CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-727

ENVIRONMENTAL ASSESSMENT/FONSI

CDER Establishment Evaluation Report
for April 24, 1997

Application: **NDA 20727/000**
Stamp: **03-JUL-1996** Regulatory Due: **03-JUL-1997**
Applicant: **MEDCO**
85 TW ALEXANDER DR
RESEARCH TRIANGLE PARK, NC 2

Priority: **4S** Org Code: **110**
Action Goal: District Goal: **03-MAR-1997**
Brand Name: **BIDIL(HYDRALAZINE HCL/ISOSORB**
Established Name:
Generic Name: **HYDRALAZINE HCL/ISOSORBIDE DI**
Dosage Form: **TAB (TABLET)**
Strength: **75/40,75/20,37.5/20,37.**

FDA Contacts:

Overall Recommendation:

Establishment: [redacted]
DMF No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **ASSIGNED INSPECTIO 25-SEP-1996**

Responsibilities:
[redacted]

Establishment: [redacted]
DMF No: [redacted]

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATI 10-JAN-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:
[redacted]

Establishment: [redacted]
DMF No: [redacted]

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATI 30-JUL-1996**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:
[redacted]

Establishment: [redacted]
DMF No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATI 30-JUL-1996**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:
[redacted]

Establishment: [ ]

DMF No: [ ]

Profile: **CSN** OAI Status: **NONE**

Last Milestone: **OC RECOMMENDATI 30-JUL-1996**

Decision: **ACCEPTABLE**

Reason: **BASED ON PROFILE**

Responsibilities:

[ ]

Appears This Way
On Original

CDER Establishment Evaluation Report
for July 01, 1997

Application: **NDA 20727/000**
Stamp: **03-JUL-1996** Regulatory Due: **03-JUL-1997**
Applicant: **MEDCO**
85 TW ALEXANDER DR
RESEARCH TRIANGLE PARK, NC 2

Priority: **4S** Org Code: **110**
Action Goal: District Goal: **03-MAR-1997**
Brand Name: **BIDIL(HYDRALAZINE HCL/ISOSORB**
Established Name:
Generic Name: **HYDRALAZINE HCL/ISOSORBIDE DI**
Dosage Form: **TAB (TABLET)**
Strength: **75/40,75/20,37.5/20,37.**

FDA Contacts:

Overall Recommendation:

ACCEPTABLE on 18-JUN-1997 by M. EGAS (HFD-322) 301-594-0095

Establishment: [redacted]
DMF No: [redacted]

Responsibilities:
[redacted]

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATI 10-JAN-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: [redacted]
DMF No: [redacted]

Responsibilities:
[redacted]

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATI 30-JUL-1996**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: [redacted]
DMF No:

Responsibilities:
[redacted]

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATI 30-JUL-1996**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: [redacted]
DMF No: [redacted]

Responsibilities:
[redacted]

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATI 30-JUL-1996**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

4 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

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

The active ingredients will be manufactured at various sites worldwide. The drug product BiDil™, is a tablet formulation manufactured from the active ingredients at Global Pharm Inc. The molecular structure of hydralazine HCl and ISDN are shown in Figures 5-1 and 5-2, respectively.

5.1 NOMENCLATURE

5.1.1 Hydralazine Hydrochloride

5.1.1.1 Chemical Name

1(2H)Phthalazinone hydrazone hydrochloride

5.1.1.2 United States Adopted Name (USAN)

Hydralazine Hydrochloride

5.1.1.3 CAS Registry Number

304-20-1

5.1.1.4 Molecular Formula and Weight

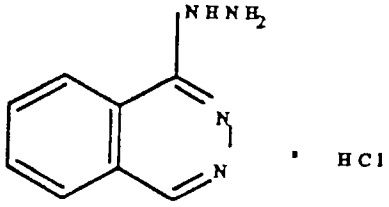
$C_8H_8N_4 \cdot HCl$; 196.64

5.1.1.5 Physical Description

White crystalline powder

Figure 5-1

Structure of Hydralazine Hydrochloride



5.2.1 Isosorbide Dinitrate (ISDN)

5.2.1.1 Chemical Name

1,4:3,6-Dianhydro-d-glucitol-2,5 dinitrate

5.2.1.2 United States Adopted Name (USAN)

Isosorbide dinitrate (ISDN)

5.2.1.3 CAS Registry Number

87-33-2 (ISDN)

64044-51-5 (Lactose)

5.2.1.4 Molecular Formula and Weight

$C_6H_8N_2O_8$ (ISDN); 236.14 (ISDN)

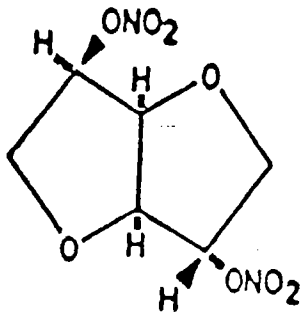
$C_{12}H_{22}O_{11}$ (Lactose); 342.30 (Lactose)

5.2.1.5 Physical Description

White crystalline powder

Figure 5-2

Structure of ISDN



5.3 IMPURITIES AND ADDITIVES

The raw materials of BiDil™ are presented in Appendix C, Table C.5-1. As seen from the table, most of the raw materials (except the active ingredients) are readily biodegradable.

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

BIDIL TABLETS

(hydralazine HCl / isosorbide dinitrate)

NDA 20-727

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF
CARDIO-RENAL DRUG PRODUCTS
(HFD-110)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-727

BIDIL TABLETS

[hydralazine HCl / isosorbide dinitrate]

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 this action 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 BiDil Tablets, Medco Research, Inc. (Research Triangle Park, NC 27709) conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a (a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Hydralazine HCl and isosorbide dinitrate are synthetic drug substances which are combined in an oral tablet administered for the treatment of congestive heart failure. Hydralazine HCl is manufactured by Sumika Fine Chemicals Co. Ltd. (Osaka 541, Japan). Isosorbide dinitrate is manufactured by EMS-Dottikon AG (Dottikon, Switzerland). Combination tablets are manufactured by Global Pharm Inc., (Don Mills, Ontario, Canada). The drug product is distributed by Medco Research, Inc. All facilities are certified to operate in accord with applicable environmental regulations. The drug product, either 37.5 mg hydralazine HCl combined with 10 or 20 mg isosorbide dinitrate or 75 mg hydralazine HCl combined with 20 or 40 mg isosorbide dinitrate will be used in hospitals, clinics and by patients in their homes.

Hydralazine HCl is extensively metabolized in-vivo. It and its metabolites will be excreted into the sewer system. Chemical and physical properties indicate that they will be restricted to the aquatic environment. Hydralazine decomposes by photolysis, slow hydrolysis and aerobic bio-transformation. As hydralazine is not expected to persist in the aquatic environment, its toxicity to aquatic organisms was not evaluated. Isosorbide dinitrate is known to be metabolized completely in-vivo. It also decomposes by photolysis. The maximum expected environmental concentrations (MEEC) of both drug substances in the aquatic environment based only on maximum production estimates for the next 5 years are less than 1 ppb and as a result, environmental effects are not expected.

Disposal includes out of specification lots, returned, unused or expired product, empty or partly used product and packaging. These will be disposed at licensed incineration facilities and landfills. Empty or partially empty packages generated in American hospitals and clinics will be disposed according to their regulations. Empty or partially empty containers from home use will be disposed in the community solid waste management system which may include landfills, incineration and recycling. Minimal quantities of unused drug may be disposed in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed 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.

7/24/1996 Florian Zielinski
DATE PREPARED BY: Florian Zielinski, Review Chemist
Division of New Drug Chemistry I

7/25/96 Robert J Wolters
DATE DIVISION CONCURRENCE: Robert J Wolters,
Division of New Drug Chemistry I

8/28/96 Nancy B Sager
DATE APPROVED: Nancy B. Sager, Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment (Ref.: Vol. 1.6, pages 1 to 78)
Material Safety Data Sheets (Ref.: Vol. 1.6, pages 47 to 52)
a) hydralazine HCl
b) isosorbide dinitrate
Compliance Statements (Ref.: Vol. 1.6, pages 75A, C & E , 76A and 78)

Original: NDA 20-727
HFD-357 FONSI File [NDA # 20-727]
HFD-357 Docket File
HFD-205 FOI COPY
HFD-110 Division File
HFD-110 CSO, Gary Buehler
HFD-110 Review Chemist, Florian Zielinski

NON-CONFIDENTIAL

Environmental Assessment of BiDil™

Medco Research, Inc.
85 T.W. Alexander Drive
Research Triangle Park, NC 27709

This Environmental Assessment (EA) Report and the Appendix A of this report containing the MSDS and the compliance certificates from the manufacturers are non-confidential. Appendix B is a confidential appendix that contains the study reports in support of the Environmental Assessment Report. Appendix C is the full EA report that contains confidential trade secrets or information from which these trade secrets can be derived. This material could be beneficial to competitors and, therefore, this appendix should not be duplicated for distribution.

TABLE OF CONTENTS

TABLE OF CONTENTS (Continued)

TABLE OF CONTENTS (Continued)

TABLE OF CONTENTS (Continued)

SECTION PAGE

TABLE OF CONTENTS (Continued)

SECTION PAGE

1. **DATE**

February 8, 1996

2. **NAME OF APPLICANT**

Medco Research, Inc.

3. **ADDRESS**

85 T.W. Alexander Drive

Research Triangle Park, NC 27709

4. **DESCRIPTION OF THE PROPOSED ACTION**

4.1 **REQUESTED APPROVAL**

Medco Research, Inc. is seeking the approval of NDA 20-727 for the manufacture, packaging, distribution and use of the drug product, BiDil™ tablets in four strengths pursuant to Section 505(b) of the Food and Drug Cosmetic Act. The BiDil™ tablets have two active ingredients: 1) hydralazine HCl [1(2H)Phthalazinone hydrazone hydrochloride]; and 2) isosorbide dinitrate [1,4:3,6-Dianhydro-d-glucitol-2,5-dinitrate; (ISDN)]. The ISDN as manufactured has 25% isosorbide dinitrate and 75% lactose. The quantity of ISDN in the tablet strengths presented below represents active ingredients only. Approval is sought for the manufacture of BiDil™ tablets of differing combinations of the two active ingredients hydralazine hydrochloride and isosorbide dinitrate as stated below in Table 4-1.

Table 4-1

BiDil™ Tablets Strengths Requiring NDA Approval

	Hydralazine (in mg)	ISDN (in mg)
1.	75	40
2.	75	20
3.	37.5	20
4.	37.5	10

The maximum forecasted quantities of the active ingredients that will be required to manufacture the drug product from 1997 to 2001 are presented in confidential Appendix C. Since the hydralazine and ISDN are two active ingredients in the drug product their amounts for each year are provided separately in this appendix.

The Environmental Assessment (EA) Report has been prepared and submitted in accordance with 21 CFR § 25.31 (a). The full EA report is presented in the Confidential Appendix C of this public EA document [Freedom of Information (FOI) Document]. The subject matter presented in the Confidential Appendix C includes proprietary information that cannot be disclosed. Appendix A of this public document (FOI document) is a non-confidential Appendix containing Material Safety Data Sheets (MSDS) for the raw materials. Appendix B is a confidential Appendix of the public document containing study reports in support of this EA.

4.2 NEED FOR ACTION

BiDil™ is the combination of hydralazine and ISDN/Lactose in one formulation that is used for the treatment of congestive heart failure.

The major effects of hydralazine are on the cardiovascular system. Hydralazine, by altering cellular calcium metabolism, interferes with the calcium movements within the vascular smooth muscle that are responsible for initiating or maintaining the contractile state. The peripheral vasodilating effect of hydralazine results in decreased

arterial blood pressure (diastolic more than systolic); decreased peripheral vascular resistance; and an increased heart rate, stroke volume, and cardiac output. The preferential dilatation of arterioles, as compared to veins, minimizes postural hypotension and promotes the increase in cardiac output.

The principal pharmacological action of isosorbide dinitrate is relaxation of vascular smooth muscle, producing a vasodilatory effect on both peripheral arteries and veins, with predominant effects on the latter. Dilation of the postcapillary vessels, including large veins, promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left-ventricular end-diastolic pressure (preload). Arteriolar relaxation reduces systemic vascular resistance and arterial pressure (afterload).

4.3 PRODUCTION LOCATIONS

Three major locations are involved in the manufacture of the drug product BiDil™ (Figure 4-1), two involved in the manufacture of two active ingredients and one location in the manufacture of drug product BiDil™ tablets. Medco Research, Inc. will be the distributor of BiDil™ tablets in the United States. Approval is sought to manufacture the formulated drug product, BiDil™ tablets, at the following locations:

1. Sumika Fine Chemicals Co. Ltd., Daiichi Karai Koraibushi Bldg., 2-7 Koraibashi 4-chome Chuo-Ku, Osaka 541, Japan - manufacturer of Hydralazine HCl.
2. EMS-DOTTIKON AG, CH-5605, Dottikon, Switzerland - manufacturer of ISDN/Lactose.
3. Global Pharm Inc., 865 York Mills Road, Unit 2, Don Mills, Ontario M3B 1Y6 Canada - manufacturer of the drug product, BiDil™ tablets.

The two active ingredients from the overseas locations will be shipped to Global Pharm Inc. for production of the drug product. All packaging operations are carried out at the Global Pharm Inc., Canada facility. Approval is also sought to manufacture and package the drug product at Global Pharm Inc., Canada, for distribution by Medco Research, Inc., 85 T.W. Alexander Drive, Research Triangle Park, NC 27709.

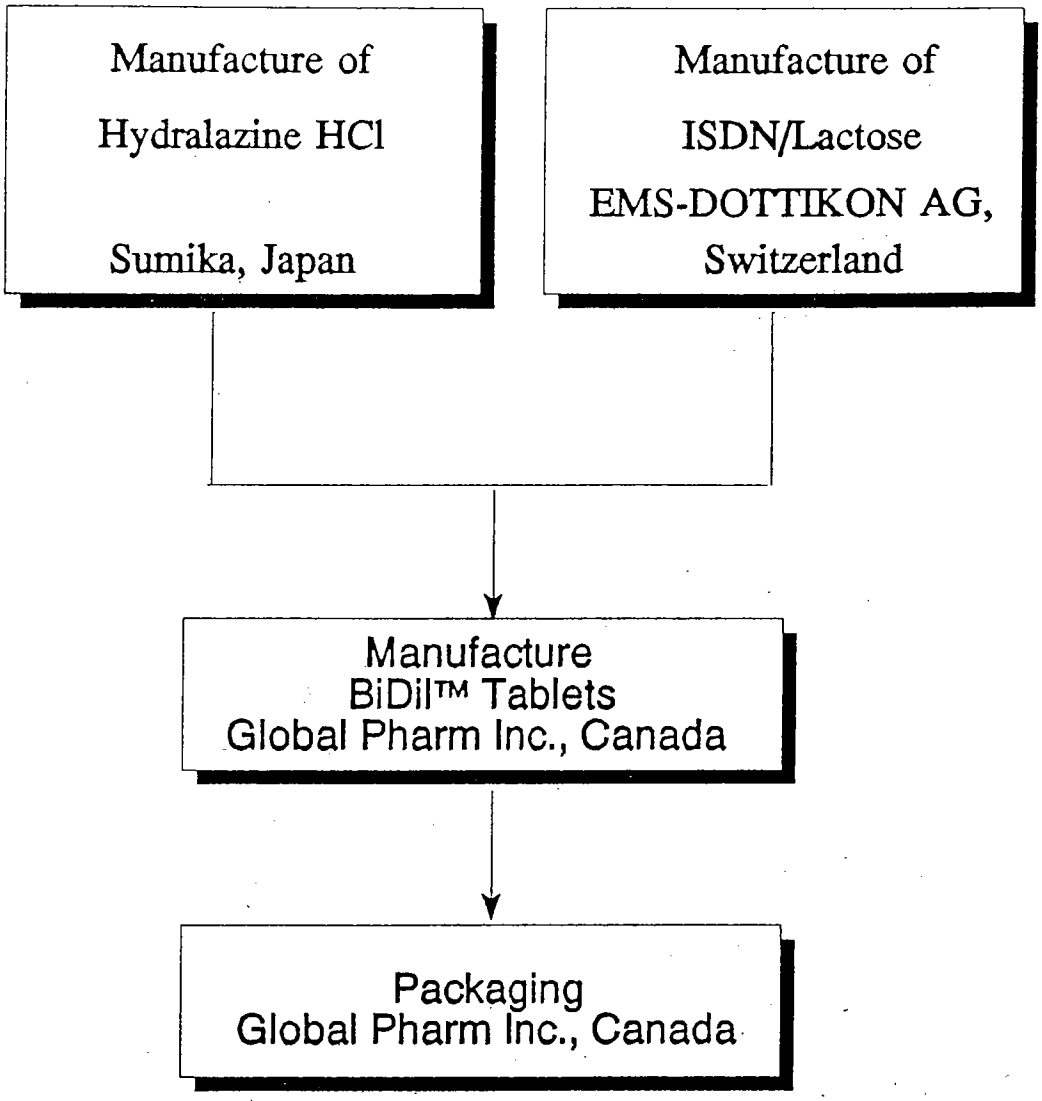


Figure 4-1
SITES RELEVANT TO THE MANUFACTURE
OF BiDil™ TABLETS

4.4 LOCATIONS OF USE AND DISPOSAL

As medication prescribed to treat congestive heart failure, BiDil™ tablets will be ingested by patients throughout the United States. The drug substances and its metabolites are excreted by patients which will enter municipal treatment systems through domestic sewage.

Off specification lots of active ingredients or any unused drug product that is returned to Medco Inc. (beyond expiration date) will be sent to one of a number of alternative contractors for incineration.

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

The active ingredients will be manufactured at various sites worldwide. The drug product BiDil™, is a tablet formulation manufactured from the active ingredients at Global Pharm Inc. The molecular structure of hydralazine HCl and ISDN are shown in Figures 5-1 and 5-2, respectively.

5.1 NOMENCLATURE

5.1.1 Hydralazine Hydrochloride

5.1.1.1 Chemical Name

1(2H)Phthalazinone hydrazone hydrochloride

5.1.1.2 United States Adopted Name (USAN)

Hydralazine Hydrochloride

5.1.1.3 CAS Registry Number

304-20-1

5.1.1.4 Molecular Formula and Weight

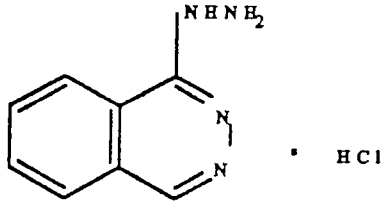
$C_8H_8N_4 \cdot HCl$; 196.64

5.1.1.5 Physical Description

White crystalline powder

Figure 5-1

Structure of Hydralazine Hydrochloride



5.2.1 Isosorbide Dinitrate (ISDN)

5.2.1.1 Chemical Name

1,4:3,6-Dianhydro-d-glucitol-2,5 dinitrate

5.2.1.2 United States Adopted Name (USAN)

Isosorbide dinitrate (ISDN)

5.2.1.3 CAS Registry Number

87-33-2 (ISDN)

64044-51-5 (Lactose)

5.2.1.4 Molecular Formula and Weight

$C_6H_8N_2O_8$ (ISDN); 236.14 (ISDN)

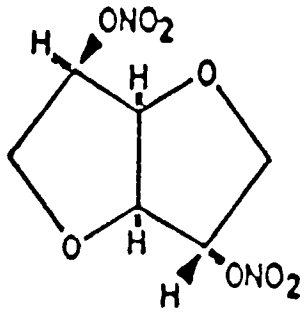
$C_{12}H_{22}O_{11}$ (Lactose); 342.30 (Lactose)

5.2.1.5 Physical Description

White crystalline powder

Figure 5-2

Structure of ISDN



5.3 IMPURITIES AND ADDITIVES

The raw materials of BiDil™ are presented in Appendix C, Table C.5-1. As seen from the table, most of the raw materials (except the active ingredients) are readily biodegradable.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

The drug product is manufactured by blending the two active ingredients, ISDN/Lactose and hydralazine HCl. This is then immediately followed by the addition of the other raw materials (Appendix C, Table C.5-1) which are then processed into the drug product, BiDil™ tablets. All processing equipment is enclosed to minimize release of the raw materials to the environment. All the components of the drug product with the exception of Opadry Dark Orange, Opadry Dark Yellow, and purified water are dispensed by modules designed for computerized weighing and dispensing in a closed system. Appendix C, Figure C.6-1 and Attachment C.15-1 illustrate this manufacturing process.

6.1 SYNTHESIS OF HYDRALAZINE HCl AT SUMIKA FINE CHEMICALS CO. LTD., JAPAN

Synthesis of the active ingredient, hydralazine HCl, is conducted by Sumika Fine Chemicals Co. Ltd., Japan. Compliance with environmental laws, occupational safety, and health by the manufacturer and governmental agency are provided in Appendix C, Attachment C.15-2 and C.15-3, respectively.

6.2 SYNTHESIS OF ISDN AT EMS-DOTTIKON AG, SWITZERLAND

Synthesis of the active ingredient ISDN is conducted by EMS-DOTTIKON AG, Switzerland. ISDN is subsequently diluted with lactose prior to shipment and use. Compliance with environmental laws, occupational safety, and health by the manufacturer and governmental agency are provided in Appendix C, Attachment C.15-2 and C.15-3, respectively.

6.3 PREPARATION OF THE DRUG PRODUCT, BiDil™ TABLETS, AT GLOBAL PHARM INC., CANADA

6.3.1 SUBSTANCES EMITTED DURING MANUFACTURING

Atmospheric Emissions

Air emissions from the manufacture of BiDil™ tablets are estimated to be [ ] Kg per lot of tablets. Equipment used in the manufacture of the tablets is equipped with Rotoclone dust collectors. The majority of the dust collected is discharged into the sanitary sewer. A small portion of dust [ ] Kg) is released into the air. No organic materials are used in the manufacturing process and thus no volatile organic emissions are anticipated.

Aqueous Wastes

Drug product which is lost into the aqueous waste stream is from equipment cleaning, exhaust air scrubbers, vacuum cleaners, etc. and is estimated to be [ ] Kg per lot of tablets. All wastewater from this facility is discharged to the Municipality of Metropolitan Toronto Privately Owned Treatment Works (POTW) where it is treated and then released.

Solid Wastes

Solid wastes from the manufacture of BiDil™ tablets represent the largest part of material loss. This is estimated to only be — Kg per lot of tablets. Dust captured in filters and vacuum cleaners, rejected tablet cores, and residuals from equipment cleaning make up the bulk of this solid waste. This waste is identified as pharmaceutical waste and disposed of by incineration. Non-hazardous waste (bottles, corrugated cardboard, fiber drums, etc.) is collected and landfilled in the Municipality of Toronto run landfill under Bill #143.

6.3.2 CONTROLS EXERCISED ON RESIDUALS AND EMISSIONS

No volatile organic emissions will be generated during production of the drug product. Emission controls consist of Rotoclone dust collectors which control the release of particulates generated during manufacturing. Aqueous wastes are sewered into the general wastewater discharge. Solid wastes are disposed of at permitted waste facilities. The manufacturing facility is not permitted to dispose of hazardous waste on site. All hazardous and pharmaceutical waste is incinerated. A spill procedure and spill control team are in place. Philip Environmental, 124 Cushman Road, St. Catharines, Ontario, Canada, has been retained to provide an emergency back up to the facility onsite spill control team.

6.3.3 COMPLIANCE OF PROPOSED ACTION WITH APPLICABLE EMISSION REQUIREMENTS

Since particulate and volatile organic emissions are insignificant, manufacturing the drug product will be in compliance with the Ontario Environmental Protection Act, Section 9. The manufacturing facility has a Certificate of Approval for air emissions from the Canadian government (Approval Numbers; 8-3358-92-006 and 8-4305-92-938). Amendment of the Certificate of Approval to include manufacturing of BiDil™ tablets is in progress.

Wastewater from manufacturing is regulated by the Municipality of Metropolitan Toronto under BY-LAW #153-89. The Global Pharm, Inc. facility is registered as a waste generator in the province of Ontario under Regulation 309 Section 15(4)

of the Environmental Protection Act. The registration number is ON0039500. Non-hazardous solid wastes will be landfilled by the Municipality of Toronto under Bill 143. Incineration of hazardous and pharmaceutical waste is conducted by Laidlaw Medical Services in Gatineau, Quebec (Provincial I.D. #L7530-07-20).

Certification of compliance with applicable emission requirements for the manufacture of drug product at Global Pharm Inc. from the facility manager is provided in Appendix A-2.

6.3.4 EFFECT OF THE PROPOSED ACTION ON COMPLIANCE WITH CURRENT EMISSION REQUIREMENTS

Emissions and releases from the manufacture of active ingredients and drug product will not exceed the limitations of current permits and proposed permit amendments. Manufacturing will be scheduled to fit within the existing framework of activities for which current and proposed emission requirements are applicable.

6.4 OCCUPATIONAL SAFETY

Employees are trained in the proper operation of equipment and chemicals used in manufacture of the drug product in order to minimize potential safety, health and environmental risks. The air handling system for each manufacturing module is separate and is filtered and monitored to maintain the exposure of chemical to personnel below all threshold values. Extensive safety training is mandated, and Material Safety Data Sheets (Appendix A-1) are available to personnel for chemicals handled in the manufacturing area. Employee training is conducted on the chemical hazards associated with manufacturing.

Specified personal protective equipment (e.g., gloves, self contained filtered air respirators, safety shoes, eye protection, disposable body suits, etc.) and engineering controls designed for the equipment (e.g., exhausts to remove dust) are adequate to protect the employees.

The safe transport of all drug-related materials is ensured by following protocols which include formal qualification of vendors, training of personnel, and rigid

specification of containers and materials. Access to drug substances and products is restricted to authorized personnel.

6.5 AMOUNT OF SUBSTANCES ENTERING THE ENVIRONMENT

Human drugs find their way into the environmental compartments (i.e., soil, air, water) through manufacture, use, disposal and accidental spills. The two major sources of environmental exposure of the drug are: 1) the patients who use the drug product; the drug product and/or its metabolites are discharged into the domestic sewer through excreta of the patients; and 2) manufacturing plants; release of the drug or its precursors or by-products through wastewater from the manufacturing plants. In either case the municipal domestic sewage could be the main recipient of these contaminant sources. The domestic sewage is finally discharged into the municipal wastewater treatment plant (WTP). The concentrations and releases in the subsections below are estimated without taking into consideration any degradation of the drug or its products at the manufacturing plants or during transport in the municipal sewage to the WTP, and, therefore, are worst case scenarios. The fate of emitted drug substances in the environment is discussed in Section 7.0 and the effects of these substances are discussed in Section 8.0, with a summary provided in Tables 7-1 and 7-2.

6.5.1 Human Elimination

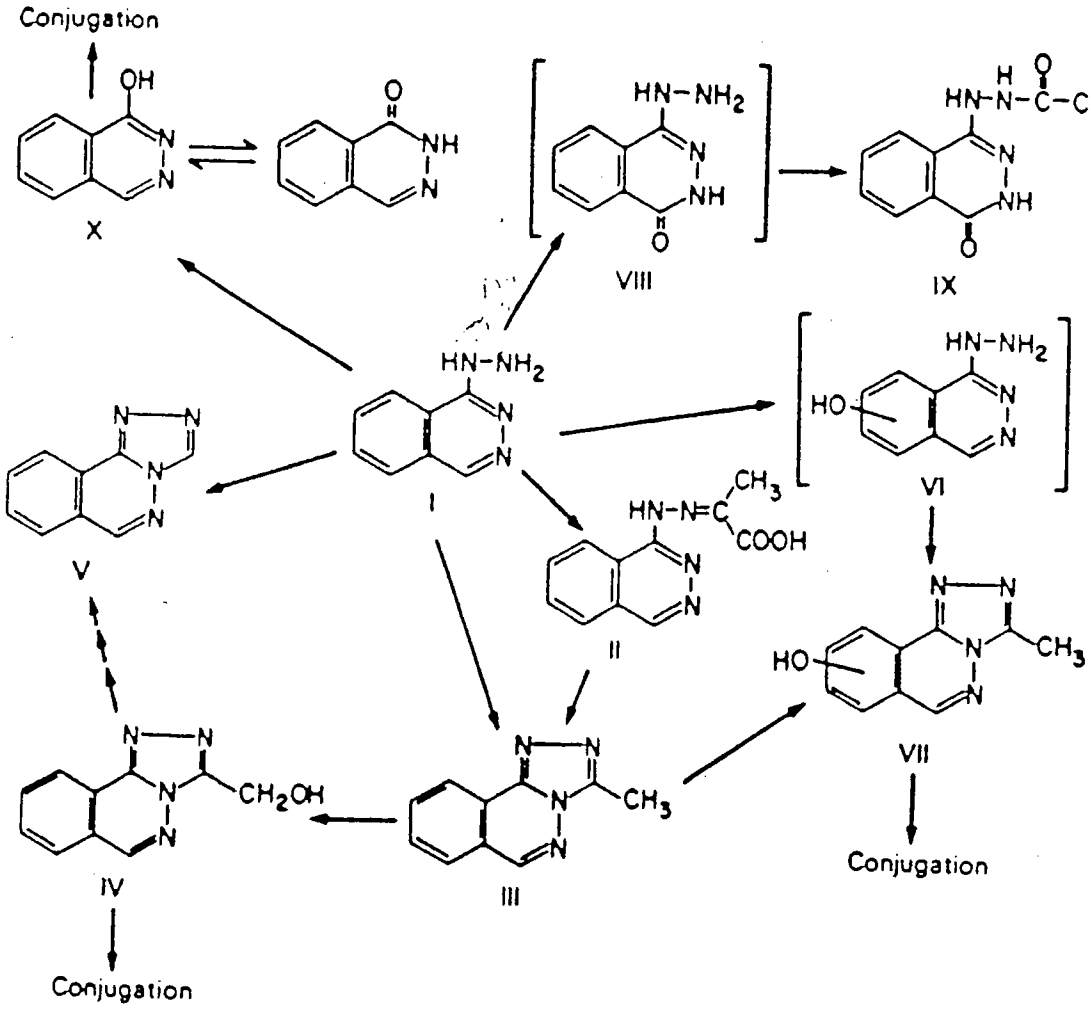
For the sake of estimation of Maximum Emitted Environmental Concentrations (MEEC), it is assumed that all the drug is consumed by patients and excreted intact through urine and feces. Hydralazine is extensively metabolized in the human body. Studies measuring the urinary excretion of radioactivity after oral administration of ^{14}C-hydralazine indicate that 52 to 90% of the dose is ultimately found in the urine. About 10% of the administered activity is found in the feces. Only small amounts of hydralazine (1 to 15%) are found in the urine. The most abundant urinary metabolite is 4-(2-acetylthydrasino-phthalazin-1-one (Figure 6-1). The major circulating metabolite of hydralazine in man is hydralazine pyruvic acid hydrazone (HPH) which is known to degrade in urine. In rats, HPH was metabolized to expired carbon dioxide (Ludden et al., 1982). Thus, hydralazine

could be eliminated substantially before being excreted through urine or feces. ISDN is known to be completely metabolized in humans to isosorbide-5-mononitrate and isosorbide-2-mononitrate (Figure 6-3). The relative concentration of these metabolites in urine and feces is not known (Bogaert, 1983). The MEEC of hydralazine HCl at the WTP is likely to range from [ ] ppb. The MEEC of ISDN at the WTP is likely to range from [ ] to 0.391 ppb. The worst case concentrations of [ ] ppb for hydralazine and [ ] ppb for ISDN are used for the risk assessment table (Tables 11-1 and 11-2).

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

Information is presented that is relevant to the environmental transport and fate of hydralazine and ISDN. Assessment of transport and fate is accomplished by an evaluation of processes affecting transport (between air, water, and soil) and processes affecting chemical and biological degradation. The methodology involved in this evaluation and its application to specific chemicals is discussed in Water-Related Environmental Fate of 129 Priority Pollutants (USEPA, 1979; Howard, et al., 1990). The procedures outlined in the Environmental Assessment Technical Assistance Handbook (USFDA, 1987) were followed to study the environmental fate of hydralazine and ISDN.

BiDil™ is a drug developed for the treatment of congestive heart disease. As stated earlier, BiDil™ has two active ingredients, hydralazine hydrochloride and ISDN. The metabolism of hydralazine and ISDN in humans is outlined in Figures 6-1 and 6-2. Hydralazine is extensively metabolized in the human body leading to production of several metabolites. ISDN is completely metabolized to isosorbide 5-mononitrate and isosorbide 2-mononitrate. Eventually, these metabolites will be found in the human excreta. Because of the structural similarity of metabolites with both the active ingredients and also as a worst-case concentration scenario that excluded human elimination, it was assumed that all hydralazine HCl and ISDN would be consumed and excreted intact. The environmental fate studies were therefore conducted with hydralazine HCl and ISDN.



I: hydralazine, 1-hydrazinophthalazine
II. hydralazine pyruvic acid hydrazone (HPH)
III: 3-methyl-s-triazolo [3,4a] phthalazine (MTP)
IV: 3-hydroxymethyl-s-triazolo [3,4a] phthalazine (HMTP)
V: s-triazolo [3,4a] phthalazine (TP)
VI: 1-hydrazino-hydroxyphthalazine
VII: 3-methyl-s-triazolo [3,4a]hydroxyphthalazine
VIII: 4-hydrazinophthalazin-1-one
IX: 4-(2-acetythydrasino)-phthalazin-1-one
X: phthalazinone

Figure 6-1

METABOLISM OF HYDRALAZINE HYDROCHLORIDE IN HUMANS

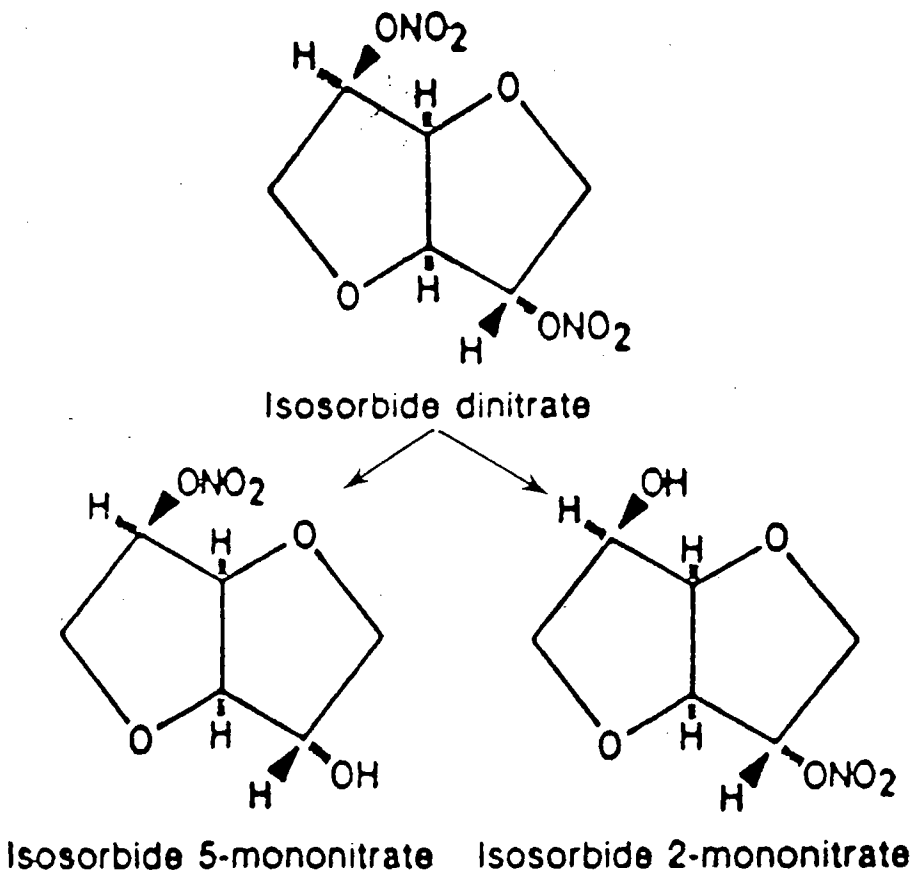


Figure 6-2
METABOLISM OF ISOSORBIDE DINITRATE IN HUMANS

7.1 AIR

Minimal or no emissions of BiDil™ are expected to be released into the atmosphere during manufacture or use of the product by patients. Hydralazine is a white to off-white odorless crystalline powder with a melting temperature of 275°C. Its relative stability (high melting temperature) in solid form suggests that volatilization in air is an unlikely phenomenon. Therefore, air emissions in its solid form are unlikely. Dust from the manufacturing of bulk drug will be trapped by vent filters that are collected and disposed of by landfilling or incineration. If any bulk drug should escape the dust collection system, it will precipitate with rain and become photolyzed in the condensing moisture. BiDil™ is a tablet formulation and no air emissions are expected during manufacture because of the containment measures that are in place. In the event of accidental release of aerosols, both hydralazine and ISDN are likely to photodegrade extensively aqueous solutions.

The raw material components of the drug product are trapped by vent filters during manufacturing will be disposed of by landfilling or incineration. All the equipment washes are also contained, collected and disposed of as liquid washes and sewered. Based on this information, manufacture and use of BiDil™ should have no impact in the "Air" environmental compartment.

7.2 WATER

BiDil™ will be introduced to the aqueous environment via elimination by patients and via releases from manufacturing. Minimal release of the drug substance is expected to the sewer and no release from manufacturing of drug product to aqueous environment (sewer) is expected due to contained handling of the wastes resulting from equipment cleaning and other operations during formulation. Biodegradation and photodegradation in the aeration and settling tanks of the WTP are expected to decrease its concentration significantly before the sewage effluent is released to surface water.

As stated in Subsection 6.5.1, the Maximum Emitted Environmental Concentration (MEEC) of BiDil™ at a typical wastewater treatment plant due to patient usage is estimated to be — μg/L (— ppb). Hydralazine is extensively metabolized in the human body and ISDN is completely metabolized. In addition to the elimination in the

human body, extensive photodegradation in the WTP will eliminate metabolites of these two active ingredients of BiDil™. The worst case Expected Environmental Concentration (EEC) in the WTP are [ ] ug/L [ ]ppb) for hydralazine HCl and [ ] µg/L [ ] ppb) for ISDN.

In the water of a sewage treatment facility, or in the surface water that dilutes the effluent, BiDil™ (or its by-products) would be affected by environmental processes that include biodegradation, photolysis, and hydrolysis. The methodology and results of the environmental fate studies conducted for hydralazine and ISDN are summarized below.

7.2.1 Aerobic Biodegradation in Water - Hydralazine Hydrochloride

The test chemical, hydralazine HCl, was tested for biodegradability in an aqueous aerobic medium at a nominal test chemical concentration of 10 mg C/L. Production of CO_2 was measured during the 28-day test period. A reference chemical (glucose) at a nominal concentration of 10 mg C/L was tested concurrently to verify the viability of the microbial inoculum. Blank systems containing no chemical were also tested to monitor the background CO_2 produced by the inoculum. The study was conducted in the dark at a temperature range of 22 ± 3 °C. The test was terminated at 28 days. The percent biodegradability was calculated as a function of the CO_2 production in the test systems as compared to the amount of material applied. After the 28-day incubation, the mean theoretical CO_2 evolved for the applied dextrose was 92.4%, verifying that the microbial inoculum was viable and active. The microbial plate count of the test solutions at day 28 also confirmed the presence of viable microorganisms. For the test chemical, hydralazine HCl, approximately 1.24% of the theoretical value of CO_2 was produced during the same incubation period. Detectable quantities of CO_2 evolution were not observed until the day 28 sampling. Total organic carbon analysis was performed at test initiation and termination for the test solutions. The mean percent of carbon removed from the test and reference systems was 0 and 97.9%, respectively. HPLC analysis was performed on the day 0 and day 28 test solutions. The percent of hydralazine HCl remaining at day 28 was determined to be 18.2% of the day 0 concentration. These results indicated that hydralazine HCl was not significantly mineralized to CO_2 under the test conditions. These results were confirmed by

the TOC analysis of the day 28 test chemical treatment media (the mean percent of carbon removed was 0%). Based on results from the HPLC analyses of the test media (which indicated that 18.9% of the test media remained as hydralazine HCl), it can be concluded that hydralazine HCl was biotransformed. A full study report is provided in Appendix B-1 and a summary of results is provided in Table 7-3.

7.2.2 Aerobic Biodegradation in Water - ISDN

The test chemical, isosorbide dinitrate (ISDN)/Lactose 25/75%, was tested for biodegradability in an aqueous aerobic medium at a nominal test chemical concentration of 10 mg C/L. Production of CO_2 was measured during the 28-day test period. A reference chemical (glucose) at a nominal concentration of 10 mg C/L was tested concurrently to verify the viability of the microbial inoculum. Blank systems containing no chemical were also tested to monitor the background CO_2 produced by the inoculum. The study was conducted in the dark at a temperature range of 22 $\pm$ 3 °C. The test was terminated at 28 days. The percent biodegradability was calculated as a function of the CO_2 production in the test systems as compared to the amount of material applied. After the 28-day incubation, the theoretical CO_2 evolved for the applied dextrose exceeded 100% of theoretical in all three replicates, verifying that the microbial inoculum was viable and active. The microbial plate count of the test solutions at day 28 also confirmed the presence of viable microorganisms.

For the test chemical, ISDN/Lactose 25/75%, approximately 89% of the theoretical value of CO_2 was produced during the same incubation period. No lag period was observed for the test chemical to begin evolving CO_2. The estimated time for 50% mineralization was 3.9 days (correlation coefficient = 0.957). Total organic carbon analysis was performed at test initiation and termination for the test solutions. The mean percent of carbon removed from the test and reference systems was 76.0 $\pm$ 2.6 and 97.8 $\pm$ 1.2, respectively. HPLC analysis was performed on the day 0 and day 28 test solutions. The mean percent of ISDN remaining at day 28 was determined to be 98.3% of the day 0 concentration, indicating that almost all the mineralization observed was from the lactose component of the test chemical. These results indicated that ISDN/Lactose 25/75% was rapidly mineralized (~89% in 28 days) under the test conditions. However, based on results

from the HPLC analyses of the test media (which indicated that 98.3% of the test media remained as ISDN) and the results from the TOC analysis of day 29 test chemical treatment media (the mean percent of carbon removed was 76.0%), it can be concluded that the mineralization was due to the lactose composition. A full study report is provided in Appendix B-2 and a summary of results is provided in Table 7-4.

7.2.3 Aqueous Photodegradation - Hydralazine Hydrochloride

The aqueous photodegradation of the test chemical, hydralazine hydrochloride (referred to as hydralazine in the report), in pH 5, 7, and 9 buffers was determined at 25 ± 3°C. A xenon arc lamp was used as the light source and illumination at the test samples was approximately the intensity of sunlight at equinox 40°N latitude. A nominal concentration of 100 μg/mL hydralazine was used for both the preliminary and definitive studies.

A preliminary study was conducted to validate the HPLC method for analysis of hydralazine in buffer solutions, determine the preliminary photolysis half-lives and define procedures and sampling schedule for the definitive study. The HPLC method showed retention time consistency for hydralazine across five concentrations ranging from 2.5 μg/mL to 25 μg/mL and the calibration curve developed from these concentrations was linear with a correlation coefficient of 0.99995, confirming the validation of HPLC method. Both direct and indirect photolysis potentials were investigated in a preliminary study. Hydralazine rapidly degraded under indirect photolysis conditions (1% acetone as a sensitizer) at all pHs, including time 0 samples which showed <21% hydralazine, suggesting too rapid a degradation in the presence of acetone. Therefore, evaluation by indirect photolysis was discontinued. There was no degradation of hydralazine in non-exposed samples that contained no acetone. The estimated half-lives of hydralazine under direct photolysis conditions was 20.9, 18.8, and 3.29 hours in pH 5, 7, and 9 buffers, respectively. Based on the preliminary study results the definitive study was conducted only under direct photolysis conditions.

For the definitive study, the measured concentrations of the dosing solution as determined by high performance liquid chromatography (HPLC) were 90.5, 90.2, and

80.4 μg/mL for the pH 5, 7, and 9 dosing solutions, respectively, against a nominal concentration of 100 μg/mL. Three replicates each of exposed samples and dark controls were analyzed by HPLC at various sampling intervals. Based on the results from HPLC analysis, the

percent photolyzed, the direct photodegradation first-order rate constant, and half-life values under experimental conditions for hydralazine are as follows:

pH	Percent Photolyzed	Rate Constants ($hour^{-1}$)	t½ (hours)
5	15.2	-3.46×10^{-3}	200
7	65.3	-3.32×10^{-2}	20.9
9	76.6	-2.19×10^{-1}	3.17

The nonexposed samples displayed no appreciable loss of hydralazine throughout the study with >93.7% of hydralazine remaining at termination for all pH levels.

A chemical actinometer, p-nitroanisole (PNA), was used as a reference chemical in the definitive study and exposure conditions were the same as the test chemical. The photodegradation first-order rate constant and half-life for PNA was -0.0532 $hour^{-1}$ and 13.0 hours, respectively. Nonexposed samples of the actinometer did not lose any PNA throughout the study.

The published quantum yield for PNA (2.82×10^{-4}) was used to calculate the hydralazine quantum yield at equinox 40 °N latitude (3). Calculated quantum yield values at equinox 40°N latitude, at pH 5, 7, and 9 were 2.92×10^{-4}, 9.88×10^{-4}, and 3.09×10^{-3}, respectively. These quantum yield values agree with values calculated from measured light intensity from the xenon lamp at pH 5, 7, and 9; and the values were 3.90×10^{-4}, 1.07×10^{-3}, and 3.02×10^{-3}, respectively. This agreement confirms that the xenon lamp simulated natural sunlight in the photolysis study.

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

The quantum yield values for hydralazine were used to estimate photolytic half-life values versus latitude and season. The half-life values for hydralazine at the surface of water at pH 5, 7, and 9 with varying season and latitude were estimated using the quantum yield values based on measured intensity values (Q_m). At pH 5, the half-lives ranged from a low of 116 hours (summer, 20° N) to a high of 1777 hours (winter, 50° N). At pH 7, the half-lives ranged from a low of 16.3 hours (summer, 20° N and 30° N) to a high of 151 hours (winter, 50° N). At pH 9, the half-lives ranged from a low of 2.83 hours (summer 30° N) to a high of 22.8 hours (winter, 50° N).

In conclusion, the test chemical, hydralazine hydrochloride, undergoes direct photodegradation in aqueous media with half-lives of 200, 20.9 and 3.17 hours in pH 5, 7, and 9 buffers, respectively. Based on these results, photodegradation appears to be a likely removal mechanism for hydralazine in the aqueous environment. A full study report is provided in Appendix B-3 and a summary of results is provided in Table 7-5.

C.7.2.4 Aqueous Photodegradation - ISDN

The aqueous photodegradation of the test chemical, isosorbide dinitrate (ISDN), was studied at a temperature of 25 ± 2 °C by exposing ISDN in pH 7 buffer sensitized with 1% acetone (indirect photolysis) to a xenon arc light source. The xenon arc light source used was approximately the intensity of sunlight at equinox 40 °N latitude. Since the test chemical was not known to dissociate, the photolysis study was conducted only at pH 7.

A preliminary study was conducted to validate the HPLC method for analysis of ISDN in buffer solutions, determine the photolysis half-lives and define procedures and sampling schedule for the definitive study. The HPLC method showed retention time consistency for ISDN across five concentrations ranging from 0.8032 to 40.16 μg/mL and the calibration curve developed from these concentrations was linear with a correlation coefficient of 0.99993, confirming the validation of the HPLC method. Both direct and indirect photolysis potentials were investigated in the preliminary study. The nominal test chemical concentration for the direct photolysis study was

12.55 μg/mL, and 10.00 μg/mL for the indirect photolysis study. ISDN degraded in less than 24 hours under indirect photolysis conditions (1% acetone as a sensitizer) at pH 7. Degradation of ISDN under direct photolysis was slow, having an estimated half-life of 269 hours at pH 7. Based on the preliminary study results, the definitive study was conducted only under indirect photolysis conditions.

For the definitive study, the measured concentrations of the dosing solution as determined by high performance liquid chromatography (HPLC) was 10.22 μg/mL against a nominal concentration of 10.00 μg/mL. Three replicates each of exposed samples and dark controls were analyzed by HPLC at various sampling intervals. Based on the results from HPLC analysis, the percent photolyzed, photodegradation first-order rate constant, and half-life values under experimental conditions for ISDN were calculated and are 86.6%, -0.0878 $hours^{-1}$ and 7.89 hours respectively. The nonexposed samples displayed no appreciable loss of ISDN throughout the study with >99% of the ISDN remaining at termination.

A chemical actinometer, *p*-nitroanisole (PNA), was used as a reference chemical. PNA was exposed to the xenon arc source for the same exposure period as the test chemical. Based on the results from HPLC analyses, a photodegradation first-order rate constant and half-life for PNA under experimental conditions were calculated to be -0.0939 $hour^{-1}$ and 7.38 hours, respectively. The nonexposed samples of the actinometer displayed no loss of PNA throughout the study.

A reaction quantum yield of 2.82×10^{-4} for PNA (3) was used in determinations of reaction quantum yields for the test chemical. The reaction quantum yield for ISDN under indirect photodegradation conditions was calculated to be 2.74×10^{-3} for the pH 7 buffer system based on the mean solar data for light intensity at equinox 40° N latitude listed in the U.S. EPA 40 CFR §796.3800 (5). The reaction quantum yield for ISDN was also calculated as 1.82×10^{-3} for the pH 7 buffer system based on measured light intensity values from the xenon light source. The quantum yield value from both calculation methods agree, therefore, quantum yield value based on measured intensity values were used for all subsequent calculations since they reflected the actual

test conditions. This agreement confirms that the xenon lamp simulated natural sunlight in the photolysis study.

The quantum yield values for ISDN were used to estimate photolytic half-life values versus latitude and season. The half-life values for ISDN at the surface of water at pH 7 with varying season and latitude were estimated using quantum yield values based on measured intensity values (Q_m). At pH 7, the half-lives ranged from a low of 27.6 hours (summer, 30°N) to a high of 168 hours (winter, 50° N).

In conclusion, this study demonstrates that ISDN undergoes indirect photodegradation in aqueous media with an experimentally measured half-life of 7.89 hours. Based on these results, photodegradation appears to be a likely removal mechanism for ISDN in the aqueous environment. A full study report is provided in Appendix B-4 and a summary of results is provided in Table 7-6.

C.7.2.5 Hydrolysis - Hydralazine Hydrochloride

The hydrolysis of hydralazine was studied in pH 5 acetate buffer, pH 7 phosphate buffer, and pH 9 borate buffer. A preliminary study was conducted to validate the HPLC method for analysis of hydralazine in buffer solutions, determine the hydrolysis potential and define procedures and sampling schedule for the definitive study. The HPLC method showed retention time consistency for hydralazine across five concentrations ranging from 2.5 μg/mL to 25 μg/mL and the calibration curve developed from these concentrations was linear with a correlation coefficient of 0.99995. The preliminary hydrolysis study was conducted at 50°C in the three aqueous buffer solutions (i.e., pH 5, 7, and 9) for a period of 5 days. The percent of hydralazine recovered after 5 days of incubation at 50°C was 3.0, 2.9, and 3.0% for pH 5, 7 and 9 buffers, respectively. These recoveries of hydralazine corresponded to percent hydrolyzed of 97.0, 97.1, and 97.0% for pH 5, 7, and 9 buffers, respectively. The preliminary study was also conducted at 25 ± 1°C in three aqueous buffer solutions for a period of 24 hours. The percent hydralazine recovered after 24 hours of incubation at 25°C was 98.5, 98.4, and 58.6% for pH 5, 7 and 9 buffers, respectively. The estimated half-lives at 25°C were 660, 950, and 32 hours for pH 5, 7, and 9 buffer systems, respectively.

The sampling schedule for the definitive study was established based on the preliminary study results.

A definitive study was conducted at a nominal test concentration of 100 μg/mL (100 ppm) in pH 5, 7, and 9 aqueous buffer solutions in a controlled environmental chamber maintained at 25 $\pm$ 1°C. For the pH 5 and 7 test systems, the mean percentage of hydralazine left in the buffers at 28 days was 84.8% and 14.1% of time 0, respectively. Following 8 days of hydrolysis at 25 °C, the mean percent of hydralazine left in pH 9 buffer was 11.9% of time 0. These recoveries of hydralazine corresponded to percent hydrolyzed of 15.2, 85.9, and 88.1% for pH 5, 7, and 9 buffers, respectively. Based on the results from HPLC analysis, the percent hydrolyzed, the hydrolysis rate constant, and half-life values for hydralazine under experimental conditions were determined in pH 5, 7, and 9 buffers and are calculated as follows:

This study demonstrated that hydralazine undergoes extensive hydrolysis at pH 9 ($t_{1/2}$, 66.4 hours) followed by pH 7 buffer ($t_{1/2}$). The hydrolysis of hydralazine at pH 5 was less pronounced with $t_{1/2}$ of 2510 hours. At an elevated temperature of 50°C, hydralazine was extensively hydrolyzed ($\geq$97%) in all three pH buffers (5, 7 and 9). These results indicate that hydrolysis could be an important removal pathway for hydralazine from the environment in warmer climates at all three pH ranges and at pH 9 in moderate climates. A full study report is provided in Appendix B-5 and a summary of results is provided in Table 7-7.

7.2.6 Hydrolysis - ISDN

A hydrolysis study with the active ingredient isosorbidedintrate (ISDN) was conducted at a nominal test concentration of 20 μg/mL (20 ppm) in three aqueous buffer solutions in a shaking water bath maintained at 50 $\pm$ 1 °C. The buffer systems were pH 5 acetate buffer, pH 7 phosphate buffer, and pH 9 borate buffer. The concentration of ISDN in each test sample at day 0 and day 5 was measured using high-performance liquid chromatography (HPLC). Following 5 days of hydrolysis at 50 °C, the mean percent of ISDN in solution from triplicate samples was 101%, 101%, and 101% of time 0 for the pH 5, 7, and 9 test systems, respectively.

The data generated during this study showed that the test chemical, ISDN, did not hydrolyze at 50 °C in the pH range between 5 and 9. Therefore, the hydrolysis rate definitive test was not performed since the test chemical concentration is greater than 90% or more of the initial concentration. The test chemical is considered hydrolytically stable. The half-life would be equal to or greater than a year at 25 °C. A full study report is provided in Appendix B-6 and a summary of results is provided in Table 7-8.

7.2.7 Probable Fate of BiDil™ in Aquatic Systems

Photodegradation, and biodegradation in the WTP will diminish or eliminate the amount of drug substance likely to be released to the natural aquatic compartment. Therefore, the actual concentrations that will be present near an effluent outfall of the WTP can be expected to be much smaller than that entering WTP and would continue to diminish in natural waters with dilution and with the passage of time due to biodegradation and photodegradation in natural surface waters. Downstream from the effluent outfall, the expected environmental concentration (EEC) of BiDil™ or its by-products is expected to be essentially zero. However, worst case estimations of EEC for hydralazine and ISDN are presented in Tables 11-1 and 11-2.

7.3 SOIL

As seen from the fate in the WTP aquatic matrix, the majority of hydralazine and ISDN in the WTP are expected to be eliminated by photodegradation and to a smaller degree, biodegradation and hydrolysis. Thus, soil is an unlikely environmental compartment.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

Since significant eliminations of hydralazine and ISDN occur in the human body and in WTP, no environmental effects studies were conducted.

9. USE OF RESOURCES AND ENERGY

The proposed action requires a moderate commitment of company resources. However, chemicals that will be used are common commodities of commerce. Moreover, no irreversible or irretrievable commitment of limited national resources will be involved. The estimated use of energy for the manufacture of BiDil™ tablets at the Global Pharm Inc. facility is [illegible] kw/hr of electricity and [illegible] of natural gas.

As discussed in Subsection 8, the environmental impact of releases from manufacturing and use of the product is negligible. Therefore, it is unlikely that threatened or endangered species could be affected.

10. MITIGATION MEASURES

Controls exercised on emissions at the Global Pharm facility are described in Section 6.3.2. Compliance of the proposed action with applicable emission requirements is described in Section 6.3.4.

Material Safety Data Sheets (MSDS) are provided in Appendix A-1. Unused drugs (past the labeled expiration date) are returned to Medco Inc. for disposal by landfilling or incineration. Waste minimization studies are an ongoing activity at Global Pharm Inc. facilities.

11. ALTERNATIVES TO THE PROPOSED ACTION

No potential adverse environmental impacts have been identified for the proposed action. Little or no release of hydralazine hydrochloride and ISDN, active ingredients of BiDil™ tablets to the environment outside WTP is expected due to elimination within the human body, extensive photodegradation, biodegradation, and hydrolysis in the WTP. Because no adverse environmental impact is expected, alternatives to the proposed action are not being considered. If this product were not manufactured (as a no-action alternative), BiDil™ would not become available as medication to treat patients with heart ailments.

Table 7-3. Aerobic Biodegradation of Hydralazine Hydrochloride in Water

One Page Summary

TEST CHEMICAL: HYDRALAZINE HYDROCHLORIDE

TITLE OF STUDY: AEROBIC BIODEGRADATION OF HYDRALAZINE HCl IN WATER

NATURE OF STUDY: AEROBIC BIODEGRADATION - ENVIRONMENTAL FATE

STUDY PERFORMED BY: [ ]

SUMMARY OF RESULTS

For the test chemical, hydralazine HCl, approximately 1.24% of the theoretical value of CO_2 was produced during the 28-day incubation period. Detectable quantities of CO_2 evolution were not observed until the day 28 sampling. Total organic carbon analysis was performed at test initiation and termination for the test solutions. The mean percent of carbon removed from the test and reference systems was 0 and 97.9%, respectively. HPLC analysis was performed on the day 0 and day 28 test solutions. The percent of hydralazine HCl remaining at day 28 was determined to be 18.2% of the day 0 concentration. Based on results from the HPLC analyses of the test media (which indicated that 18.9% of the test media remained as hydralazine HCl), it can be concluded that hydralazine HCl was biotransformed significantly.

Removal of Hydralazine HCl from Test Solutions

Carboy	Hydralazine HCl Conc. Day 0 (µg/mL)	Hydralazine HCl Conc. Day 28 (µg/mL)	Hydralazine HCl Concentration (as Percent of Day 0)
Test-1	[		]
Test-2	[		]
Test-3	[		]
Average	21.29	3.86	18.2
Standard Deviation	0.16	1.5	7.1

ENVIRONMENTAL SIGNIFICANCE

Hydralazine hydrochloride was biotransformed extensively as indicated by the removal of >70% of hydralazine from the test solutions, indicating potential for removal from WTP through this process.

Table 7-4. Aerobic Biodegradation of Isosorbide Dinitrate in Water
One Page Summary

TEST CHEMICAL: Isosorbide dinitrate (ISDN)

TITLE OF STUDY: AEROBIC BIODEGRADATION OF ISDN IN WATER

NATURE OF STUDY: AEROBIC BIODEGRADATION - ENVIRONMENTAL FATE

STUDY PERFORMED BY: [ ]

SUMMARY OF RESULTS

The test chemical, isosorbide dinitrate (ISDN)/Lactose 25/75%, was tested for biodegradability in an aqueous aerobic medium at a nominal test chemical concentration of 10 mg C/L. For the test chemical, ISDN/Lactose 25/75%, approximately 89% of the theoretical value of CO_2 was produced during the 28 day incubation period. No lag period was observed for the test chemical to begin evolving CO_2. The estimated time for 50% mineralization was 3.9 days (correlation coefficient = 0.957). Total organic carbon analysis was performed at test initiation and termination for the test solutions. The mean percent of carbon removed from the test and reference systems was 76.0 ± 2.6 and 97.8 ± 1.2, respectively. HPLC analysis was performed on the day 0 and day 28 test solutions. The mean percent of ISDN remaining at day 28 was determined to be 98.3% of the day 0 concentration, indicating that almost all the mineralization observed was from the lactose component of the test chemical.

Concentration of ISDN on Day 0 and Day 28 by HPLC Analysis

Carboy	ISDN Conc. Day 0 (µg/mL)	ISDN Conc. Day 28 (µg/mL)	ISDN Concentration (as % of Day 0)
Test-1	[ ]		[ ]
Test-2	[ ]		[ ]
Test-3	[ ]		[ ]
Average	6.34	6.23	98.3
Standard Deviation	0.10	0.02	1.36

ENVIRONMENTAL SIGNIFICANCE

Biodegradation is not an important removal pathway for the lactose component (75%) of ISDN in the WTP.

Table 7-5. Aqueous Photodegradation of Hydralazine Hydrochloride
One Page Summary

TEST CHEMICAL: HYDRALAZINE HYDROCHLORIDE

TITLE OF STUDY: DETERMINATION OF THE AQUEOUS PHOTODEGRADATION OF HYDRALAZINE

NATURE OF STUDY: PHOTODEGRADATION - ENVIRONMENTAL FATE

STUDY PERFORMED BY: [redacted]

SUMMARY OF RESULTS

The aqueous photodegradation of the test chemical, hydralazine hydrochloride (referred to as hydralazine in the report), in pH 5, 7, and 9 buffers was determined at 25 ± 3°C. A xenon arc lamp was used as the light source and illumination at the test samples was approximately the intensity of sunlight at equinox 40°N latitude. A nominal concentration of 100 µg/mL hydralazine was used.

The measured concentrations of the dosing solution as determined by high performance liquid chromatography (HPLC) were 90.5, 90.2, and 80.4 µg/mL for the pH 5, 7, and 9 dosing solutions, respectively, against a nominal concentration of 100 µg/mL. Three replicates each of exposed samples and dark controls were analyzed by HPLC at various sampling intervals. Based on the results from HPLC analysis, the percent photolyzed, the direct photodegradation first-order rate constant, and half-life values under experimental conditions for hydralazine are as follows:

pH	Percent Photolyzed	Rate Constants ($hour^{-1}$)	t½ (hours)
5	15.2	-3.46×10^{-3}	200
7	65.3	-3.32×10^{-2}	20.9
9	76.6	-2.19×10^{-1}	3.17

The nonexposed samples displayed no appreciable loss of hydralazine throughout the study with >93.7% of hydralazine remaining at termination for all pH levels.

In conclusion, the test chemical, hydralazine hydrochloride, undergoes direct photodegradation in aqueous media with half-lives of 200, 20.9 and 3.17 hours in pH 5, 7, and 9 buffers, respectively. Based on these results, photodegradation appears to be a likely removal mechanism for hydralazine in the aqueous environment.

ENVIRONMENTAL SIGNIFICANCE

The rapid photodegradation of hydralazine hydrochloride in the aqueous buffers of pH 7 and 9 suggests that photodegradation may be a major removal pathway in the wastewater treatment plant (WTP). Because of this reason, the potential for hydralazine hydrochloride to reach aquatic or terrestrial compartment outside of the WTP may be minimal, suggesting no significant environmental impact through human use.

Table 7-6. Aqueous Photodegradation of Isosorbide Dinitrate
One Page Summary

TEST CHEMICAL: Isosorbide dinitrate (ISDN)

TITLE OF STUDY: DETERMINATION OF AQUEOUS PHOTODEGRADATION OF ISDN

NATURE OF STUDY: PHOTODEGRADATION - ENVIRONMENTAL FATE

STUDY PERFORMED BY: [illegible]

SUMMARY OF RESULTS

The aqueous photodegradation of the test chemical, isosorbide dinitrate (ISDN), was studied at a temperature of 25 ± 2 °C by exposing ISDN in pH 7 buffer sensitized with 1% acetone (indirect photolysis) to a xenon arc light source. The xenon arc light source used was approximately the intensity of sunlight at equinox 40 °N latitude. Since the test chemical was not known to dissociate, the photolysis study was conducted only at pH 7.

The measured concentrations of the dosing solution as determined by high performance liquid chromatography (HPLC) was 10.22 μg/mL against a nominal concentration of 10.00 μg/mL. Three replicates each of exposed samples and dark controls were analyzed by HPLC at various sampling intervals. Based on the results from HPLC analysis, the percent photolyzed, photodegradation first-order rate constant, and half-life values under experimental conditions for ISDN were calculated and are 86.6%, -0.0878 hours^{-1} and 7.89 hours respectively. The nonexposed samples displayed no appreciable loss of ISDN throughout the study with >99% of the ISDN remaining at termination.

pH	Percent Photolyzed	Rate Constants (hour^{-1})	t½ (hours)
7	86.6	-0.0878	7.89

In conclusion, this study demonstrates that ISDN undergoes indirect photodegradation in aqueous media with an experimentally measured half-life of 7.89 hours. Based on these results, photodegradation appears to be a likely removal mechanism for ISDN in the aqueous environment.

ENVIRONMENTAL SIGNIFICANCE

The rapid photodegradation of ISDN in the aqueous buffer of pH 7 suggests that photodegradation may be a major removal pathway in the wastewater treatment plant (WTP). Because of this reason, the potential for ISDN to reach aquatic or terrestrial compartment outside of the WTP may be minimal, suggesting no significant environmental impact either through human use or manufacturing.

Table 7-7. Hydrolysis of Hydralazine Hydrochloride
One Page Summary

TEST CHEMICAL: HYDRALAZINE HYDROCHLORIDE

TITLE OF STUDY: HYDROLYSIS AS A FUNCTION OF pH OF HYDRALAZINE

NATURE OF STUDY: HYDROLYSIS - ENVIRONMENTAL FATE

STUDY PERFORMED BY: [ ]

SUMMARY OF RESULTS

A definitive study was conducted at a nominal test concentration of 100 μg/mL (100 ppm) in pH 5, 7, and 9 aqueous buffer solutions in a controlled environmental chamber maintained at 25 ± 1°C. For the pH 5 and 7 test systems, the mean percentage of hydralazine left in the buffers at 28 days was 84.8% and 14.1% of time 0, respectively. Following 8 days of hydrolysis at 25 °C, the mean percent of hydralazine left in pH 9 buffer was 11.9% of time 0. These recoveries of hydralazine corresponded to percent hydrolyzed of 15.2, 85.9, and 88.1% for pH 5, 7, and 9 buffers, respectively.

Based on the results from HPLC analysis, the percent hydrolyzed, the hydrolysis rate constant, and half-life values for hydralazine under experimental conditions were determined in pH 5, 7, and 9 buffers and are calculated as follows:

pH	Percent Hydrolyzed	Rate Constant $hour^{-1}$	Half-life (hours)
5	15.2	-2.77×10^{-4}	2510
7	85.9	-3.10×10^{-3}	224
9	88.1	-1.04×10^{-2}	66.4

This study demonstrated that hydralazine undergoes extensive hydrolysis at pH 9 ($t_{1/2}$, 66.4 hours) followed by pH 7 buffer ($t_{1/2}$). The hydrolysis of hydralazine at pH 5 was less pronounced with $t_{1/2}$ of 2510 hours. At an elevated temperature of 50°C, hydralazine was extensively hydrolyzed (≥97%) in all three pH buffers (5, 7 and 9). These results indicate that hydrolysis could be an important removal pathway for hydralazine from the environment in warmer climates at all three pH ranges and at pH 9 in moderate climates.

ENVIRONMENTAL SIGNIFICANCE

Hydrolysis is an important removal pathway for hydralazine from the environment in warmer climates (≥97% removed at 50°C at all three pH ranges and at pH 9 in modern climates.

Table 7-8. Hydrolysis of Isosorbide Dinitrate
One Page Summary

TEST CHEMICAL: Isosorbide dinitrate (ISDN)

TITLE OF STUDY: HYDROLYSIS AS A FUNCTION OF pH OF ISDN

NATURE OF STUDY: HYDROLYSIS - ENVIRONMENTAL FATE

STUDY PERFORMED BY: [redacted]

SUMMARY OF RESULTS

A hydrolysis study with the active ingredient isosorbidedintrate (ISDN) was conducted at a nominal test concentration of 20 µg/mL (20 ppm) in three aqueous buffer solutions in a shaking water bath maintained at 50 ± 1 °C. The buffer systems were pH 5 acetate buffer, pH 7 phosphate buffer, and pH 9 borate buffer. The concentration of ISDN in each test sample at day 0 and day 5 was measured using high-performance liquid chromatography (HPLC). Following 5 days of hydrolysis at 50 °C, the mean percent of ISDN in solution from triplicate samples was 101%, 101%, and 101% of time 0 for the pH 5, 7, and 9 test systems, respectively.

The data generated during this study showed that the test chemical, ISDN, did not hydrolyze at 50 °C in the pH range between 5 and 9. Therefore, the hydrolysis rate definitive test was not performed since the test chemical concentration is greater than 90% or more of the initial concentration. The test chemical is considered hydrolytically stable. The half-life would be equal to or greater than a year at 25 °C.

pH	Concentration (Day 0)	Concentration (Day 5)	Percent of Initial Measured Dose	Percent Hydrolyzed
5	20.5 ± 0	20.8 ± 0.1	101	1.5
7	20.6 ± 0	20.8 ± 0.1	101	-0.97
9	20.5 ± 0	20.7 ± 0.2	101	-0.98

ENVIRONMENTAL SIGNIFICANCE

ISDN is hydrolytically very stable and hydrolysis is not a removal pathway for ISDN in the environment.

12. PREPARERS

Ranga Velagaleti, Ph.D
Director
Environmental Fate and Assessment Division
Analytical Biochemistry Laboratories, Inc.
7200 East ABC Lane
Columbia, Missouri 65202

Wes Winberry, B.S.
Program Manager
Environmental Fate and Assessment Division
Analytical Biochemistry Laboratories, Inc.
7200 East ABC Lane
Columbia, Missouri 65202

The preparers' resumes are provided in Appendix C, Attachment C.15-4.

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

13. CERTIFICATION

PREPARERS

The undersigned certify that the information presented is true, accurate, and complete for preparation of the Environmental Assessment Report in accordance with 21 CFR 25.31(a).

Signature Ranga Velagaleti Date 2-8-96

Title Director, Environmental Fate and Assessment

Signature Wes Winter Date 2-8-96

Title Program Manager, Environmental Fate and Assessment

SPONSOR

The undersigned certifies that the information presented herein and provided to Ranga Velagaleti by Medco Research, Inc. (applicant) is true, accurate, and complete to the best of our knowledge.

Signature Anne McKay Date 8/13/96

Title Director, Regulatory Affairs

14. REFERENCES

1. Bogaert, M.G. 1983. Clinical Pharmacokinetics of Organic Nitrates. Clinical Pharmacokinetics 8:410-421.

2. Howard, P.H. Sage, G.W. Jarvis, W.F., and Gray, D.A., eds., 1990. Handbook of Environmental Fate and Exposure Data for Organic Chemicals. Chelsea, Michigan: Lewis Publishers.

3. Ludden, T.M.; McNay, Jr., J.L.; Shepherd, A.M.M.; and Lin, M.S. 1982. Clinical Pharmacokinetics of Hydralazine. Clinical Pharmacokinetics 7:185-205.

4. Metcalf & Eddy, Inc., 1979. Wastewater Engineering: Treatment, Disposal, Reuse. Revised by G. Tchobanoglous. New York: McGraw-Hill Book Company.

5. Pharmaceutical Manufacturers Association (PMA), 1991. Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA. PMA, Washington, D.C.

6. U.S. Environmental Protection Agency (USEPA), 1979. Water-Related Environmental Fate of 129 Priority Pollutants. Prepared by M.A. Callahan, M.W. Slimak, N.W. Gabel, I.P. May, C.F. Fowler, et al., for the Office of Water Planning and Standards, U.S. Environmental Protection Agency, Washington, D.C., EPA-440/4-79.029ab.

7. U.S. Food and Drug Administration (USFDA), 1987. Environmental Assessment Technical Assistance Handbook. Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration, Washington, D.C., FDA/CFSAN-87/30. (NTIS PB87-175345).

15. APPENDICES

APPENDIX A-1

Material Safety Data Sheets

MATERIAL SAFETY DATA SHEET

This form may be used comply with OSHA'S Hazard Communication Standard, 29 CFR 1910. 1200. To be valid. all information required by § 1910. 1200(g) of the Standard must appear on this form. Consult the Standard for specific requirements. Note:Blank spaces are not permitted. if any item is not applicable, or no information is avaliable, the space must be marked to indicate that.

IDENTITY(As Used on Label and List) Hydralazine Hydrochloride

SECTION I

Manufacturer's Name Sumika Fine Chemicals Co., Ltd.	Emergency Telephone Number 06 (OSAKA) 473 - 0331
Address(Number,Street City,state,and ZIP Code) 1-21, Utajima 3-Chome, Nishiyodogawa-ku, Osaka, Japanc.(555)	Telephone Number for Information 06 (OSAKA) 473 - 0331 Date Prepared September 16, 1989 Signature of Preparer(optional) K. Tanaka

Section II — Hazardous Ingredients/Identity Information

Hazardous Components (Specific Chemical Identity;Common Name(s))	OSHA PEL	ACGIH TLV	Other Limits Recommended	%(optional)
Not Applicable				

Section III — Physical/Chemical Characteristics

Boiling Point	Not Applicable	Specific Gravity(H_2O=1)	Not Applicable
Vapor Pressure(mm Hg	Not Applicable	Melting Point	270 - 280° (decomposition)
Vapor Density(AIR=1)	Not Applicable	Evaporation Rate (Butyl Acetate=1)	Not Applicable
Solubility in Water	40 mg/ml Water		
Appearance and odor	White crystalline powder. Odorless.		

Section IV — Fire and Explosion Hazard Data

Flash Point(Method Used)	Not Applicable	Flammable Limits Not Applicable	LEL	UEL
Extinguishing Media	Water spray, dry chemical, carbon dioxide or foam.			
Special Fire Fighting Procedures	As with all fires, evacuate, personnel safe area. Firefighters should use self-contained breathing equipment and protective clothing.			
Unusual Fire and Explosion Hazards	This material is assumed to be combustible. When heated to decomposition material emits toxic fumes.			

Section V — Reactivity Data

Stability	Unstable		Conditions to Avoid
	Stable	X	

Incompatibility (Materials to Avoid): Not Applicable

Hazardous Decomposition or Byproducts: When heated to decomposition material emits toxic fumes.

Hazardous Polymerization	May Occur		Conditions to Avoid
	Will Not Occur	X	

Section VI — Health Hazard Data

Route(s) of Entry: Inhalation? X Skin? X Ingestion? X

Health Hazards (Acute and Chronic)

LD50 : irn - rat 34 mg/kg

: ipr - mus 83 mg/kg

: scu - mus 73 mg/kg

Carcinogenicity: NTP? Not Applicable IARC Monographs? Group 3 OSHA Regulated? Not Applicable

Signs and Symptoms of Exposure: Toxic effect occur frequently with hydralazine, particularly tachycardia, severe headache and nausea.

Medical Conditions Generally Aggravated by Exposure: Hypersensitivity to material

Emergency and First Aid Procedures: Persons developing serious hypersensitivity reactions must receive immediate medical attention.

Section VI — Precautions for Safe Handling and Use

Steps to be Taken in Case material is Released or Spilled: Vacuum or sweep up spillage. Avoid contact. Place spillage in appropriate container for waste disposal.

Waste Disposal Method: Dispose of waste in accordance with all applicable Federal, State and local laws.

Precautions to be Taken in Handling and Storing: Store in tight container. Avoid contact with eyes, skin or clothing. Avoid breathing dust or mist.

Other Precautions: Unkown

Section VII — Control Measures

Respiratory Protection (Specify Type): NIOSH approved respirater

Ventilation	Local Exhaust	Recommended	Special	Unknown
	Mechanical (General)	Recommended	Other	Not Applicable
Protective Gloves	Rubber		Eye Protection	Safety Goggles

Other Protective Clothing or Equipment: Unknown

Work/Hygienic/Maintenance Practices: Wear proper musk, gloves and safety goggles. After work, wash sufficiently face and hands, and rinse out the mouth. Wash and keep clean clothing.

SUMIKA FINE CHEMICALS CO., LTD.

1-21, UTAJIMA 3-CHOME
NISHIYODOGAWA-KU
OSAKA (555), JAPAN

PHONE: (06)473-0331
FAX : (06)474-2468
TELEX: 524-8275 YODOPH J

No.

Date : May 31, 1994

CERTIFICATE OF ANALYSIS

We hereby certify that the following commodity has been manufactured by our company and that the relative statements below are true and correct.

PRODUCT	Hydralazine Hydrochloride BP93				
LOT NO	405006		QUANTITY	500 kg	NO. 11 20

Determination		Specification	Result
Characteristics		white or almost white crystalline powder	pass test
Identification	A. IR B. UV C. chlorides	pass test pass test pass test	pass test pass test pass test
Acidity		pH 3.5 to 4.2	3.8
Clarity of solution		pass test	pass test
Colour of solution		not more intensely coloured than reference solutions GY6	pass test
Heavy metals		not more than 20 ppm	pass test
Hydrazine (TLC)		pass test	pass test
Loss on drying		not more than 0.5 %	0.2 %
Sulphated ash		not more than 0.1 %	0.0 %
Assay		not less than 98.5 % and not more than 101.0 %	100.0 %

The merchandise meets all BP 1993 Specifications.

Manufacturing Date : May 14, 1994
Expiry Date : May 13, 1997

SUMIKA FINE CHEMICALS CO., LTD.

S. Salkawa

S. Salkawa, Manager

Quality Control Department

1. Product-Characterisation

1.1. Name of Product ISOSORBIDEDINITRATE / LACTOSE 25/75 %

1.2. Synonym(s) ..... ISDN/Lactose 25/75 % .....

1.3. Prod-No EMS P 1004

1.4. CAS-RN 87-33-2 ISDN
64044-51-5 LACTOSE

1.5. Molecular Weight 236.14 (ISDN)

1.6. Formula $C_6H_8N_2O_8$ ISDN

1.7. Aspect of the Mixture
.... white, crystalline powder, no distinct odour .....

2. Physical Constants (ISDN)

2.1. Melting Point 69 °C

2.2. Boiling Point ...°C

2.3. Solidification Point ... °C

2.4. Density (..°C) ..... g/ml

2.5. Bulk Density ... kg/m³

2.6. Vapor Pressure (..°C) .... mbar

2.7. Solubility (20°C) 1.1 g/l (in water); freely soluble in many organic solvents (f.e. alcohol, ether, acetone)

3. Fire and Explosion Hazard Data

3.1. Flash Point ... °C

3.2. Temp of Ignition ... °C

3.3. Explosion Limits lower: ..... upper: .....

3.4. Decomposition Temp. about 150 °C, ISDN is an explosive

3.5. Maximum Heat Medium Temperature (Method 'Geigy-Kühner') 70°C

3.6. Hazardous Decomposition Products:
..... toxic fumes of CO_2, CO, NO_x, NH_3 .....

3.7. Incompatabilities: sensitive to alkaline hydrolysis .....

3.8. Additional Information: ISDN is an explosive .....

4. Transport Regulations (Mixture)

IMDG-Code: 4.1 RID/ADR: 4.1 / 23 b UN-No : 2907

ADNR : 4.1 / 23 b ICAO/IATA-DGR : 4.1 / UN-No 2907

Customs Tariff No. : CH 3003.9000 / HS 3003.90

Additional Information: Packaging Group II
.....

5. Security Regulations

R-Sentences: none .....

S-Sentences: none .....

Additional Informations: .....
.....

---

6. Protective Measure / Storage / Handling

6.1. Technical Protective Measures
work only in clean rooms, attend to a good ventilation of rooms
.....
.....

6.2. Personal Protective Measures
Respiration: ..yes... Eyes: ..yes....
Skin : ..yes... Others: .....

6.3. Working Hygiene
ISDN may cause headache .....
.....

6.4. Fire- and Explosion Protection
mixture is to be stored in a dry and cool place in well closed containers .....

6.5. Waste Disposal
burning .....
.....

---

7. Emergency, Fire and First Aid Procedures

7.1. In case of Released or Spilled Material
wipe together and hold for waste disposal (burning) .....
.....

7.2. Extinguishing Media adapted: Foam, Dry Chemical, CO_2, Water spray .....
incompatibile: .....

7.3. First Aid
remove contaminated persons to fresh air; .....
wash skin and eyes with plenty of water .....
.....

7.4. Additional Informations
pure ISDN is a highly explosive !! .....
.....

---

8. Health Hazard Data (ISDN)

8.1. Instruction Sheets Hommel: none Kühn-Birett: none

8.2. Literature Information
RTECS/ LZ 4385000 MSD Book: .. .. none .. ..
Sax; Dangerous Properties: none Merck-Index 10, 5074
Chapman/Hall; Dictionary of Organic Compounds: ..... none .....

8.3. Tox-Data oral: LD_{50} (rat) 747 mg/kg LD_{50} (mouse) 1050 mg/kg
intraperitoneal: LD_{50} (rat) 620 mg/kg LD_{50} (mouse) 720 mg/kg

8.4. Additional Information
registered in EINECS Master Inventory I (1987), No 2017409 ....
registered in EPA/TSCA Inventory (1989) .....

9. Ecology

9.1. Toxicity for Water Organism
.....
..... not known .....

9.2. Toxicity for Fishes
.....
..... not known .....

9.3. Additional Information
.....
.....

10. Additional Indications

ISDN itself is an explosive substance .....
The mixture 25/75% with lactose is harmless .....
.....
.....
.....

Note:

All the above informations are based on our today's knowledge.

Date: December 20, 1993
Superseded: January 06, 1993

MS-Dottikon AG Tel 057-26-11-55
Fax 057-24-21-20

Quality / Analytical Department
Dr.M.Aellen

(MSP1004E)

CABOT
Cabot Corporation
Cab-O-Sil Division
P.O. Box 188
Tuscola, IL 61953-0188
(217) 253-3370
(800) 222-6745
(800) 252-3705 (IL)

Technical Data

Information about Cab-O-Sil fumed silica,
a Cabot performance chemical.

MATERIAL SAFETY DATA SHEET

CODE	DATE ISSUED	DATE REVISED	ISSUED BY
CAB-O-SIL®	January, 1985	April, 1990	Regulatory Compliance Office

CHEMICAL NAME OR COMPOSITION
Silicon Dioxide, Amorphous — CAS #112945-52-5

HAZARD RATING


TRADE NAME & SYNONYMS
CAB-O-SIL Fumed Silica, Colloidal Silica, Pyrogenic, Amorphous, Synthetic Silica

CHEMICAL FAMILY	MOLECULAR FORMULA
Oxide	SiO_2

SECTION II - SIGNIFICANT COMPONENTS AND CONTAMINANTS

CAS NO.	COMPONENT	PERCENT	PERMISSIBLE EXPOSURE LIMIT	ACGIH Total Dust
112945-52-5	Silica, amorphous, fumed, cryst.-free	99 plus	20 mppcf	10 mg/m³

SECTION III - PHYSICAL DATA

PHYSICAL CHARACTERISTICS
Fine White Powder, Odorless

BOILING POINT	FREEZING POINT	SPECIFIC GRAVITY (WATER = 1.0)
NA	NA	2.2

VAPOR PRESSURE (mm Hg. at 20° C)	pH
NA	4.0 (4% Aqueous Slurry)

VAPOR DENSITY (AIR = 1)	SOLUBILITY IN WATER
NA	Insoluble

SECTION IV - FIRE AND EXPLOSION HAZARD DATA

FLASH POINT (SPECIFY METHOD)	FLAMMABLE (EXPLOSIVE) LIMITS (PERCENTAGE BY VOLUME)	
	LOWER EXPLOSIVE LIMIT	UPPER EXPLOSIVE LIMIT
NA	NA	NA

FIRE EXTINGUISHING MEDIA
NA

SPECIAL FIRE FIGHTING PROCEDURES
NA

UNUSUAL FIRE AND EXPLOSION HAZARDS
See Section IX

TOXICITY CAB-O-SIL fumed silica is not considered a potential carcinogen by IARC, NTP, or OSHA. Primary route(s) of entry: Inhalation. Non-toxic Oral LD50 = Greater than 5000 mg/kg.

EFFECTS OF OVEREXPOSURE	ACUTE None known other than possible temporary discomfort due to inhalation of dust concentration above the permissable exposure limit.
	CHRONIC None known

EMERGENCY AND FIRST AID PROCEDURES

Flush eyes with plenty of water.

For inhalation discomfort, move victim to fresh air.

GENERAL REACTIVITY

Stable

INCOMPATABILITY (MATERIALS TO AVOID)

None

HAZARDOUS DECOMPOSITION PRODUCTS

None

HAZARDOUS POLYMERIZATION	CONDITIONS TO AVOID
None	NA

STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED

Spilled CAB-O-SIL fumed silica is not a hazardous waste under U.S. Federal RCRA regulations.

WASTE DISPOSAL METHOD

CAB-O-SIL fumed silica may be swept up or vacuumed for normal disposal.

CONTAINER DISPOSAL

Ordinary methods for non-hazardous waste.

EYE PROTECTION	GLOVES
Safety goggles recommended	Not necessary

RESPIRATORY

NIOSH approved dust respirator recommended for concentrations above TLV (10mg/m³)

VENTILATION	OTHER
Adequate for dusty environments	None

Dry powdered materials can build static electrical charges when subjected to friction.

Proper precautions, when using CAB-O-SIL fumed silica in the presence of flammable or explosive liquids, should be taken to prevent accidents. (See NFPA-77 Static Electricity)

CAB-O-SIL fumed silica is not restricted/non-hazardous

MATERIAL SAFETY DATA SHEET Explotab® Page 1 of 4

EDWARD MENDELL CO., INC.
2981 Route 22, Patterson, NY, USA 12563-9970 Tel: + (914) 878-4414; Fax: + (914) 878-4484
Church House, 48 Church Street, Reigate, Surrey, RH2 0SN, U.K. Tel: + (44) 737 222323; Fax: + (44) 737 222545

1. PRODUCT

Product Name:	[redacted]
Other Names:	Sodium starch glycolate NF; Sodium starch glycollate BP
Chemical Name:	Starch carboxymethyl ether, sodium salt
Molecular Formula:	Not applicable.
Molecular Weight:	Estimated 500,000 - 1,000,000

2. PRODUCT INFORMATION

Chemical Description:	Cross-linked, low substituted carboxymethyl ether of potato starch.
CAS:	9063-38-1
EINECS:	Not Available
Supply Class:	Non-hazardous.

3. HAZARDS IDENTIFICATION

Hazard Class:	Not Regulated
Health Hazard:	May be harmful if ingested in great quantity. May be irritating to eyes and if inhaled as dust.

4. FIRST AID MEASURES

Eyes:	Irrigate thoroughly with water. If discomfort persists obtain medical attention.
Skin:	Wash off thoroughly with soap and water.
Ingestion:	No hazard anticipated from ingestion incidental to industrial exposure. Wash out mouth thoroughly with water. In severe cases obtain medical attention.
Inhalation:	Non-hazardous; nuisance dust. Remove from exposure. If irritation persists obtain medical attention.

5. FIRE FIGHTING MEASURES

Extinguishing Media:	Water, dry powder, CO_2
Fire and Explosion Hazards:	Combustible. Dust explosion hazard. Avoid conditions of dust

	concentrations
Protective Measures:	Normal precautions against smoke inhalation.
Hazardous Decomposition:	CO_2, H_2O, and typical combustion by-products.

6. ACCIDENTAL RELEASE MEASURES (SPILLAGE)

Personal Precautions:	Dust mask, gloves, (c)overalls and goggles recommended.
Environmental Precautions:	Non-hazardous. Spills of this material are not subject to any special reporting requirements under current environmental legislation in either the USA or European Union.
Recovery:	Sweep up product and dispose of in accordance with local regulations

7. STORAGE AND HANDLING (IN NORMAL USE)

Storage:	Store in well closed container to avoid moisture uptake (hygroscopic) and contamination by other materials.
Ventilation:	Use local ventilation. Dusting may occur.
Handling:	Dust mask, gloves, (c)overalls and goggles recommended. Cleaning procedures should minimize any dust creation.

8. EXPOSURE CONTROLS / PERSONAL PROTECTION (NORMAL USE)

Occupational Exposure Limits:	Non-hazardous nuisance dust. OSHA Permissible Exposure Limit (PEL) for nuisance dusts: 15 mg/m³ total dust and 5 mg/m³ respirable fraction.	
Engineering measures:	Use local ventilation. Dusting may occur.	
Personal Protective Equipment:	Respiratory:	Dust mask recommended
	Hand:	Gloves recommended.
	Eye:	Goggles recommended.
	Other:	(C)overalls recommended.

9. PHYSICAL/CHEMICAL PROPERTIES

Appearance:	White to off-white fine powder.
Odour:	Odourless.
pH (as delivered):	Not applicable.
Viscosity:	Not applicable.

Boiling Point:	Not applicable.
Flash Point:	Not applicable.
Vapour Pressure:	Not applicable.
Vapour Density:	Not applicable.
Relative Density (SG):	Particle density 1.5 g/ml
Solubility:	Practically insoluble in methylene chloride; insoluble but swells in contact with water.

10. STABILITY AND REACTIVITY

Stability:	Stable under recommended conditions of storage.
Conditions to avoid:	High temperature, high humidity.
Materials to avoid:	Oxidizing substances.
Recommended Materials for Process/Handling Equipment:	Normal materials used in the construction of processing equipment for the food/pharmaceutical industries.

11. TOXICOLOGICAL INFORMATION

Short Term:	None known. No hazard anticipated incidental to industrial exposure.
Eyes:	None known. No hazard anticipated incidental to industrial exposure. Mechanical irritant. May cause scratching to eye surfaces.
Skin:	None known. No hazard anticipated incidental to industrial exposure.
Ingestion:	None known. No hazard anticipated incidental to industrial exposure.
Inhalation:	None known. No hazard anticipated incidental to industrial exposure.
Long Term Effects:	No evidence of carcinogenic, mutagenic, or teratogenic effects.

12. ECOLOGICAL INFORMATION

Biocompatibility:	No data.
Aquatic Toxicity:	No data.
Other:	None known.

MATERIAL SAFETY DATA SHEET Explotab®

13. DISPOSAL CONSIDERATIONS

May be disposed of in accordance with local regulations.

14. TRANSPORT INFORMATION (REGULATIONS)

Packaging (Size & Description):	50kg polyethylene lined fibreboard drums.
Transport Classification:	Not Regulated
Identification Number:	Not applicable.
Proper Shipping Name:	Not applicable.
ICAO/IATA/IMDG Class:	Not applicable.
Subsidiary Risk:	Not applicable.
Packing Group:	Not applicable.
ADR Class:	Not applicable.
Transport Hazard Symbol:	None.
Hazard Iden. Number:	Not Regulated
Emergency Action Code:	Not applicable.
Other:	None.

15. REGULATORY INFORMATION (Supply & Labelling)

Supply Classification:	Not Regulated
Hazard Pictogram:	Not required.
Risk Phrases:	This material is generally regarded as safe when handled and used in an appropriate manner.
Safety Phrases:	This material is generally regarded as safe when handled and used in an appropriate manner.
Other Applicable Regulations:	None known

16. OTHER INFORMATION

None

Date: May 2, 1994, JRG

The above information is believed to be correct but is not purported to be all inclusive and shall be used as a guide. Mendell shall not be held liable for any damage resulting from handling or from contact with the above product.

MATERIAL SAFETY DATA SHEET

This document has been prepared to meet the requirements of the U.S. OSHA Hazard Communication Standard, 29 CFR 1910.1200; the EEC Directive, 91/155/EEC and other regulatory requirements.

1. Company and Product Identification

FMC CORPORATION
Pharmaceutical and Bioscience Division
1735 Market Street
Philadelphia, PA 19103 (U.S.A.)

FMC CORPORATION NV
Avenue Louise 480-B9
1050 Brussels, Belgium

Chemical Name : Microcrystalline Cellulose
Brand Name : Avicel® PH 101, 102, 103, 105, 112, 200
Chemical Family : Carbohydrate
Formula : $(C_6H_{10}O_5)_x$
Synonyms : Microcrystalline Cellulose, MCC

EMERGENCY TELEPHONE NUMBERS:

U.S.A. & Canada		Europe	
Medical	(303) 595-9048	Medical	01 (303) 595-9048
Chemtrec	(800) 424-9300	Transportation	01 (202) 483-7616
Plant	(302) 451-0100	Plant (Cork)	353 21 354 133
General Information:	(215) 299-6000	Brussels	32 2 645 5511

2. Composition/Information on Ingredients

Ingredient Name	CAS #	EEC Symbol and Risk Phrases
Microcrystalline Cellulose	9004-34-6	Not classified as dangerous

3. Hazards Identification

Emergency Overview:

Accumulation of overhead settled dust may form explosive concentrations in air when disturbed and dispersed.

Potential Health Effects:

Minimally irritating to the eyes and non-irritating to the skin. No adverse human effects known.

4. First Aid Measures

Eyes : Flush with water for at least 15 minutes. If irritation occurs and persists, obtain medical attention.
Skin : Wash with plenty of soap and water. Get medical attention if irritation occurs and persists.
Inhalation : Remove to fresh air. If breathing difficulty or discomfort occurs and persists, obtain medical attention.
Ingestion : Drink plenty of water. Never give anything by mouth to an unconscious person. If any discomfort persists, obtain medical attention.

Notes to Medical Doctor: This compound has very low toxicity. Treatment is symptomatic and supportive only.

5. Fire Fighting Measures

Extinguishing Media : Water

Unusual Fire and Explosion Hazard : Accumulation of overhead settled dust may form explosive concentrations in air when disturbed and dispersed. The propagation of flame through air-floated dusts takes place usually following a small explosion which shakes down accumulated dust. According to NFPA 68 (Explosion Venting Guide), the Hazard Class of Dust Deflagrations for microcrystalline cellulose is St-1, the lowest hazard class.

Special Fire Fighting Procedures : For fires involving this material, do not enter any enclosed or confined fire space without wearing full protective clothing and self-contained breathing apparatus (SCBA) approved for firefighting. This is necessary to protect against the hazards of heat, products of combustion and oxygen deficiency. Do not breathe smoke, gases or vapors generated.

Hazardous Decomposition Products : None known

6. Accidental Release Measures

Maintain good housekeeping practices to minimize accumulation of settled dust, especially on overhead surfaces. Sweep up the spilled material and dispose of in accordance with the waste disposal method outlined in Section 13, "Disposal Considerations".

7. Handling and Storage

Use local exhaust or general dilution ventilation to control exposure to dust. Always use safe lifting techniques when manually moving containers, especially when shipping containers weighing more than 50 pounds (22.7 kg). To protect quality, store in a tight container in a dry place.

8. Exposure Controls/Personal Protection

Recommended Personal Protective Equipment

Respiratory : Whenever dust in the worker's breathing zone cannot be controlled with ventilation, workers should wear respirators which are approved by NIOSH/MSHA (or equivalent agency) for protection against airborne dust.

Eyes : Whenever airborne dust concentrations are high, appropriate protective eyewear, such as monogoggles, should be worn to prevent eye contact.

Gloves : Not required.

Special Clothing and Equipment : Not required.

Exposure Limits

Exposure Limit: Cellulose

	Inhalable Dust	Respirable Dust	STEL
Belgium (TWA)	10 mg/m3	–	–
France (TWA)	–	10 mg/m3	–
Switzerland (TWA)	–	6 mg/m3	–
United Kingdom (TWA)	10 mg/m3	5 mg/m3	20 mg/m3
USA (ACGIH TWA)	10 mg/m3	–	–
USA (OSHA TWA)	15 mg/m3	5 mg/m3	–

9. Physical/Chemical Properties

Appearance	: White, free flowing powder	Solubility in Water (% by Weight)	: Insoluble
Odor	: Odorless	Evaporation Rate (butyl acetate = 1)	: Not applicable
Melting Point	: Not applicable	Flash Point	: Not applicable
Boiling Point	: Not applicable	Flammable Limits (Air)	
		Upper	: Not applicable
Vapor Pressure	: Not applicable	Lower	: Not applicable
Vapor Density (Air = 1)	: Not applicable	Autoignition Temperature	
		Minimum Ignition Temp	: 420°C
pH (as is)	: Not applicable	Explosive Properties	: St-1
pH (in soln)	: 5.0-7.0 as an 11% solids dispersion	Oxidizing Properties	: Not applicable
Specific Gravity (H_2O = 1)	: Bulk density, 0.3 g/cc	Partition Coefficient (Kow)	: Not applicable
% Volatiles by Volume	: Approximately 5% water, by weight	Fat Solubility	: Not available

10. Stability and Reactivity

Stability : Stable

Hazardous Decomposition Products : None known

Conditions/Materials to Avoid (Incompatibility): None known

11. Toxicological Information

Eye Contact : Minimally irritating (rabbit). FMC Study Numbers I82-621, I82-626.

Skin Contact : Non-irritating, Primary Irritation Index (rabbit) = 0/8.0. FMC Study Number I82-625. Non-sensitizing (guinea pig). FMC Study Number I91-1184.

Skin Absorption : Dermal LD50 > 2 g/kg (rabbit). FMC Study Numbers I82-620, I82-624.

Inhalation : No mortality at maximum attainable concentration. 4 hour LC50 > 5.05 mg/l (rat). FMC Study Numbers I82-622, I82-627.

Ingestion : Oral LD50 > 5 g/kg (rat). FMC Study Number I82-623.

Acute Effects From Overexposure : No significant hazard in animal toxicity tests.

Chronic Effects From Overexposure : A 90 day animal study showed no adverse effects when administered in the diet (FMC Study Number I92-1464). This product was negative (non-mutagenic) in the Ames test (FMC Study Number I91-1189). No adverse human effects known. Microcrystalline cellulose is considered an inert dust which is not toxic to the lung when exposures are properly controlled.

Carcinogenicity: IARC: No NTP: No Other (OSHA, ACGIH): No

12. Ecological Information

Environmental Fate: Biodegradation in soil: Inherently biodegradable (FMC Study Number I92-1300).

Environmental Effects:

Rainbow Trout: 96 hr LC50 > 100%, Saturated solution. (NOEC = 100%), FMC Study Number I92-1297.

Daphnia: 48 hr LC50 > 100%, Saturated solution (NOEC = 100%), FMC Study Number I92-1298.

Algae: 96 hr EC50 > 100%, Saturated solution (NOEC = 12.5%), FMC Study Number I92-1299.

13. Disposal Considerations

No special disposal methods are suggested. It is the user's responsibility to comply with all applicable local, state, and federal laws, rules, regulations, and standards.

14. Transportation Information

U.S. DOT	: Not regulated in Title 49 of the U.S. Code of Federal Regulations as a hazardous material.
Shipping Name	: National Motor Freight Classification Item 71390, Flour Cellulose, Edible.
UN (IMO/IMDG)	: Not Applicable
Marpol Designation	: None
Canada (TDG)	: Not Applicable

15. Regulatory Information

U.S. TSCA Inventory	: Yes
U.S. SARA Title III	
Section 311/312	: None
Section 313 (40 CFR 372)	: This product does not contain any toxic chemicals subject to the reporting requirements of Section 313 of Title III of the Superfund Amendments and Reauthorization Act of 1986 (SARA) and 40 CFR part 372.
California Proposition 65	: This product does not contain any chemicals currently on the California list of known carcinogens and reproductive toxins.
Canada WHMIS	: Not a controlled product under the Canadian Workplace Hazardous Materials Information System (WHMIS).
EEC EINECS No.	: 232-674-9 Cellulose 231-595-7 Hydrochloric acid Note: Under the EINECS reporting guidelines, the reactants are reportable; the post-reacted natural polymer is not reportable.
EEC Symbols	: Not classified as dangerous
EEC Risk Phrases	: Not classified as dangerous
EEC Safety Advise Phrases	: Not classified as dangerous
Additional Regulatory Information	: Avicel®PH Microcrystalline Cellulose meets the standards set forth in the United States Pharmacopeia/National Formulary, European Pharmacopoeia, British Pharmacopoeia, The Pharmacopoeia of Japan and the Food Chemicals Codex. Microcrystalline cellulose is generally recognized as safe (GRAS) by qualified experts and is in accordance with the United States Food and Drug Administration. FMC maintains a Drug Master File at the U.S. Food and Drug Administration to support the safe use of Avicel PH in drug products. The Avicel PH products are manufactured in accordance with Current Good Manufacturing Practice and are in compliance with the Federal Food, Drug and Cosmetic Act, as Amended.

16. Other Information

NFPA Designation 704

		Degree of Hazard	Degree of Hazard Code
Red	Fire:	1	4 = Extreme
Blue	Health:	0	3 = High
Yellow	Reactivity:	0	2 = Moderate
White	Special Hazard:	None	1 = Slight
			0 = Insignificant

Prepared by: FMC Corporation
Sections Revised: New Format

Material Safety Data Sheet
May be used to comply with
OSHA's Hazard Communication Standard,
CFR 1910.1200. Standard must be
suited for specific requirements.

U.S. Department of Labor
Occupational Safety and Health Administration
(Non-Mandatory Form)
Form Approved
OMB No. 1218-0072

IDENTITY (As Used on Label and List)
Anhydrous Lactose, NF

Note: Blank spaces are not permitted. If any item is not applicable, or no information is available, the space must be marked to indicate that.

Section I

Manufacturer's Name Quest International	Emergency Telephone Number Chemtrec: 1-800-424-9300
Address (Number, Street, City, State, and ZIP Code) P.O. Box 630 Norwich, New York 13815	Telephone Number for Information 607-334-9951
	Date Prepared 5/24/94
	Signature of Preparer (optional)

Section II — Hazardous Ingredients/Identity Information

Hazardous Components (Specific Chemical Identity; Common Name(s))	OSHA PEL	ACGIH TLV	Other Limits Recommended	% (optional)
NONE				

Section III — Physical/Chemical Characteristics

Boiling Point	N.A.	Specific Gravity (H_2O = 1) Bulk Density	Approx. 8
Vapor Pressure (mm Hg.)	Negligible	Melting Point	Decomposes
Vapor Density (AIR = 1)	Negligible	Evaporation Rate (Butyl Acetate = 1)	N.A.

Solubility in Water: 20g/100 ml @75°C

Appearance and Odor: White Powder, Nearly Odorless

Section IV — Fire and Explosion Hazard Data

Flash Point (Method Used) Unknown	Flammable Limits Unknown	LEL UK	UEL UK

Extinguishing Media: Water, CO_2

Special Fire Fighting Procedures: None Required

Unusual Fire and Explosion Hazards: None

Section V — Reactivity Data

Stability			Conditions to Avoid
	Unstable		
	Stable	X	

Incompatibility (Materials to Avoid)

Hazardous Decomposition or Byproducts

Hazardous Polymerization			Conditions to Avoid
	May Occur		
	Will Not Occur	X	

Section VI — Health Hazard Data

Route(s) of Entry: Inhalation? Skin? Ingestion?

Health Hazards (Acute and Chronic) Not a Health Hazard

Carcinogenicity: NTP? IARC Monographs? OSHA Regulated?

Not a Carcinogen

Signs and Symptoms of Exposure

Medical Conditions Generally Aggravated by Exposure

Emergency and First Aid Procedures None Required

Section VII — Precautions for Safe Handling and Use

Steps to Be Taken in Case Material is Released or Spilled

Sweep or Vacuum

Waste Disposal Method Normal solid waste disposal

Precautions to Be Taken in Handling and Storing

No special precautions

Other Precautions

Section VIII — Control Measures

Respiratory Protection (Specify Type) Not required

Ventilation			
	Local Exhaust	Special	
	Mechanical (General)	Other	

Protective Gloves Not Required Eye Protection Not Required

Other Protective Clothing or Equipment Not Required

Work/Hygienic Practices Normal

M A T E R I A L S A F E T Y D A T A S H E E T

NOTICE: The information and recommendations contained herein are based upon data believed to be correct. However, no guarantee or warranty of any kind, expressed or implied is made with respect to the information contained herein.

HAZARD RATINGS

HEALTH = 0
FLAMMABILITY = 0
REACTIVITY = 0

0=Minimal 1=Slight 2=Moderate 3=Serious 4=Severe

SECTION I

MANUFACTURER'S NAME: Colorcon - A Division of Berwind Pharmaceutical Services, Inc.

ADDRESS: Moyer Blvd., West Point, Pa. 19486

EMERGENCY TELEPHONE NUMBER: CHEMTREC:1-800-424-9300

PRODUCT CLASS: Dry film coating concentrate

TRADE NAME: Opadry

MANUFACTURER'S ID CODE: [redacted]

SECTION II
HAZARDOUS INGREDIENTS

The materials listed in this Data Sheet are classified as non-hazardous in accordance with the definition set forth in 29CFR 1910.1200. Ingredients contained in this product are not subject to SARA TITLE III requirements.

SECTION III
PHYSICAL DATA

BOILING RANGE: N/A

VAPOR DENSITY (VS AIR): N/A

EVAPORATION RATE(VS BUTYL ACETATE): N/A

PERCENT VOLATILE (W/W)= N/A

LIQUID DENSITY (VS WATER): N/A

APPEARANCE AND ODOR: Odorless Dark orange powder.

SECTION IV
FIRE AND EXPLOSION DATA

FLASH POINT: N/A

EXTINGUISHING MEDIA:

CO2
Dry Chemical
Water Fog

FLAMMABLE LIMITS: Lel: N/A
Uel:

SPECIAL FIRE FIGHTING PROCEDURES:

None.

UNUSUAL FIRE AND EXPLOSION HAZARDS: None.

SECTION V
HEALTH HAZARD DATA

EFFECTS OF OVEREXPOSURE: None.

PRIMARY ROUTE(S) OF ENTRY: Inhalation

EMERGENCY AND FIRST AID PROCEDURES:

In case of accidential eye contact, flush eyes with water. If irritation exists, obtain medical attention.

SECTION VI
REACTIVITY DATA

PRODUCT STABILITY: Stable

CONDITIONS TO AVOID: None known.

SECTION VII
SPILL OR LEAK PROCEDURES

PROCEDURE WHEN MATERIAL SPILLED OR RELEASED: Sweep up and discard into proper waste container. Avoid contact with water until after all material has been swept up. Area can then be washed down with water.

WASTE DISPOSAL METHOD: Dispose of in accordance with Federal, State and Local regulations.

SECTION VIII
SPECIAL PROTECTION INFORMATION

VENTILATION: Sufficient to prevent inhalation of dust.

RESPIRATORY PROTECTION: An approved dust respirator should be worn.

PROTECTIVE CLOTHING: Gloves and coveralls recommended to protect from dust.

EYE PROTECTION: Safety goggles.

OTHER PROTECTIVE EQUIPMENT:

SECTION IX
SPECIAL PRECAUTIONS

HANDLING AND STORING: Store in cool, dry area. Keep containers closed.

OTHER PRECAUTIONS: In accord with good industrial practices, handle with due care and avoid personal contact. Wash exposed skin areas with soap and water.

MATERIAL SAFETY DATA SHEET

NOTICE: The information and recommendations contained herein are based upon data believed to be correct as of the date of issue. No guarantee or warranty of any kind, expressed or implied is made with respect to the information contained herein.

HAZARD RATINGS

HEALTH	= 0
FLAMMABILITY	= 0
REACTIVITY	= 0

0 = Minimal 1 = Slight 2 = Moderate 3 = Serious 4 = Severe

SECTION I - PRODUCT IDENTIFICATION

MANUFACTURER'S NAME:	COLORCON, A DIVISION OF BERWIND PHARMACEUTICAL SERVICES
ADDRESS:	MOYER BLVD., WEST POINT, PA 19486
EMERGENCY TELEPHONE NUMBER:	CHEMTREC: 800/424-9300
PRODUCT CLASS:	Dry Film Coating Concentrate
TRADE NAME:	OPADRY
MANUFACTURER'S ID CODE:	YS-1-12725

SECTION II - INGREDIENT DATA

HAZARDOUS COMPONENT:	CAS:	EXPOSURE LIMITS: (ACGIH)	(OSHA)
Titanium Dioxide	13463-67-7	10 MG/M3	10 MG/M3

PENNSYLVANIA RIGHT-TO-KNOW:

Hydroxypropyl Methylcellulose	9004-65-3	Not Established
Polyethylene Glycol	Trade Secret	Not Hazardous
FD&C Pigments	Trade Secret	Not Hazardous

WHMIS:
None

SECTION III - PHYSICAL DATA

BOILING RANGE: N/A

VAPOR DENSITY (VS. AIR): N/A

EVAPORATION RATE (VS. BUTYL ACETATE) N/A

PERCENT VOLATILE (W/W): N/A

LIQUID DENSITY: N/A

FREEZING POINT: None

ODOR THRESHOLD: Odorless

AUTO IGNITION TEMPERATURE: N/A

APPEARANCE AND ODOR:
Yellow Odorless powder

SECTION IV - FIRE/EXPLOSION DATA

FLASH POINT: N/A

FLAMMABLE LIMITS - LEL: N/A

- UEL: N/A

RATE OF BURNING: N/A

SENSITIVITY TO STATIC DISCHARGE: See explosion hazards

EXTINGUISHING MEDIA:
Water spray or fog, CO2, dry chemical

SPECIAL FIRE FIGHTING PROCEDURES:
Fire fighters should wear self contained breathing apparatus operated in positive pressure mode and full turn out gear.

UNUSUAL FIRE AND EXPLOSION HAZARDS:
Product may form explosive mixtures with the proper air proportions and source of ignition, similar to grain dust. Keep clouds of such dust away from possible ignition sources.

SECTION V - HEALTH HAZARDS

EFFECTS OF OVEREXPOSURE:
Can cause transient eye, nose and throat irritation. May cause coughing and chest discomfort.

ROUTES OF ENTRY: Inhalation

FIRST AID PROCEDURES:
Eye Contact: Flush with water for at least 15 minutes.

Skin Contact: Wash with mild soap and water.

Inhalation: Remove victim to fresh air.

As in all cases of over exposure, if irritation persists, seek medical attention.

SECTION VI - TOXICITY DATA

CHRONIC EFFECTS: No specific data available.

TARGET ORGANS: No specific data available.

CARCINOGENITY: NTP: No IARC: No OSHA: No

SECTION VII - REACTIVITY

PRODUCT STABILITY: Stable

CONDITIONS TO AVOID: Heat, sparks, flame and other ignition sources. Avoid the generation of dust layers and clouds.

HAZARDOUS POLYMERIZATION: Will not occur.

MATERIALS TO AVOID:
Oxidizing materials.

DECOMPOSITION PRODUCTS:
Carbon monoxide, carbon dioxide

SECTION VIII - SPILL PROCEDURES

LARGE SPILLS:
Moisten slightly with water to avoid producing dust. Surfaces subject to spills or dusting with this product can become slippery when wet. Sweep or shovel moistened material into proper waste containers. Do not sweep dry material, as this will produce dust concentrations in the air.

SMALL SPILLS:
Vaccum material or moisten slightly with water and place into proper waste container.

WASTE DISPOSAL:
This product is not a hazardous waste under RCRA regulations. Consult State and Local regulations for proper waste disposal method.

SECTION IX - PROTECTION DATA

VENTILATION:
General air circulation, use local exhaust to collect excessive dust at point of generation. Dust collection systems should be provided with explosion venting and automatic fire protection. Discharge from ventilation systems should comply with applicable air pollution regulations.

RESPIRATORY PROTECTION:
A Niosh approved dust respirator if airborne concentrations exceed TLV limits or for allergic individuals.

PROTECTIVE CLOTHING:
Gloves

EYE PROTECTION:
Safety glasses or goggles. Contact lens should not be worn when handling this product. Contacts may intensify any exposures.

OTHER PROTECTIVE EQUIPMENT:

SECTION X - SPECIAL PRECAUTIONS

HANDLING AND STORAGE:
Avoid handling procedures which suspends or accumulates dust. Avoid breathing dust. Wash after handling.

OTHER PRECAUTIONS:
Avoid excessive contact with eyes, skin and clothing. Throughly clean all equipment, piping and vessels before beginning maintenance or repairs.

SECTION XI - REGULATORY

CLASSIFICATIONS:
Not regulated under DOT regulations.
This product is considered hazardous under the OSHA hazard communicaiton standard.

SARA TITLE III (Community Right-to-know):

SECTION 311/312:
This product is categorized as an immediate health hazard.

SECTION 313:
This product does not contain any chemicals listed in section 313 above de minimis levels.

TOXIC SUBSTANCE CONTROL ACT:
All materials contained in this product are listed on the TSCA inventory.

STATE RIGHT-TO-KNOW:
N/A

APPENDIX A-2

Statements of Compliance from Manufacturers

Sumika Fine Chemicals Co., Ltd., Japan

Sumika Fine Chemicals Co., Ltd.

Daiichi Kasai Koraibashi Bldg
3-7, Koraibashi 4-chome
Chuo-ku, Osaka 541, Japan
TEL:06-231-0070 FAX:06-231-0016

1/5

May 28, 1996

Ms. Anne Mckay
Regulatory Affairs
Medco Research Inc.
Post Office Box 13886
Research Triangle Park NC 27709
U.S.A.

Dear Ms. Mckay:

Reference is made to my fax to you dated May 15th.

As I promised, I am sending you the copies of Certificates which we obtained from Governor of Gifu Prefecture and Governor of Anpachi-town as per attached. (I am sending them directly to you instead of through our agent.)

If you have any question or request, please feel free to contact us.

Very truly yours,

SUMIKA FINE CHEMICALS CO., LTD.

K. Ikuta, Manager
International Business Dept.

Encl.

証　明　書

岐阜県知事

　　　梶原　拓　殿

平成　7年　4月　28日

岐阜県安八郡安八町[illegible]3750番地

住化ファ[illegible]株式会社岐阜工場

当工場の生産活動に係る　水質汚濁防止法　第5条　第1項及び第7条第1項の規定に基づく届出ならびに　大気汚染防止法　第6条第1項（第7条　第1項、第8条　第1項）の規定により、ばい煙発生施設の届出については下記の通り受理されていることを証明願います。

記

（水質汚濁防止法関係）

届出項目	届出年月日	受理年月日	受理番号
特定施設許可設置届	平成　2年　6月15日	平成　2年　8月21日	大垣保環第　82号の16
特定施設の構造等変更届	平成　5年11月19日	平成　5年12月21日	大垣保環第118号の2

（大気汚染防止法関係）

施設の名称	届出年月日	受理年月日	受理番号
ばい煙発生施設（廃棄物焼却炉）設置届	平成　2年　6月25日	平成　2年　6月29日	大垣保環第82号の20
ばい煙発生施設（廃棄物焼却炉）変更届	平成　3年12月20日	平成　3年12月25日	大垣保環第57号の11

上記のとおり相違ないことを証明します。

大垣保環第143号

平成　7年　4月28日

岐阜県知事　　梶原　拓

Mr. Hajime Hirai
General manager of Gifu Plant of
Sumika Fine Chemicals Co., Ltd.

Certificate

This is to certify that a Convention for Environmental Preservation was concluded under the Provision of Article 67, Para 2 of the Ordinance for Prevention of Pollution of Gifu Prefecture in the matter of the following agreement relating to the manufacture of the substance produced in Gifu Plant.

Convention	Convention date
Convention for Environmental Preservation	December 1, 1993

April 21, 1995
Masaharu Niwa
Governor of Anpachi-cho

5/5

証　明　書

安八郡安八町長
丹　羽　正　治　殿

平成 7 年 4 月 21 日

岐阜県安八郡安八町牧[illegible]八町3750番地
住化ファインケム株式会社岐阜工場
工場長　平井

Cor

当工場の生産活動に伴わり、環境基本法並びに岐阜県公害防止条例第６７条の２項に基づく「環境保全協定」が締結されていることを証明願います。

記

協　定　書　名	協 定 年 月 日
環境保全に関する協定書	平成　5年12月　1日

上記のとおり相違ないことを証明します。

平成　7年　4月21日

岐阜県安八郡安八町長　　丹　羽　正　治

Mr. Hajime Hirai
General manager of Gifu Plant of
Sumika Fine Chemicals Co., Ltd.

Certificate

This is to certify that a license was issued under Article 5, Para 1 and Article 7, Para 1 of the Law for the Prevention of Water Pollution and under Article 6, Para 1, Article 7, Para 1 and Article 8, Para 1 of the Law for the Prevention of Air Pollution.

Application	License date	License No.
Application for license for installation of a designated facility	June 21, 1992	O-H No. 82-16
Application for license for change in the structure etc. of a designated facility	December 21, 1993	O-H No. 118-2
Application for licence for installation of an incinerator	June 20, 1990	O-H No. 82-20
Application for license for change in the structure etc. of an incinerator	December 25, 1993	O-H No. 57-11

April 28, 1995
Taku Kaiwara
Governor of Gifu Prefecture

EMS-DOTTIKON AG, Switzerland

BAUDEPARTEMENT DES KANTONS AARGAU
Abteilung Umweltschutz

Entfelderstrasse 16
Telefon 064 21 27 28
Telefax 064 21 17 30
Marcel Schmid

5001 Aarau, Juli 1995

Food an Drug
Administration

U.S.A.

ENVIRONMENTAL PROTECTION CERTIFICATE

1. The company EMS-Dottikon AG operates facilities for pharmaceutical manufacturing at the following address

   EMS-DOTTIKON AG
   CH-5605 Dottikon
   Switzerland

2. These production facilities may only operate in accordance with permits issued by the responsible authorities. In the permits are laid down the purpose for which buildings and plants may be used and the legal conditions with which the company must comply.

3. The above described permits cover the preparation of pharmaceutical products containing ISDN active substance.

4. All buildings and plants of the company EMS-Dottikon AG must comply with the federal and cantonal laws and regulations concerning safety, protection of the environment and working conditions. Compliance is enforced by the cantonal authorities.

5. The relevant departments of the cantonal authorities perform periodic inspections.

6. On the basis of the inspections performed it can be confirmed that there exists no indication of violation of the applicable laws and regulations.

BAUDEPARTEMENT
Chef Abteilung Umweltschutz

Dr. Jürg W. Tschopp

DRUG-02.DOC

Global Pharm. Inc., Canada

Global Pharm Inc.

In summary of the status report (attached) on the environmental compliance of the facility, the facility is in compliance with all relevant regulations. The facility also has a program in place to ensure compliance to all Health and Safety regulations.

To the best of my knowledge there is no historical or archeological significance to the manufacturing facility located at 865 York Mills Road, Don Mills, Ontario Canada.

J. Thorogood
Manager, Engineering and Maintenance.