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Division of Dockets Management
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Food and Drug Administration
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RE: FDA's Draft Guidances on Premarketing Risk Management, Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, and Development and Use of Risk Minimization Action Plans [Docket Nos. 2004D-0187, 2004D-0188, and 2004D-0189]

To Whom It May Concern:

These comments are submitted in response to FDA's *Federal Register* publication announcing the public availability for comment of the following draft documents: Draft Guidances for Industry on Premarketing Risk Assessment; Good Pharmacovigilance Practices and Pharmaco-epidemiologic Assessment; Development and Use of Risk Minimization Action Plans [*Federal Register*: May 5, 2004 (Volume 69, Number 87)].

The University of California, San Francisco Center for Consumer Self Care has as its mission helping consumers and patients take a central role in their own health care. We achieve our mission by applying our experience in medicines, dietary supplements, in-home diagnostic devices, and lifestyle practices to: engage national, state, and local stakeholders on significant health policy issues and initiatives affecting access to, as well as the cost, quality and behavioral outcomes of, self-care; conduct policy-relevant research to advance the knowledge and practice of self-care; share with consumers and health professionals relevant, reliable, evidence-based information on responsible self-care; educate health practitioners and students about the theory and practice of self-care.

As part of Congress' second reauthorization of the Prescription Drug User fee Act (PDUFA III), the Food and Drug Administration (FDA) agreed to certain performance goals, including development of guidance for industry on risk management for drug and biological products. Issued in May 2004 in draft form, the guidance is in three parts addressing pre-marketing risk assessment, post-marketing pharmacovigilance, and the development of Risk Minimization Action Plans ("RiskMAPs")[1].

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These guidances are important steps to keep the public aware of FDA's evolving operational framework for protecting and promoting the public health, thereby also setting forth FDA's expectations of industry's responsibilities in the lifecycle management of drugs and biologics, and providing a baseline of learning for professionals new to the areas of drug development, postmarketing surveillance, and lifecycle product management.

However, FDA's drafts are weak in expressing the current conceptual framework evolving among health professionals for improving the standard of health care. These weaknesses include: (a) omission of an explicit overarching perspective of patient-centered health care; (b) miscasting Risk Minimization Action Plans (RiskMAPs) as only applicable for special situations, when preferably every product should be the subject of a systematic benefit-risk management action plan; and (c) an unbalanced emphasis on safety over benefit in defining what should be a systems approach aimed at optimizing patient outcomes. These shortcomings are discussed in this commentary with a view to engaging a broader dialogue to refine the overall perspective of the draft guidance.

Converging Health Trends Signaling A New Health Care Paradigm – Patient-Centered Care

Significant health trends have converged creating a crisis in health care. The first wave of the aging baby boomers turns 65 in 2011, with an estimated 70 million people over age 65 years by 2020. Seniors have a higher chronic disease burden. According to the Centers for Disease Control (CDC), seven of every 10 Americans who die each year (i.e., more than 1.7 million) die of a chronic disease.[2] Obesity is at worldwide epidemic proportions due to modern-day lifestyle choices leading to less activity and poor dietary choices.[3] Obesity cuts across all ages, and is associated with increased morbidity and mortality from cancer, cardiovascular disease, diabetes and other diseases.[4]

Yet today, it doesn't seem the practice of health care is doing as well as it might in easing suffering and preventing premature death. For example, leading researchers and policymakers convened by the Institute of Medicine to assess how to improve health of patients in the 21st century[5] concluded, "More than 50% of patients with diabetes, hypertension, tobacco addiction, hyperlipidemia, congestive heart failure, asthma, depression and chronic atrial fibrillation are currently managed inadequately,[6,7,8,9,10,11,12] and 18,000 Americans die each year from heart attacks because they did not receive preventive medications, although they were eligible for them." [13]

Inadequate management of the health of patients can stem from multiple sources, including: the health care practitioner; the patient; and the allied support personnel (e.g., outpatient laboratory technicians) contributing to the patient's care. As a result, leading experts have begun to shape a different vision of health care to improve disease outcomes and health promotion strategies. This vision is based on reframing our perspective on how patients, health practitioners and other health professionals interact to achieve

successful therapeutic and preventive approaches to chronic disease management, and how the many health professionals involved in each patient's care must interact as a team in delivering optimal health care to the individual. The term describing this new approach to health care has been termed patient-centered care[14] – i.e., care provided with respect to, and responsive to, individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions. This perspective is dramatically different from the disease-centered approach by physicians and the drug-centered approach by pharmacists in a paternalistic model of health care.

Patent-Centered Health Care as an Essential Part of the Overarching Perspective

In looking at the FDA's perspective on this changing health care paradigm, it's instructive to review the 1999 FDA white paper, *Managing the Risks from Medical Product Use: Creating a Risk Management Framework,* which was a formative element in the development of the current draft risk management guidance.[15] The agency's risk management white paper was developed at the direction of then FDA Commissioner Jane Henney, who formed a special task force from the Centers for Biologics Evaluation and Research, Devices and Radiological Health and Drug Evaluation and Research to respond to critics citing slow approval times compared to overseas markets and others claiming inadequate premarketing approaches to predict safety premarketing. Specifically, in defining the model for premarketing and postmarketing risk management activities, the inter-Center task force appropriately called for a systems framework to medical product risk management, to "enable a better integration of the efforts of all the involved parties." However, the task force then identified the prescriber (i.e., physicians) as the center of the postmarketing model of risk-managed health care, with the patient, pharmacist and nurse as secondary elements.[16] This is essentially a drug-centered paternalistic model of health care that falls short of embracing an integration of a fully utilized health care team.

In assessing the draft guidances relative to the white paper, it is noteworthy that there is no identification of the "prescriber" as the central in-use decision maker in the postmarketing environment. Yet, at the same time, there is no acknowledgement in any of the three parts of the draft risk management guidance that the overarching approach to drug development and postmarketing pharmacovigilance should be patient-centered. A more forward-looking view would acknowledge the important contributions of the entire health care team (physicians, pharmacists, nurses and patients/consumers) to enhancing benefits of, and reducing risks from, medical products. Such acknowledgement would emphasize the potential for each element of the health care team to participate in risk management action plans and would place focus on the goals and objectives of health communication, as such communication is the catalyst for moving patients and consumers from higher-risk/lower-benefit to lower-risk/higher benefit outcomes.

Finally in this regard, a patient-centered approach during premarketing drug development does not remove the emphasis on learning about drug-drug or drug-disease interactions, for example, but rather recognizes the ultimate goal of most pharmaceutical therapy is self care by the patient or consumer in a collaborative healthcare model of

patient/consumer-centered care. The emphasis is not on what does the drug do, but rather how is the drug's toxicity expressed in the context of use, as modified by appropriate risk management strategies undertaken by the entire health care team.

RiskMAPs for Every Medical Product

There is a second aspect of the three-part guidance that impacts the overarching perspective that should be fostered by FDA in its communications to industry about optimizing outcomes of drug therapy. Specifically, the draft guidance describes risk management as a continuous process, as follows:

> "Risk management is an iterative process of (1) assessing a product's benefit-risk balance, (2) developing and implementing tools to minimize risks while preserving benefits, (3) evaluating tool effectiveness and re-assessing the benefit-risk balance, and (4) making adjustments, as appropriate, to the risk minimization tools to improve the benefit-risk balance. The four-part process <u>should be continuous throughout a product's lifecycle</u>, with the results of risk assessment informing the sponsor's decisions regarding risk minimization." (emphasis added)

Yet, in that part of the draft guidance dealing with risk minimization plans, FDA makes a distinction between routine risk-related and risk minimization action plans (RiskMAPs). FDA states the former is provided by the Food Drug Cosmetic Act at section 503(b) (21 U.S.C. 353(b) regarding limiting drugs to prescription status, FDA regulations regarding spontaneous adverse event reporting, and FDA-approved professional labeling, while the latter is defined as "a strategic safety program designed to meet specific goals and objectives in minimizing known risks of a product while preserving its benefits." FDA posits that RiskMAPs would be used for a small number of products, such as Accutane (i.e., use of a registry), among others.

What are the implications of this distinction in risk minimization approaches between routine and presumably extraordinary types of safety situations? Certainly, FDA's definition of risk management does not distinguish among products; FDA specifically states (see quoted excerpt above) that risk management should be "continuous throughout a [meaning "any"] product's lifecycle." Along the same lines, FDA's definition of a RiskMAP (i.e., a strategic safety program designed to meet specific goals) would seem to apply to both routine and extraordinary situations – i.e., to all products. A "routine" approach to labeling with the placement of specific "liver toxicity" warnings on the label and monitoring AERs to determine if such warnings are adequate requires a strategic on-going approach to safety, just as the creation and management of a registry program for a potential teratogen.

Only if companies systematically plan risk assessment and risk minimization activities for each product will they meet FDA's expectations for lifecycle risk management and for identifying unexpected situations that may require special approaches. Because safety issues arise unpredictably both in the drug development phase or even late in a product's marketing history (e.g., issues arising in relation to

aspirin and Reye's syndrome[17], gastric alcohol dehydrogenase[18], and hemorrhagic stroke[19]; benzocaine and methemoglobinemia[20]; in-use confusion relating to dosing drops and liquid forms of pediatric fever reducers[21], among others), an on-going strategic safety plan designed to meet specific goals is needed for every drug and biologic products, even if the scope and nature of each product's risk management plans will be uniquely derived from a continuum of possible activities. It is difficult to see what is gained by FDA's contrivance of a category called RiskMAP, when from a patient-centered viewpoint safety is best achieved by continuous lifecycle risk management, that engages a systems approach to risk management with use of different risk minimization tools as needed in accordance with the safety challenges than may arise. FDA should state this perspective explicitly in the draft guidance, saying that a company should have an on-going risk management action plan in place for every product they market or have in development.

Benefit-Risk Management as an Essential Part of the Overarching Perspective

The third overarching aspect relating to FDA's three-part draft risk management guidance relates to FDA's less than adequate emphasis on benefits management throughout a product's lifecycle. According to the inter-Center Task Force on Risk Management, the "goals are to maximize benefit, minimize risk" by balancing the benefits to be gained with the potential risks of using a product."[22] Thus, the benefits side of the equation is just as important from both a public health and patient-centered, context as the safety side of the equation. For a marketed product, new dosage forms, new indications, and new approaches to improving adherence through self management programs tied to specific therapies are important product improvements -- not just financially for the company in lifecycle product marketing, but also for the patient. While FDA acknowledges this at several points in the guidance, it is not accomplished in as definitive a way as it could and should be. Hence, "benefit-risk management" should be the preferred overarching concept and terminology, with "benefit-risk management action plans" (i.e., BenefitRiskMAPs) strategically defined and appropriately tailored by companies for the specific objectives of optimizing treatment and minimizing in-use risk for every medical product marketed or in development by a company.

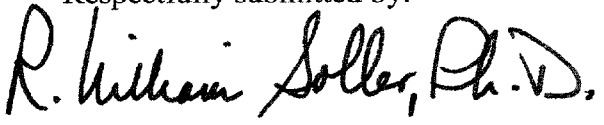
After all, acceptable benefit-risk is the ultimate goal of drug development and continued marketing, and it is a concept most properly considered in its duality; thus, the exposition of relevant guidances should not be done separately. Use of an umbrella phrase encompassing both the benefit and risk elements of the regulatory standard of approval and continued marketing would appropriately reframe the three-part guidance recommending companies use a systems approach to benefit-risk management of medical products in patient-centered health care.

Summary

In summary, FDA has taken important steps in issuing the three-part guidance. However, the agency has yet to articulate a patient-centered approach to drug development, the drug approval process, or post-marketing benefit/risk management.

Now, the agency has the opportunity to do this in finalizing the guidance documents, thereby aligning its expectations for industry with the evolving collaborative care approach taking hold in U.S. clinical and community practice settings. Further, FDA does a disservice in distinguishing routine from special types of risk minimization. Every product should have its own benefit-risk management action plan, tailored to where the product resides along a continuum of potential risk and risk management tools. Finally, the draft guidance documents should be more firmly framed in the context of optimizing benefit and minimizing risk, to the point of using and explaining the terms, "benefit-risk management" and "benefit-risk management action plans." At a minimum, if the introductory paragraphs that are repeated in each of the three parts of the draft guidance were to be recast to incorporate the concepts conveyed herein, then there would likely be a greater impact on both promoting and protecting the public health, and therefore in meeting the individual patient's and consumer's needs for appropriately safe and optimally effective drugs and biologics.

Respectfully submitted by:



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1 Food and Drug Administration.: Draft Guidances on (a) Premarketing Risk Assessment, (b) Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, (c) Development and Use of Risk Minimization Action Plans. *Federal Register*: May 5, 2004 (Volume 69, Number 87).

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