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Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**Re: Docket No. 2004N-0279. Drug Information Association/Food and Drug Administration Workshop: Pharmacogenomic Combination Product Co-Development.** Meeting on July 29, 2004. Published in the FR on July 13, 2004.

Abbott Laboratories (Abbott) is one of the leading companies in health care products employing more than 55,000 people in over 130 countries. As a manufacturer of pharmaceutical drugs, biologicals, devices, and *in vitro* diagnostic products, Abbott has been committed to the development of innovative, safe and effective products spanning a wide range of patient care management. We support the Agency's efforts to develop the guidance to industry on the co-development of *in vitro* diagnostics and drug/biologic (pharmaceutical) products. We are pleased to have the opportunity to work with the Agency and other stakeholders on the development of this guidance.

We believe that the questions raised in the presentation by Lois Hinman, Ph.D., at the FDA/DIA Pharmacogenomics Combination Product Co-development Workshop of July 29, 2004, provide an excellent framework for the envisioned guidance. Abbott submits the following additional comments.

To avoid unnecessary confusion Abbott recommends minimal use of the term 'combination product' in this guidance, and especially that the term not be used in its title. We suggest the following title: Guidance to Industry on the "Co-development of In Vitro Diagnostics and Drug or Biologic Products."

Abbott welcomes the proposed role of the Office of Combination Products as a coordinator of activities of the various FDA Centers during review of *in vitro* diagnostic and pharmaceutical products that may be used in conjunction with each other. Further, Abbott recognizes principles applied to combination products may aid in the co-development of *in vitro* diagnostic and pharmaceutical products and recommends the guidance document acknowledge such situations. For example, when the same clinical trial supports both the *in vitro* diagnostic and pharmaceutical product, recognition of

2004N-0279

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either the drug or device GCP authorities as controlling may be appropriate. Further, one agency inspection of clinical trial sites coordinated by a lead center is more appropriate than two separate inspections conducted by each center.

Historically, *in vitro* diagnostic and pharmaceutical products used in conjunction with one another have not been designated as combination products. With much success, CDRH has reviewed the marketing application of the *in vitro* diagnostic product, while CDER or CBER has reviewed the pharmaceutical product application. It should be recognized in the guidance that FDA does not plan to change this practice, especially as it relates to the application review of these products.

As the list of examples below demonstrates, the safe and effective use of a broad range of therapeutic products is dependent, at least indirectly, on diagnostic products. Only in certain situations would such interdependency between a diagnostic and a therapeutic product constitute a "combination product." Therefore, it is essential that any FDA guidance on pharmacogenomic co-development clearly articulate the scope of its applicability. This may be achieved by clearly defining the meaning of the term "combination product co-development" for the purposes of the guidance. Such definition should clarify whether the guidance only pertains to therapeutic and diagnostic products "where both will be **necessary** in the clinical management of patients" or to other co-development situations as well. Discussion of the meaning of the term "necessary in the clinical management of patients" may also be needed to avoid misapplication of the guidance to products that, in fact, are not the intended subjects of the guidance.

We recommend that the following scenarios be taken into consideration when defining the scope of applicability of this guidance and any future regulatory framework.

- A single *in vitro* diagnostic may be clinically useful in conjunction with multiple pharmaceutical products.
- Multiple *in vitro* diagnostic products or home brew tests may be available in conjunction with a pharmaceutical product.
- A research assay may be used during development of a pharmaceutical product but never developed into an *in vitro* diagnostic product.
- An *in vitro* diagnostic may be developed for a condition and not specifically for a certain therapeutic agent, but will nonetheless be indicated in the therapeutic agent label.
- Decisions regarding the development of an *in vitro* diagnostic to be used in conjunction with a pharmaceutical product may be made during late stages of pharmaceutical product development.
- An *in vitro* diagnostic may also be developed after a pharmaceutical product is already in the market.

**Abbott**

Docket No. 2004N-0279

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Flexibility in the guidance will have the salutary effect of encouraging and facilitating the implementation of innovative approaches.

At the FDA/DIA of July 29, 2004 workshop, timeframes of the development of an *in vitro* diagnostic test in relation to a pharmaceutical product development were discussed. We believe the guidance should avoid definition of timeframes for stages of *in vitro* diagnostic development that are based on stages of pharmaceutical development.

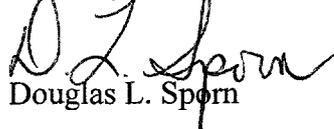
Abbott recommends, instead, the use of decision trees as tools to illustrate the processes for the co-development of *in vitro* diagnostics and pharmaceutical products. Decision trees focus on the important generic situations that may arise in the development of *in vitro* diagnostic and pharmaceutical products for use with each other. Furthermore, the guidance should not include case studies such as those presented at the July 29, 2004 FDA/DIA workshop. Focus can easily be diverted to specific (possibly irrelevant) aspects of a case study, away from the central issues of broad application.

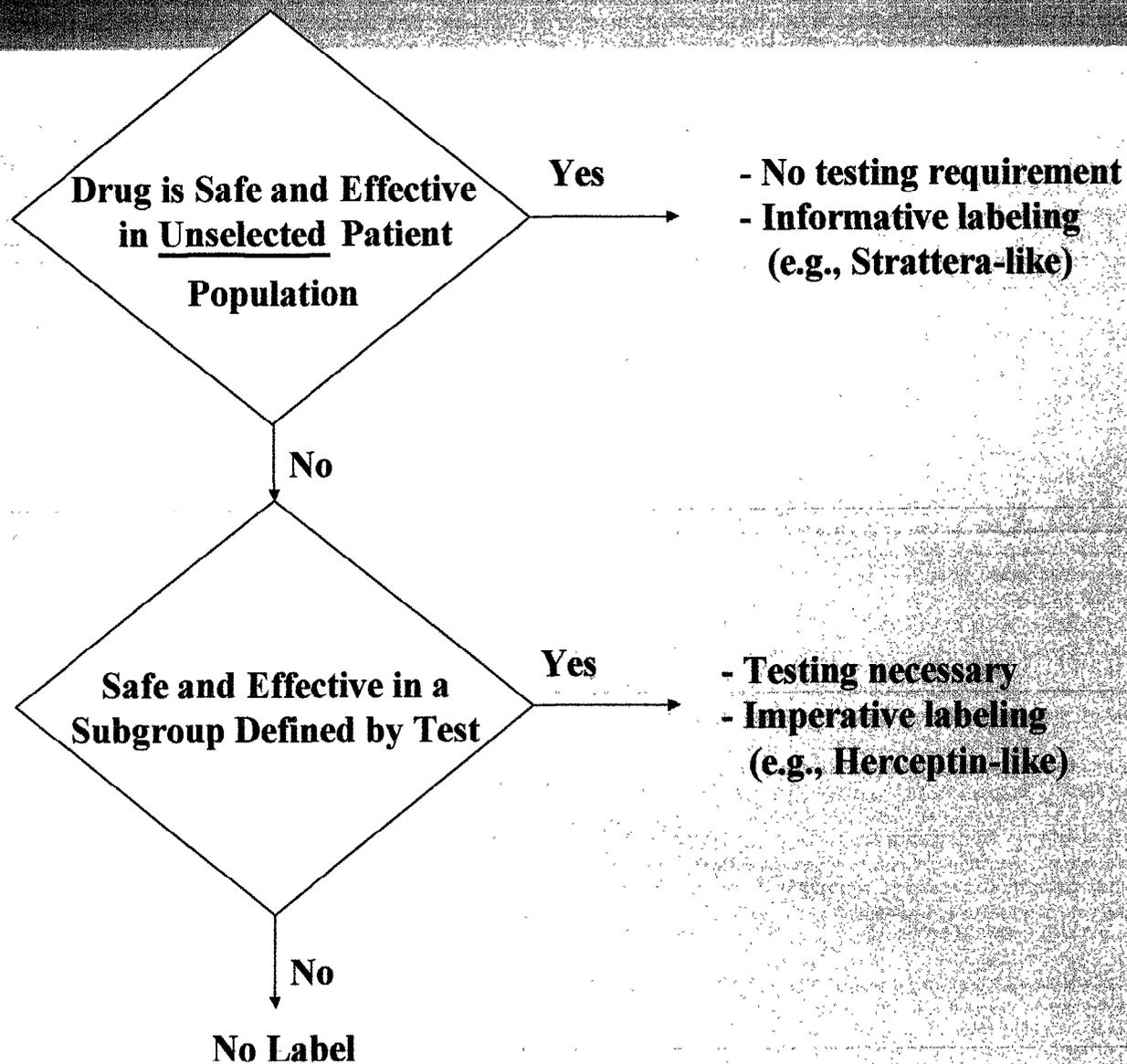
Specifically, Abbott recommends use of the attached decision tree that was presented during the labeling panel discussion at the recent FDA/DIA workshop.

Abbott requests that the guidance document provide a clear delineation between clinical and analytical test characteristics, and also between biomarker assays and *in vitro* diagnostic tests. There is considerable need for clear distinctions due to common use of words that have different meanings between diagnostics and pharmaceuticals, or between research and clinical applications. For example, it must be made clear whether 'sensitivity' refers to the likelihood of a positive test result given the presence of a target analyte in a sample, or to the likelihood of a positive test result given the presence of an indicated health condition in a patient. Similarly, validation of a biomarker is a research activity that has very different standards from either analytical or clinical validation of an *in vitro* diagnostic product, which in turn differ substantially from each other. Consistent use of modified nouns such as 'analytical sensitivity', 'clinical sensitivity', 'biomarker validation', 'analytical validation' and 'clinical validation' will greatly assist sponsors to interpret FDA's intentions in this guidance.

We thank the Agency for their consideration of our comments. Should you have any question, please contact Ivone Takenaka, Ph.D. at (847)-935-9011 or by FAX at (847) 938-3346.

Sincerely,

  
Douglas L. Sporn



# Strattera™ -like Labeling

- “X is metabolized primarily through the CYP2D6 enzymatic pathway. People w/ reduced activity in this pathway (PMs) have higher plasma concentrations of X compared w/ people with normal activity (EMs).
- Laboratory tests are available to identify CYP2D6 PMs.

# Herceptin<sup>®</sup>-like Labeling

- Detection of X protein overexpression is necessary for selection of patients appropriate for Y therapy.
- Overexpression of X by tumors was an entry criterion of the clinical studies described.
- The commercial assays (A and B) are appropriate assays in the selection of patients for Y therapy.