# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 40-298

## ADMINISTRATIVE

Telecon

**Date:** 030998

**Time:** 1015 H

**ANDA #:** 40-298

**Firm:** Mylan

**Drug:** Extended Phenytoin Sodium Capsules USP, 100 mg

**Participants:** Gregg Davis, FDA and Laura Deiricgi, Mylan

**Phone #:** 304-599-2595 x6600

**Agenda:**

I called Mylan and asked for a revision. The ANDA batch theoretical yield was capsules but Mylan proposed a scaled-up batch of capsules. I asked for a revised blank batch record to reflect a scale-up.

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

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ANDA Number: 40-298 Date of Submission: February 27, 1998

Applicant's Name: Mylan Pharmaceuticals Inc.

Established Name: Extended Phenytoin Sodium Capsules USP, 100 mg

Labeling Deficiencies:

1. CONTAINER

   Satisfactory in draft

2. INSERT

   a. GENERAL

      It is preferable to use "mL" than "ml" throughout the text.

   b. DESCRIPTION

      i. We encourage you to revise the chemical name to be same as the second name appearing in the official monograph for your product in USP 23. In addition, revise the molecular weight to read "274.25" to be in accordance with USP 23.

      ii. Second paragraph:

         A) First sentence:

            ...100 mg phenytoin sodium. [delete "USP", redundant]

         B) The two ingredients contained in imprinted ink, and n- may be dissipated in the manufacturing process. If this is the case, you may delete these from the listing of inactive ingredients.

   c. INDICATIONS AND USAGE (First paragraph) - Revise to read as follows:

...the control of tonic-clonic (grand mal) and psychomotor (temporal lobe) seizures.

d. CONTRAINDICATIONS

... patients with a history of hypersensitive...

e. WARNINGS

i. First paragraph:

A) Penultimate sentence:

The event of an allergic or hypersensitivity reaction, more rapid ...

B) Last sentence:

...be an anticonvulsant drug...

ii. Last paragraph, last sentence:

... delivery and to the neonate...

f. PRECAUTIONS

i. General - Fourth paragraph, last sentence:

...succinamides,... [spelling]

ii. Drug Interactions - Item 1:

A) ...estrogens, ethosuximide, $H_2$-antagonists,... [add "ethosuximide"]

B) ... succinamides,... [spelling]

g. HOW SUPPLIED

We encourage you to relocate "Rx only" to the TITLE.

Please revise your labels and 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 your last submission with all differences annotated and explained.

/S/

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

# 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? | | | |
| 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 bioequivalency values: insert to study. List Cmax, Tmax, T ½ 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

   a. **Dilantin® KAPSEALS** (approved October 30, 1987 according to the stamp on the labeling. However, this approval could not be verified in the COMIS) and **Dilantin-125®** (Phenytoin Oral Suspension, USP) approved March 23, 1990 as supplements SLR-018 & 019.

   b. Unless specific information associated with the dosage form, more current approved labeling for **Dilantin-125®** was used for side-by-side comparison.

2. 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 1635 (Volume B.1.2).

3. PATENTS/EXCLUSIVITIES - No pending issue

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   RLD: Store below 30°C (86°F). Protect from light and moisture.

   ANDA: Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light and moisture.

5. DISPENSING STATEMENT

   RLD - Dispense in tight, light-resistant container as defined in the USP.

   ANDA - Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

6. PACKAGING CONFIGURATIONS

   RLD: 100s, 1000s, U/D 100s, Memo pack containing 84 U/D capsules (28 day dosage regimen)

   ANDA - 100s and 1000s.

7. The capsules have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See Vol.B.1.3, P.2032

8. This capsule preparation reflects capsule-shaped tablet encapsulated with hard-shell gelatin capsules.

9. CLOSURE

CONTAINER ; HDPE
100s: CRC
1000's: Non-CRC See vol.B.1.2, p.1975 & 1976

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**Date of Review: August 28, 1998**

**Date of Submission: February 27, 1998**

**Primary Reviewer: Chan Park** /S/ **Date:** 9/8/98

**Team Leader:** /S/ **Date:** 9/8/98

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cc:

ANDA: 40-298
DUP/DIVISION FILE
HFD-613/CParek/CHoppes (no cc)

Review

CC: ANDA 40-298
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Nerurkar for BioSign Off List
HFD-655/ J. Lee R.S. 8/10/98
BIO DRUG FILE NNN 8/17/98

Printed in Final on

BIOEQUIVALENCY - ACCEPTABLE

1. **FASTING STUDY** (STF) Strengths: 100 mg
Clinical: Mylan **Outcome:** **AC**
Analytical: Mylan

5. **STUDY AMENDMENT** (STA)6/25/98 Strengths: 100 mg
**Outcome:** **AC**

OUTCOME DECISIONS:
**AC** - Acceptable **NC** - No Action

WINBIO COMMENTS:
Fasting study now complete and acceptable.

2.1

# APPROVAL SUMMARY

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

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ANDA Number: 40-298 Date of Submission: September 28, 1998

Applicant's Name: Mylan Pharmaceuticals Inc.

Established Name: Extended Phenytoin Sodium Capsules USP, 100 mg

**APPROVAL SUMMARY** (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

**CONTAINER LABELS: 100s & 1000s**

**Satisfactory in FPL as of 9/28/98 submission**

**PROFESSIONAL PACKAGE INSERT LABELING:**

**Satisfactory in FPL as of 9/28/98 submission**

**REVISIONS NEEDED POST-APPROVAL - INSERT:**

**DESCRIPTION - Second paragraph, last sentence:**

**"1½ to 3 hours" rather than "1 to 3 hours". The firm has committed that the outsert will be revised to add "½" prior to release of production copies. (P.23 of the 9/28/98 submission)**

**BASIS OF APPROVAL:**

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Dilantin®

ANDA Number: **Dilantin® KAPSEALS** (ANDA 84-349; approved October 30, 1987 according to the stamp on the labeling. However, this approval could not be verified in the COMIS) and **Dilantin-125®** (Phenytoin Oral Suspension, USP) approved March 23, 1990 as supplements SLR-018 & 019.

NDA Drug Name: **Dilantin® KAPSEALS**

ANDA Firm: Parke Davis

Date of Approval of ANDA Insert and supplement #: See above

Has this been verified by the MIS system for the ANDA?
No

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: **Dilantin® KAPSEALS**

Other Comments:

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   b. Unless specific information associated with the dosage form, more current approved labeling for **Dilantin-125®** was used for side-by-side comparison with the exception of INDICATIONS AND USAGE section.

   c. As discussed with the firm on September 25, 1998, Chan Park and Charlie Hoppoes of the Agency had allowed the firm to model the INDICATIONS AND USAGE section after the Dilantin Capsules insert labeling, not after the Oral Suspension.

2. 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 1635 (Volume B.1.2).

3. PATENTS/EXCLUSIVITIES - No pending issue

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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8. This capsule preparation reflects capsule-shaped tablet encapsulated with hard-shell gelatin capsules.

9. CLOSURE

CONTAINER ; HDPE
100s: CRC
1000's: Non-CRC See vol.B.1.2, p.1975 & 1976

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**Date of Review: October 7, 1998**

**Date of Submission: September 28, 1998**

**Primary Reviewer: Chan Park** /S/

**Date:** 10/8/98

**Team Leader:**

**Date:** /S/ 10/9/98

cc:

ANDA: 40-298
DUP/DIVISION FILE
HFD-613/CPark/CHoppes (no cc)

Review