CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER _____

ADMINISTRATIVE DOCUMENTS

TELEPHONE MEMO

To: David Guzek (Abbott Laboratories)
(847)937-6845

CC: ANDA 75-241 Furosemide Injection USP, 10 mg/mL

From: Saundra T. Middleton

Date: December 1, 1997

Subject: Container data package

Mr. Guzek, was asked to submit the full plastic syringe data package for the plastic container.

In addition, the 356h form should be resubmitted and filled-out completely, i.e., Holder of Approved Application and Proposed Indication.

The above information should be submitted within 10 business days.

Mr. Guzek, will see that the above information is sent ASAP.

E L E C T R O N I C M A I L M E S S A G E

Date: 09-Dec-1997 04:41pm EST
From: William Rickman
RICKMAN
Dept: HFD-615 MPN2 113
Tel No: 301-827-5862 FAX 301-594-0174

TO: SHIRLEY A L II (ORA) (SII@ORA.FDA.GOV @INTERNET)
TO: STEVE P SENIO (ORA) (SSENIO@ORA.FDA.GOV @INTERNET)

Subject: RE: Methods Verification

Shirley,

OGD has accepted for filing ANDA for g/mL from :

Abbott Laboratories
Att: Thomas Willer
200 Abbott Park Rd.
D 99 AP30
tt Park, IL 60064-3537
8 -937-7867

CDER Establishment Evaluation Report
for December 10, 1997

Application: **ANDA 75241/000**
Stamp: **03-NOV-1997** Regulatory Due:
Applicant: **ABBOTT LABS**
200 ABBOTT PARK RD
ABBOTT PARK, IL 600643537

Priority:
Org Code: **600**
Action Goal:
District Goal: **03-JAN-1999**
Brand Name:
Established Name: **FUROSEMIDE**
Generic Name:
Dosage Form: **INJ (INJECTION)**
Strength: **10 MG/ML SYRINGE**

FDA Contacts: **J. WILSON III (HFD-617) 301-827-5848 , Project Manager**
V. SAYEED (HFD-629) 301-827-5848 , Team Leader

Overall Recommendation:

Establishment: **1021343**
ABBOTT LABORATORIES
HWY 301 NORTH
ROCKY MOUNT, NC 27804

DMF No:
AADA No:

Profile: **SVT** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC 10-DEC-1997**

Responsibilities:
FINISHED DOSAGE MANUFACTURER

Establishment: **1411365**
ABBOTT LABORATORIES
1400 SHERIDAN RD
NORTH CHICAGO, IL 60064

DMF No:
AADA No:

Profile: **NEC** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC 10-DEC-1997**

Responsibilities:
FINISHED DOSAGE STABILITY TESTER

Establishment:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC 10-DEC-1997**

Responsibilities:
DRUG SUBSTANCE MANUFACTURER

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-241 Date of Submission: October 31, 1997

Applicant's Name: Abbott Laboratories

Established Name: Furosemide Injection USP, 10 mg/mL (Plastic Syringe)

Labeling Deficiencies:

1. CONTAINER - 4 mL, mL, & 10 mL *Ansyr*™ Single-dose Syringe

   Include the statement "Discard unused portion.".

2. CARTON - 4 mL, mL, & 10 mL

   a. Revise the net quantity statement to read "x mL Single-dose Syringe" and delete the statement "Single-dose unit" on the side panel.

   b. Increase the prominence of the statement "For I.V. or I.M. use.". We encourage you to relocate this statement to the main panel.

   c. We encourage the inclusion of the statement "Contains no preservative." as the last sentence in the text "Each mL ..." .

   d. We note that your trademark " is more prominent than the established name of your drug products. We ask you to reduce the prominence of the trademark ` _ .

3. INSERT

   a. DESCRIPTION

      i. We encourage you to relocate the RAO numbers and revision date to follow the HOW SUPPLIED section.

ii. First paragraph:

We encourage the inclusion of the statement "Contains no preservative." as the last sentence.

iii. Revise the molecular weight to read "330.75" to be in accordance with USP 23.

b. CLINICAL PHARMACOLOGY

It is preferable to use "mcg" rather than "μg" when referring to micrograms.

c. PRECAUTIONS (Carcinogenesis, Mutagenesis, Impairment of Fertility):

Delete the last paragraph.

d. OVERDOSAGE - third paragraph:

i. Relocate the second sentence to begin as a new paragraph.

ii. Relocate the last sentence to begin as a new last paragraph.

e. HOW SUPPLIED

i. Include "Discard ununsed portion.".

ii. We encourage the inclusion of the statement "Do not remove from carton until ready for use.".

Please revise your container labels and carton and package insert labeling, as instructed above, and submit in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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 the last submitted labeling with all differences annotated and explained.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

NOTES/QUESTIONS TO THE CHEMIST:

1. Do you concur with the last two paragraphs under DESCRIPTION section regarding the firm's proposed container? firm is being asked for additional information on this subject in mail 5-15-98

2. Has the firm submitted the supporting data for the validation of calibration on the container labels? If yes, is it acceptable? Firm is being asked for this information in mail 5-15-98

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		x	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	

Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling (continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			x
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			x
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	x		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		x	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	

Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. MODEL LABELING

   Lasix® Injection - Hoechst Marion Roussel, Inc; revised June, 1995, and approved March 6, 1996.

2. INACTIVE INGREDIENTS

   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of Components and Composition appearing on page 1-47, 48 & 49. (Volume 1.1).

3. The firm claims that they submit this application in accordance with MAPP 6020.2, "Applications for Parenteral Products in Plastic Immediate Containers.", issued September 6, 1996.

4. The firm states that this application is the seventh in a series of submissions of drug products in plastic syringes. The firm has submitted full data package for the plastic containers in the previous applications, NDA (50% Dextrose Injection USP, 50 mL in Plastic Syringe) and ANDA (Iopamidol Injection, Plastic Syringe), and hence, the firm did not include same information in this application. (Refer to the firm's cover latter for the original submission).

5. PATENTS/EXCLUSIVITIES

   No pending issue. The firm's statement is accurate.

6. The "description and solubility" of the drug products found in the DESCRIPTION section is identical with those described in the innovator's insert labeling.

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   NDA - Store at controlled room temperature 15°-30°C (59°-86°F). Do not use if solution is discolored. Protect syringe from light.

   ANDA - Store at controlled room temperature 15°-30°C (59°-86°F). Do not use if solution is discolored or contains particulate. Protect from light.

8. PACKAGING CONFIGURATIONS

NDA - 4mL, & 12 mL
ANDA - 4mL, , & 12 mL

9. CONTAINER/CLOSURE SYSTEM

Elastomeric closures and plastic syringe (p.5-22, vol.1.5)

Date of Review: December 29, 1997

Date of Submission: October 31, 1997

Cycle # 1 (FPL)

Primary Reviewer: Chan Park 1/5/98 **Date:**

Team Leader: John Grace 1/14/98 **Date:**

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cc:

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RECORD OF TELEPHONE CONVERSATION

Dr. Vilayat Sayeed, Dr. Melissa Maust and Bonnie McNeal called Sponsor to discuss Sponsor's fax of February 25, 1999 requesting clarification of Minor deficiencies letter.

The first question was on chemistry comment 3. The Agency stated that this was not a fill volume issue but a gradation accuracy issue. The second paragraph of the Sponsor's fax explains what the Agency is asking. The Sponsor was asked to provide their methodology and that would answer all questions.

On Chemistry comment 6, the Sponsor asked if both nl and 10 ml containers must go on stability. The Agency responded that our policy has been that each size must go on stability. If the Sponsor wants to request a waiver post-approval, they must submit a document requesting this which will be reviewed within the Agency.

Sponsor will respond to deficiency letter as soon as possible.

Filename:
v/firmsam/abbott/telecons/75241-0302.doc

/s/

DATE
March 2, 1999

APPLICATION NUMBER

75-241

TELECON

INITIATED BY APPLICANT/ FDA
FDA

PRODUCT NAME
Furosemide Injection, USP

FIRM NAME
Abbott Laboratories

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Jessie Lee, Manager, Regulatory Affairs

TELEPHONE NUMBER
847-937-5613

SIGNATURE /s/ 5-99

cc: ANDA 75-241
D.J. File

OFFICE OF GENERIC DRUGS
ABBREVIATE NEW DRUG APPLICATION

ADDENDUM

ANDA: 75-241

DRUG PRODUCT: Furosemide

FIRM: Abbott Laboratories

DOSAGE FORM: Injection

STRENGTH: 10 mg/mL

In response to telephone conversations held on May 12 and May 13, 1999 between Dr. A. Rudman (Deputy Director, Office of Generic Drugs) and Dr. J. Lee (Abbott Laboratories), the firm has provided a telephone amendment dated May 14, 1999.

Firstly, due to the lack of prior-approved bracketing stability protocol per the Agency's request, the firm withdrew all appropriate documents related to the , size for the above referenced drug product without prejudice to re-filing the appropriate information at a later date.

Secondly, as requested by OGD, the firm proposed the drug product release and stability specification limits for the Total Impurities of NMT and NMT respectively. Abbott provided the following information:

(a) a revised draft of the analytical method (Determination of Furosemide, ; Furosemide Injection, USP) including the appropriate calculations (Exhibit I),
(b) revised final product specifications (Exhibit II), and
(c) the annotated marketed stability product stability protocols (Exhibit III/4 mL fill in 5-mL syringe and 10 mL fill in 10-mL syringe).

Thirdly, the firm deleted the size from the "HOW SUPPLY" section of the labeling. In order to standardize the presentation of information in their drug inserts, the

firm also indicated that the "R_x only" statement in the Title section will not be included. The statement is already shown on the container and carton labels of the drug product. The firm referenced FDAMA 1997, Section 125 (Revised: July 1998). A copy of the labeling is provide in Exhibit IV. The final printed labeling will be forwarded to the Agency. This issues will be reviewed by the Labeling Division.

In conclusion, all issues (excluding those to be reviewed by the Labeling Division) discussed between OGD and Abbott Laboratories have been satisfactorily addressed.

CHEMIST: /S/ DATE: 5/25/99

cc:

Endorsements:

5/26/99

OFFICE OF GENERIC DRUGS
ABBREVIATE NEW DRUG APPLICATION

ANDA APPROVAL SUMMARY

ANDA: 75-241

DRUG PRODUCT: Furosemide

FIRM: Abbott Laboratories

DOSAGE FORM: Injection

STRENGTH: 10 mg/mL

cGMP STATEMENT/EIR UPDATE STATUS:
The establishment evaluation request is acceptable (November 30, 1998/J.D. Ambrogio) for (Drug Substance Manufacturer), Abbott Laboratories - Rocky Mount, NC (Drug Product Manufacturer and Testing), and Abbott Laboratories - (Stability Testing).

BIO STUDY:
The firm requested a bio-waiver of bioavailability test requirements per 21 CFR 320.22(b)(1), therefore, no in-vivo or in-vitro studies were conducted with the subject drug.

The Bio-review (J. Lee-02/17/98) recommends that the waiver of an in-vivo bioavailability study be granted.

VALIDATION (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
The drug substance and the drug product are both USP compendial. FDA methods validation are not required.

STABILITY (ARE CONTAINER USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?):

The containers used in the accelerated and room temperature studies are the same as proposed in the application.

LABELING:
Label issues have been resolved and label is satisfactory (J. Barlow - ~~03/12/99~~ 5/27/99).

STERILIZATION VALIDATION (IF APPLICABLE):
The product is nto 5 or 10 mL plastic syringes which are subsequently sterilized. The product is to be parametrically released.

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS O.K.?):
The executed batches were, Lot No. 24-577-DK (mL syringe) and Lot No. 23-010-DK syringe). The executed batches were packaged in the proposed container/closure systems.

The Drug Master File currently acceptable by this reviewer.

PROPOSED PRODUCTION BATCH (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?):
The proposed production batch will be produced in the manner and same size as the bio batch. The executed batch in size; this is a ten-fold (10X) increase.

CHEMIST: David J. Cummings DATE: 4/23/99

cc:

Endorsements: