TAB 2

OTC WEIGHT CONTROL RULEMAKING CHRONOLOGY

Feb 1982 - Advisory Panel Report published in the FEDERAL REGISTER

Sept 1990 - Senator Ron Wyden hearing:
Dr. Paul Raford testifies on PPA abuse and ADRs

Oct 1990 - Proposed Rule - Certain Active Ingredients (Removes 111 Category II and III weight control ingredients from the OTC market)

May 1991 - Public Meeting on PPA safety, efficacy, and misuse

Aug 1991 - Final Rule - Removes 111 Category II and III ingredients (PPA and benzocaine are Cat. I)

June 1992 - Stroke data sent to consultants (Jack Whisnant, Mayo Clinic, Steven Kittner, U. Maryland, Janet Daling, U. Washington)

July 1992 - Consultants agree that data do not support an increased risk of stroke associated with PPA

Nov 1992 - Feedback Meeting Nonprescription Drug Manufacturers Association (NDMA): proposal for PPA/Stroke study

Mar 1993 - NDMA submits draft protocol for case-control study of PPA and stroke

Mar 1993 - FDA Feedback Letter to NDMA re PPA safety: will place PPA in Category III, should conduct safety study

May 1993 - Epidemiology Branch reviews protocol

June 1993 - Feedback Letter on the PPA/stroke case-control protocol.

Aug 1993 - Feedback Meeting: PPA/Stroke Study Protocol

Oct 1993 - NDMA response to feedback meeting

Nov 1993 - Epidemiology review of NDMA response

May 1994 - Effectiveness Feedback Letter:
4 studies support efficacy of controlled-release (CR) combined with diet - CR will need NDA at final rule - studies do not support immediate-release

Sep 1994 - Case-control safety study begins (expected 4 years)

PHENYLPROPANOLAMINE HYDROCHLORIDE (PPA)

- Pre-1982 PPA weight control dosages:
  25-37.5 mg single doses; 75-mg timed-release dose
  75 mg total daily limit.

- September, 1976
  NASAL DECONGESTANT Advance Notice of Proposed Rulemaking
  (Advisory Panel Report)
  Advisory Panel recommends Category I adult doses:
  25 mg/4 hrs. or 50 mg/8 hrs.
  150 mg total daily limit.

- February, 1982
  WEIGHT CONTROL Advance Notice of Proposed Rulemaking
  (Advisory Panel Report)
  Advisory Panel recommends Category I adult doses:
  25-50 mg single doses
  150 mg total daily limit.

  SAFETY ISSUE: reports that PPA causes elevation of blood pressure.

  FDA limits weight control doses:
  25-37.5 mg single dose, 75-mg timed release
  75mg total daily limit.

  FDA requests blood pressure studies.

- January, 1985
  NASAL DECONGESTANT PROPOSED RULE:
  PPA deferred because of safety issues.

- FDA REVIEWS BLOOD PRESSURE STUDIES.
  CONCLUSIONS:
  1. PPA causes a biphasic BP response.
  2. Pressor/depressor effects are dose-related.
  3. Effects on BP diminish with repeated dosing.
  4. FDA concludes that single doses up to 50 mg are safe, and pressor effects are small compared to normal variations in BP.

- Small number of ADRs in Spontaneous Reporting System:
  possibility of a relationship between PPA use and an increased risk of hemorrhagic stroke.
  1. Most reports: weight control (25% use), excess dose
  2. Few reports: cough-cold (75% use), doses $\geq$ weight control
  3. Degree of underreporting unknown.

CONCLUSION: no convincing evidence of a causal relationship; no need to remove PPA from market.

- FDA REVIEWS WEIGHT CONTROL EFFICACY STUDIES:
  CONCLUSION: 75-mg controlled release effective when used with a reduced-calorie diet.

- March, 1993 Letter to NDMA:
  PROPOSED RULES WILL PLACE PPA NASAL DECONGESTANT AND WEIGHT CONTROL DRUGS IN CATEGORY III.
  Industry submits protocol for safety study of PPA and hemorrhagic stroke.

- September, 1994
  Safety study begins.