

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
40136

CORRESPONDENCE



ANDA 40-136

Food and Drug Administration
Rockville MD 20857

Luitpold Pharmaceuticals, Inc
Attention: Audrey Bialeski
One Luitpold Drive
Shirley, NY 11967

DEC 4 1996

Dear Madam:

This is in reference to your abbreviated new drug application dated February 17, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Hydralazine Hydrochloride Injection USP, 20 mg/mL.

Reference is also made to your amendment dated June 21, 1996.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

- A. Chemistry Deficiencies

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

Chem. Deficiencies

B. Microbiology Deficiencies

1. The antimicrobial preservatives efficacy tests (APET's) performed for the subject drug product using Aspergillus niger did not meet compendial requirements. USP 23 Chapter <51> states that.. "the concentration in the test preparation immediately after inoculation is between 100,000 and 1,000,000 microorganisms per mL." You should repeat the APET's for A. niger only and submit a data summary which meets USP acceptance criteria.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

1. The drug master file (DMF) you referenced, DMF [redacted] for your supplier of the drug substance, Hydralazine Hydrochloride USP, was reviewed and found to be deficient. The holder of DMF [redacted] has been informed of these deficiencies. All the deficiencies in DMF [redacted] must be adequately addressed before approval of this application.
2. You indicate that "prior to becoming an approved component vendor, manufactured lots of product using the vendor's components are placed on stability and monitored". Please acknowledge that any change to the container/closure system requires a supplement as per 21 CFR 314.70(b).

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MINOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

RSI

cc Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-136

Luitpold Pharmaceuticals, Inc.
Attention: Audrey L. Bialeski
One Luitpold Drive
Shirley, NY 11967

OCT 25 1995

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letters dated April 5, 1995, and June 1, 1995; and your amendments dated May 10, 1995, and October 4, 1995.

NAME OF DRUG: Hydralazine Hydrochloride Injection USP, 20 mg/mL

DATE OF APPLICATION: February 17, 1995

DATE OF RECEIPT: February 22, 1995

DATE ACCEPTABLE FOR FILING: October 5, 1995

We will correspond with you further after we have had the opportunity to review your application.

Please identify any communications concerning this application with the number shown above.

Should you have questions concerning this application contact:

James Wilson
Consumer Safety Officer
(301) 594-0310

Sincerely yours,

/S/ *10/24/95*
Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Luitpold Pharmaceuticals, Inc.
Attention: Audrey L. Bialeski
One Luitpold Drive
Shirley, NY 11967

JUN 1 1995

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated February 17, 1995, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Hydralazine Hydrochloride Injection USP, 20 mg/mL.

Reference is also made to our "Refuse to File" letter dated April 5, 1995, and your amendment dated May 10, 1995.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

You have failed to provide a complete side-by-side comparison of the formulation of your proposed drug product with that of the reference listed drug product. While we note that you have provided qualitative and quantitative comparisons between your proposed drug product and the reference listed drug product, you have failed to characterize any differences between your proposed drug product and the reference listed drug and provide information to demonstrate these differences do not affect the safety of the proposed drug product [21 CFR 314.94(a)(9)(iii)]. This information to demonstrate safety should include, but is not limited to: (a) examples of approved drug products administered by the same route of administration which contain the same inactive ingredients, and that are within the same concentration range, (b) a description of the purpose of the inactive ingredients when different inactive ingredients are included in the proposed drug product, (c) a comparison of the physical and chemical properties (e.g. pH, osmolarity, tonicity) of the proposed drug product with that of the reference listed drug, and (d) information to show that the inactive ingredients do not adversely affect these properties.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

/S/

6/1/95

Yana Ruth Mille
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-136

cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett

Endorsement: HFD-615/Prickman, Acting Chief 5/16/95 date
HFD-615/WRussell, CSO 5/16/95 date
HFD-610/JPhillips, Chief, LRB 5/16/95 date
HFD-623/RKishore, Sup.Chem. R. Kishore date
WP File\russell\40\40-136
F/T by Fox 5/16/95
ANDA Refuse to File!

APR 5 1995

Luitpold Pharmaceuticals, Inc.
Attention: John Purpura
One Luitpold Drive
Shirley, NY 11967

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated February 17, 1995, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Hydralazine Hydrochloride Injection USP, 20 mg/mL.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

You have failed to provide a side-by-side comparison of the formulation of your proposed drug product with that of the reference listed drug product. You must demonstrate that the proposed drug product is qualitatively and quantitatively the same as the reference listed drug product. In addition, if any qualitative or quantitative differences do exist between your proposed drug product and the reference listed drug, you must provide information to demonstrate these differences do not affect the safety of the proposed drug product [21 CFR 314.94(a)(9)(iii)]. This information to demonstrate safety should include, but is not limited to: (a) examples of approved drug products administered by the same route of administration which contain the same inactive ingredients, and that are within the same concentration range, (b) a description of the purpose of the inactive ingredients when different inactive ingredients are included in the proposed drug product, (c) a comparison of the physical and chemical properties (e.g. pH, osmolarity, tonicity) of the proposed drug product with that of the reference listed drug, and (d) information to show that the inactive ingredients do not adversely affect these properties.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

In addition, you failed to provide a side-by-side comparison of your proposed package insert with the approved package insert for the reference listed drug with all differences annotated and explained [314.94(a)(8)(iv)]. Please provide this annotated comparison.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

IS/

4/5/95

Yana Ruth Mille
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-136
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett

Endorsement: HFD-615/Prickman, Acting *W. Prickman* *4/4/95* date
HFD-615/WRussell, CSO *W. Russell* date
HFD-610/JPhillips, Chief, IRB *J. Phillips* *4/4/95* date
HFD-623/Chem Branch *R. [unclear]* date *4-5-95*
A:\rtfanda\40-136
F/T File 4-4-95
ANDA Refuse to File!

1,1
ANDA 40-136

FEB - 8 1996

Luitpold Pharmaceuticals, Inc.
Attention: Audrey L. Bialeski
One Luitpold Drive
Shirley NY 11967

Dear Madam:

Reference is made to your abbreviated new drug application dated February 17, 1995, submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Hydralazine Hydrochloride Injection USP, 20 mg/mL.

The following comments pertain **only** to bioequivalency issues in the February 17, 1995 submission.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

15/10/95

ANDA 40-136

Luitpold Pharmaceuticals, Inc
Attention: John Purpura
One Luitpold Drive
Shirley, NY 11967

Dear Sir:

This is in reference to your abbreviated new drug application dated February 17, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Hydralazine Hydrochloride Injection USP, 20 mg/mL.

Reference is also made to your amendments dated May 10, 1995 and October 4, 1995.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

Chem Deficiencies

C. Microbiology Deficiencies

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

1. In reference to your assay method for the drug product, please be informed that since the product is an official article in the United States Pharmacopeia (USP), the approval to use an analytical procedure that differs from that in the USP does not release you from any obligations to comply with the methods and procedures in the USP. Therefore, in the event of a dispute, only the results obtained by the official methods and procedures in the USP will be considered conclusive.
2. Please be informed that DMF facility references were provided for two of the alternative suppliers of vials,

For emergency use - only in patients unable to take oral medication.

- b.. We encourage the inclusion of a pH range as seen in your package insert labeling (DESCRIPTION).

4. INSERT

a. DESCRIPTION

- i. First paragraph, last line, "...Hydrazinophthalazine...", (capital "H").
- ii. Include the molecular formula of hydralazine hydrochloride, " $C_8H_8N_4HCl$ ".

b. PRECAUTIONS

- i. Revise to read "hydralazine", rather than } throughout this section with the following exceptions:

- Second paragraph in the Laboratory Tests subsection (should read "hydralazine hydrochloride").
- In the Pediatric Use subsection.

- ii. Pediatric Use

...in pediatric patients have...

c. HOW SUPPLIED

See General Comment.

Please revise your labels and labeling, as instructed above, and submit final print labeling. To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained. Please note that we reserve the right to request further changes in your labels and/or labeling based upon further changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 4/18/96

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 40-136
Dup File
Division File
Field Copy
HFD-600/Reading File
HFD-82

Endorsements:

HFD-623/M.Maust/2-26-96 *M. Maust 4/11/96*
HFD-623/A. Rudman, Ph.D./3-23-96 *Vilayet H. Sayed 4/11/96*
HFD-617/J.Wilson/CSO/3-26-96 *Jim White 4/15/96*
HFD-613/J.White/J.Phillips for/4-10-96 *Phillips for 4/14/96*
HFD-623/K.Muhvich, Ph.D./ *KH Muhvich 4/15/96* *J. Phillips 4/17/96*

NOT APPROVABLE: MAJOR AMENDMENT



LUITPOLD

June 13, 1997

NEW CORRESP

NC

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

VIA TELEFAX AND FEDERAL EXPRESS

EXPEDITED REVIEW

Hydralazine HCl Injection, USP - 20 mg/mL

ANDA 40-136

Teleconference June 11, 1997

Dear Mr. Wilson:

Reference is made to the abbreviated new drug application for Hydralazine HCl Injection, USP, 20 mg/mL dated February 17, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act and granted Expedited Review. Reference is also made to the amendments dated May 10, and October 4, 1995, June 21, 1996, January 22, March 6, March 21, and May 29, 1997.

As discussed in the teleconference between FDA and Luitpold on June 11, 1997, the precision of the impurity/degradant calculation has been improved by using phthalazine as the standard. Chromatographic analysis of USP reference standards confirms similar absorptivity for phthalazine and the degradants/impurities identified.

As agreed during the teleconference, all issues have been resolved and this application may be approved.

Please contact me at (516) 924-4000 extension 459 if you require any further information. FAX communications should be made to (516) 345-0335.

Sincerely,

LUITPOLD PHARMACEUTICALS, INC.

Robert J. Anderson, B.A., J.D.
Associate Director, Regulatory Affairs

RJA/rs

RECEIVED
JUN 16 1997
GENERIC DRUGS

Hydralazine HCL Injection, USP- 20 mg/mL
ANDA 40-136 - Minor Telephone Amendent
May 29, 1997
Page 2 of 2

The specification for total impurity/degradation was tightened, based on results of the 18 month stability test station since, as previously discussed, data for the 12 month test station is not available. See Attachment II.

All values are within the tightened specification after recalculation with the more accurate method. Therefore, identification of the peaks should not be necessary. However, after extensive research and testing was performed, were identified as at retention times of 2.3 minutes and 2.8 minutes respectively.

Please contact me at (516) 924-4000 extension 459 if you require any further information. FAX communications should be made to (516) 345-0335.

Sincerely,

LUITPOLD PHARMACEUTICALS, INC.



Robert J. Anderson, B.A., J.D.
Associate Director, Regulatory Affairs

RJA/rs



LUITPOLD

March 21, 1997

FAXED

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

VIA TELEFAX AND FEDERAL EXPRESS

**Hydralazine HCl Injection, USP - 20 mg/mL
ANDA 40-136
Minor Telephone Amendment**

Dear Mr. Wilson:

Reference is made to the abbreviated new drug application dated February 17, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, for Hydralazine HCl Injection, USP, 20 mg/mL. Reference is also made to the amendments dated May 10 and October 4, 1995, June 21, 1996, January 22 and March 6, 1997.

This Minor Telephone Amendment is submitted in response to the FDA Telephone contact of March 13, 1997 requesting the following additional information.

Chromatographic purity profiles for the drug substance and drug product have been summarized for two raw material RR numbers (same manufacturer lot number), and the drug product at initial, 12, 18 and 32 month stability (see Attachment I). Chromatograms have also been provided for each of the samples. Note that the 12 month stability test point was actually tested at 14 months.

Each impurity peak is assigned a number based on retention time. The Hydralazine peak was used as an internal standard to establish the Relative Retention Time Ratio (retention time of impurity ÷ retention time of hydralazine) for each peak.

At the 12 month time point, detected total impurities are %. Due to an oversight, impurity was not measured. However, the 18 month samples show at %, resulting in a total impurity level of % if combined with the 12 month data. Based on this data, the Finished Product specification for Chromatographic Purity was established at % for total impurities with an alert limit of %.



LUITPOLD

March 6, 1997

VIA TELEFAX AND FEDERAL EXPRESS

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

Hydralazine HCl Injection, USP; 20 mg/mL
ANDA 40-136
Minor Telephone Amendment

Dear Mr. Wilson:

Reference is made to the abbreviated new drug application dated February 17, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, for Hydralazine HCl Injection, USP, 20 mg/mL. Reference is also made to the amendments dated May 10 and October 4, 1995, June 21, 1996 and January 22, 1997.

This Minor Telephone Amendment is submitted in response to the FDA telephone contact of February 13, 1997 requesting the following additional information.

Luitpold Pharmaceuticals, Inc. hereby commits to include extractables testing as part of the stopper release for the first three lots of stoppers received and annually one lot thereafter, to qualify the vendor.

A revised Post Approval Stability Commitment has been provided in Attachment I. A statement has been included that an expiration date extension will be based on stability data from three production batches.

In addition to the upright sample data previously submitted for Sterility, Bacterial Endotoxins and AME, we have performed Sterility and Bacterial Endotoxins testing for the inverted samples at the 32 month time point. This represents a worst case scenario since it is well beyond the proposed expiration date of 12 months. All results meet specifications.

The Antimicrobial Preservative Effectiveness Study (previously submitted on February 17, 1995) demonstrated a minimum effectiveness level of %. A more stringent specification of % was established to further ensure the preservative remains above the minimum effective level throughout the product's proposed 12 month shelf life. Preservative concentration was monitored via analysis for both upright and inverted samples at 12 and 18 months. Preservative levels well above the % limit have been shown for all stability test stations, including those beyond the proposed 12 month shelf life.

MAR 07 1997

Hydralazine HCl Injection, USP; 20 mg/mL
ANDA 40-136 - Minor Telephone Amendment
March 6, 1997
Page 2 of 2

The Chromatographic Purity specification for Finished Product and Stability testing is based on consideration of all peaks eluting on the column during the assay determination, not just the impurity limit for the drug substance. Review of the chromatographs for upright and inverted samples tested at the 18 month time point shows approximately % degradation for the upright samples and % for the inverted. Therefore, Luitpold has established the Chromatographic Purity specification at % with an internal alert limit of % for the Finished Product and Stability Monographs. Copies of the chromatographs have been included as Attachment II.

Please contact me at (516) 924-4000 extension 459 if you require any further information. FAX communications should be made to (516) 345-0335.

Sincerely,

LUITPOLD PHARMACEUTICALS, INC.



Robert J. Anderson, B.A., J.D.
Associate Director, Regulatory Affairs

RJA/ab



Original

LUITPOLD

January 22, 1997

Office of Generic Drugs, CDER
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

VIA FEDERAL EXPRESS

Hydralazine HCl Injection, USP; 20 mg/mL
ANDA 40-136
Minor Amendment - Request For Expedited Review

NDA ORIGINATOR

jm

Dear Sir/Madam:

Reference is made to the abbreviated new drug application dated February 17, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, for Hydralazine HCl Injection, USP, 20 mg/mL. Reference is also made to the amendments dated May 10 and October 4, 1995, June 21, 1996 and to the FDA letter dated December 4, 1996.

Luitpold Pharmaceuticals, Inc. requests expedited review of this amendment based on public health need as defined in the Office of Generic Drugs's Policy and Procedure Guide #18-90. There is a medical emergency due to the shortage of Hydralazine HCl Injection, USP available to the medical community. This shortage has been confirmed with Mr. Harvey Greenberg of the OGD Drug Shortage Committee.

We have provided our responses in **comment**/response format.

A. Chemistry Deficiencies

1. You state that you have revised all appropriate manufacturing steps to include minimum and maximum mixing times. Please specify the steps in which these changes took place.

Minimum and maximum mixing times have been added to the following manufacturing steps in the Master Formula:

Page Number	Step Number(s)
3b	1
3c	
3d	

RECEIVED

JAN 24 1997

Madame
1/30/97

Copies of these pages (as provided in Attachment III of the comment dated June 21, 1996) are included in Attachment I.

GENERIC DRUGS

- 5. The inspection worksheets and the supplier's certification statements provided in attachment V are not adequate for the release of the container/closure components. If you are using the vendor's COA and in-house physical and chemical identification testing, these should be included as part of your in-house COA for these components.**

The information required for the release of containers and closures by Luitpold is summarized on the respective inspection worksheets. Each shipment of components received at Luitpold must be accompanied by the Vendor's Certificate of Compliance/Analysis. As part of the release procedures, the Vendor COA is reviewed. Acceptance of the Vendor COA is documented by the approval of the package by the Departmental Supervisor.

Additionally, Luitpold performs physical inspection and chemical identification testing. The latter portion of the container inspection worksheet specifies the Vendor COA must be attached to the worksheet. The closure inspection worksheet also provides a Lab Specification section to document the inclusion of the Vendor's Certificate of Analysis and an IR Spectrum of the rubber closure. Release of each lot of components includes the review and approval of the inspection worksheet and vendor documentation. Copies of the inspection worksheets have been included in Attachment V.

Based on the Agency's recommendation, Luitpold commits to revise the format of the container/closure inspection worksheets to improve clarity.

- 6. You have responded adequately to comment 8.b., however, the revised stability protocol only includes the storage temperature, not the position of the vials for the annual stability batches. Please include the storage position as part of the statement for the annual stability batches.**

A revised Post Approval Stability Commitment which includes the position of the vials for the annual stability batches is provided in Attachment VI.

- 7. Please commit to updating the Particulate Matter Test <788> as per USP supplement 5 (effective November 15, 1996).**

The Finished Product and Stability Specifications have been updated to reflect the Particulate Matter Test <788> as per USP supplement 5. See Attachment IV.

- 8. Please include an APHA color test and specification for the drug product at release and on stability.**

The Finished Product and Stability Specifications have been updated to include a Color of Solution test and specification based on USP 23 Chapter <631>, Color and Achromicity. Please refer to Attachment IV.

9. You indicate that there is a decrease in pH over time for this product. Please provide the room temperature shelf-life stability data to support the requested expiration period.

The room temperature shelf life stability data which supports the requested 12 month expiration period is provided in Attachment VII. All test results are within specifications through the proposed expiration period.

10. On page 251 of the original submission, you indicate that the color of the solution (I assume you mean the drug product solution) intensified over time. This discoloration was attributed to trace amounts of _____ present in the stopper formulation, and therefore, you changed to a stopper with a _____ coating. How do you intend to provide assurance that the discoloration, _____ is no longer a concern (6). In addition, please explain how you will monitor and control the extractables from the _____ stopper used in this product.

Changing the stopper formulation to the _____ with _____ coating has provided the assurance that the discoloration, _____ are no longer a concern for Hydralazine Hydrochloride Injection, USP. This assurance is further demonstrated by the acceptable 18 month room temperature shelf-life stability data included in Attachment VII. Luitpold has also updated the Finished Product and Stability specifications to include a Color of Solution test based on USP 23 Chapter <631>, see Attachment IV.

With regard to the extractables from the _____ stopper used for the Hydralazine product, it has been demonstrated in the June 21, 1996 amendment that the _____ coating is effective in preventing the leaching of extractables from the rubber into the solution. Data from the _____ describing the extractable characteristics of the rubber and _____ coating was also provided in the original submission and the June 21, 1996 amendment.

B. Microbiology Deficiencies

1. The antimicrobial preservative efficacy test (APET's) performed for the subject drug product using Aspergillus niger did not meet compendial requirements. USP 23 Chapter <51> states that .."the concentration in the test preparation immediately after inoculation is between 100,000 and 1,000,000 microorganisms per mL." You should repeat the APET's for A. niger only and submit a data summary which meets USP acceptance criteria.

As recommended, the antimicrobial preservative efficacy test has been repeated for Aspergillus niger. The retest conforms to USP 23 Chapter <51> which requires a concentration of between 100,000 and 1,000,000 microorganisms per mL in the test preparation immediately after inoculation. A data summary has been included in Attachment VIII.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

- 1. The drug master file (DMF) you referenced, DMF _____ for your supplier of the drug substance, Hydralazine Hydrochloride USP, was reviewed and found to be deficient. The holder of DMF _____ has been informed of these deficiencies. All the deficiencies in DMF _____ must be adequately addressed before approval of this application.**

_____ has responded to the deficiency letter referencing DMF _____ in a letter to the FDA dated December 27, 1996. A copy of the first page of their response letter is included in Attachment IX.

- 2. You indicate that "prior to becoming an approved component vendor, manufactured lots of product using the vendor's components are placed on stability and monitored". Please acknowledge that any change to the container/closure system requires a supplement as per 21 CFR 314.70(b).**

Luitpold acknowledges that any change to the container/closure system will require a supplement as per 21 CFR 314.70(b).

Please contact me at (516) 924-4000 extension 459 if you require any further information. FAX communications should be made to (516) 345-0335.

Sincerely,

LUITPOLD PHARMACEUTICALS, INC.



Robert J. Anderson, B.A., J.D.
Associate Director, Regulatory Affairs

RJA/ab



LUITPOLD

RECEIVED

JUN 24 1996 *Via Federal Express*

GENERIC DRUGS

*Labeling approval
7/5/96 C.P. 12*

June 21, 1996

Office of Generic Drugs, CDER
Division of Chemistry I
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

**RE: Hydralazine Hydrochloride Injection, USP; 20 mg/mL
ANDA 40-136
Major Amendment**

ORIG AMENDMENT
12

Dear Sir/Madam:

Reference is made to our abbreviated new drug application dated February 17, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, for Hydralazine Hydrochloride Injection, USP, 20 mg/mL.

Reference is also made to our amendments dated May 10, 1995 and October 4, 1995 and to the FDA letter dated April 18, 1996.

We have provided our response in **comment/response** format.

A. Chemistry Deficiencies

- 1. The following deficiencies are related to the drug substance:**

5

✓

2. **The lot number on the COA for the Sodium Hydroxide does not correspond with the lot number on the executed batch records. Please provide the COA for the lot of sodium hydroxide that was used in the test batch.**

3. **The following deficiencies are related to the manufacturing instructions:**

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

- 4. Please include impurity specifications, individual and total, for both release and stability testing. Also, please identify the impurities present in the product.**

Impurities are monitored as part of the testing of the raw material. As stated in USP 23, our raw material monograph includes a test for chromatographic purity with an established limit of not more than 1.0% total impurities. We have tightened our controls for the raw material by including a limit for each individual impurity of not more than %. According to the Guideline on Impurities in New Drug Substances, as published in the Federal Register Notice of January 4, 1996, "Identification of impurities below apparent levels of % is generally not considered necessary." Impurities in the raw material will be monitored with the same specifications for both release and stability as part of our annual retest program.

Copies of our revised raw material specifications and monograph have been included for review in Attachment IV.

- 5. The following deficiencies are related to the components of the container/closure system:**
- a. Please provide an acceptable vendor qualification program for alternative suppliers of the container/closure components. In addition, when an alternative component supplier is used, please commit to placing one lot of the product on stability.**

Luitpold's vendor qualification program includes a thorough review of the vendor's past performance and evaluation of the vendor's responses to the Quality Questionnaire. Prior to becoming part of the Approved Component Vendor list manufactured lots of product using the vendor's components are placed on stability and monitored. Evaluation of the above information will determine the acceptance of the specific vendor from our Approved Component Vendor List. An audit of the vendor's facility may also be conducted.

In addition, we also commit to put one lot of product on stability when an alternative component supplier is used.

- b. **Please provide tests and specifications for incoming identification and release of the components that are specified as part of the container/closure system for this product. Please provide a COA for the actual lot of components used in the manufacture of this test batch specifying the lot numbers on the COA.**

Acceptance of components received by Luitpold is based on the vendor's COA and the results of our physical inspection and chemical identification testing. Copies of the worksheets used to record these results, in addition to the vendor's COA (certifications of testing) for the actual lots of components used in the manufacture of the test batch have been included for review, please refer to Attachment V. Currently we also perform the USP <661> Powdered Glass Test and Arsenic Test annually for the glass containers and generate an IR spectrum for each lot of rubber closures received.

- c. **Please confirm that the biological reactivity testing was performed on the actual lot of rubber stoppers used in this test batch.**

The biological reactivity testing was performed using the _____ All results passed and copies of the test reports were supplied by _____ and included by Luitpold in its original application for Hydralazine HCl Injection, USP. For ease of review we have included in Attachment VI, the test reports and a letter from the _____ certifying the testing methods have not changed from USP 22 to USP 23.

- d. **On page 515 you state that container/closure integrity testing was performed but no results were provided. Please provide the results of this testing and provide assurance that the flip-seals were also tested for fit and seal integrity.**

We have provided the results for the container/closure validations performed in September 1994 and September 1995 for the _____ mm _____ stopper, the _____ USP flint _____ glass vial and the royal blue flip-off seal. For each of the validations performed, the immersion test, the shipping test and the warehouse test, it was found that the flip-off seals fit properly and the seal integrity remained intact for each study. Copies of the data packages have been included for review in Attachment VII.

- e. **Please provide test data for the seal integrity of the flip-off seals with the stopper and the vial.**

Test data for the seal integrity of the flip-off seals used in conjunction with the stopper and the vial has been included. Please refer to the response provided for item 5d.

- f. **Please provide a detailed description of the extractables from the original stopper and provide data to assure that this will not be an issue with the stopper. Please include an incoming release test for extractables.**

A detailed description of the extractables from the stopper was included as part of the original application on page 485. A detailed description of the extraction characteristics for the film was also included as page 491 of the original application.

As a confirmation of the vendor's supplied information we have performed an extractable study using y and

The study consisted of vials which were filled with 1 mL of Water for Injection, USP. units were stoppered with the original rubber stopper and units with the rubber stopper. All samples were inverted using cycle for finished product units (minutes). After the samples were analyzed and the results are as follows:

	rubber stopper	rubber stopper
Zinc	ppm	ppm
Absorption at 200 nm	AU	AU

The results of the study demonstrate the stopper is effective in preventing extractables from the rubber penetrating the solution. Pages 485 and 491 of our original submission have been included for review as Attachment VIII.

6. **Please provide an upper specification for the assay test for the in-process release of the bulk solution (page 387).**

The in-process specifications for the assay test used for the release of the bulk solution have been revised to %. A copy of the bulk solution specifications for Hydralazine HCl Injection, USP has been included for review as Attachment IX.

7. The in-process glass reconciliation on page 376 indicates that _____ pieces are available for filling but previously you stated a test batch size of _____ pieces. Please explain this difference.

The test batch size of _____ pieces is the theoretical batch size, calculated from the _____ L target compounding volume and the _____ mL target fill volume (i.e. _____ vials).

The actual yield after filling was _____ vials. Due to samples being taken for preliminary process evaluation, _____ L compounded was not filled into vials. Samples of the bulk solution were collected to study the formulation process, in addition to a bulk bioburden holding time study. The volume not filled is accounted for on page 376 of the original ANDA, as summarized below. Note total solution accountability equals ____%. Please refer to Attachment X for a copy of page 376 of the original ANDA.

Volume Not Filled:	L
Bulk samples:	L
Supply lines:	L
Filter:	L
Mixing Vessel:	L
Volume Loss:	<u>L</u>
Total:	L

8. Please revise your post-approval stability commitment to include the following:

- a. Please rephrase "first three commercial production lots" to read "first three production lots".

We have rephrased our post-approval stability commitment to state "first three production lots," rather than "first three commercial production lots."

- b. Please specify the storage conditions (temperature and position).

We have specified the storage conditions as follows: the first three production lots and each annual stability lot thereafter will be stored at _____ °C in upright and inverted positions.

c. Please include an initial test point.

The initial test point for our stability studies is taken from our finished product test results for each lot placed on stability. Our stability commitment has been revised to include this clarification.

d. Please indicate that one production batch of each container/closure system and each size will be added to the stability program.

A statement indicating that one production batch of each container/closure system and each size will be added to the stability program, has been added to our stability commitment.

A copy of our revised post-approval stability commitment has been included for review as Attachment XI, with the changes highlighted.

9. Sterility testing is currently accepted for maintenance of sterility testing over the shelf life of a drug product. However, the Office highly recommends that a container/closure integrity test be performed instead. The container/closure test should be performed at expiry of the stability protocol and the sensitivity of the test method should be demonstrated.

A conference call was held on May 6, 1996 between FDA and Luitpold Pharmaceuticals, Inc. to discuss the item above. Representing FDA were Mr. Ken Muhvich, Microbiologist and Ms. Melissa Maust, Chemist. Dr. Chin Wu, Mr. Mark Rosen and Ms. Audrey Bialeski represented Luitpold.

Mr. Muhvich stated the sterility testing currently being performed by Luitpold is perfectly acceptable to the Agency. It is recommended for our consideration that some type of physical test using the drug product be performed in the future, as the Agency prefers seal integrity testing over sterility testing. Mr. Muhvich suggested loss of gas or dye testing as possible methods, but stated anything that is scientifically sound would be accepted.

Based on the discussion of May 6, 1996, Luitpold commits to future examination of various types of physical tests for possible inclusion in our analysis program.

B. Labeling Deficiencies

1. GENERAL COMMENT:

Revise your storage recommendation to appear as follows:

Store between 15°-30°C (59°-86°F)

We have revised our labeling storage recommendation to appear as follows:
"Store between 15°-30°C (59°-86°F)."

2. CONTAINER

See General Comment.

Our container labels have been revised in accordance with the General Comment.

3. CARTON

- a. Include the following statement as seen on the carton labeling of the listed drug:**

For emergency use - only in patients unable to take oral medication.

Our carton labeling has been revised to include the following statement as seen on the reference listed drug, "For emergency use - only in patients unable to take oral medication."

- b. We encourage the inclusion of a pH range as seen in your package insert labeling (DESCRIPTION).**

Our carton labeling has been revised to include the pH range as seen in our package insert labeling (DESCRIPTION).

4. INSERT

a. DESCRIPTION

- i. First paragraph, last line,
"...Hydrazinophthalazine...", (capital "H").**

The DESCRIPTION section, first paragraph, last line, "...Hydrazinophthalazine...", has been revised to include a capital "H."

- ii. **Include the molecular formula of hydralazine hydrochloride, "C₈H₈N₄HCl".**

We have revised our product insert to include the molecular formula of hydralazine hydrochloride, "C₈H₈N₄HCl," in the DESCRIPTION section.

b. PRECAUTIONS

- i. **Revise to read "hydralazine", rather than throughout this section with the following exceptions:**

- **Second paragraph in the Laboratory Tests subsection (should read "hydralazine hydrochloride").**
- **In the Pediatric Use subsection.**

The PRECAUTIONS section of our product insert has been revised to read "hydralazine," rather than with the following exceptions: the second paragraph in the Laboratory Tests subsection and in the Pediatric Use subsection.

- ii. **Pediatric Use**

...in pediatric patients have...

Our product insert has been revised to read "...in pediatric patients have..." in the Pediatric Use subsection.

c. HOW SUPPLIED -

See General Comment.

The HOW SUPPLIED section of our product insert has been revised in accordance with the General Comment.

Please revise your labels and labeling, as instructed above, and submit final print labeling. To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained. Please note that we reserve the right to request further changes in your labels and/or labeling based upon further changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

We have provided, in accordance with 21 CFR 314.94(a)(8)(iv), a side-by-side comparison of our proposed labeling with the last submission with all differences annotated and explained. Also as requested, we have included final printed labeling for our container, carton and product package insert. See Attachment XII.

C. Microbiology Deficiencies

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

1. In reference to your assay method for the drug product, please be informed that since the product is an official article in the United States Pharmacopeia (USP), the approval to use an analytical procedure that differs from that in the USP does not release you from any obligations to comply with the methods and procedures in the USP. Therefore, in the event of a dispute, only the results obtained by the official methods and procedures in the USP will be considered conclusive.

We acknowledge that Hydralazine HCl Injection is an official article in the United States Pharmacopeia (USP), and in the event of a dispute, only the results obtained by the official methods and procedures in the USP will be considered conclusive.

2. Please be informed that DMF facility references were provided for two of the alternative suppliers of vials, {

Luitpold acknowledges that DMF facility references have been provided for two of the alternative suppliers of vials, {

This concludes our amendment to this application. We appreciate your time and attention to this application. Please contact me at (516) 924-4000 ext. 497 if you require any further clarification or information.

Sincerely,

LUITPOLD PHARMACEUTICALS, INC.



Audrey Bialeski, Supervisor
Regulatory Affairs



LUITPOLD

*Refer to file
MA 5/15/95
AMENDMENT
CPA
5/15/95*

May 10, 1995

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Hydralazine Hydrochloride Injection, USP; 20 mg/mL
ANDA 40-136
Amendment

Dear Sir/Madam:

Reference is made to our abbreviated new drug application dated February 17, 1995 submitted under Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Hydralazine Hydrochloride Injection, USP; 20 mg/mL.

Reference is also made to your correspondence dated April 5, 1995 requesting certain information to be submitted within thirty days of the date of that correspondence to amend our application. Based on our conversation with Mr. William Russell, C.S.O. for our application, the following Attachments I and II contain the requested information.

In accordance with 21 CFR 314.101(d)(3), we submit in Attachment I, a side-by-side comparison of the formulation of our proposed drug product with that of the reference listed drug product.

Attachment II contains the side-by-side comparison of our proposed package insert with the approved package insert for the reference listed drug product in accordance with 21 CFR 314.94 (a)(8)(iv). As requested, all differences are annotated and explained.

This concludes our amendment to this application which we believe to be sufficiently complete to merit a technical review. Please do not hesitate to contact me at (516) 924-4000 ext. 459 if you require any further clarification or information.

Sincerely,

LUITPOLD PHARMACEUTICALS, INC.

Audrey Bialeski, Acting Supervisor
Regulatory Affairs

RECEIVED

MAY 12 1995

GENERIC DRUGS



LUITPOLD

505(j)(2)(A)
info for acceptable
for filing
10/12/95
10/13/95

BIOAVAILABILITY

AMENDMENT

October 4, 1995

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2733

**RE: Hydralazine Hydrochloride Injection, USP; 20 mg/mL
ANDA 40-136
Amendment**

RECEIVED

OCT 05 1995

Dear Sir/Madam:

GENERIC DRUGS

Reference is made to our abbreviated new drug application dated February 17, 1995 submitted under Section 505(j) of the Federal, Food, Drug and Cosmetic Act for Hydralazine Hydrochloride Injection, USP; 20 mg/mL.

Reference is also made to your correspondence dated April 5, 1995, our amendment dated May 10, 1995, and your correspondence dated June 1, 1995.

Luitpold Pharmaceutical's version of Hydralazine HCl Injection, USP contains the same active and inactive ingredients in the same concentrations as the reference listed drug Apresoline® to the extent that the names, amounts, or proportions of inactive ingredients are required by regulation to be disclosed in labeling (see 21 CFR 201.100(b)(5)). The listed drug manufacturer, CIBA-GEIGY Limited has chosen not to include information about ingredients added to adjust the pH in their labeling for Apresoline® HCl Injection as allowed by 21 CFR 201.100(b)(5)(iii). CIBA-GEIGY Limited has also chosen not to list Water for Injection in the package insert for the reference listed drug, Apresoline® HCl Injection. In accordance with 21 CFR 201.100(b)(5)(iii) the vehicle, if not listed, must be Water for Injection. This is the same vehicle used by Luitpold Pharmaceuticals, Inc. for Hydralazine HCl Injection, USP.

Luitpold Pharmaceuticals, Inc. is providing the following information to demonstrate that the pH adjusting solutions used for its Hydralazine HCl Injection, USP do not effect the safety of the drug product. Sodium Hydroxide and Hydrochloric Acid are commonly used for pH adjustment in parenteral products. These compounds do not introduce any new moieties especially since

the active ingredient, Hydralazine HCl, USP is supplied as the Hydrochloride salt and the USP glass vials contain sodium oxide which decomposes in solution to form sodium hydroxide. In regards to the change in tonicity from our pH adjustment, the maximum amounts of 1N Hydrochloric Acid and/or 1N Sodium Hydroxide that can be added to our 200 Liter batch is 1 Liter of each solution. The maximum theoretical milliosmols (where both solutions are used) that could be added is:

$$\frac{2 \text{ Liters} \times 1\text{N}}{200 \text{ Liters}} \times 1000 = 10 \text{ mOsmol/L}$$

where each one normal solution is equivalent to one Osmol and the 1000 is used to convert from Osmols to mOsmols. This maximum amount of 10 mOsmol/L is insignificant to the product's theoretical osmolarity of 1000 mOsmol/L and actual osmolarity of 1000 mOsmol/L.

We have provided as Attachment I, a side-by-side comparison of the osmolarity of the reference listed drug and Luitpold's Hydralazine HCl Injection, USP. The theoretical osmolarity was calculated based on the formula provided in the insert for the reference listed drug and found to be 1,571 mOsmol/L. A routine test dilution (1:10 with Water for Injection) was calculated to fall between the Osmometer's two calibration standards of 100 and 500 mOsmol/L. The average actual osmolarity found for two lots of Apresoline® was 1,515 mOsmol/L. Luitpold's Hydralazine HCl Injection, USP was found to be 1,553 mOsmol/L. There is a 1.5 to 3.5% difference in the values obtained for the two products which is not statistically significant. The finished product testing and the osmolarity results clearly demonstrate a full side-by-side comparison of the formulations of Luitpold's Hydralazine HCl Injection, USP and CIBA-GEIGY's Apresoline®.

The results provided above, together with the information previously submitted, supports a complete comparison of the formulation of our proposed drug product with that of the reference listed drug product. This concludes our amendment to this application which we believe to be sufficiently complete to merit a technical review. Please do not hesitate to contact me at (516) 924-4000 ext. 459 if you require any further clarification or information.

Sincerely,

LUITPOLD PHARMACEUTICALS, INC.



Audrey Bialeski, Acting Supervisor
Regulatory Affairs



LUITPOLD

*Refuse to file
LU 2/27/95
Chase
4/13/95*

February 17, 1995

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Hydralazine Hydrochloride Injection, USP; 20 mg/mL
Original Submission

Dear Sir or Madam:

Pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act and under the provisions of 21 CFR 314.94, Luitpold Pharmaceuticals, Inc. is submitting an abbreviated new drug application for Hydralazine Hydrochloride Injection, USP.

This original application contains three volumes provided in duplicate (archival - blue and review - red) and divided into appropriately referenced sections. Pages are consecutively numbered in the bottom center of each page. Copies of a complete table of contents are provided in the front of every volume. While Hydralazine HCl Injection is a USP article, the compendial method for the drug product is not stability indicating. We are providing appropriately validated alternative stability indicating assay methods for hydralazine and the methyl and propyl paraben preservative system. Two additional copies of our methods validation package (Section XVI) in black pressboard binders are also submitted herein in accordance with Attachment B of OGD P&P Guide #30-91.

We appreciate your attention to this application. All inquires and correspondence regarding this application should be addressed to Mr. John Purpura, Manager Regulatory Affairs at (516) 924-4000 ext. 459.

Sincerely,

LUITPOLD PHARMACEUTICALS, INC.

John Purpura, Manager
Regulatory Affairs

RECEIVED

FEB 22 1995

GENERIC DRUGS