300.

EMERGENCY OVERVIEW: Irbesartan is an antihypertensive agent (lowers blood pressure). Material has low minimum ignition energy. Control static discharges to prevent ignition. Very strong explosion pressure. See Health Effects section for additional information.

2. COMPOSITION/ INFORMATION ON INGREDIENTS

COMPONENTS	HAZARDOUS (Y/N)	CONCENTRATION (WT %)	CAS NUMBER	EXPOSURE GUIDELINE
Irbesartan	Y	100	138402-11-6	0.03 mg/cu. m. BMS-EG[1]

[1] BMS-EG- Bristol-Myers Squibb Pharmaceutical Group Exposure Guideline (TWA 8-10 hour).

3. HEALTH HAZARDS IDENTIFICATION

EFFECTS OF OVEREXPOSURE

Routes of Entry:

1. ***Inhalation:*** If material becomes airborne there is potential for inhalation. The extent of systemic absorption of the material after inhalation is not known.

2. ***Skin contact***: Exposure may occur via skin contact if gloves and protective clothing are not worn. The extent of systemic absorption of the material after skin contact is not known.

3. ***Ingestion:*** Ingestion of large quantities of this material in an occupational setting would not be expected to occur. Ingestion of trace amounts of the material might occur if material contacts the hands and hands are not washed prior to eating drinking or smoking. Irbesartan is well absorbed after ingestion.

Acute

Ingestion: Inadvertent ingestion of trace amounts of this material would not be expected to result in symptoms. Therapeutic doses can lower blood pressure in persons with high blood pressure. Ingestion of therapeutic doses by persons with normal blood pressure has occasionally resulted in a sudden fall in blood pressure when changing from a reclining to a standing position. Nausea, vomiting and headache have been reported in a few patients receiving therapeutic doses of this drug.

Inhalation: There is no information concerning the potential for this material to produce symptoms after inhalation. Most dusts may cause mechanical irritation (sneezing, tearing of the eyes) after high exposure. Systemic toxicity may be possible.

Skin Contact

a. ***Toxic***: There is no information concerning the potential for this material to produce symptoms after inhalation.
b. ***Irritation***: Irbesartan is not a skin irritant.
c. ***Sensitization***: The sensitization potential has not been evaluated.

Eye Contact: Material is not an eye irritant.

Chronic: Drug is an angiotensin II receptor antagonist. In persons with normal blood pressure, repeated exposure (50-100 mg/day) may result in a sudden fall in blood pressure when changing from the reclining to a standing position. In persons with high blood pressure, headaches have occasionally been reported after therapeutic doses.

Exposure Guideline Summary:

Carcinogen Lists ***IARC***: No. ***NTP***: No. ***OSHA***: No.

Target Organs: Specific target organs for toxicity have not been identified. Compound exerts pharmacological effects on the cardiovascular system.

Medical Conditions Aggravated by Exposure:

Medical Surveillance Recommendation: If exposure exceeds the exposure guideline, personnel should be monitored for orthostatic hypotension, complete blood count, and liver function tests.

FOR MORE INFORMATION REFER TO SECTION 11: TOXICOLOGICAL INFORMATION.

4. FIRST AID MEASURES

Ingestion: Get medical attention immediately. Vomiting may be induced if a person is conscious and not experiencing convulsions. Never give anything by mouth to an unconscious person.

Inhalation: Remove exposed person to fresh air. If person is not breathing give artificial respiration. If breathing is difficult administer oxygen. Get medical attention.

Skin Contact: Remove contaminated clothing. Wash thoroughly with soap and water. If signs of irritation (redness, swelling, itching, etc.) develop or persist, seek medical attention.

Eye Contact: Hold eyelids apart and flush with plenty of water for 15 minutes. Get medical attention immediately.

Note to physicians: Irbesartan is an angiotensin II antagonist and lowers blood pressure at therapeutic doses.

5. FIRE FIGHTING MEASURES

Flash point: Not applicable.
Autoignition Temperature: 510 degrees C for a dispersed dust cloud.
Flammability limits
LEL: Not applicable.
UEL: Not applicable.

Combustibility of Dusts: Easily ignitable in presence of electrostatic or electric spark. Provide appropriate bonding and grounding protection to control static charges. Powder handling equipment such as dust collectors, dryers, and mills may require additional protective measures, i.e., explosion venting.

Extinguishing Media: In case of fire use water, carbon dioxide, foam, or dry chemical.

Firefighting Instructions: *Firefighters should wear* self-contained breathing apparatus (SCBA), flame and chemical resistant clothing, boots and gloves. Evacuate personnel to upwind direction, remove unneeded material and cool container(s) with water from maximum distance.

Hazardous Combustion Products: CO, CO_2, NO_x.

Unusual Hazards: Avoid sparks, heat and/or open flame.

6. ACCIDENTAL RELEASE MEASURES

Spill/Clean-up: Wearing suitable protective clothing, vacuum powder using a HEPA (high efficiency particulate air) filtered vacuum, or moisten and pick-up so as to minimize dust generation. Place into a suitable container for disposal. The spill area should be cleaned thoroughly with detergent and water and ventilated after material has been picked up. A laboratory coat or gown, impermeable gloves (latex or nitrile), a respirator with HEPA filters or cartridges and eye protection should be worn as a minimum precaution. Additional protective clothing/equipment may be needed depending on the quantity spilled and the extent of the spill.
SEE SECTION 8 FOR SPECIFICS OF PERSONAL PROTECTIVE CLOTHING

AND EQUIPMENT.

7. HANDLING AND STORAGE

Handling Precautions: Avoid static electricity build-up prior to and while handling irbesartan. Do not spill contents. Minimize dust generation.

Container Requirements: Stored as bulk drug using conducting drums and/or anti-static liners.

Storage Conditions: Store irbesartan in a dry place at or below room temperature in a tightly closed container. Protect from moisture.

8. EXPOSURE CONTROLS AND PERSONAL PROTECTION

Ventilation Requirements: Keep airborne concentrations below exposure guideline of 0.03 mg/m3 for irbesartan by enclosure of processes or local exhaust ventilation, as required.

Respiratory Protection: It is advisable to consult an industrial hygienist when selecting a respirator, especially when larger quantities are to be handled or if material is to be handled together with solvents or other compounds. For powder handling, when engineering controls are not sufficient to control exposure, wear an approved* respirator with HEPA filters or cartridges, or supplied air. A self-contained breathing apparatus should be available for emergency use.

*NIOSH approves respiratory protection in the U.S.

Eye Protection: Wear safety glasses (ANSI Z87.1).

Protective Gloves: Wear impervious (latex or nitrile) gloves if the potential exists for dermal contact.

Special Clothing: Wear laboratory coat or protective coveralls, whenever the potential for contact with the powder exists.

Hygiene: Wash hands after handling compound and before eating, smoking, using lavatory, and at end of day.

9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance/Physical State/Color: Practically white crystalline powder.
Boiling point: Not applicable.
Evaporation rate: Not applicable.
Flash point: Not applicable.
Freezing point/Melting point (degrees C): 185 degrees C; decomposition with gas evolution.
Octanol/water partition coefficient: Log Kow = 2.85 at pH 5; Log Kow = 1.13 at pH 7; Log Kow < 1 at pH 9.
Odor (threshold): Not available.
pH: Not available.
Solubility in water: Practically insoluble; 3.34 mcg/ml at pH 5; 302 mcg/ml at pH 7; 758 mcg/ml at pH 9.
Specific gravity: 1.30.
Vapor density (Air = 1): If adequate temperatures caused material to volatilize, its vapor density would be greater than 1 (heavier than air).
Vapor Pressure: less than 1 E -07 torr at 25 degrees C.
Viscosity: Solid material.
Dissociation Constant: pKa is 4.79 at 25 degrees C.

10. STABILITY AND REACTIVITY

Stability: Stable at room temperature. When material is heated as a bulk powder or as an aerated powder, an exotherm did not develop.

Incompatibilities: Avoid strong oxidizing agents.

Conditions of Reactivity: None identified under normal conditions of storage and handling.

Hazardous Decomposition Products: CO, CO2, NOx.

Hazardous Polymerization: Will not occur.

Explosion data relative to mechanical impact: No specific data.

Explosion data relative to static discharge:

Explosion Severity Factor (Kst): 383 bar-m/s
Explosion Class: ST-3, very strong explosion pressure.

Minimum Ignition Energy: < 3 mJ
Powder Resistivity: > 10 exponent 14 ohm.m
Charge Decay Time: 35 Hours (estimated).
Limiting oxygen concentration: 9.8-11.5%

Material exhibits very strong explosion characteristics if ignited as a dust cloud. Material is highly susceptible to accumulating static charges during processing and uncontrolled static discharge may result in igniting a dust cloud under certain conditions due to the low minimum ignition energy. Provide suitable bonding and grounding for containers and process equipment to control static charges. Powder handling equipment such as dust collectors, dryers, and mills may require additional protective measures (e.g. explosion venting).

11. TOXICOLOGICAL INFORMATION

RTECS # (U.S.):

ACUTE

LD 50:
Acute oral LD50 (rat) > 2000 mg/kg;
Acute oral LD50 (mouse) >2000 mg/kg;

LC 50: Not available.

CHRONIC

Repeated Dose Studies: In monkeys or rats treated daily for six months with oral doses (90 mg/kg) of irbesartan, mild decreases in blood pressure, decreased heart weight in females and mild to moderate hypertrophy and hyperplasia of the juxtaglomerular cells of the kidney were noted. In some female rats lesions of the glandular stomach were noted. Also in rats, decreased liver weights, slight changes in red blood cell parameters, and other slight changes in clinical chemistry and electrolyte values were noted.

Carcinogenicity: This compound was not carcinogenic when evaluated in CD1 mice or Wistar rats.

Mutagenicity: In the mouse bone marrow micronucleus study, oral administration of irbesartan indicated no genotoxicity at doses up to 4000 mg/kg/day. Irbesartan was negative for mutagenicity in the Ames test, in

V79 fibroblasts and in a DNA repair assay. It was not clastogenic in primary human lymphocytes.

Teratogenicity: Teratogenic effects were not observed in pregnant rabbits at doses up to 30 mg/kg/day. Slight maternal toxicity was seen at a dose of 10 mg/kg/day with more marked maternal toxicity (some abortions and resorptions) at 30 mg/kg/day. Teratogenic effects were not observed in pregnant rats at doses up to 450 mg/kg/day although maternal toxicity was noted from doses of 50 mg/kg/day or greater.

Reproductive Effects: The compound did not alter the fertility of male and female rats at doses up to 650 mg/kg/day. Some adverse effects on the F1 fetus were seen at doses from 50 mg/kg and greater.

Toxicological synergistic products: No studies of interactions with other drugs have been conducted. It is likely that irbesartan exposure would add to the effect of other antihypertensive medications.

12. ECOLOGICAL INFORMATION

Ecotoxicological Information:

Microbial Inhibition Assay: The compound did not inhibit most organisms at concentrations up to 1000 mg/l. The minimum inhibitory concentration for Bacillus megaterium was 800 mg/l.

Daphnia magna Acute Toxicity Assay - 24 and 48 hr EC50s were 203 and 191 mg/l, respectively. 48 hr no effect concentration was 86.4 mg/l.

Chemical Fate Information: Hydrolysis and photodegradation in aqueous environments may be primary routes of depletion in the environment. The hydrolytic route is quite dependent on pH.

Hydrolysis Half-life: $\geq$ 1 year, pH 5; 40 days, pH 7; 2.3 days, pH 9;

Aerobic Aqueous Biodegradation - Compound was not readily biodegraded.

Aqueous Photodegradation Half-life: < 10 hours at pHs ranging from 5-9.

Aerobic Soil Biodegradation - This compound has half-lives ranging from 641 to 4759 days in various soils. Only a small percentage of compound was metabolized during a 64 day test period.

Soil Adsorption/Desorption - Depending on soil type the Koc values varied from 110 to 869, suggesting that mobility of the compound in the soil may depend on such factors as pH and cation exchange capacity.

13. DISPOSAL CONSIDERATIONS

Disposal: Dispose of in accordance with National, State, Local, and applicable country regulations. Incineration is recommended.

14. TRANSPORT INFORMATION

DOMESTIC

Proper shipping name: Not classified.
Hazard Class, UN Number, Packing Group: Not classified.
Label requirements: Not applicable.
Placard requirements: Not applicable.

INTERNATIONAL

Proper shipping name: Not classified.
Hazard Class, UN Number, Packing Group: Not classified.
Label requirements: Not applicable.
Placard requirements: Not applicable.

Refer to Federal and international regulations for additional information.

15. REGULATORY/STATUTORY INFORMATION

U.S. Federal: Based on criteria of the OSHA Hazard Communication Standard, the hazards of this material include: effects on cardiovascular system.

International: See EC Labeling below.

EC Labeling: The following are risk and safety advice phrases for Irbesartan:

S33- Take precautionary measures against static discharges.

S36/37- Wear suitable protective clothing and gloves.
S38- In case of insufficient ventilation wear suitable respiratory equipment.

16. OTHER INFORMATION

November 22, 1996: The MSDS for Irbesartan, dated August 9, 1996, was updated to include changes to sections 1, 2, 3, and 11 (primarily health effects and toxicology information).

8-9-96: The MSDS for Irbesartan, dated 3-3-95, was updated in Section 3 to include additional health effects information, in Sections 9, 10 and 12 to include additional physical/chemical properties, stability and fate and effects data, and in section 15 to include additional regulatory information.

3-3-95: The MSDS for Irbesartan (BMS 186295-01) was updated to include additional Fire and Explosion and Stability information, and information in Section 15.

1-4-95: The MSDS of 06-21-94 for BMS 186295-01 was updated here to include additional toxicology and fire data, as well as proposed generic name of irbesartan.

06-21-94: This is the first MSDS to be issued by the Bristol-Myers Squibb Pharmaceutical Group for this material.

This compound is a drug substance intended for use under the direction of a physician. As a general precaution, personnel who handle drug substances should avoid contact (ingestion, inhalation, skin, and eye contact) with these substances. Smoking, drinking, or eating should not be allowed in the areas where this material is used.

This material safety data sheet is intended for use by personnel who handle this material as part of their job responsibilities. It does not address the therapeutic use of this material. Information concerning the therapeutic use of this drug substance should be obtained from formulated product package inserts and other appropriate references.

The information contained in this MSDS is believed to be accurate and represents the best information available at the time of preparation. However, we make no warranty, express or implied, with respect to such information, and we assume no liability from its use. MSDS136e.

NON-CONFIDENTIAL APPENDIX

SECTION A2

Environmental Certification Statement
Sanofi Chimie, Aramon, France

USINE D'ARAMON
ROUTE D'AVIGNON
30390 ARAMON
TEL. : (33) 66 57 71 71
FAX : (33) 66 57 72 91
Telex 490 004

sanofi
CHIMIE

Aramon, July 25 1996

Bristol-Myers Squibb
Pharmaceutical Research Institute
Regulatory Affairs Department
P.O. Box 4000
Princeton, NJ 08543-4000
U.S.A.

Re: Drug Substance IRBESARTAN
Certification of Compliance
with Environmental Regulations

Dear Sirs,

Pursuant to U.S. Executive Order 12114 "Environmental Effects Abroad of Major Federal Actions", the undersigned official certifies that all irbesartan manufacturing facilities named below are in compliance with, or on an enforceable schedule to be in compliance with all local and national environmental laws and all emission requirements set forth in all permits, and that approval and the subsequent increase in production at the facilities named below is not expected to affect compliance with current emission requirements or compliance with environmental laws.

Sincerely yours,

Pierre Chastagnier

Title: Plant Manager
Facilities: Aramon Facilities
Date: July 25 1996

TABLE 3.5.4.2

TEST FOR CHROMOSOME ABERRATIONS BY *IN VITRO* HUMAN LYMPHOCYTE METAPHASE ANALYSIS; RESEARCH WITHOUT METABOLIC ACTIVATION

COMPOUND SR 47436 **SAMPLING TIME : 24 hours**

COMPOUND	DOSES µg/ml		GAPS PER CELL	BREAKS PER CELL	NUMBER OF ABNORMAL CELLS/ NUMBER OF CELLS OBSERVED	TOTAL OF NUMERICAL ABERRATIONS	TOTAL OF CELLS CARRYING STRUCTURAL ABERRATIONS	
							EXCLUDING CELLS WITH GAPS ONLY	INCLUDING CELLS WITH GAPS ONLY
SOLVENT CONTROL	0	m	0.025	0.02	No. ABNORMAL CELLS	0	4	9
		s	*0.157*	*0.14*	No. CELLS OBSERVED	200	200	200
MITOMYCIN C	0.25	m	0.15	2	No. ABNORMAL CELLS	0	79	79
		s	*0.359*	*1.781*	No. CELLS OBSERVED	100	100	100
		t	3.326	11.1	CHI 2	0	197.513	178.503
		p	<0.001	<0.001	p	N.S.	<0.001	<0.001
SR 47436	300	m	0.04	0.33	No. ABNORMAL CELLS	0	58	63
		s	*0.196*	3.046	No. CELLS OBSERVED	200	200	200
		t	0.845	6.076	CHI 2	0	53.617	49.39
		p	N.S.	<0.001	p	N.S.	<0.001	<0.001
	100	m	0.035	0.06	No. ABNORMAL CELLS	0	11	18
		s	*0.184*	*0.258*	No. CELLS OBSERVED	200	200	200
		t	0.585	1.927	CHI 2	0	2.494	3.217
		p	N.S.	N.S.	p	N.S.	N.S.	N.S.
	30	m	0.045	0.035	No. ABNORMAL CELLS	0	6	15
		s	*0.208*	*0.21*	No. CELLS OBSERVED	200	200	200
		t	1.085	0.84	CHI 2	0	0.103	1.596
		p	N.S.	N.S.	p	N.S.	N.S.	N.S.
HISTORICAL CONTROL DATA Mean of 9 studies [range]			0.032 [0.02-0.05]	0.033 [0.015-0.045]	No. ABNORMAL CELLS	0.3 [0-1]	6.2 [3-8]	10.2 [4-15]

m = mean ; s = standard deviation ; t = Student's t ; N.S. = not statistically significant at the threshold of $p<0.05$

Cultures treated with SR 47436, in the presence of S-9 mix, showed no increase in the frequency of aberrant cells at the 24 hour sampling time. However, at the 48 hour sampling time, a statistically significant ($p < 0.05$) increase in breaks per cell was observed at high (300 µg/ml) and low (30 µg/ml) concentrations. The intermediate concentration (100 µg/ml) induced no variation (Table 3.5.4.3). According to the sponsor, the variation observed has no biological relevance since the frequency of breaks observed at 300 µg/ml was only slightly beyond the accepted range and no increase in the number of aberrant cells was seen. Further, the slight increase in aberrant cells noted at the low concentration (30 µg/ml) was in one culture only and was not observed at the next higher concentration, 100 µg/ml. Thus, the sponsor concludes that at the highest (toxic) concentration (300 µg/ml), the response of SR 47436 in cultured human lymphocytes was equivocal in the absence of metabolic activation. At non-toxic concentrations, no clastogenic activity was observed with or without metabolic activation. A second study (section 3.5.5) was initiated by the sponsor to confirm these findings.

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TABLE 3.5.4.3

TEST FOR CHROMOSOME ABERRATIONS BY *IN VITRO* HUMAN LYMPHOCYTE METAPHASE ANALYSIS; RESEARCH WITH METABOLIC ACTIVATION

COMPOUND **SR 47436**

SAMPLING TIME : 48 hours

COMPOUND	DOSES µg/ml		GAPS PER CELL	BREAKS PER CELL	NUMBER OF ABNORMAL CELLS/ NUMBER OF CELLS OBSERVED	TOTAL OF NUMERICAL ABERRATIONS	TOTAL OF CELLS CARRYING STRUCTURAL ABERRATIONS	
							EXCLUDING CELLS WITH GAPS ONLY	INCLUDING CELLS WITH GAPS ONLY
SOLVENT CONTROL	0	m	0.045	0.01	No. ABNORMAL CELLS	0	2	10
		s	*0.231*	*0.1*	No. CELLS OBSERVED	200	200	200
SR 47436	300	m	0.035	0.055	No. ABNORMAL CELLS	0	9	14
		s	*0.184*	*0.269*	No. CELLS OBSERVED	200	200	200
		t	0.479	2.218	CHI 2	0	3.365	0.709
		p	N.S.	<0.05	p	N.S.	N.S.	N.S.
	100	m	0.025	0.03	No. ABNORMAL CELLS	0	6	11
		s	*0.157*	*0.171*	No. CELLS OBSERVED	200	200	200
		t	1.013	1.428	CHI 2	0	1.148	0.05
		p	N.S.	N.S.	p	N.S.	N.S.	N.S.
	30	m	0.035	0.075	No. ABNORMAL CELLS	1	13	20
		s	*0.184*	*0.3*	No. CELLS OBSERVED	200	200	200
		t	0.479	2.907	CHI 2	0	6.926	3.604
		p	N.S.	<0.01	p	N.S.	<0.01	N.S.
HISTORICAL CONTROL DATA Mean of 9 studies [range]			0.036 [0.02-0.05]	0.028 [0.015-0.05]	No. ABNORMAL CELLS	0 [0-0]	5.5 [3-10]	12 [7-14]

m = mean ; s = standard deviation ; t = Student's t ; N.S. = not statistically significant at the threshold of p<0.05

3.5.5. SR 47436: *In Vitro* Chromosomal Aberration Test in Human Lymphocytes (Second Study) (Report #RS0006930709/01; Study #MAF010). Vol. 46

This GLP study was conducted in the laboratory of for Sanofi Recherche, Montpellier Cedex, France between April 21, 1993 and May 27, 1993. The aim of the study was to evaluate the ability of the test compound to induce chromosomal aberrations using human lymphocytes cultured *in vitro*, with and without metabolic activation. This is a repeat study performed in a different contract laboratory as the results of the previous study were not unequivocal in establishing freedom from clastogenic activity for SR 47436.

Methods

Whole blood cultures were established from blood taken from a single healthy female volunteer. Phytohemagglutinin was added to stimulate the lymphocytes to divide. The mammalian liver post-mitochondrial fraction (S-9 mix, 2%) used for metabolic activation was prepared from male Sprague Dawley rats induced with Aroclor 1254. Blood cultures were treated with solvent (DMSO), SR 47436 (batch 92.02) or positive controls (4-nitroquinoline 1-oxide, - S-9; cyclophosphamide, + S-9) and the following scheme illustrates the number of cultures and the treatment pattern used in the study.

SUMMARY OF TREATMENT AND HARVEST TIMES

Duration of treatment, h		20	44	3	3
Recovery, h		0	0	17	41
Harvest time after start of treatment*, h		20	44	20	44
Treatment regime	S-9 mix	Number of cultures used for each treatment			
Solvent control	- +	4 -	4 -	4 4	- 4
SR 47436	- +	2 -	2 -	2 2	- 2
Positive control	- +	2 -	- -	- 2	- -

* 1½ hr before harvest, colchicine was added to arrest dividing cells in metaphase.

The selection of SR 47436 dose levels was based on mitotic index. A dose range from 33.26 to 1400 µg/ml was used in the assay. The highest dose selected for the assay in general produces a 50-80% reduction in MI compared with the control or is the dose which produces precipitation. One hundred metaphases from each culture were analyzed for chromosome aberrations. Only cells with 44-46 chromosomes were considered acceptable for analysis of structural aberrations. The test substance was to be considered as clearly positive in the assay if: (a) statistically significant increase

in the proportion of cells with structural aberrations (excluding gaps) occurred at one or more concentrtions, (b) the proportion of aberrant cells at such data points exceeded the normal range. Increases in number of cells with gaps or increases in the proportion of cells with structural aberrations not exceeding the normal range or occurring only at very high or very toxic concentrations were likely to be concluded as "equivocal" by the sponsor.

Results

Complete mitotic inhibition was observed at several doses following various treatment regimes. The following doses were selected for further analysis.

Treatment, hr (incubation + recovery)	± S-9 mix	Concentrations of SR 47436	Mitotic inhibition§
20 + 0	-	78.84, 105.1, 140.2 µg/ml	54%
3 + 17	+	249.2, 332.2, 443 µg/ml	62%
44 + 0	-	186.9 µg/ml	66%
3 + 41	+	443 µg/ml	21%
3 + 17	-	590.6 µg/ml	41%

§inhibition at highest analyzed dose

The majority of cultures treated with SR 47436, in the presence or absence of S-9 mix, exhibited frequencies of cells with structural chromosome aberrations which were similar to and not significantly different from those observed in concurrent solvent controls. However, a statistically significant increase in aberrant cell frequencies over concurrent control levels was observed at the dose analyzed for the group 44 + 0 hours treatment, in the absence of S-9. No biological significance is attributed to this finding since the increase was against a zero background of aberrant cells in control cultures. Further, the increase was seen in only one culture and the replicate culture exhibited aberrant cell frequencies within the normal range (Table 3.5.5.1A). Also, the analyzed dose, 186.9 µg/ml, was cytotoxic since this dose induced 66% mitotic inhibition.

Frequencies of cells with numerical aberrations which exceeded the historical and concurrent control ranges were observed only in two replicate cultures treated in the presence of S-9 at the 3 + 41 hr sample time. Though the mitotic inhibition induced by SR 47436 at 443 µg/ml was 21%, the sponsor does not consider the finding as alarming since the frequencies were close to the accepted range (Table 3.5.5.1B). It is not clear why the sponsor did not test concentrations below the maximum dose. The rest of the SR 47436-treated cultures exhibited acceptable frequencies of cells with numerical aberrations.

Positive control compounds, both in the absence and presence of S-9 mix, induced a statistically significant increase in the frequency of cells with structural aberrations but not numerical aberrations. The sponsor adds that the importance of numerical aberrations in *in vitro* human

lymphocyte cultures is not clear. Based on historical control data, the sponsor concludes that SR 47436 does not induce structural chromosome aberrations in cultured human peripheral blood lymphocytes when tested to its limit of toxicity in either the absence or presence of S-9. This is incorrect since SR 47436 at concentrations of 300 µg/ml in the previous study and 186.9 µg/ml in the present study (both in the absence of S-9 mix) increased the frequency of cells with structural aberrations ($p < 0.05$ when compared to concurrent control). The present study only confirmed the observations made in the previous study.

TABLE 3.5.5.1
STUDY TO EVALUATE CLASTOGENIC EFFECT OF SR 47436 ON CULTURED HUMAN BLOOD LYMPHOCYTE: CELLS WITH STRUCTURAL AND NUMERICAL ABERRATIONS

A. 44 hours treatment - S-9, 0 hours recovery

Treatment (µg/ml)	Replicate	Cells scored	Structural aberrations		Numerical aberrations		Mitotic index (mean)
			including gaps	excluding gaps	Total	%	
Solvent	C	100	1	0	0	0	5.5
	D	100	3	0	1	1.0	5.0
	Totals	200	4	0	1	0.5	(5.3)
SR 47436 186.9	A	100	3	1	2	2.0	2.2
	B	100	4	3	3	2.9	1.4
	Totals	200	7	4*	5	2.4	(1.8)
Historical control		2800	2.3 [0-7][a]	0.9 [0-4][a]		1.1 [0-5][a]	

B. 3 hours treatment + S-9, 41 hours recovery

Treatment (µg/ml)	Replicate	Cells scored	Structural aberrations		Numerical aberrations		Mitotic index (mean)
			including gaps	excluding gaps	Total	%	
Solvent	A	100	0	0	1	1.0	5.7
	B	100	2	0	1	1.0	3.7
	Totals	200	2	0	2	1.0	(4.7)
SR 47436 443	A	100		3	5	4.8	
	B	100	3	0	4	3.8	
	Totals	200	9	3[NS]	9	4.3	(3.7)
Historical control		2800	1.7 [0-5][a]	0.8 [0-4][a]		0.8 [0-3][a]	

*: $p \leq 0.05$, NS: not significant
Number highlighted exceed the historical negative control ranges
[a]: normal range calculated as follows: mean number of aberrant cells per 100 (± 2.58 x SD) and values rounded to the nearest whole number

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3.5.6. SR 47436: *In Vivo* Micronucleus Study in Mice (Report #RS0006930107/01; Study #MUT040). Vol. 46

This GLP study was conducted in the laboratory of for Sanofi Recherche, Montpellier Cedex, France between October 15, 1992 and December 4, 1992. The aim of the study was to evaluate the clastogenic or aneugenic effects of SR 47436 in mice (*in vivo*).

Methods

A preliminary toxicity test was conducted using groups of 5 male and 5 female (weight: 21-30 g, age: 5-6 weeks) OF1 mice ( ). Suspension of SR 47436 (batch 92.02) in 10% w/v gum arabic was administered orally (25 ml/kg) by gavage as single dose of 2500 or 4000 mg/kg. A dose higher than 4000 mg/kg was not administered because of solubility limitations. Animals were not fasted before treatment. The mortality rate was determined over a period of 48 hours. There were no deaths and the 4000 mg/kg dose was retained for the main study.

Five groups of 10 mice (details as above) were used for this study. The design of the experiment was as follows:

Group #	#Males	#Females	Sacrifice/Sampling Time
1 (negative control)	5	5	24 hours
2 (negative control)	5	5	48 hours
3 (positive control) (cyclophosphamide 50 mg/kg, i.p.)	5	5	24 hours
4 (SR 47436)	5 (+ 2)¶	5 (+ 2)	24 hours
5 (SR 47436)	5 (+ 2)	5 (+ 2)	48 hours

¶: 2 animals of each sex at each time were treated, in parallel, but were sacrificed only in case of mortality in the main group.

Animals were sacrificed 24 or 48 hr after treatment. Bone marrow was isolated from both femurs and smears were prepared for evaluation. Two slides per animal were read; for each animal, the number of polychromatic erythrocytes (PCE) having one or more micronuclei (MN) was determined for at least 1000 or, preferably 2000 PCE. The test substance was considered to be negative if there was no statistically significant increase in the number of MN observed at either of the 2 sampling times.

Results

There were no deaths. A statistically significant decrease in the ratio of PCE to NCE was observed in treated group relative to control group at both 24 hr ($p < 0.01$) and 48 hr ($p < 0.05$) sampling times. These changes possibly reflect the slight cytotoxic effect of SR 47436 at the selected high

dose, 4000 mg/kg. No increase in MN-PCE was found in the animals treated with SR 47436, two sexes combined or males and females apart, compared with the control. On the other hand, cyclophosphamide induced a significant increase in the number of MN-PCE, compared to the vehicle control group. Thus, it can be concluded that SR 47436 has no clastogenic activity in the micronucleus test in mice.

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3.5.7. SR 47436/HCTZ: Ames Reverse-Mutation Assay in Salmonella typhimurium and E. coli (Report #RS0042960523/02; Study #94660). Vol. 21

This GLP study was conducted by the department of Genetic Toxicology of Bristol-Myers Squibb Pharmaceutical Research Institute, Syracuse, NY between May 24 and June 7, 1994.

The Ames test permits the detection of gene mutations induced by the test compound or its metabolites in histidine-requiring strains of *Salmonella typhimurium* and in tryptophan-requiring *E. coli*. In the presence of a genotoxic agent, tester strains revert from histidine or tryptophan dependence (auxotrophy) to histidine or tryptphan independence (prototrophy). The Salmonella strains are capable of detecting DNA base pair substitutions and frameshift-type mutations. The E. coli WP2 uvrA strain is capable of detecting DNA base pair substitutions. SR 47436/HCTZ was evaluated for its ability to increase the reversion frequency at the histidine locus in *Salmonella typhimurium* strains TA1535, TA1537, TA 98 and TA100, and tryptophan locus in E. coli tester strain WP2 uvrA in the presence and absence of a rat liver metabolic activation system (S-9 mix).

SR 47436 (batch 93.06)/HCTZ (batch 48192) (dissolved in DMSO) was tested in a range finding assay with strains TA100 and WP2 uvrA at concentrations ranging from 0.5/0.5 to 2500/2500 µg/plate. All dose levels were tested in duplicate cultures both with and without S-9 mix. Slight to marked cytotoxicity was observed in tester strain TA100 at SR 47436/HCTZ concentrations ≥500/500 µg/plate. Slight cytotoxicity was observed in tester strain WP2 uvrA at a SR 47436/HCTZ concentration of 2500/2500 µg/plate. The histidine$^+$ and tryptophan$^+$ revertant counts seen in this range finding assay were not elevated in any of the SR 47436/HCTZ-treated cultures when compared to the negative control levels.

In the definitive mutation assay, the test and control articles were evaluated in triplicate cultures with all tester strains in each study in the presence and absence of S-9 mix. The S-9 mixture included 6% (v/v) Aroclor 1254-induced male Sprague-Dawley rat liver homogenate with the appropriate buffer and cofactors. SR 47436/HCTZ was evaluated at concentrations of 50/50, 100/100, 200/200, 400/400 and 800/800 µg/plate in S. typhimurium strains, and 200/200, 400/400, 800/800, 1600/1600 and 2500/2500 µg/plate in strain WP2 uvrA, both with and without S-9 mix. The reference positive controls used were: sodium azide (in TA1535 and TA100 strains), 9-aminoacridine (in TA1537), 2-nitrofluorene (in TA98) in the absence of S-9 mix, and 2-aminoanthracene in all five tester strains in the presence of S-9 mix. For all strains, exposure to SR 47436/HCTZ resulted in revertant frequencies similar to or less than observed in the concurrent solvent (DMSO) (negative) control cultures. Slight to marked cytotoxicity (reduction of the bacterial background lawn) was observed in tester strains TA100, TA1535 and TA98 both with and without S-9 mix, at concentrations of SR 47436/HCTZ ≥ 400/400 µg/plate. Moderate and marked cytotoxicities were observed in tester strain TA1537 at a SR 47436/HCTZ concentration of ≥ 800/800 µg/plate, with and without S-9 activation, respectively. Slight cytotoxicity was observed in tester strain WP2 uvrA, both with and without S-9 mix, at 2500/2500 µg/plate.

SR 47436/HCTZ was reevaluated in a confirmatory assay conducted under almost identical

conditions at concentrations of 50/50 to 2500/2500 µg/plate. The results of this assay were essentially the same as the results of the previous assay. All positive and negative control values in both assays were within acceptable limits. Thus, the results suggest that SR 47436/HCTZ is non-mutagenic in the Ames reverse-mutation assay up to and including cytotoxic dose levels.

AUG 21 1997

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

(Irbesartan/Hydrochlorothiazide)
Tablet
20-758

Sanofi Pharmaceuticals, Inc.

U. S. FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Cardio-Renal Drug Products
(HFD-110)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-758

(Irbesartan/Hydrochlorothiazide)

Tablet

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that it will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Irbesartan/Hydrochlorothiazide, Sanofi Pharmaceuticals, Inc., has prepared an environmental assessment (attached) in accordance with *21 CFR 25.31a(a)*, which evaluates the potential environmental impact of the manufacture, use and disposal of the product. The maximum expected environmental concentration is at a level that normally relieves the applicant from completing format items 7, 8, 9, 10, 11, and 15 in accordance with the Tier 0 approach specified in the *Guidance for Industry for the submission of an Environmental Assessment in Human Drug Applications and Supplements.*

Irbesartan/Hydrochlorothiazide is a chemically synthesized drug which is administered as a tablet in the treatment of hypertension. The drug substances will be manufactured by Sanofi Chimie, Aramon, France and a contract manufacturers. The drug product will be manufactured by Bristol-Myers Squibb, U.S. Pharmaceutical Group, Evansville, Indiana. The finished drug product will be used in hospitals, clinics and by patients in their homes.

Irbesartan/Hydrochlorothiazide may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance will be landfilled and rejected or returned drug product will be disposed of at a licensed incinerator. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or

partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

August 19, 1997
Date

PREPARED BY
Carl J. Berninger, Ph.D.
Environmental Scientist
Environmental Assessment Team
Center for Drug Evaluation and Research

8/21/97
Date

CONCURRED
Nancy B. Sager
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment (FOI copy)
Material Safety Data Sheets for drug substances

Copies:

HFD-110

Kathleen Bongiovanni, PM
Original to NDA 20-757, through Kathleen Bongiovanni, PM
Division File for NDA 20-758

HFD-205

FOI Copy

HFD-357

EA File
Docket File
C. Berninger

file name: c:\fonsi\20758e01.fcb

APPEARS THIS WAY
ON ORIGINAL

TELEPHONE CONFERENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE:	August 21, 1997
FROM:	Carl J. Berninger, Ph.D. (HFD 110) CJB
NDA NUMBER:	20-757 and 20-758
NAME OF FIRM:	Sanofi Pharmaceuticals, Inc. (Bristol-Myers Squibb)
SUBJECT:	Correction of page numbers in Section 13, Certification
NAME OF PERSON:	Ms. Debbie McCloskey

Ms. Debbie McCloskey certified that in Irbesartan, NDA 20-757, Environmental Assessment, FOI version, the certification, Section 13 should refer to pages 004-032 rather than the given 004-037 as releasable.

In addition, she certified that in Irbesartan/Hydrochlorothiazide, NDA 20-758, Environmental Assessment, FOI version, the certification, Section 13 should refer to pages 004-037 rather than the given 004-032 as releasable.

She will follow this Telephone conversation with an official submission to the same effect as soon as possible.

APPEARS THIS WAY
ON ORIGINAL

ENVIRONMENTAL ASSESSMENT (FOI)

AMENDED

Irbesartan/Hydrochlorothiazide Tablets NDA #20-758

ENVIRONMENTAL ASSESSMENT
Irbesartan/Hydrochlorothiazide Tablets NDA #20-758

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ENVIRONMENTAL ASSESSMENT
Irbesartan/Hydrochlorothiazide Tablets NDA #20-758

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Format 1 Section No.

Page No.

ENVIRONMENTAL ASSESSMENT
Irbesartan/Hydrochlorothiazide Tablets NDA #20-758

1. **DATE** July 24, 1997

2. **NAME** Sanofi Pharmaceuticals, Inc.

3. **MAILING ADDRESS** 90 Park Avenue
New York, New York 10016

4. **DESCRIPTION OF PROPOSED ACTION**

A. **Requested Approval**

Sanofi Pharmaceuticals, Inc. has filed a NDA pursuant to Section 505(b) of the Federal Food, Drug and Cosmetic Act for Irbesartan/Hydrochlorothiazide 75/12.5mg and 150/12.5mg Tablets. An Environmental Assessment is being submitted pursuant to 21 CFR § 25.31 a(a) for Irbesartan/Hydrochlorothiazide Tablets. This environmental assessment provides detailed information for the new drug substance, irbesartan. Detailed information has not been provided for hydrochlorothiazide as the latter drug substance has been approved for and is in widespread use in humans since 1959.

B. **Need for Action**

Irbesartan/Hydrochlorothiazide Tablets are indicated for the treatment of hypertension. The hydrochlorothiazide is added to the combination tablets to enhance the therapeutic effect of irbesartan.

C. **Production Locations**

1. New Drug Substance

Irbesartan, the active ingredient in the final product, which is the subject of the proposed action, is manufactured by Sanofi Chimie, Route d'Avignon, 30390 Aramon, France, DMF number 10,310 and Contract Manufacturer #2 (refer to the Confidential Appendix B8 for the name, locations and DMF number).

A detailed presentation of the synthesis and in-process controls of irbesartan is given in Sanofi Chimie's type II DMF. Only the manufacturing process from the final intermediate to irbesartan was summarized in NDA 20-758. The proprietary intermediates listed in the NDA are manufactured at Sanofi Chimie, Aramon, France and Contract Manufacturer #2. Refer to the Confidential Appendix B7 for the manufacturing scheme from the final intermediate to the drug substance, irbesartan. The information included in the Confidential Appendix B7 is taken directly from NDA 20-758.

ENVIRONMENTAL ASSESSMENT
Irbesartan/Hydrochlorothiazide Tablets NDA #20-758

The plant of Sanofi Chimie, Aramon, France is located about 2 miles (3 kilometers) north of Aramon, a town of about 3,000 inhabitants in the Provence region of southern France between Arles and Avignon. The facility is located on the Rhone River in a hilly area with a dry, warm climate.

The manufacturing site consists of approximately 50 acres with about 30 buildings housing manufacturing operations, quality control, warehouses, maintenance, process development laboratories and administrative and management offices. The facility is zoned industrial.

The operations at the facility include manufacturing and warehousing of bulk intermediates and fine pharmaceutical chemicals. The Prefectural Order No. 89-006N of January 30, 1989 authorizes Sanofi Chimie Aramon to handle chemical and pharmaceutical substances in the Aramon facility where Irbesartan will be manufactured.

Waste management, minimization and spill prevention programs, policies and procedures have been instituted to ensure proper compliance with all site regulations. A waste water treatment facility receives all waste water from the plant. After treatment, the water is discharged to the Rhone River in accordance with established permit limitations.

2. Hydrochlorothiazide

Hydrochlorothiazide is a generic drug substance used in conjunction with irbesartan in the Irbesartan/Hydrochlorothiazide Tablets final product and will be sourced from the Contract Manufacturer #1. Refer to the Confidential Appendix B1 for the name, location and DMF number.

3. New Drug Product

Irbesartan/Hydrochlorothiazide Tablets, the market presentation, will be formulated and packaged at the Bristol-Myers Squibb, U.S. Pharmaceutical Group; 2400 W. Lloyd Expressway, Evansville, Indiana, 47721.

The Evansville plant is located on a 60-acre site adjacent to the Ohio River, within the city of Evansville in Vanderburgh County. The immediate neighborhood includes a school and residential areas, as well as other industrial and commercial businesses. The upper soil is silty clay.

There are no known rare or endangered species inhabiting the area surrounding the facility; there are also no nature preserves or protected areas nearby. The site is within the 100-year flood plain of the Ohio River.

ENVIRONMENTAL ASSESSMENT
Irbesartan/Hydrochlorothiazide Tablets NDA #20-758

D. Locations of Use

Irbesartan/Hydrochlorothiazide Tablets, will be used worldwide for the treatment of hypertension. Irbesartan/Hydrochlorothiazide Tablets will be used by trained professionals in hospitals and clinics, as well as patients in their homes. It is anticipated that its distribution will be primarily to well-developed countries, particularly in the United States, Canada, and Europe.

E. Disposal Sites

1. New Drug Substance

Rejected new drug substance received in Evansville, Indiana will be disposed of as non-hazardous solid waste at an approved and permitted landfill in accordance with all federal, state and local regulations. Refer to the Confidential Appendix B3 for information on the approved landfill.

2. Drug Product

The Bristol-Myers Squibb (BMS), Distribution Center located in Mt. Vernon, Indiana, is the designated pharmaceutical finished product goods processing center for other BMS distribution centers located in the United States and its territories. North America Technical Operations Logistics has contracted with a third party processor of returned goods, The Ballantine Group, Franklin, NJ, to process the returns of finished pharmaceuticals from direct and indirect customers. Finished product that is expired, damaged, unwanted or unsalable is returned to the Mt. Vernon facility from other BMS Distribution Centers, or The Ballantine Group from customers where it is checked and inventoried pending QC disposition. In accordance with Company approved standard operating procedure, returned goods may be placed back into inventory subject to certain conditions, sent back to a processing site for further evaluation, or directed for disposal. All returns awaiting final disposition are held in a security zone within the facility in quarantine status.

ENVIRONMENTAL ASSESSMENT
Irbesartan/Hydrochlorothiazide Tablets NDA #20-758

Irbesartan/Hydrochlorothiazide Tablets slated for disposal are segregated at the facility as a non-hazardous off-specification pharmaceutical. Non-hazardous off-specification pharmaceuticals are packed by facility personnel and loaded for transport to a Company approved, permitted incineration facility. Transportation is provided by an approved carrier. The shipping papers (manifests) are prepared by facility personnel and accompany the waste shipment to the disposal facility. The disposal facility acknowledges receipt by signing and returning copies of the manifest to the originating facility (Mt. Vernon facility or The Ballantine Group).

As an additional security feature, destruction events may be witnessed by a firm independent from the disposal company. A written report is produced which confirms the identity and condition of the truck seal upon arrival at the disposal facility, net weight, time required for disposal and the names and signatures of the witnessing persons (when applicable). In addition all disposal facilities confirm in writing to Logistics management, the date(s) on which the actual destruction of said materials occurred. Refer to Confidential Appendix, Section B3 for a listing of the potential disposal sites.

Irbesartan/Hydrochlorothiazide Tablets used at U.S. hospitals, pharmacies or clinics, empty or partially empty packages will be disposed of according to in-house procedures. Empty or partially empty Irbesartan/Hydrochlorothiazide Tablets containers used in the home will typically be disposed of by a community's solid waste management system which includes landfills, incineration and recycling, although minimal quantities of unused drug may be disposed of in the sewer system.

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

i. Irbesartan

A. Nomenclature

i. Established Name: Irbesartan
ii. Brand/Proprietary Name: Not Approved
iii. Chemical Names

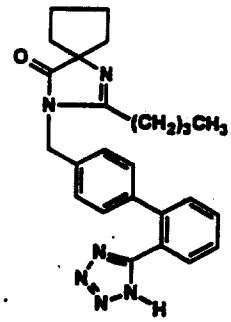
1. Chemical Abstract Name: 1,3-Diazaspiro[4.4]non-1-en-4-one,2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl methyl]-(9CI)
2. Systematic Chemical Name: 2-Butyl-3-[p-(-o-1H-tetrazol-5-ylphenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one

B. Chemical Abstract Service Number: 138402-11-6

C. Molecular Formula: $C_{25}H_{28}N_6O$

D. Molecular Weight: 428.54

E. Structure



F. Physical Description - White to off-white crystalline powder.

G. Additives
Refer to Section 6.A of this document for a listing of additives expected to be emitted into the environment during the manufacture of Irbesartan and Irbesartan/Hydrochlorothiazide Tablets.

H. Impurities
There are no impurities in the new drug substance at levels greater than one percent (1%).

II. Hydrochlorothiazide

A. Nomenclature

i. Established Name: Hydrochlorothiazide
ii. Brand/Proprietary Name: Hydrochlorothiazide
iii. Chemical Names

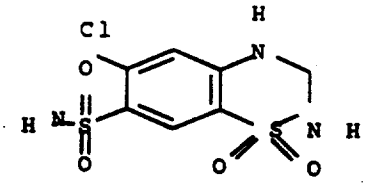
1. Chemical Abstract Name: 2H-1,2,4-Benzothiadiazine-7-Sulfonamide,6-Chloro-3,4-dihydro-,1,1-dioxide

B. Chemical Abstract Service Number: 58-93-5

C. Molecular Formula: $C_7H_8ClN_3O_4S_2$

D. Molecular Weight: 297.75

E. Structure:



F. Physical Description: White to practically white crystalline powder.

G. Additives: Refer to Section 6.A of this document for a listing of additives expected to be emitted during the manufacture of Irbesartan/Hydrochlorothiazide Tablets.

H. Impurities: Refer to the Contract Manufacturer #1, DMF, as specified in Confidential Appendix B1.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

Irbesartan may be introduced into the environment from: 1) the manufacture of irbesartan new drug substance, 2) the manufacture of the final products, 3) the site of patient use and 4) the disposal of the drug product.

The new drug substance, irbesartan and proprietary intermediates listed in the Confidential Appendix B7 are manufactured at a foreign facility by Sanofi Chimie and Contract Manufacture #2. A letter certifying the following statements for the manufacturing facilities are attached in the Non-Confidential Appendix A2 for Sanofi Chimie and Confidential Appendix B8 for Contract Manufacturer #2; 1) that it is in compliance with all local and national environmental laws; 2) that it is in compliance with, or are on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and 3) that approval and the subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws.

Hydrochlorothiazide is manufactured at a foreign facility by Contract Manufacturer #1. A letter certifying the following statements for the manufacturing facility is attached in the Confidential Appendix B1; 1) that it is in compliance with all local and national environmental laws; 2) that it is in compliance with, or are on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and 3) that approval and the subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws.

The following is a description of the introduction of substances into the environment from the final product manufacturing site, the site of patient use, and disposal of the drug product.

ENVIRONMENTAL ASSESSMENT
Irbesartan/Hydrochlorothiazide Tablets NDA #20-758

A. Substances Expected to be Emitted

Refer to the Confidential Appendix B4 for substances expected to be emitted from the final product manufacturing facility.

B. Controls Exercised

1. Air Emissions

Air emissions of particulates at the Bristol-Myers Squibb Evansville site from Irbesartan/Hydrochlorothiazide Tablets processes are controlled through the use of dust-control equipment, principally wet scrubbers, that are registered by the city of Evansville Environmental Protection Agency (EPA).

2. Liquid Waste

Wastewater from the Evansville manufacturing site is discharged into a Publicly Owned Treatment Works (POTW), specifically the city of Evansville's Westside Wastewater Treatment Plant.

3. Solid Waste

Irbesartan/Hydrochlorothiazide Tablets are not listed hazardous waste as defined by 40 CFR Section 261. All non-hazardous solid waste generated from the manufacture of Irbesartan/Hydrochlorothiazide Tablets is disposed of at an approved and permitted incinerator, in accordance with all federal, state and local regulations.

4. Drug Product

Irbesartan, drug product waste may be generated as losses in manufacturing equipment, dust removed from HVAC filters and minor sources. Disposal of irbesartan/hydrochlorothiazide material is scheduled for an approved incinerator listed in the Confidential Appendix B3.

Disposal of rejected, returned, and off-specification drug product is previously described in Section 4.E.2 of this document.

C. Citation of and Statement of Compliance with Applicable Emission Requirements

After due inquiry and discussion with personnel charged with responsibility for such matters, applicant certifies that all necessary actions have been or will be taken so that emissions, discharges and wastes from the production of Irbesartan/Hydrochlorothiazide Tablets will be in compliance with applicable environmental, occupational health and safety standards and national, federal, state and local emission regulations and permits or with applicable consent orders and administrative orders and directives for its facility in Evansville, Indiana.

ENVIRONMENTAL ASSESSMENT
Irbesartan/Hydrochlorothiazide Tablets NDA #20-758

Material Safety Data Sheets for Irbesartan and Hydrochlorothiazide are included in the Non-Confidential Appendix A1.

The Evansville facility is under the jurisdiction of the city of Evansville's local Environmental Protection Agency (EPA). The city of Evansville EPA is governed by the Indiana Department of Environmental Management who is under the jurisdiction of the United States Environmental Protection Agency, Region 5.

1. Citations of Applicable Federal, State and Local Regulations

   Listed below are citations of applicable Federal, State and local emission requirements and laws:

   i. **Federal - United States**

   Major environmental statutes with regulations promulgated by the United States Environmental Protection Agency that may impact pharmaceutical manufacturing include:

   Air Quality: Clean Air Act of 1977 as amended 1990; 42 United States Code (U.S.C.) §§ 7401-7671q; 40 Code of Federal Regulations (C.F.R.) Parts 50-88

   Waste: Resource Conservation and Recovery Act 1976 as amended by the Hazardous and Solid Waste Act Amendments 1984; 42 U.S.C. §§ 6901-6992; 40 C.F.R. Parts 240-281

   Remediation: "Superfund," Comprehensive Environmental Response, Compensation and Liability Act of 1980; 42 U.S.C. §§ 9601-9675; 40 C.F.R. Parts 300-311

   Water: Clean Water Act of 1972; 33 U.S.C. §§ 1251-1387; 33 C.F.R. Parts 320-330, 335-338; 40 C.F.R. Parts 104-140, 230-233, 401-477

   Chemicals: Emergency Planning and Community Right-to-Know Act of 1986 (Superfund Amendments and Reauthorization Act Title III, SARA Title III) 42 U.S.C. §§ 11001-11050; 40 C.F.R. Parts 350, 355, 370, 372; Pollution Prevention Act of 1990; 42 U.S.C. §§ 13101-13209

   Energy: Atomic Energy Act of 1954; 42 U.S.C. §§ 2011-2297g-2; 10 C.F.R. Parts 0-171, 760-766, 810-962; Energy Reorganization Act of 1974; 42 U.S.C. §§ 5801-5891; 10 C.F.R. Parts 88, 40.7, 50.7, 70.7, 708; Low-Level Radioactive Waste Policy Act of 1980; 42 U.S.C. §§ 10 C.F.R. Parts 61-62; Regulations implemented by the Atomic Energy Commission

   Occupational Safety & Health: Occupational Safety and Health Act of 1970; 29 U.S.C. §§ 651-78; 29 C.F.R. Parts 1900-1910

ii. State - Indiana

Solid Waste Management Rules
329 IAC Article 2

Solid Waste Management Air Pollution Control Rules
326 IAC Article 2

Permit Review Rules
326 IAC Article 3

Monitoring Requirements Water Pollution Control Rules
327 IAC Article 5

Industrial Wastewater Pretreatment Programs (NPDES)
327 IAC 13-10-3, Sewer Use Ordinance

Indiana Occupational Safety & Health Act (IOSHA)
Title 22, Article 8, Chapter 1.1

iii. Local - Evansville, Indiana

Evansville Ordinance 5.53, Wastewater Discharge Regulations (local sewer ordinance).

2. Emission Permits

Listed in the following section are the emission permits and/or registrations, according to air, liquid and solid waste streams. Confidential information on permit numbers, authorizing agency and expiration dates are contained in the Confidential Appendix B5 for the manufacture of Irbesartan/Hydrochlorothiazide Tablets.

i. Air Emissions

Dust control equipment used at the BMS Evansville site for Irbesartan/Hydrochlorothiazide Tablets processes is registered by the city of Evansville EPA. An annual fee for operation is required by Evansville EPA under ID #015. The city of Evansville EPA inspects the site at least annually and is responsible for issuing the permits and registrations.

ii. Liquid Waste

The wastewater from the Evansville manufacturing site discharges into a Publicly Owned Treatment Works (POTW), specifically the city of Evansville's Westside Wastewater Treatment Plant (NPDES permit number IN0032956). The Evansville plant's industrial pretreatment permit from the city of Evansville is registered under Mead Johnson & Company.

iii. Solid Waste

The non-hazardous solid waste generated in the Irbesartan/Hydrochlorothiazide Tablets manufacture is sent to an approved and permitted incinerator, in accordance with all federal, state and local regulations. Refer to the Confidential Appendix B3 for a listing of the applicable disposal site(s).

D. Discussion of the Effect of Approval on Compliance with Current Emission Requirements

The proposed action involved no new construction at the Bristol-Myers Squibb production facility in Evansville, Indiana. Hence, there was no impact on land use, water quality or other natural resources from construction activities.

The estimated fifth year production volume in the United States is listed in the Confidential Appendix B2.

Considering the estimated fifth year production volumes, the manufacturing of Irbesartan/Hydrochlorothiazide Tablets should not have an adverse impact on the environment nor on compliance with current emission permits or registrations at the final product manufacturing site.

E. Expected Introduction Concentration

Irbesartan/Hydrochlorothiazide Tablets are administered to patients orally and will enter the environment primarily through the sanitary wastewater systems, at the location where the product is administered.

The estimated fifth year production volume of irbesartan drug substance and hydrochlorothiazide, estimated from projected total sales volumes of Irbesartan/Hydrochlorothiazide Tablets and the companion filing Irbesartan Tablets (NDA #20-757) in the United States, are listed in the Confidential Appendix B2.

ENVIRONMENTAL ASSESSMENT
Irbesartan/Hydrochlorothiazide Tablets NDA #20-758

i. Expected Introduction Concentration From Use

The expected introduction concentration is calculated using the fifth year volume for the new drug substance, irbesartan and for generic drug substance, hydrochlorothiazide.

The Expected Introduction Concentration (EIC) entering the aquatic environment from patient use is determined as follows:

EIC-Aquatic (ppm) = A x B x C x D x E

Where

A = kg/year production
B = 1/liter per day entering POTWs*
C = year/365 days
D = 10^6 mg/kg
E = pharmacologic activity of irbesartan and its metabolites excreted in the urine and feces relative to pharmacologic activity of administered dose.**

* 1.115 X 10^{11} liters per day entering Publicly Owned Treatment Works (POTWs), source: 1992 Needs Survey, Report to Congress, September 1993, EPA 832-R-93-002.

** Refer to the Confidential Appendix B2 for description of the pharmacological activity of irbesartan and its metabolites.

EIC-Aquatic (ppm) = Refer to the Confidential Appendix B2 for the EIC value.

The EIC for irbesartan and hydrochlorothiazide relate to the estimated concentration in waters discharged from POTWs which service domestic residences, hospitals and clinics. This concentration is expected to undergo further dilution by surface flow (average factor of 10), which would result in an Expected Environmental Concentration (EEC) an order of magnitude less than the EIC. Therefore, the Maximum Expected Environmental Concentration (MEEC) is the Expected Introduction Concentration as calculated in Confidential Appendix B2.

The MEEC (EIC) values are less than 1 part per billion for irbesartan and hydrochlorothiazide and this EA qualifies for tier 0, as defined in Section III.D.7.c in the FDA CDER's guidance to industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements that was issued in November 1995.

ii. Expected Introduction Concentration from Disposal

An expected introduction concentration for disposal was not calculated because as previously described in Section 4.E.2, irbesartan/hydrochlorothiazide drug product wastes will be disposed of in approved and permitted disposal facilities. Refer to Section 4.E.2 of this environmental assessment for further information on disposal practices.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

As determined in Section 6.E.i, this EA qualifies for tier 0 and the information for EA format items 7, 8, 9, 10, 11 and 15 are not necessary. However, Section 15 is included in this EA to report confidential information from Sections 1 - 6 and 12 - 13.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

As determined in Section 6.E.i, this EA qualifies for tier 0 and the information for EA format items 7, 8, 9, 10, 11 and 15 are not necessary. However, Section 15 is included in this EA to report confidential information from Sections 1 - 6 and 12 - 13.

9. USE OF RESOURCES AND ENERGY

As determined in Section 6.E.i, this EA qualifies for tier 0 and the information for EA format items 7, 8, 9, 10, 11 and 15 are not necessary. However, Section 15 is included in this EA to report confidential information from Sections 1 - 6 and 12 - 13.

10. MITIGATION MEASURES

As determined in Section 6.E.i, this EA qualifies for tier 0 and the information for EA format items 7, 8, 9, 10, 11 and 15 are not necessary. However, Section 15 is included in this EA to report confidential information from Sections 1 - 6 and 12 - 13.

11. ALTERNATIVES TO THE PROPOSED ACTION

As determined in Section 6.E.i, this EA qualifies for tier 0 and the information for EA format items 7, 8, 9, 10, 11 and 15 are not necessary. However, Section 15 is included in this EA to report confidential information from Sections 1 - 6 and 12 - 13.

ENVIRONMENTAL ASSESSMENT
Irbesartan/Hydrochlorothiazide Tablets NDA #20-758

12. **LIST OF PREPARERS**

Eileen P. Hayes, Sc.D., DABT, B.S., Pharmacy, Northeastern University; Sc.D., Toxicology, Harvard School of Public Health; post-doctoral training, Department of Pathology, Brigham & Women's Hospital/Harvard Medical School; served on the faculties of the Toxicology Programs at Northeastern University and UMDNJ - Robert Wood John Medical School/Rutgers University; Diplomate of the American Board of Toxicology, practicing professional since 1979 with experience in occupational and environmental toxicology and chemical metabolism.

James Kearney, MS, Environmental Health, University of Cincinnati; BA, Biology, University of Buffalo; Certified Industrial Hygienist; Certified Safety Professional; practicing professional since 1980 with experience in industrial hygiene, safety and environmental protection.

Beth L. Bidstrup, MHS, Industrial Hygiene and Safety, The Johns Hopkins University; BS, Industrial Hygiene and Environmental Toxicology, Clarkson University; Certified Industrial Hygienist, practicing professional since 1986 with experience in industrial hygiene, safety and product stewardship.

13. **CERTIFICATION**

The undersigned official certifies that the information presented is true, accurate and complete to the best of the knowledge of Sanofi Pharmaceuticals, Inc. and Bristol-Myers Squibb Company.

The undersigned officials certifies that the environmental assessment summary document (pages 004 - 032) contains non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR §1506.6.

See memo dated 8/2/97
C.J.B

Signature _____ Date 11/08/1997

Sanofi Pharmaceuticals, Inc.

Signature Robert Simon Date 14/8/97
Robert Simon, Executive Director
Worldwide Regulatory Affairs
Bristol-Myers Squibb Company

ENVIRONMENTAL ASSESSMENT
Irbesartan/Hydrochlorothiazide Tablets NDA #20-758

14. REFERENCES

1. Guidance for Industry "For the Submission of an Environmental Assessment in Human Drug Applications and Supplements," Food and Drug Administration Center for Drug Evaluation and Research (CDER), November 1995, CMC 6, pages 1-E1.

2. "Disposition and Bioavailability of Irbesartan in Healthy Male Subjects after Intravenous and Oral Administration of [^{14}C]Irbesartan in Solution, and Oral Administration of Irbesartan Capsule," N.N. Vachharajani, Report Accession Number 910054507, February 12, 1996.

3. "Investigator Brochure - Irbesartan and Irbesartan/Hydrochlorothiazide," Bristol-Myers Squibb Pharmaceutical Research Institute, September 28, 1995.

*4. "Biotransformation of [^{14}C]BMS 186295 in Human Subjects," T. J. Chando, Report Accession Number 910054075, March 12, 1996.

5. "Mass-Balance and Absolute Bioavailability of Irbesartan in Healthy Male Subjects After 50 mg Intravenous and 150 mg Oral Administration of [14C] Irbesartan Solution," N.N. Vachharajani, Report Accession Number 910056233, April 17, 1996.

6. "Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA." Pharmaceutical Manufacturers Association, version 7, July 1991.

7. "Technical Assistant Document," FDA Environmental Assessment Technical Assistance Handbook NTIS PB 87-175345-, March, 1987.

8. National Environmental Policy Act (NEPA), 42 USC 4332, (1969) 83 Stat. 853.

9. FDA Final Rule for Compliance with National Policy Act: Policy and Procedure, Federal Register 50 FR 16636, 21 CFR 25, April 16, 1985.

*10. "Inhibitory Effects of SR 47436 Metabolites of [125I] AII Binding to Human Aortic Smooth Muscle Membranes," J.C. Breliere and J. Gougat, Report Number RS0038960806/01, August 6, 1996.

**11. M.B. Cohen, "Recovery in Radiolabel Studies", I.O.M. to D.W. Everett, May 3, 1995.

* Reports are from other sections of the NDA #20-757 and are included in the Confidential Appendix B6 as supplementary reference documents for the discussion of the pharmacologic activity of irbesartan and its metabolites.

** Report was not included in NDA 20-757 but is included in the Confidential Appendix B6.

ENVIRONMENTAL ASSESSMENT
Irbesartan/Hydrochlorothiazide Tablets NDA #20-758

15. APPENDICES

Appendices Index

A. Non-Confidential

1. Material Safety Data Sheet (MSDS) for Irbesartan and Hydrochlorothiazide
2. Environmental Certification Statement -Sanofi Chimie, Aramon, France.

B. Confidential

1. Contract Manufacturer #1 and Environmental Certification Statement
2. Manufacturing 5th Year Volumes and Expected Introduction Concentration
3. Disposal Facilities
4. Substances Expected to be Emitted
5. Facility Permit and/or Registration Information
6. Reference Documents Supporting the Pharmacologic Activity of Irbesartan and Its Metabolites
7. Synthesis Schematic for the Manufacture of Irbesartan from the Final Intermediate
8. Contract Manufacturer #2 and Environmental Certification Statement

NON-CONFIDENTIAL APPENDIX

SECTION A1

Material Safety Data Sheet (MSDS) for Irbesartan and Hydrochlorothiazide

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

BRISTOL-MYERS SQUIBB
PHARMACEUTICAL GROUP
P.O. BOX 191
NEW BRUNSWICK, NJ 08903
908-519-3843.

Product Identification: Irbesartan.

Chemical Name: 2-n-Butyl-3-((2'-(1H-tetrazol-5-yl) biphenyl-4-yl)methyl)-1,3-diazaspiro(4,4)non-1-en-4-one.
Synonym: SR 47436, BMS 186295-01
How Supplied: Bulk dry powder in fiber drums.
Product Use: Treatment of hypertension.
Chemical Family: Tetrazole, diazaspironone.

Molecular Formula: $C_{25}H_{29}N_6O$ ***CAS #***: 138402-11-6

EMERGENCY CONTACTS

Health: 908-519-3843 (Monday through Friday, daytime) at other times contact Chemtrec or the local poison control center.

Transportation: CHEMTREC (800)424-9300.

EMERGENCY OVERVIEW: Irbesartan is an antihypertensive agent (lowers blood pressure). Material has low minimum ignition energy. Control static discharges to prevent ignition. Very strong explosion pressure. See Health Effects section for additional information.

2. COMPOSITION/ INFORMATION ON INGREDIENTS

COMPONENTS	HAZARDOUS (Y/N)	CONCENTRATION (WT %)	CAS NUMBER	EXPOSURE GUIDELINE
Irbesartan	Y	100	138402-11-6	0.03 mg/cu. m. BMS-EG[1]

1 BMS-EG- Bristol-Myers Squibb Pharmaceutical Group Exposure Guideline (TWA 8-10 hour).

3. HEALTH HAZARDS IDENTIFICATION

EFFECTS OF OVEREXPOSURE

Routes of Entry:

1. ***Inhalation:*** If material becomes airborne there is potential for inhalation. The extent of systemic absorption of the material after inhalation is not known.

2. ***Skin contact***: Exposure may occur via skin contact if gloves and protective clothing are not worn. The extent of systemic absorption of the material after skin contact is not known.

3. ***Ingestion:*** Ingestion of large quantities of this material in an occupational setting would not be expected to occur. Ingestion of trace amounts of the material might occur if material contacts the hands and hands are not washed prior to eating drinking or smoking. Irbesartan is well absorbed after ingestion.

Acute

Ingestion: Inadvertent ingestion of trace amounts of this material would not be expected to result in symptoms. Therapeutic doses can lower blood pressure in persons with high blood pressure. Ingestion of therapeutic doses by persons with normal blood pressure has occasionally resulted in a sudden fall in blood pressure when changing from a reclining to a standing position. Nausea, vomiting and headache have been reported in a few patients receiving therapeutic doses of this drug.

Inhalation: There is no information concerning the potential for this material to produce symptoms after inhalation. Most dusts may cause mechanical irritation (sneezing, tearing of the eyes) after high exposure. Systemic toxicity may be possible.

Skin Contact

a. ***Toxic***: There is no information concerning the potential for this material to produce symptoms after inhalation.
b. ***Irritation***: Irbesartan is not a skin irritant.
c. ***Sensitization***: The sensitization potential has not been evaluated.

Eye Contact: Material is not an eye irritant.

Chronic: Drug is an angiotensin II receptor antagonist. In persons with normal blood pressure, repeated exposure (50-100 mg/day) may result in a sudden fall in blood pressure when changing from the reclining to a standing position. In persons with high blood pressure, headaches have occasionally been reported after therapeutic doses.

Exposure Guideline Summary:

Carcinogen Lists ***IARC***: No. ***NTP***: No. ***OSHA***: No.

Target Organs: Specific target organs for toxicity have not been identified. Compound exerts pharmacological effects on the cardiovascular system.

Medical Conditions Aggravated by Exposure:

Medical Surveillance Recommendation: If exposure exceeds the exposure guideline, personnel should be monitored for orthostatic hypotension, complete blood count, and liver function tests.

FOR MORE INFORMATION REFER TO SECTION 11: TOXICOLOGICAL INFORMATION.

4. FIRST AID MEASURES

Ingestion: Get medical attention immediately. Vomiting may be induced if a person is conscious and not experiencing convulsions. Never give anything by mouth to an unconscious person.

Inhalation: Remove exposed person to fresh air. If person is not breathing give artificial respiration. If breathing is difficult administer oxygen. Get medical attention.

Skin Contact: Remove contaminated clothing. Wash thoroughly with soap and water. If signs of irritation (redness, swelling, itching, etc.) develop or persist, seek medical attention.

Eye Contact: Hold eyelids apart and flush with plenty of water for 15 minutes. Get medical attention immediately.

Note to physicians: Irbesartan is an angiotensin II antagonist and lowers blood pressure at therapeutic doses.

5. FIRE FIGHTING MEASURES

Flash point: Not applicable.
Autoignition Temperature: 510 degrees C for a dispersed dust cloud. .
Flammability limits
LEL: Not applicable.
UEL: Not applicable.

Combustibility of Dusts: Easily ignitable in presence of electrostatic or electric spark. Provide appropriate bonding and grounding protection to control static charges. Powder handling equipment such as dust collectors, dryers, and mills may require additional protective measures, i.e., explosion venting.

Extinguishing Media: In case of fire use water, carbon dioxide, foam, or dry chemical.

Firefighting Instructions: *Firefighters should wear* self-contained breathing apparatus (SCBA), flame and chemical resistant clothing, boots and gloves. Evacuate personnel to upwind direction, remove unneeded material and cool container(s) with water from maximum distance.

Hazardous Combustion Products: CO, CO_2, NO_x.

Unusual Hazards: Avoid sparks, heat and/or open flame.

6. ACCIDENTAL RELEASE MEASURES

Spill/Clean-up: Wearing suitable protective clothing, vacuum powder using a HEPA (high efficiency particulate air) filtered vacuum, or moisten and pick-up so as to minimize dust generation. Place into a suitable container for disposal. The spill area should be cleaned thoroughly with detergent and water and ventilated after material has been picked up. A laboratory coat or gown, impermeable gloves (latex or nitrile), a respirator with HEPA filters or cartridges and eye protection should be worn as a minimum precaution. Additional protective clothing/equipment may be needed depending on the quantity spilled and the extent of the spill.
SEE SECTION 8 FOR SPECIFICS OF PERSONAL PROTECTIVE CLOTHING

AND EQUIPMENT.

7. HANDLING AND STORAGE

Handling Precautions: Avoid static electricity build-up prior to and while handling irbesartan. Do not spill contents. Minimize dust generation.

Container Requirements: Stored as bulk drug using conducting drums and/or anti-static liners.

Storage Conditions: Store irbesartan in a dry place at or below room temperature in a tightly closed container. Protect from moisture.

8. EXPOSURE CONTROLS AND PERSONAL PROTECTION

Ventilation Requirements: Keep airborne concentrations below exposure guideline of 0.03 mg/m3 for irbesartan by enclosure of processes or local exhaust ventilation, as required.

Respiratory Protection: It is advisable to consult an industrial hygienist when selecting a respirator, especially when larger quantities are to be handled or if material is to be handled together with solvents or other compounds. For powder handling, when engineering controls are not sufficient to control exposure, wear an approved* respirator with HEPA filters or cartridges, or supplied air. A self-contained breathing apparatus should be available for emergency use.

*NIOSH approves respiratory protection in the U.S.

Eye Protection: Wear safety glasses (ANSI Z87.1).

Protective Gloves: Wear impervious (latex or nitrile) gloves if the potential exists for dermal contact.

Special Clothing: Wear laboratory coat or protective coveralls, whenever the potential for contact with the powder exists.

Hygiene: Wash hands after handling compound and before eating, smoking, using lavatory, and at end of day.

9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance/Physical State/Color: Practically white crystalline powder.
Boiling point: Not applicable.
Evaporation rate: Not applicable.
Flash point: Not applicable.
Freezing point/Melting point (degrees C): 185 degrees C; decomposition with gas evolution.
Octanol/water partition coefficient: Log Kow = 2.85 at pH 5; Log Kow = 1.13 at pH 7; Log Kow < 1 at pH 9.
Odor (threshold): Not available.
pH: Not available.
Solubility in water: Practically insoluble; 3.34 mcg/ml at pH 5; 302 mcg/ml at pH 7; 758 mcg/ml at pH 9.
Specific gravity: 1.30.
Vapor density (Air = 1): If adequate temperatures caused material to volatilize, its vapor density would be greater than 1 (heavier than air).
Vapor Pressure: less than 1 E -07 torr at 25 degrees C.
Viscosity: Solid material.
Dissociation Constant: pKa is 4.79 at 25 degrees C.

10. STABILITY AND REACTIVITY

Stability: Stable at room temperature. When material is heated as a bulk powder or as an aerated powder, an exotherm did not develop.

Incompatibilities: Avoid strong oxidizing agents.

Conditions of Reactivity: None identified under normal conditions of storage and handling.

Hazardous Decomposition Products: CO, CO2, NOx.

Hazardous Polymerization: Will not occur.

Explosion data relative to mechanical impact: No specific data.

Explosion data relative to static discharge:

Explosion Severity Factor (Kst): 383 bar-m/s
Explosion Class: ST-3, very strong explosion pressure.

Minimum Ignition Energy: < 3 mJ
Powder Resistivity: > 10 exponent 14 ohm.m
Charge Decay Time: 35 Hours (estimated).
Limiting oxygen concentration: 9.8-11.5%

Material exhibits very strong explosion characteristics if ignited as a dust cloud. Material is highly susceptible to accumulating static charges during processing and uncontrolled static discharge may result in igniting a dust cloud under certain conditions due to the low minimum ignition energy. Provide suitable bonding and grounding for containers and process equipment to control static charges. Powder handling equipment such as dust collectors, dryers, and mills may require additional protective measures (e.g. explosion venting).

11. TOXICOLOGICAL INFORMATION

RTECS # (U.S.):

ACUTE

LD 50:
Acute oral LD50 (rat) > 2000 mg/kg;
Acute oral LD50 (mouse) >2000 mg/kg;

LC 50: Not available.

CHRONIC

Repeated Dose Studies: In monkeys or rats treated daily for six months with oral doses (90 mg/kg) of irbesartan, mild decreases in blood pressure, decreased heart weight in females and mild to moderate hypertrophy and hyperplasia of the juxtaglomerular cells of the kidney were noted. In some female rats lesions of the glandular stomach were noted. Also in rats, decreased liver weights, slight changes in red blood cell parameters, and other slight changes in clinical chemistry and electrolyte values were noted.

Carcinogenicity: This compound was not carcinogenic when evaluated in CD1 mice or Wistar rats.

Mutagenicity: In the mouse bone marrow micronucleus study, oral administration of irbesartan indicated no genotoxicity at doses up to 4000 mg/kg/day. Irbesartan was negative for mutagenicity in the Ames test, in

V79 fibroblasts and in a DNA repair assay. It was not clastogenic in primary human lymphocytes.

Teratogenicity: Teratogenic effects were not observed in pregnant rabbits at doses up to 30 mg/kg/day. Slight maternal toxicity was seen at a dose of 10 mg/kg/day with more marked maternal toxicity (some abortions and resorptions) at 30 mg/kg/day. Teratogenic effects were not observed in pregnant rats at doses up to 450 mg/kg/day although maternal toxicity was noted from doses of 50 mg/kg/day or greater.

Reproductive Effects: The compound did not alter the fertility of male and female rats at doses up to 650 mg/kg/day. Some adverse effects on the F1 fetus were seen at doses from 50 mg/kg and greater.

Toxicological synergistic products: No studies of interactions with other drugs have been conducted. It is likely that irbesartan exposure would add to the effect of other antihypertensive medications.

12. ECOLOGICAL INFORMATION

Ecotoxicological Information:

Microbial Inhibition Assay: The compound did not inhibit most organisms at concentrations up to 1000 mg/l. The minimum inhibitory concentration for Bacillus megaterium was 800 mg/l.

Daphnia magna Acute Toxicity Assay - 24 and 48 hr EC50s were 203 and 191 mg/l, respectively. 48 hr no effect concentration was 86.4 mg/l.

Chemical Fate Information: Hydrolysis and photodegradation in aqueous environments may be primary routes of depletion in the environment. The hydrolytic route is quite dependent on pH.

Hydrolysis Half-life: $\geq$ 1 year, pH 5; 40 days, pH 7; 2.3 days, pH 9;

Aerobic Aqueous Biodegradation - Compound was not readily biodegraded.

Aqueous Photodegradation Half-life: < 10 hours at pHs ranging from 5-9.

Aerobic Soil Biodegradation - This compound has half-lives ranging from 641 to 4759 days in various soils. Only a small percentage of compound was metabolized during a 64 day test period.

Soil Adsorption/Desorption - Depending on soil type the Koc values varied from 110 to 869, suggesting that mobility of the compound in the soil may depend on such factors as pH and cation exchange capacity.

13. DISPOSAL CONSIDERATIONS

Disposal: Dispose of in accordance with National, State, Local, and applicable country regulations. Incineration is recommended.

14. TRANSPORT INFORMATION

DOMESTIC

Proper shipping name: Not classified.
Hazard Class, UN Number, Packing Group: Not classified.
Label requirements: Not applicable.
Placard requirements: Not applicable.

INTERNATIONAL

Proper shipping name: Not classified.
Hazard Class, UN Number, Packing Group: Not classified.
Label requirements: Not applicable.
Placard requirements: Not applicable.

Refer to Federal and international regulations for additional information.

15. REGULATORY/STATUTORY INFORMATION

U.S. Federal: Based on criteria of the OSHA Hazard Communication Standard, the hazards of this material include: effects on cardiovascular system.

International: See EC Labeling below.

EC Labeling: The following are risk and safety advice phrases for Irbesartan:

S33- Take precautionary measures against static discharges.

S36/37- Wear suitable protective clothing and gloves.
S38- In case of insufficient ventilation wear suitable respiratory equipment.

16. OTHER INFORMATION

November 22, 1996: The MSDS for Irbesartan, dated August 9, 1996, was updated to include changes to sections 1, 2, 3, and 11 (primarily health effects and toxicology information).

8-9-96: The MSDS for Irbesartan, dated 3-3-95, was updated in Section 3 to include additional health effects information, in Sections 9, 10 and 12 to include additional physical/chemical properties, stability and fate and effects data, and in section 15 to include additional regulatory information.

3-3-95: The MSDS for Irbesartan (BMS 186295-01) was updated to include additional Fire and Explosion and Stability information, and information in Section 15.

1-4-95: The MSDS of 06-21-94 for BMS 186295-01 was updated here to include additional toxicology and fire data, as well as proposed generic name of irbesartan.

06-21-94: This is the first MSDS to be issued by the Bristol-Myers Squibb Pharmaceutical Group for this material.

This compound is a drug substance intended for use under the direction of a physician. As a general precaution, personnel who handle drug substances should avoid contact (ingestion, inhalation, skin, and eye contact) with these substances. Smoking, drinking, or eating should not be allowed in the areas where this material is used.

This material safety data sheet is intended for use by personnel who handle this material as part of their job responsibilities. It does not address the therapeutic use of this material. Information concerning the therapeutic use of this drug substance should be obtained from formulated product package inserts and other appropriate references.

The information contained in this MSDS is believed to be accurate and represents the best information available at the time of preparation. However, we make no warranty, express or implied, with respect to such information, and we assume no liability from its use. MSDS136e.

MATERIAL SAFETY DATA SHEET

Sigma Chemical Co.
P.O. Box 14508
St. Louis, MO 63178
Phone: 314-771-5765

Aldrich Chemical Co., Inc.
1001 West St. Paul
Milwaukee, WI 53233
Phone: 414-273-3850

Fluka Chemical Corp.
980 South Second St.
Ronkonkoma, NY 11779
Phone: 516-467-3535

This information valid through April 30, 1997

SECTION 1. - - - - - - - - - - CHEMICAL IDENTIFICATION- - - - - - - - - -
CATALOG #: H4759
NAME: HYDROCHLOROTHIAZIDE

SECTION 2. - - - - - COMPOSITION/INFORMATION ON INGREDIENTS - - - - - -
CAS #: 58-93-5
MF: C7H8CLN3O4S2
EC NO: 200-403-3

SYNONYMS

AQUARILLS * AQUARIUS * BREMIL * 6-CHLORO-3,4-DIHYDRO-2H-1,2,4-BENZOTHIADIAZINE-7-SULFONAMIDE 1,1-DIOXIDE * 6-CHLORO-3,4-DIHYDRO-7-SULFAMOYL-2H-1,2,4-BENZOTHIADIAZINE 1,1-DIOXIDE * 6-CHLORO-7-SULFAMOYL-3,4-DIHYDRO-2H-1,2,4-BENZOTHIADIAZINE 1,1-DIOXIDE * CHLOROSULTHIADIL * CHLORSULFONAMIDODIHYDROBENZOTHIADIAZINE DIOXIDE * CHLORZIDE * CIDREX * DICHLOROSAL * DICHLOTIAZID * DICHLOTRIDE * DICLOTRIDE * 3,4-DIHYDRO-6-CHLORO-7-SULFAMYL-1,2,4-BENZOTHIADIAZINE-1,1-DIOXIDE * DIHYDROCHLOROTHIAZID * DIHYDROCHLOROTHIAZIDE * 3,4-DIHYDROCHLOROTHIAZIDE * DIHYDROXYCHLOROTHIAZIDUM * DIREMA * DISALUNIL * DRENOL * DYAZIDE * ESIDREX * ESIDRIX * FLUVIN * HCTZ * HCZ * HIDRIL * HIDROCHLORTIAZID * HIDRORONOL * HYDROTHIDE * HIDROTIAZIDA * HYDRIL * HYDRO-AQUIL * HYDROCHLOROTHIAZID * HYDROCHLOROTHIAZIDE * HYDROCHLORTHIAZIDE * HYDRODIURETIC * HYDRO-DIURIL * HYDROSALURIC * HYPOTHIAZID * HYPOTHIAZIDE * IDROTIAZIDE * IVAUGAN * JEN-DIRIL * MASCHITT * MEGADIURIL * NCI-C55925 * NEFRIX * NEO-CODEMA * NEOFLUMEN * ORETIC * PANURIN * RO-HYDRAZIDE * SU 5879 * THIARETIC * THIURETIC * URODIAZIN * VETIDREX *

SECTION 3. - - - - - - - - - - HAZARDS IDENTIFICATION - - - - - - - - -
LABEL PRECAUTIONARY STATEMENTS

HARMFUL
HARMFUL IF SWALLOWED.
MAY CAUSE SENSITIZATION BY INHALATION AND SKIN CONTACT.
PHOTOSENSITIZER.
TARGET ORGAN(S):
KIDNEYS
WEAR SUITABLE PROTECTIVE CLOTHING.

SECTION 4. - - - - - - - - - - FIRST-AID MEASURES- - - - - - - - - -
IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS.
CALL A PHYSICIAN.
IN CASE OF SKIN CONTACT, FLUSH WITH COPIOUS AMOUNTS OF WATER FOR AT LEAST 15 MINUTES. REMOVE CONTAMINATED CLOTHING AND SHOES. CALL A PHYSICIAN.
IF INHALED, REMOVE TO FRESH AIR. IF BREATHING BECOMES DIFFICULT, CALL A PHYSICIAN.
IN CASE OF CONTACT WITH EYES, FLUSH WITH COPIOUS AMOUNTS OF WATER FOR AT LEAST 15 MINUTES. ASSURE ADEQUATE FLUSHING BY SEPARATING THE EYELIDS WITH FINGERS. CALL A PHYSICIAN.

SECTION 5. - - - - - - - - - - FIRE FIGHTING MEASURES - - - - - - - - -
EXTINGUISHING MEDIA

CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.
SPECIAL FIREFIGHTING PROCEDURES
WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO PREVENT CONTACT WITH SKIN AND EYES.
UNUSUAL FIRE AND EXPLOSIONS HAZARDS
EMITS TOXIC FUMES UNDER FIRE CONDITIONS.
TION 6. - - - - - - - - - ACCIDENTAL RELEASE MEASURES- - - - - - - - - -
WEAR RESPIRATOR, CHEMICAL SAFETY GOGGLES, RUBBER BOOTS AND HEAVY RUBBER GLOVES.
SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.
AVOID RAISING DUST.
VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.
SECTION 7. - - - - - - - - - - - HANDLING AND STORAGE- - - - - - - - - - -
REFER TO SECTION 8.
SECTION 8. - - - - - - - EXPOSURE CONTROLS/PERSONAL PROTECTION- - - - - -
NIOSH/MSHA-APPROVED RESPIRATOR.
USE ONLY IN A CHEMICAL FUME HOOD.
COMPATIBLE CHEMICAL-RESISTANT GLOVES.
CHEMICAL SAFETY GOGGLES.
SECTION 9. - - - - - - - - PHYSICAL AND CHEMICAL PROPERTIES - - - - - - -
APPEARANCE AND ODOR
SOLID.
PHYSICAL PROPERTIES
MELTING POINT: 269-270'C
SOLUBILITY:
WATER -INSOLUBLE
METHANOL-SOLUBLE
SECTION 10. - - - - - - - - - -STABILITY AND REACTIVITY - - - - - - - - -
STABILITY
STABLE.
HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS
CARBON MONOXIDE, CARBON DIOXIDE
NITROGEN OXIDES
SULFUR OXIDES
HYDROGEN CHLORIDE GAS
HAZARDOUS POLYMERIZATION
WILL NOT OCCUR.
SECTION 11. - - - - - - - - - - TOXICOLOGICAL INFORMATION - - - - - - - -
ACUTE EFFECTS
HARMFUL IF SWALLOWED.
MAY BE HARMFUL IF ABSORBED THROUGH THE SKIN.
MAY BE HARMFUL IF INHALED.
MAY CAUSE ALLERGIC REACTION.
PHOTOSENSITIZER.
EXPOSURE CAN CAUSE:
NAUSEA, DIZZINESS AND HEADACHE
OTHER SYMPTOMS MAY INCLUDE ERYTHEMA MULTIFORME, VOMITING, DIARRHEA, AND MUSCLE SPASM.
CHRONIC EFFECTS
TARGET ORGAN(S):
KIDNEYS
RTECS #: DK9100000
2H-1,2,4-BENZOTHIADIAZINE-7-SULFONAMIDE, 6-CHLORO-3,4-DIHYDRO-, 1,1-DIOXIDE
TOXICITY DATA

ORL-WMN LDLO:2500 UG/KG/5D-I	AJMEAZ 70,1163,81
ORL-RAT LD50:2750 MG/KG	TXAPA9 1,333,59
IPR-RAT LD50:234 MG/KG	27ZIAQ -,124,73
SCU-RAT LD50:1270 MG/KG	27ZIAQ -,124,73
IVN-RAT LD50:990 MG/KG	JPETAB 140,249,63

ORL-MUS LD50:1175 MG/KG FRZKAP (1),44,83
IPR-MUS LD50:578 MG/KG 27ZIAQ -,77,65
SCU-MUS LD50:1470 MG/KG 27ZIAQ -,124,73
IVN-MUS LD50:590 MG/KG JPETAB 134,273,61
UNR-MUS LD50:1100 MG/KG FRZKAP (5),26,83
IVN-DOG LD50:250 MG/KG 27ZIAQ -,124,73
IVN-RBT LD50:461 MG/KG 27ZIAQ -,124,73

TARGET ORGAN DATA

PERIPHERAL NERVE AND SENSATION (SPASTIC PARALYSIS WITH/WITHOUT SENSORY CH
BEHAVIORAL (CONVULSIONS OR EFFECT ON SEIZURE THRESHOLD)
BEHAVIORAL (COMA)
VASCULAR (BP LOWERING NOT CHARACTERIZED IN AUTONOMIC SECTION)
LUNGS, THORAX OR RESPIRATION (ACUTE PULMONARY EDEMA)
LUNGS, THORAX OR RESPIRATION (CYANOSIS)
LUNGS, THORAX OR RESPIRATION (OTHER CHANGES)
GASTROINTESTINAL (NAUSEA OR VOMITING)
NUTRITIONAL AND GROSS METABOLIC (CHANGES IN: NA)
NUTRITIONAL AND GROSS METABOLIC (CHANGES IN: Cl)
NUTRITIONAL AND GROSS METABOLIC (BODY TEMPERATURE INCREASE)
NUTRITIONAL AND GROSS METABOLIC (OTHER CHANGES)
ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES (RTECS) DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR COMPLETE INFORMATION.

SECTION 12. - - - - - - - - - - ECOLOGICAL INFORMATION - - - - - - - - - -

DATA NOT YET AVAILABLE.

SECTION 13. - - - - - - - - - - DISPOSAL CONSIDERATIONS - - - - - - - - - -

DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN IN A CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER. OBSERVE ALL FEDERAL, STATE AND LOCAL ENVIRONMENTAL REGULATIONS.

SECTION 14. - - - - - - - - - - TRANSPORT INFORMATION - - - - - - - - - -

CONTACT SIGMA CHEMICAL COMPANY FOR TRANSPORTATION INFORMATION.

TION 15. - - - - - - - - - - REGULATORY INFORMATION - - - - - - - - - -

EUROPEAN INFORMATION

HARMFUL
R 22
HARMFUL IF SWALLOWED.
R 42/43
MAY CAUSE SENSITIZATION BY INHALATION AND SKIN CONTACT.
S 36
WEAR SUITABLE PROTECTIVE CLOTHING.

REVIEWS, STANDARDS, AND REGULATIONS

OEL=MAK
IARC CANCER REVIEW:HUMAN INADEQUATE EVIDENCE IMEMDT 50,293,90
IARC CANCER REVIEW:ANIMAL INADEQUATE EVIDENCE IMEMDT 50,293,90
IARC CANCER REVIEW:GROUP 3 IMEMDT 50,293,90
EPA GENETOX PROGRAM 1988, INCONCLUSIVE: HISTIDINE REVERSION-AMES TEST
EPA TSCA SECTION 8(B) CHEMICAL INVENTORY
NTP CARCINOGENESIS STUDIES (FEED);EQUIVOCAL EVIDENCE:MOUSE
NTPTR* NTP-TR-357,89
NTP CARCINOGENESIS STUDIES (FEED);NO EVIDENCE:RAT
NTPTR* NTP-TR-357,89

SECTION 16. - - - - - - - - - - OTHER INFORMATION- - - - - - - - - - -

THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT PURPORT TO BE ALL INCLUSIVE AND SHALL BE USED ONLY AS A GUIDE. SIGMA, ALDRICH, FLUKA SHALL NOT BE HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING OR FROM CONTACT WITH THE ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR PACKING SLIP FOR ADDITIONAL TERMS AND CONDITIONS OF SALE.

NON-CONFIDENTIAL APPENDIX

SECTION A2

Environmental Certification Statement
Sanofi Chimie, Aramon, France

USINE D'ARAMON
ROUTE D'AVIGNON
30390 ARAMON
TÉL. : (33) 66 57 71 71
FAX : (33) 66 57 72 91
Telex 490 004

sanofi CHIMIE

Aramon, July 25 1996

Bristol-Myers Squibb
Pharmaceutical Research Institute
Regulatory Affairs Department
P.O. Box 4000
Princeton, NJ 08543-4000
U.S.A.

Re: Drug Substance IRBESARTAN
Certification of Compliance
with Environmental Regulations

Dear Sirs,

Pursuant to U.S. Executive Order 12114 "Environmental Effects Abroad of Major Federal Actions", the undersigned official certifies that all irbesartan manufacturing facilities named below are in compliance with, or on an enforceable schedule to be in compliance with all local and national environmental laws and all emission requirements set forth in all permits, and that approval and the subsequent increase in production at the facilities named below is not expected to affect compliance with current emission requirements or compliance with environmental laws.

Sincerely yours,

Pierre Chastagnier

Title: Plant Manager
Facilities: Aramon Facilities
Date: July 25 1996