DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

SHERMAN

AUG 26 1997

TRANSMITTED VIA FACSIMILE

Preeti I. Pinto, M.S.
Senior Regulatory Affairs Associate
The DuPont Merck Pharmaceutical Company
Barley Mill Plaza
Wilmington, DE 19880-0027

Re: NDA 9-218
Coumadin (warfarin sodium tablets, USP) Crystalline
MACMIS File ID #5702

Dear Ms. Pinto:

This letter is in reference to The DuPont Merck Pharmaceutical Company's (DuPont) submissions, dated December 10, 1996, March 27, 1997, and July 8, 1997, of promotional materials under cover of Form FDA 2253 for Coumadin (warfarin sodium tablets, USP) Crystalline. These submissions included a slide presentation,[1] a press release[2] and promotional brochures[3]. The Division of Drug Marketing, Advertising, and Communications (DDMAC), in consultation with the Division of Gastro-Intestinal and Coagulation Drug Products and the Office of Generic Drugs, has reviewed these promotional materials and has concluded that they are false and/or misleading under the Federal Food, Drug, and Cosmetic Act and the regulations promulgated thereunder. Our specific objections follow:

Misleading Statements Concerning Bioequivalence

The slide presentation contains information that states or suggests that generic drug products, such as warfarin, that have been shown to be bioequivalent to a reference drug (Coumadin) and approved as such by FDA may not be therapeutically equivalent. DuPont relies on limited data and allegations of intra-subject variability to conclude that such products may not be used

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1 The slide kit is entitled "Anatomy of a Narrow Therapeutic Index Drug."

2 DuPont Merck press release dated March 26, 1997, concerning approval of generic warfarin sodium tablets by Barr Laboratories.

3 These brochures include, but are not limited to, CU-32212 and CU-32228.

interchangeably. This presentation is false and/or misleading and results in the misbranding of DuPont's Coumadin, 21 CFR 201.6(a).

All products approved under NDAs and ANDAs are considered safe and effective when used as labeled. DuPont's suggestions that generic products are held to a lower standard for approval implies that generic products are less safe and/or effective than branded products. It is misleading to suggest that generic products that FDA has determined are bioequivalent to Coumadin, may not be therapeutically equivalent to the reference product without substantial evidence to support such a claim. The information relied on by DuPont is not persuasive and does not support its claims. All FDA approved dosage forms of generic drugs classified as therapeutically equivalent and coded AB can be substituted for the reference product with the full expectation that the substituted product will produce the same clinical effect and safety profile.[4]

Misleading Recommendations for PT Testing and Monitoring

In the promotional brochures and press release cited above, DuPont refers to the performance of additional testing or monitoring when switching from one formulation of warfarin to another. For example, DuPont states in a press release that "[o]nce a patient is stabilized on Coumadin,

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[4] According to the Approved Drug Products, 17th Edition, 1997, FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable *in vitro* standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; and (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations.

For those products designated as AB, an evaluation of therapeutic equivalence is assigned to pharmaceutical equivalents only if the approved application contains adequate scientific evidence establishing through *in vivo* and/or *in vitro* studies the bioequivalence of the product to a selected reference product. FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.

...he or she should not be switched to another formulation of warfarin sodium without the knowledge and approval of the patient and his or her physician so additional monitoring can be performed." To support this statement, DuPont refers to the statement in its approved product labeling that "[t]o ensure adequate control, it is recommended that additional PT tests are done when other warfarin products are interchanged with Coumadin...."

DuPont's reference to, and use of, this statement in its promotional brochures and press release is misleading. The statement in the approved product labeling was included in labeling at a time when there were warfarin products available in the marketplace, such as warfarin potassium, that were not bioequivalent or therapeutically equivalent to Coumadin. Under those circumstances, the statement in labeling was true and not misleading. However, in the current environment, there are no currently marketed inequivalent products and there is at least one product that FDA has determined is bioequivalent and therapeutically equivalent to Coumadin. Thus, this statement in labeling is misleading and has been used by DuPont in a misleading manner.

Lack of Fair Balance

Finally, although DuPont describes warfarin as a "dangerous" drug, it fails to provide fair balance in its promotional materials by failing to disclose the impact of changes in diet or travel on the therapeutic response and the risks of significant drug-drug interactions. Moreover, DuPont should disclose that an International Normalized Ratio (INR) greater than 4.0 appears to provide no additional therapeutic benefit in most patients and is associated with a higher risk of bleeding.

Recommended Actions

In response to the issues raised in this letter, DuPont should:

(1) immediately suspend all promotional activities and materials that convey or contain the allegedly violative claims or information identified in this letter until these allegations are resolved;

(3) submit a written response to DDMAC on or before September 6, 1997, acknowledging its intent to comply with the above request and describing the steps that it has taken to ensure that these activities and the use of these materials have been suspended.

DuPont should address any correspondence or additional questions to Stephen Sherman at the Division of Drug Marketing, Advertising, and Communications, HFD-40, Rm 17 B-17, 5600 Fishers Lane, Rockville, Maryland 20857. In addition, DuPont's response to the issue of revising the approved product labeling should be directed to the Director of the Division of Gastro-Intestinal and Coagulation Drug Products. DDMAC reminds DuPont that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS ID #5702, in addition to the NDA number.

Sincerely,

Minnie Baylor-Henry , R.Ph., J.D.
Director
Division of Drug Marketing,
Advertising, and Communications

Lilia Talarico, M.D.
Acting Director
Division of Gastro-Intestinal and
Coagulation Drug Products