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DUPLICATE

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August 10, 1998



Ms. Minnie Baylor-Henry
Director, Drug Marketing, Advertising
And Communications Division
Office of Drug Evaluation I, CDER
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Promotional Use of Health Care Economic Information -
Recommended Approach for Implementing FDAMA §114

Dear Ms. Baylor-Henry:

Under the FDA Modernization Act of 1997 (FDAMA), certain "health care economic information" is permitted to be distributed by pharmaceutical manufacturers to defined categories of managed care decision makers.¹ We understand that the FDA is currently in the process of developing a Guidance for Industry on this topic. Bristol-Myers Squibb Company is a research-based manufacturer of prescription drugs and other health care products which will be subject to the Guidance ultimately implemented. We would, therefore, like to take this opportunity to pass along some initial thoughts about the type of information which should qualify for distribution under this portion of FDAMA.

The statute provides that certain health care economic information ("HCEI") shall not be considered false and misleading if it is based upon "competent and reliable scientific evidence", rather than the normal (and higher) standard of "adequate and well-controlled trials". However, HCEI qualifies for this relaxed standard of proof under the statute only if the information "directly relates to an indication approved under Section 505 [of the FD&C Act] or under Section 351(a) of the Public Health Service Act..."²

It is clear from the legislative history that Congress was willing to accept less restrictive treatment

¹FDAMA §114; 21 U.S.C. 352(a).

²Id.

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of HCEI only with respect to approved indications.³ This requirement provided assurance that any efficacy claims incorporated into HCEI would already have been demonstrated through adequate and well-controlled trials. FDAMA clearly does not permit a manufacturer to promote an efficacy claim that would otherwise be prohibited through "gamesmanship" -- i.e., weaving an unapproved claim together with economic data and characterizing the mixture as "health care economic information". Given the Congressionally-mandated requirement that HCEI relate only to approved indications, we are concerned that the possibility that HCEI could be inappropriately used as a vehicle to make unapproved claims about health outcome endpoints.

FDA carefully limits a drug's labeling to the health claims proven by well-controlled studies. If a particular drug is clinically shown to have a beneficial effect only on surrogate markers (e.g., blood pressure, cholesterol reduction) the drug's labeling is limited to claims about these surrogates. On the other hand, if the NDA sponsor performs clinical studies demonstrating a beneficial impact on health outcome endpoints (e.g., reduction in mortality and major morbidity) the drug's labeling can reflect these outcome benefits.

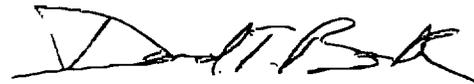
It would be very helpful if the Guidance to Industry currently being drafted by FDA could clarify that health outcomes claims for a drug that are not part of the product's approved labeling fail to qualify as "health care economic information" governed by Section 114 of FDAMA. A separate section of the FDA Modernization Act includes a process and safeguards regarding off-label dissemination. The statute does not authorize off-label promotion in the guise of an economic claim.

To further elucidate this point, the FDA may want to consider setting forth in its Guidance document certain specific examples of the proper application of the statute in this regard. Five such examples are provided in the House report on FDAMA.⁴ These illustrate the intent of Congress to prohibit health outcomes claims that are not supported by substantial evidence derived from adequate clinical trials.

Finally, we would point out that allowing unwarranted health outcomes claims to be incorporated into HCEI significantly dilutes the incentive for manufacturers to perform registrational-quality studies necessary to definitively prove health outcomes benefits.

If you have any questions concerning the above, please call me.

Sincerely,



David T. Bonk

³See H.R. Report No. 105-310, at pp. 65-66. This portion of the House Report appears as an attachment to this letter.

⁴Id. See Attachment.

105TH CONGRESS 1st Session	HOUSE OF REPRESENTATIVES	REPORT 105-310
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**PRESCRIPTION DRUG USER FEE REAUTHORIZATION AND
DRUG REGULATORY MODERNIZATION ACT OF 1997**

OCTOBER 7, 1997.—Committed to the Committee of the Whole House on the State
of the Union and ordered to be printed

Mr. BILEY, from the Committee on Commerce,
submitted the following

R E P O R T

together with

ADDITIONAL VIEWS

[To accompany H.R. 1411]

[Including cost estimate of the Congressional Budget Office]

The Committee on Commerce, to whom was referred the bill (H.R. 1411) to amend the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act to facilitate the development and approval of new drugs and biological products, and for other purposes, having considered the same, report favorably thereon with an amendment and recommend that the bill as amended do pass.

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the Secretary must encourage sponsors to submit supplemental applications or conduct further research based on these studies.

Sec. 10. Health care economic information

This section amends section 502(a) (21 U.S.C. 352(a)) of the FDCA to specify that health care economic information will not be considered false and misleading if the information directly relates to an approved indication for such drug and is based on competent and reliable information. It establishes that a health care economic statement may be submitted to a formulary committee, managed care organization, or similar entity with drug selection responsibilities.

The proposal defines "health care economic statement as" any analysis that identifies, measures, or compares the economic consequences, including the costs of the represented health outcomes, of the use of a drug to the use of another drug, to another health care intervention, or to no intervention."

The purpose of section 10 is to make it possible for drug companies to provide information about the economic consequences of the use of their products to parties that are charged with making medical product selection decisions for managed care or similar organizations. Such parties include formulary committees, drug information centers, and other multidisciplinary committees within health care organizations that review scientific studies and technology assessments and recommend drug acquisition and treatment guidelines. The provision is limited to analyses provided to such entities because such entities are constituted to consider this type of information through a deliberative process and are expected to have the appropriate range of expertise to interpret health care economic information presented to them to inform their decision-making process, and to distinguish facts from assumptions. This limitation is important because it will ensure that the information is presented only to parties who have established procedures and skills to interpret the methods and limitations of economic studies. The provision is not intended to permit manufacturers to provide such health care economic information to medical practitioners who are making individual patient prescribing decisions nor is it intended to permit the provision of such information in the context of medical education.

Health care economic information is defined as an analysis that identifies, measures, or compares the economic consequences of the use of the drug to the use of another drug, another health care intervention, or no intervention. Incorporated into economic consequences are the costs of health outcomes. Data about health outcomes associated with the use of a drug, other treatments, or no treatment are therefore incorporated into the economic analysis. This provision limits such incorporation to health outcomes that are directly related to the approved use of the drug and are determined based on competent and reliable scientific evidence. The provision presumes that the current standard practice of including full disclosure of all assumptions and health outcomes used in the economic analysis will continue.

The type of health care economic information that can be provided pursuant to this section is that which is directly related to

an approved labeled indication. To illustrate this point, economic claims based on preventing disease progression would ordinarily not be considered to be directly related to an approved indication for the treatment of symptoms of a disease, for a drug for which the use in prevention of disease progression has not been approved. For example, rheumatoid arthritis drugs are approved for the treatment of symptoms and not for the prevention of deformity. Therefore, economic claims based in part on an assumption of prevention of deformity would not be considered directly related to the approved indications for these drugs.

Similarly, economic claims based on prolonging patient survival would not be considered directly related and would not, therefore, be permitted under this subsection, for agents approved for the symptomatic treatment of heart failure, but not approved for prolonging survival in heart failure patients. This provision also is not intended to provide manufacturers a path for promoting off-label indications or claiming clinical advantages of one drug over another when such claims do not satisfy FDA's evidentiary standards for such claims.

However, the provision would permit health care economic information that includes reasonable assumptions about health care economic consequences derived from, but not explicitly cited in, the approved indication that are supported by competent and reliable scientific evidence. The nature of the evidence needed will depend on how closely related the assumptions are to the approved indication and to the health significance of the assumptions. For example, modeling the resource savings of insulin therapy to achieve tight control of blood sugar in Type 1 diabetes could include cost savings associated with the prevention of retinopathy (an eye disease) and nephropathy (kidney disease) based on well-controlled study(ies) that demonstrate that control of blood sugar levels with insulin leads to a reduction of such consequences. Because prevention of retinopathy and nephropathy could not simply be assumed to be a result of blood sugar control, these prevention claims would have to be shown by well-controlled study(ies) before inclusion as health care outcome assumptions.

In contrast, economic claims that model, based on observational studies in a population of women, the economic consequences of prevention of fractures due to osteoporosis would be permitted for drugs already approved for prevention of fractures due to osteoporosis. This is possible because observational data may be considered competent and reliable for making an assumption about the secondary consequences of an osteoporotic fracture once the primary prevention has been established. Similarly, the long-term economic consequences of the prevention of meningitis by haemophilus influenza vaccine could be modeled using population-based data once the primary prevention claim is established.

The standard of competent and reliable scientific evidence (49 Federal Register 30, 999, (August 2, 1984)) supporting health care economic information provided under this subsection takes into account the current scientific standards for assessing the various types of data and analyses that underlie such information. Thus, the nature of the evidence required to support various components of health care economic analyses depends on which component of

the analysis is involved. For example, the methods for establishing the economic costs and consequences used to construct the health care economic information would be assessed using standards widely accepted by economic experts. The methods used in establishing the clinical outcome assumptions used to construct the health care economic analysis would be evaluated using standards widely accepted by experts familiar with evaluating the merits of clinical assessments. In addition, the evidence needed could be affected by other pertinent factors. The competent and reliable standard is not intended to supplant the current FDCA definition of "false and misleading."

Under the FDA's current postmarketing reporting regulations, health care economic information as defined in this section must be submitted to the FDA at the time it is initially provided to a formulary committee or other similar entity. In addition, pursuant to this provision, the FDA will have access, upon request, to any data or other information related to the substantiation of the health care economic information. Such information will be evaluated by the Secretary to determine if the health care economic information meets the requirements of this section. This includes, for example, health outcome data, health resource utilization data, and other information related to the economic consequences of the use of the drug. It would not include, for example, confidential corporate financial data, including confidential pricing data.

Sec. 11. Clinical investigations

In 1962, Congress amended the new drug provisions of the law to require that the FDA approve the marketing of a new drug on the basis of substantial evidence of effectiveness. The statutory definition of substantial evidence requires adequate and well-controlled investigations, including clinical investigations, on the basis of which experts qualified by training and experience may fairly and responsibly conclude that the drug will have the effect it is represented to have under the conditions of use set forth in the labeling. On some occasions in the past, the FDA has stated that this always requires at least two well-controlled investigations. On other occasions, the FDA has stated that it requires only one well-controlled investigation in appropriate circumstances. In practice, the agency has approved many new drugs on the basis of one well-controlled investigation, where other evidence was available to confirm the effectiveness of the drug.

This legislation amends the law to codify current FDA practice. It authorizes the FDA, in its discretion, to approve an NDA on the basis of one adequate and well-controlled clinical investigation and confirmatory evidence obtained prior to or after that investigation, where the FDA concludes that such data and evidence are sufficient to constitute substantial evidence of effectiveness. The FDA will also retain its inherent administrative discretion to waive this requirement completely, as it has done in the past, where it would be unethical or unnecessary.

The FDA has itself recognized in recent guidance that substantial evidence of effectiveness may consist of one adequate and well-controlled investigation and confirmatory evidence consisting of earlier clinical trials, pharmacokinetic data, or other appropriate