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
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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

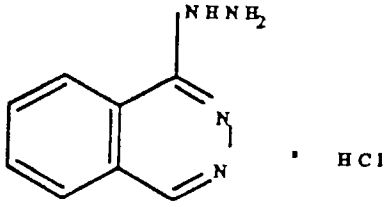
$C_8H_8N_4 \cdot HCl$; 196.64

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)

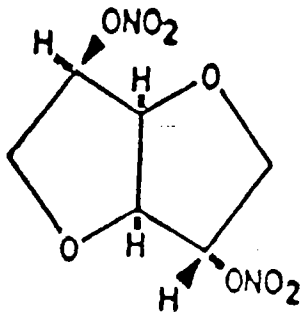
$C_{12}H_{22}O_{11}$ (Lactose); 342.30 (Lactose)

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.

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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.

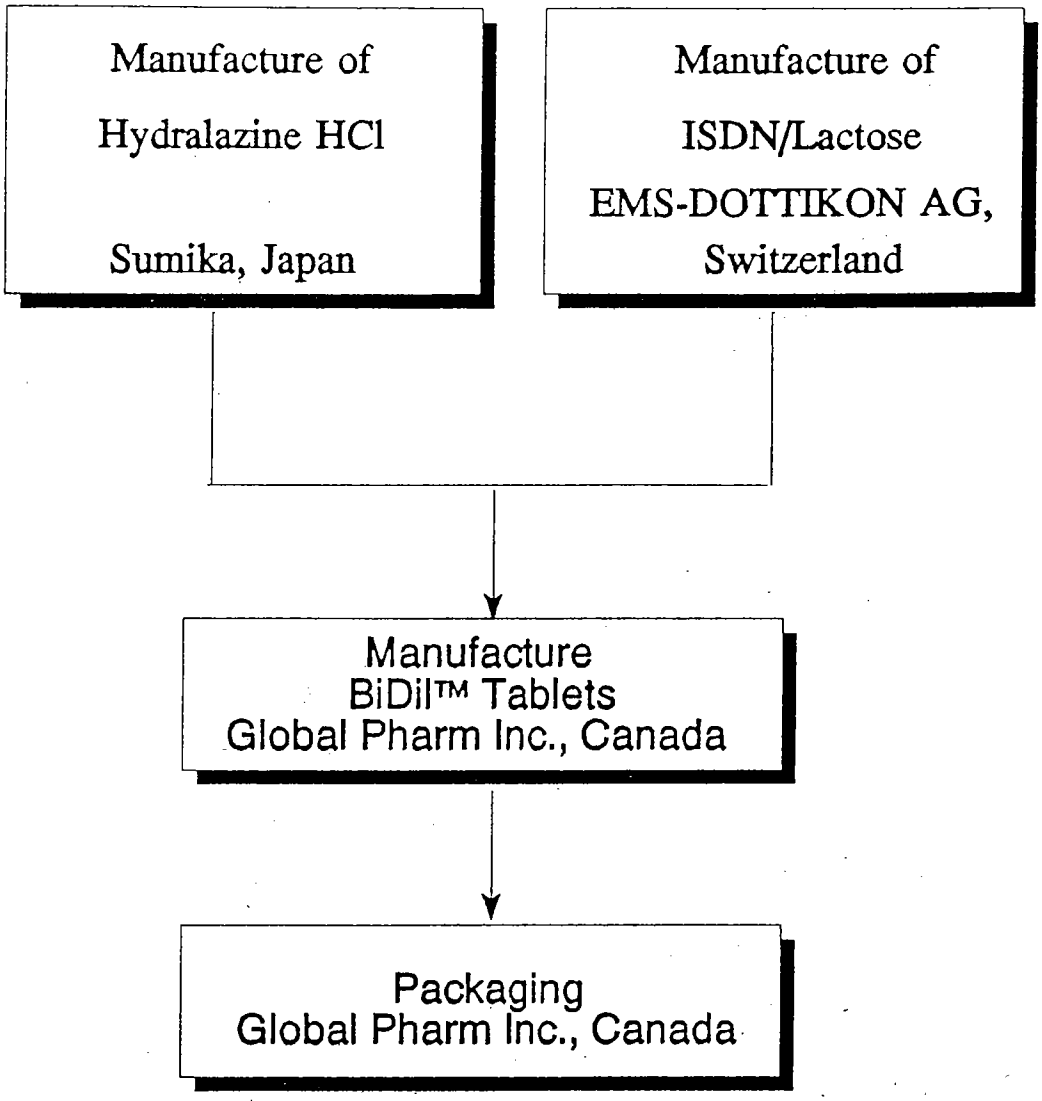


Figure 4-1
SITES RELEVANT TO THE MANUFACTURE
OF BiDil™ TABLETS

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

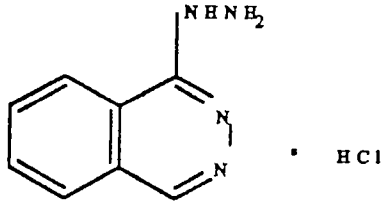
$C_8H_8N_4 \cdot HCl$; 196.64

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)

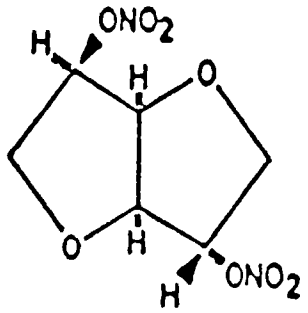
$C_{12}H_{22}O_{11}$ (Lactose); 342.30 (Lactose)

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

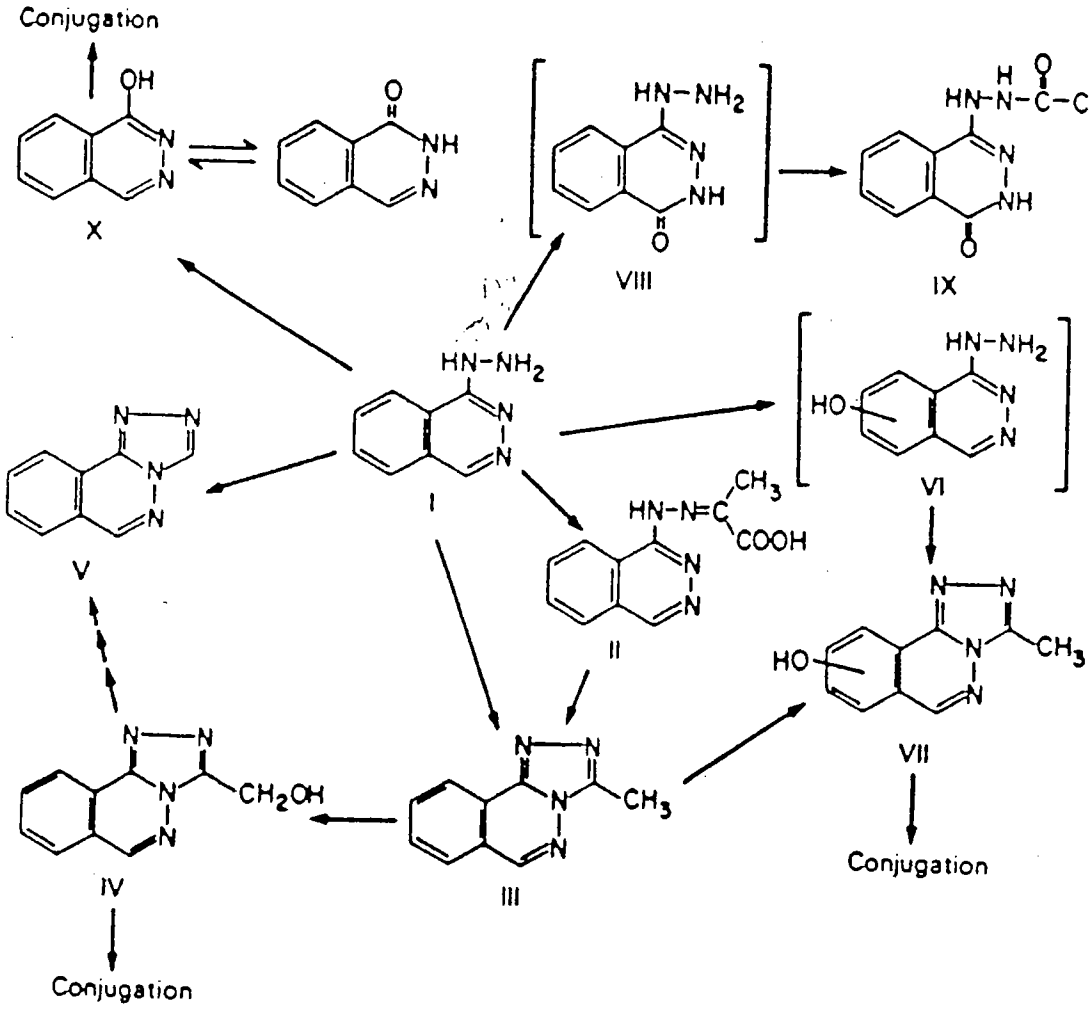
For the sake of estimation of Maximum Emitted Environmental Concentrations (MEEC), it is assumed that all the drug is consumed by patients and excreted intact through urine and feces. Hydralazine is extensively metabolized in the human body. Studies measuring the urinary excretion of radioactivity after 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

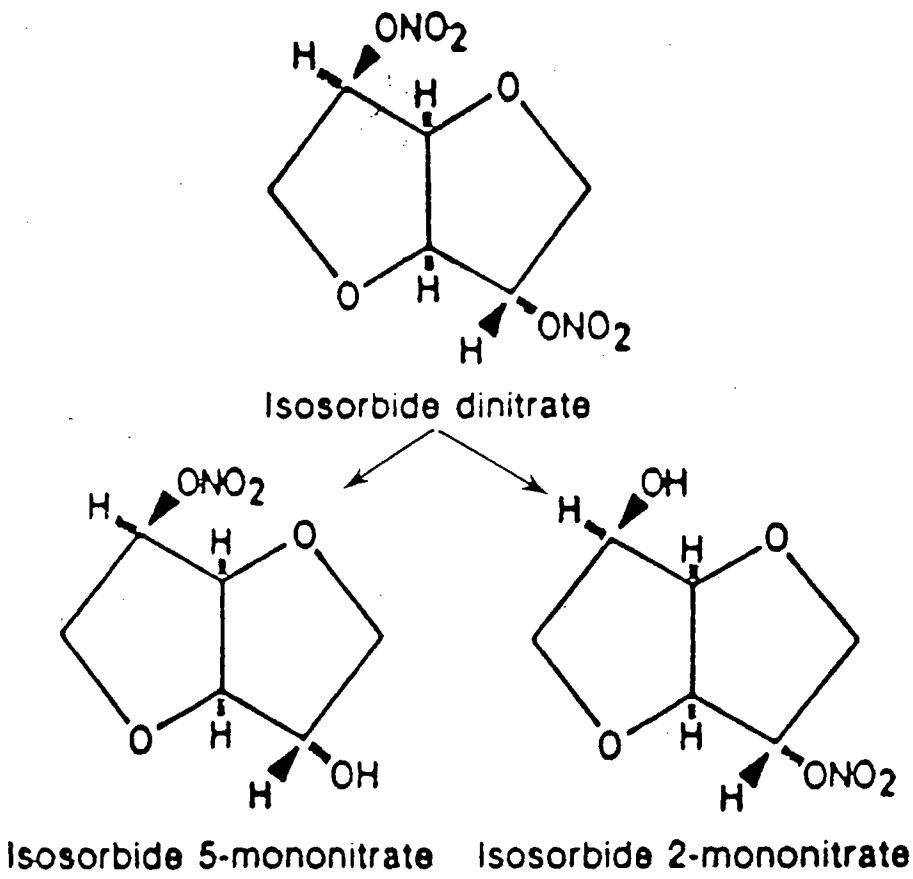


Figure 6-2
METABOLISM OF ISOSORBIDE DINITRATE IN HUMANS

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