



July 6, 2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: [Docket No. 2004D-0187] – Draft Guidance for Industry on Premarketing Risk Assessment - Request for Comments

Merck & Co., Inc. is a leading worldwide, human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline has produced many important pharmaceutical products available today. These products have saved the lives of or improved the quality of life for millions of people globally.

Merck supports regulatory oversight of pharmaceutical product development and welcomes guidance for compliance that is based on sound scientific principles and good judgment. As a leading pharmaceutical company, Merck has extensive experience in thoroughly evaluating our products from discovery to approval and throughout their marketing life to assure that they continue to provide health benefits with minimum risk. Therefore, we are well qualified to comment on the risk assessment and risk management draft guidance documents issued by FDA on May 5, 2004¹. Herein, we are providing comment on the draft guidance for industry entitled: *Premarketing Risk Assessment*.

General Comments

We commend the FDA for its efforts in the development of guidance for industry on good practices for risk assessment, risk management, and pharmacovigilance, and particularly for its prior issuance² of the three concept papers to encourage discussion of these important topics. The practice of issuing concept papers describing novel regulatory approaches, prior to issuance of draft guidance documents, is fully supported by Merck. The concept papers provide an additional opportunity for interested parties to provide

¹ 69 FR 25130, Docket No. 2004D-0187

² 68 FR 11120, Docket No. 02N-0528

comment and are a valuable tool when guidance documents describing new regulatory concepts are developed. We fully recognize the extra efforts that the concept papers precipitate and we appreciate the agency's continued commitment to this approach.

Risk assessment and risk management must be considered as part of a continuum from discovery through the marketing life of a product. As such, we are requesting that throughout the three companion guidance documents, the life-cycle approach to risk management be stressed. Because risk assessment and risk management occupy a continuum from discovery through the marketing life of a product, practices adopted in the pre-marketing phase are likely to influence plans for the future. It is critical to note that decisions made in the premarketing phase will impact future risk management activities.

We are encouraged that the draft guidance takes into account that the “*..characteristics of an appropriate safety database are product-specific.*” (Line 238). It must be noted that some of the elements specified for a sponsor to consider when developing a premarketing safety database should be assessed on a case-by-case basis (long-term controlled safety studies, diverse safety database, and exploration of dose effects). These measures would greatly increase study size if expected to provide a meaningful increment in safety information. This would lead to longer pre-market development times, ultimately delaying availability of new therapies to the public and increasing their cost. The current process for pre-market evaluation of new drugs, which may include some or all of these measures when deemed necessary, often in consultation with FDA, is highly successful in bringing safe and effective drugs to market while focusing resources on products that require special consideration for safe use. We are requesting that the case-by-case assessment of the elements of premarketing risk assessment be stressed throughout the document as a means to bring about positive public health gain.

Specific Comments

IV. GENERATING RISK INFORMATION DURING CLINICAL TRIALS

A. Size of the premarketing safety database

Lines 143 - 234: The International Council on Harmonization (ICH) published guidance (E1³) on the size of the pre-marketing safety database for products used for long-term treatment of non-life-threatening conditions and we support the reference to this document beginning on Line 175. This draft document provides additional guidance on the appropriate size of safety database for other categories of products (products only for acute use, products only for serious or life-threatening conditions). It also lists reasons, in

³ E1: The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions.

addition to those discussed in the ICH guidance, why a larger database might be appropriate.

Recommendations: The ICH E1 guidance establishes a population exposure benchmark for assessing clinical safety for drugs intended for long-term treatment of non-life-threatening conditions, including a discussion of factors that may call for a larger data base for such products. This is a category of drugs that, because of the need for chronic use for non-life-threatening indications, demands evidence of a reasonably benign safety profile. The stated philosophy of ICH E1 is that the safety evaluation during clinical drug development will characterize well those events with an incidence of about 1% while not expecting to characterize rare adverse events (those occurring in less than 1 in 1000 patients). In addition, ICH E1 is clear that the actual patient exposure for a specific drug will be determined by the information available on the drug, the drug class, and any post-marketing surveillance requirement. We believe the underlying philosophy of ICH E1 is sound and, given the ICH benchmark for drugs indicated for chronic use in non-life-threatening conditions, is applicable to other product categories in making reasonable determinations about population exposure to assess clinical safety. We recommend against attempts to standard numbers for pre-market exposure in regulatory guidance for therapies of all varying durations and degrees of disease severity (acute use, serious or life-threatening diseases, and others).

We do not believe there is a need to add to the list of reasons included in ICH E1 for a larger database. The additional reasons suggested in the draft guidance (lines 220 - 226) are vague and add little to the discussion in the existing guidance. Vaccines, for example, represent a unique product class with an excellent clinical safety record that confirms that current practices for premarket evaluation are highly effective. Therefore, we believe that vaccines represent an example that is out of context in this discussion. The suggestion that a larger database may be necessary when a very safe alternative to the investigational product is available is to suggest that the new product must not only be "safe and effective", but must be as safe and effective or more so compared to existing therapy. Such comparative safety and efficacy is not a requirement under the FD&C Act, and the sample size requirements to provide meaningful data when between group comparisons are needed make such evaluations impractical except in specific situations where it will, no doubt, be recognized without additional formal guidance. In addition, the context of the disease being treated, the pre-clinical and early phase clinical safety assessment of the new drug, the efficacy of the alternative marketed product, and the potential efficacy advantages of the new drug to existing therapy all warrant consideration in determining the appropriate pre-market exposure for a given situation and, in some cases, may obviate the need for a larger population.

As discussed in the ICH E1 guidance, the recommendation of 1500 patients is a general benchmark but the actual numbers for a specific development program need to be justified on a case-by-case basis. It should be most applicable to products with new

mechanisms of action. Patient years and duration of exposure should be addressed. A substantially smaller database should be acceptable for compounds in the same class of approved products, or for combinations of products already in the marketplace.

B. Considerations for Developing a Premarketing Safety Database

1. Long-Term Controlled Safety Studies (Lines 250-277)

This section takes the general position that “*it may be preferable in some circumstances*” to have long-term controlled safety data (lines 253-255). As indicated in our comments on the concept paper, we do not believe that justification for this conclusion is provided. The record of the industry and of the FDA in developing and approving new products with appropriate labeling confirms that, for the overwhelming majority of new drugs, current practices work very well. Indeed, as noted in this section, “*Generally, serious events that rarely occur spontaneously...are of significance and interpretable whenever they occur since the expected rate is essentially zero in populations of any feasible size*” (lines 262-264). Further, long-term controlled safety studies are not without their own concerns. It should be acknowledged that long-term placebo studies may not be ethical depending on the disease, and active-control studies may not provide a useful assessment of those adverse events that are shared across compounds. Even as an “ideal,” this suggestion is flawed in that the ideal would surely involve consideration of reasonable costs of development, existence of prior safety signals, the likelihood of such studies to provide meaningful additional safety information, and the public health cost of delaying access to new safe and effective therapies.

Recommendation: The guidance document should discuss *both* the benefits and disadvantages of long-term controlled safety studies and describe situations in which they may be recommended in the pre-marketing phase of development in spite of their limitations. Discussion should include the objectives best achieved with such studies and include discussion of power and typical duration. The guidance should not appear to recommend or imply that such studies should be considered for all programs.

D. Developing Comparative Safety Data (Lines 368-397)

The draft guidance indicates that one situation in which comparative studies (studies that include an arm with a well-characterized agent in addition to the test product) would be useful when there is a need to characterize background rates of certain adverse events. The adverse event profile of the new drug may appear high when, in fact, it is typical for that of other drugs. We believe that the term “*background rates*” is incorrect, and what is being examined in this example is the expected adverse event profile for type of drug being administered. “Background rates” implies an epidemiologic assessment.

It should be noted that it is unlikely that comparative safety studies of any reasonably attainable size would be sufficiently powered to differentiate safety differences between available therapy and the new product, especially for rare event.

There is an implication in lines 382 – 385 that when there is "*well-established related therapy*," a new product must be safer or more effective than available therapy. As noted above, this is not a requirement of the FD&C Act. Furthermore, it is unlikely that any two drugs will have the same side effect profile varying only in intensity. It is generally accepted that, even within the same class, a choice of therapies is desirable as some patients do better on one than on another. Developing comparative safety data is, in essence, raising significant regulatory hurdles for new products of the same type as currently approved therapies.

Recommendation: In finalizing the guidance document, FDA needs to present more clearly when good practice calls for comparative data in a development program with attention paid to the practical considerations such as study size and power to detect differences. It should also consider the regulatory application of such data; particularly when a single comparative study would suffice and when a replicate study would be necessary.

V. SPECIAL CONSIDERATIONS FOR RISK ASSESSMENT

B. Risk Assessment and Minimizing the Potential for Medication Errors (Line 473 – 517)

This section describes premarketing risk assessment on the product's proprietary and established names, labeling, inserts and other components of the overall product packaging. A discussion of a medication error prevention analysis (MEPA) is provided (Lines 478 – 488). The Agency has adequately described the role of the U.S. Adopted Names Council (USAN) and that sponsors use risk assessment techniques, as appropriate, to evaluate established names prior to submission to USAN (Lines 500 – 510).

Recommendation: Until methods for testing names and packaging have been validated to have predictive value in reducing medication error potential, it is premature to include recommendations for such testing in regulatory guidance (Lines 494 and following, e.g. Failure Mode and Effects Analysis, FMEA).

Instead of recommending testing of unproven value, FDA should work with State medical boards and other State regulators of health professionals to address practice issues that are significant causes of medication errors. State laws defining the elements of a "complete prescription" to include specific directions for use would eliminate prescriptions with directions such as "as directed." A requirement to include the indication in the directions ("one tablet daily for blood pressure") would clarify many potentially misleading orders.

Additional information in a prescription order is important to help identify the required product or to signal the need for clarification when handwriting or poor oral communication creates confusion. We believe that FDA should direct resources towards evaluating and validating current and proposed testing practices to determine their legitimacy before seeking any recommendations for their use. Finally, for this section, it should be noted in the guidance that established names may already be in existence for second-entry products.

VI. DATA ANALYSIS AND PRESENTATION

C. Analyzing Dose Effect as a Contribution to Risk Assessment (Line 729 – 767)

This section describes analysis of event rates by dose for certain adverse events and also notes demographic subgroup analyses. Line 743 – 745 states: *In addition, when specific demographic or baseline disease-related subgroups may be at particular risk of incurring adverse events, exploration of dose response relationships by subgroup is important.*

Recommendation: To put the subgroup analysis in proper perspective, we suggest that the following line be added to the paragraph (Line 745): *They [subgroup analyses] have the potential to provide a more reliable and relevant estimate of risk for important subgroups of the target patient population; alternatively, multiplicity issues could result in an apparent signal that may not exist.*

G. Long-term Follow-up (Line 872 – 881)

The draft guidance recommends that “*all subjects be followed to the end of the study or even after the formal end of the study*”.

Recommendation: It is important to note in the text of the final document that the safety follow-up period is most often specified in the clinical study protocol and the length of the follow-up period will be based on considerations such as those noted in the draft guidance (long half-life, deposition in certain organs, potential for irreversible effects). Long-term follow-up is not without disadvantages, such as, despite the *best efforts* of the sponsor, patients are lost to follow-up (as noted in Line 868), and there is often ambiguity in what tests to perform on the patients. Potential issues with the quality of the long-term follow-up data need to be addressed in the text of the final guidance in order to prevent unrealistic expectations. Additionally, discussion between the Agency and the sponsor concerning the potential for long-term follow-up is an integral part of good review management practices and these discussions should be fostered on a case-by-case basis depending on the type of product in development.

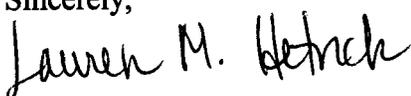
Conclusion

We commend the Food and Drug Administration for issuance of the three concept papers, followed by draft guidance documents, on premarketing risk assessment, risk minimization action plans, and good pharmacovigilance practices and pharmacoepidemiologic assessment. These documents, along with the public workshop on April 9, 10, and 11, 2003 represent an extraordinary effort on the part of the Agency to convey its preliminary thoughts on these issues and to stimulate discussion with stakeholders.

The call for guidance on risk assessment, risk management, and pharmacovigilance activities in the PDUFA III goals is neither an expression of concern that current efforts are inadequate nor a call for more intense surveillance. It simply a call to document those practices that represent the best of what we are doing now. Risk management, itself, is not new to drug development. As an industry, in conjunction with the FDA, we have been conducting pre-approval tests of increasing intensity and complexity on potential products for decades; we have been collecting, monitoring, and evaluating spontaneous reports on marketed products and taking appropriate action to minimize risks. Likewise, we have carried out Phase 4 programs based on commitments made to the Agency at the time of approval to address potential, often theoretical, risks that had not been resolved at the time of approval. It is the best of these practices that the guidance is intended to capture, along with fostering international harmonization with the approach.

We appreciate the opportunity to share our comments with respect to FDA's Draft Guidance for Industry: Premarketing Risk Assessment. Please do not hesitate to contact me, should you have any questions.

Sincerely,


for Donald M. Black, MD, MBA
Vice President
Global Regulatory Policy