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MERCK
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Dockets Management Branch (HFA-305)
Food and Drug Administration
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RE: Docket No. 00N-1484: Safety Reporting Requirements for Human Drug and Biological Products - *Proposed Rule*

Merck & Co., Inc. is a leading worldwide, human health product company. Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations. Merck's R & D pipeline has produced many of the important pharmaceutical products on the market today.

Merck supports regulatory oversight of pharmaceutical products throughout their life cycle and welcomes regulatory revisions that are 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. All of our products undergo continuous safety assessment. Safety reporting to regulatory agencies is an integral part of the process. Therefore, we are well qualified to comment on the proposed rule, "Safety Reporting Requirements for Human Drug and Biological Products," issued by FDA on March 14, 2003.[1]

General Comments

Section II.B. of the preamble to the proposed rule (68 FR 12412) summarizes FDA's rationale for the proposed amendment to the current safety reporting rules. The rationale includes the following goals:

1. To harmonize with the International Conference on Harmonization (ICH) and Council for International Organizations of Medical Sciences (CIOMS) recommendations;
2. To increase the quality of safety reports through a risk-based approach that focuses more resources on serious adverse drug experiences than on non-serious ones;

[1] 68 FR 12406, March 14, 2003

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3. To eliminate unnecessary reporting burdens on industry imposed by differences in regional format and content requirements in the EU, Japan, and the U.S.; and
4. To provide a systematic approach for collecting information on medication errors.

We commend the FDA for undertaking revision of its safety reporting regulations to improve safety surveillance of pharmaceutical products, focus attention on preventable factors that contribute to medication errors, eliminate inefficiencies, and achieve greater international harmony by implementing certain recommendations of the ICH and CIOMS. We fully support the FDA's public health objective to take all necessary steps to achieve maximum benefit from today's pharmaceuticals through effective assessment, management, and minimization of risk.

We also appreciate the challenge inherent in prospectively selecting those regulatory changes that will promote the achievement of these important goals over changes that may produce unintended consequences contrary to attainment of the objectives of the regulatory revision. The odds of "getting it right" are improved by carefully weighing the views of all stakeholders with expertise in safety assessment of pharmaceuticals, both during development and after approval. We appreciate the opportunity to provide comments and recommendations on the proposed rule that we believe will enhance its effectiveness in achieving its intended objectives.

FDA and regulators in other ICH regions have adopted MedDRA as the Medical Dictionary for regulatory activities. The use of this single standard medical terminology has facilitated the global exchange of information regarding drug safety in support of the public health. We strongly support and encourage the continued use of MedDRA for these purposes.

The proposed rule provides for extensive revisions to the safety reporting requirements for human drug and biological products. While we support the overall direction of FDA's proposal, we believe the following general provisions warrant further consideration if the Agency's objectives for this regulatory revision are to be fully realized:

1. <u>The meaning of "reasonable possibility" within the definition of *Suspected Adverse Drug Reaction*</u> [<u>Proposed 21 CFR 310.305(a), 312.32(a), and 314.80(a), 600.80(a)</u>]

> *Suspected adverse drug reaction (SADR) means a noxious and unintended response to any dose of a drug product for which there is a reasonable possibility that the product caused the response. <u>In this definition, the phrase "a reasonable possibility" means that the relationship cannot be ruled out.</u> (Emphasis added)*

Although the proposed FDA definition of a SADR is based on the ICH E2A "pre-approval clinical experience" definition of an adverse drug reaction (Section IIA2), the

ICH E2A document further explains (Section IIIA1) that, "The expression 'reasonable causal relationship' is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship." In addition, the FDA proposal is inconsistent with the EU Clinical Trials Directive on ADR reporting. Both of these documents convey the concept that "reasonable causal relationship" means there is evidence to support an association with the drug. This evidence may include temporal relationship, the pharmacology of the drug, positive rechallenge, and other factors. Similarly, confounding factors including concurrent conditions, the underlying disease process, and concomitant medications are also taken into account.

In contrast, the FDA's definition uses a negative test that is impossible to refute. The proposed definition will result in classifying any adverse experience occurring after drug administration to be an SADR by virtue of a temporal relationship and the inability to definitely rule out a causal association. The proposed definition does not represent a true harmonization between FDA and ICH.

Hence, every reported serious event in a clinical trial will, by default, be reportable to FDA, regardless of confounding factors or the remoteness of the relationship in the judgment of the investigator or sponsor. The integrity of controlled clinical trials will be seriously compromised by unblinding patients in larger numbers as a result of the indiscriminate reporting that the application of this definition will require.

The proposed changes were applied to the data from the Reduction of Endpoints in Non-insulin Dependent Diabetes Mellitus with the Angiotensin II Receptor Antagonist Losartan (RENAAL) Trial in order to assess the effect of the proposed definition of an SADR on an actual clinical trial. The primary outcome from the RENAAL trial was re-analyzed before and after applying the changes described in the proposed rule. The RENAAL trial was carried out to assess the specific effect of losartan potassium on composite and renal outcomes, and to explore the implications of dihydropyridine calcium channel blockers as concurrent therapy on composite and renal outcomes in 1513 participants with established nephropathy and hypertension associated with type 2 diabetes. The study demonstrated significant reductions in the rate of progression of renal disease as measured by a reduced incidence of primary endpoints including the occurrence of a composite event consisting of doubling of serum creatinine (SCr), occurrence of end-stage renal disease (ESRD), or death in patients receiving losartan, independent of effects on blood pressure. Because of the baseline illness in the patient population, patients were likely to experience serious adverse experiences which did not necessarily require discontinuation from the trial.

The proposed changes were implemented by removing patients with a serious adverse event (SAE) 7 days after the SAE was reported. The primary endpoint was the occurrence of a composite event consisting of doubling of SCr, ESRD, or death. SAEs often represented a manifestation of disease progression before occurrence of the primary endpoint.

Implementing the proposed SADR definition had a dramatic effect. In the original analysis, 686 of the 1513 patients entered in the study provided an endpoint or completed the trial and 827 (54.7%) were censored. Applying the proposed rule reduced the number of patients with an endpoint by 61% (i.e., from 686 to 269) and increased the number of censored patients by about half to 1244 (82.2%).

This loss of endpoints caused the trial to lose statistical significance. The original analysis (Table 1) demonstrated a positive treatment effect (43.5% vs. 47.1% with endpoints in the Losartan vs. control groups, respectively) with p = 0.022. Application of the proposed rule caused the treatment effect to lose statistical significance (16.6% vs. 18.9%) with p=0.055 (Table 2). This is not a small impact: failure to achieve statistical significance would have had drastic consequences for acceptance of the result by the medical community and regulatory approval of a labeling change.

Even if nominal significance had been preserved, the credibility of the finding would have been damaged because only 18% of the patients either experienced an endpoint or completed the trial.

This example illustrates the potential damage of the proposed reporting requirement to the sensitivity of trials that could have demonstrated meaningful clinical effects, especially in very sick populations that are inherently difficult to study, by prematurely removing patients who are willing, and whom the investigator judges are able, to continue in the trial, and thereby losing the opportunity to observe endpoints.

Table 1. Effect of Proposed Rule on Event Occurrence. Primary Endpoint is Composite Event = Doubling of SCr, ESRD, or Death

Treatment Group	Losartan				Placebo			
	Completion/Event Occurrence				Completion/Event Occurrence			
	No*		Yes		No*		Yes	
Analysis	N	%	N	%	N	%	N	%
Original	424	56.5	327	43.5	403	52.9	359	47.1
After applying proposed rule	626	83.4	125	16.6	618	81.1	144	18.9

*includes patients censored due to unblinding of SAEs

Table 2. Effect of Proposed Rule on Statistical Significance of Treatment Effect

Analysis	DF	Parameter Estimate	Standard Error	Chi-Square	**Significance** Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Original	1	-0.17545	0.07665	5.2403	**0.0221**	0.839	0.722	0.975
After applying proposed rule	1	-0.23679	0.12323	3.6921	**0.0547**	0.789	0.62	1.005

In addition to having an adverse impact on the ability to do clinical trials in sick patient populations, the proposed definition of an SADR will flood investigators and IRBs with reports that have little or no relevance to the safety of the trial. Because this definition goes beyond the usual meaning of "reasonable," it has the potential to confuse investigators, healthcare workers, the public, and the lay media. It will mandate the accumulation of data that are not only unlikely to contribute to understanding the safety profile of the drug, but may, in fact, obscure it by reducing the ratio of signal to noise. As such, it will decrease the sponsor's ability to provide meaningful data to the FDA, investigators, and patients. Furthermore, as a result of loss from studies of increased numbers of patients for whom the blind is broken but who would not ordinarily be discontinued from studies, it will threaten the ability of clinical trials to yield meaningful results.

Another potential impact of the proposed definition of SADR is on the design of studies in patients with serious medical conditions. Specifically, patient inclusion criteria could be adjusted to limit the enrollment of patients likely to experience serious adverse experiences during the study period. The goal of such a limitation would be to decrease the numbers of patients to be dropped from the analysis for events related to their primary (or other) illness and thus enhance the proportion of patients completing the study. A number of consequences would follow from this intentional pre-study censoring of the more ill patient. The proportion of patients actually experiencing a study endpoint could be reduced, thereby requiring exposure of more patients to experimental agents and increasing study costs. More importantly, limiting the study population would limit the applicability of study results and potentially result in withholding an effective treatment from those patients likely to experience the greatest benefit.

Indeed, the Agency itself appears to recognize the weakness of this proposed regulatory definition and its potential to lead to over-reporting of events that occur in clinical trials that are unlikely to be a result of exposure to the drug. FDA notes, *"Because such 'over-reporting' may make it more difficult for FDA and the sponsor, manufacturer or applicant to recognize adverse events that are really caused by a drug or biological product, the agency wants to minimize receipt of this type of safety report, but in a way that does not compromise receipt of useful safety reports that are perceived as remotely related to an administered drug or biological product but that occur, in fact, as a result of the product."* (68 FR 12418). FDA, in fact, suggested that a sponsor may propose alternative reporting methods that, with Agency agreement, the sponsor could use instead. For example, the agency proposed that a sponsor may list known consequences of the disease in study protocols that, if reported, would not be submitted to FDA in an expedited manner but would be monitored and submitted only if or when, in comparison to a control, there was evidence to suggest that the product under study may be causing these events. We do not favor promulgating a regulatory definition that largely eliminates clinical judgment in reporting coupled with an *ad hoc* exemption mechanism. We believe this inevitably would lead to different standards across clinical programs, between

different sponsors of studies, and across FDA review divisions based on differing judgments with respect to alternative proposals that are accepted as equal.

FDA has proposed an alternative definition of SADR that eliminates the phrase "a reasonable possibility." Specifically, the agency offered the following alternative definition for comment:

> *A noxious and unintended response to any dose of a drug product for which a relationship between the product and the response to the product cannot be ruled out.*

On its face, this definition may be preferable in that, by its own terms, it literally confines itself to those events that are considered a response to a drug product. However, in the agency's discussion of this alternative, it describes the meaning of the two definitions as the same. To avoid confusion, therefore, it would be necessary for FDA to define "response to a drug product" as meaning that the relationship cannot be ruled out. This, then, would offer no advantage over the other definition in terms of either its potential for confusion, its elimination of clinical judgment in the reporting of events, and its precipitation of over-reporting.

Recommendation:

(a) Merck recommends that the FDA-proposed definition and interpretation be revised for consistency with the ICH E2A Guideline for pre- and post-marketing situations.

(b) Merck recommends that FDA further harmonize with international initiatives by adopting the CIOMS VI and EU Clinical Trials Directive recommendations regarding reports to investigators. Specifically, submission of periodic line listings to investigators during Phases I through III, which are accompanied by a summary of the evolving safety profile, instead of individual expedited reports.

2. Full data set for post-marketing serious SADRs [Proposed 310.305(a), 314.80(a), 600.80(a); Preamble, Section III.A.5.]

Although the definition of "full data set" would only require "completion of all *applicable* elements" on the various forms, it is predictable that there will be disagreement over what is or is not applicable and, therefore, sponsors are likely to err on the side of completing all elements to avoid being cited by the agency for incomplete reports. Completion of all elements on Form 3500A, VAERS, CIOMS is an administrative exercise and may not be necessary to provide the information needed to evaluate the report. For example, at a recent meeting[2] concerning ICH E2B/M2 transfer of reports from industry to FDA, a review of manufacturer, consumer, and health care provider "serious AE reports" for a selected vaccine indicated that 90-100% of the reports

[2] E*Prompt meeting April 2, 2003, Washington, DC.

consistently excluded up to six fields on the VAERS form, none of which were identified as "key fields" (i.e., items 15, 16, 18, 20, 23 - vaccine administrative information).

Recommendation: Merck recommends an identification of the critical data elements or key fields which constitute a "full data set" for an individual case safety report. Identification of key fields alleviates the problem of changing the definition of a "full data set" depending on the form or method of transmission used by the sponsor. [Note: The key fields for reporting are boxed on the VAERS form already]. A good concise clinical narrative coupled with the requisite key fields would provide value to Agency evaluators without expenditure of an inordinate amount of resources to obtain data that may, in many instances, be irrelevant to evaluating the SADR.

3. The requirement for "active query" [Proposed 310.305(a), 314.80(a), 600.80(a); Preamble Section III.A.6.]

Merck supports the Agency objective to obtain complete, accurate, timely information on serious SADRs, always expedited reports, and medication errors. We support a focused line of questioning and the use of specific questionnaires to obtain relevant clinical information to evaluate a spontaneous report. We do not support *mandated*, direct verbal contact with the reporter to obtain follow-up information as essential to effective data collection for every "serious" report, as defined in safety reporting regulations. There must be flexibility in the data collection process given the time constraints on practicing physicians. Furthermore, internationally, the process of obtaining follow up data must follow local requirements, which may preclude direct contact with the health care provider by the pharmaceutical company. Direct contact with the original reporter by telephone or "other interactive means such as video conference" as a *mandate* for obtaining follow-up information will likely overburden already overworked health care providers, compromise complete and accurate reporting, and actually serve as a deterrent for future adverse experience reporting to the company or to the Agency.

Recommendation: Merck strongly recommends against imposing a regulatory mandate on the manner in which follow-up information must be obtained. This appears to be precisely the kind of requirement FDA seeks to eliminate - one for which an applicant can be cited for being out of compliance, not because the applicant provided insufficient information, but because the information was not obtained in the prescribed way. It should be sufficient for FDA to define the information necessary to complete a full data set and to stipulate the time frames for reporting without mandating the use of active query as an essential tool for obtaining that information. We believe the effect this mandate will eventually have on spontaneous reporting should not be underestimated.

Manufacturer should exercise diligence and judgment in attempting to obtain complete data.

4. The definition of medication error and the proposal for handling potential errors [Proposed 21 CFR 310.305(a), 314.80(a), 600.80(a); Preamble section III.A.8.]

The proposed rule would incorporate the following definitions into the safety reporting regulations:

> *Medication error: "Any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: Prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use."*
>
> *Actual medication error: "...a medication error that involves an identifiable patient whether the error was prevented prior to administration of the product or, if the product was administered, whether the error results in a serious SADR, non-serious SADR, or no SADR;"*
>
> *Potential medication error: "...an individual case safety report of information or complaint about product name, labeling, or packaging similarities that does not involve a patient."*

If finalized, the rule would require an expedited 15 day report of all actual and potential medication errors, active query to obtain additional information, and 30-day follow-up reports under certain circumstances.

While Merck supports the reporting of complete information on medication errors, we disagree with defining as "potential medication errors" reports about product names and labeling or packaging similarities in the absence of an event or identifiable patient. We also disagree with requiring expedited reports for the category of "potential errors" as they are defined in the proposed rule. Under the proposal, potential errors would trigger active query and follow-up reports -- the same level of reporting and follow-up as required for serious and unexpected adverse reactions.

Companies currently put forth a significant amount of time and effort in the selection of a trademark for a product. The goal of this process is to select a unique global trademark that is acceptable for the product, is not misleading or confusingly similar to another trademark, and can be safely used by healthcare professionals and patients around the world. This process is briefly summarized as follows:

- Hundreds of names are generated for consideration before the list is reduced to a manageable number of candidates,
- Search results are subjected to legal review to evaluate the trademark candidates for the likelihood of confusion (e.g., degree of similarity in appearance, pronunciation, connotation, goods, and channels of trade),

- Candidates are reviewed by independent practicing pharmacists and other practicing health care providers to screen for medication error potential, not only by appearance and sound but also appearance of a handwritten prescription or hospital order. The dosage form, strength(s), regimen, and route of administration are also considered.
- In the U.S., upon selection of a trademark, an application is filed with the U.S. Patent and Trademark Office (PTO). The PTO conducts its own independent search for potential confusion with other registered or pending trademarks. As part of the PTO approval process, the application is published to provide the public, including other companies, the opportunity to oppose an application if they believe they may be damaged by its approval.

Medical errors are a serious problem in any health care system. Medical errors include surgical errors, diagnostic errors, and a number of other unintended actions that result in patient harm or death. Medication errors relating to the misprescribing or misdispensing of medications are a subset of medical errors. Medication error or confusion can result from a combination of a number of different factors: illegible handwriting, poor auditory conditions when receiving verbal orders, incomplete prescribing information, distractions in the pharmacy, poor lighting, inadequate training of staff, over-worked personnel, and similarity in drug names.

Due to the multiplicity of factors that contribute to medication errors, there are errors that cannot be prevented by labeling or packaging because they result from practice and health care system conditions that are beyond the control of the pharmaceutical industry and the FDA. Given the various factors that may be involved in a medication error, there is clearly a need for a systems-based approach that engages other stakeholders in the health care system such as physicians, pharmacists, nurses, and third party payers to improve patient safety. State medical and pharmacy boards and national professional associations should be encouraged to establish minimum standards for prescription orders and dispensing. For example, the elimination of "take as directed" as allowable instructions to the patient on a legally acceptable prescription would provide the pharmacist or nurse with an important cue to the correct interpretation of a prescription order.

Given the extensive process undertaken by industry to select a unique trademark and the FDA's attention to avoidance of sound-alike and look-alike names, Merck believes that the potential for trademarks to contribute to medication errors has been significantly reduced. Therefore, the likelihood of any single speculative report being definitive of an unforeseen potential that a trademark may lead to confusion is extremely low. This is especially true for any marketed product for which millions of prescriptions have been written and dispensed without more than a handful of reports of confusion. Accordingly, we strongly urge the Agency to reconsider its proposal to require submission of "potential" medication errors in an expedited manner. Submission of 15-day reports regarding complaint or speculation of a possible medication error in the absence of objective evidence of an error (and a patient) is not justifiable as an effective use of

resources for either the company or the Agency and does not constitute an effective risk assessment strategy. The possibility also exists that this mechanism could be utilized by competitors to prompt the change of another company's trademark and thereby facilitate a competitive edge in the marketplace.

We believe that the broad scope of the definition of medication error, combined with the use of MedDRA terminology and the number of lower level terms (LLTs) that map to a preferred term (PT) of "medication error", will likely lead to the expedited submission of reports that may not have been intended by the Agency. Such events include LLTs of "drug maladministration", "expired drug used", "inappropriate dose of drug administered" (even if prescribed by physician), "inappropriate schedule of drug administration", and "inappropriate formulation of drug administered". The number and type of reporter terms that are mapped to an LLT of "drug maladministration" are extensive and include such things as: crushed tablets, split tablet in half/quarters/thirds, chewed tablet, improperly stored, accidental ingestion, accidentally sprayed in eye, dissolved tablet in water, IM instead of SQ injection, inadvertent needle stick, administered recalled lot, prescribed for off-label uses, among many others.

The proposed use of "active query" to obtain a minimum data set and/or full data set for all medication error reports, as outlined in the Proposed Rule, presents a significant concern. We believe this may actually have the unintended effect of reducing reporting of medication errors as well as SADRs in general by health care professionals. The intrusive nature of the active query proposal may discourage reporting of errors if the reporter of the error knows it will result in an "inquisition" and systems analysis by the pharmaceutical company and that the information ultimately becomes available to the public through Freedom of Information. In addition, the proposal does not differentiate between actual and potential medication errors in terms of active query and therefore implies that potential medication errors, which only need an identifiable reporter and a suspect drug or biologic, would be subject to the same follow up efforts (and/or 30-day reports of attempts made) in order to attain a "full data set", which by definition, doesn't exist.

Recommendation:

(a) Merck recommends that the proposed requirement for expedited submission of potential medication errors be reconsidered. Such reports are speculative and, taken individually, are uninterpretable. Furthermore, the cascade of active query, 15-day follow-up reports and 30-day reporting requirements that would be triggered under the proposed rule will deflect pharmacovigilance resources from productive activities simply to fulfill these requirements in the absence of any objective evidence of risk.

(b) Merck proposes that actual medication error reports be submitted in an expedited manner if a serious SADR is also reported. In the absence of a serious SADR (i.e., a non-serious SADR or no SADR, whether or not the drug was administered), we propose that these reports be described in the Periodic report. We believe that review of medication

error data as an aggregate will enable both the sponsor and Agency to better utilize resources and to conduct a more meaningful assessment of the risk involved.

Merck believes that many of the concerns outlined in the Proposed Rule will be substantially reduced with the implementation of the Agency's initiative regarding bar coding of labels, as evidenced by the statistics cited in the introduction to that Proposed Rule[3]. Similarly, the use of computer physician order entry (CPOE) systems, bar code readers at the point of care, and possibly automated dispensing systems would address other systems-based issues outside of the pharmaceutical industry's purview and has the potential to significantly minimize medication errors and improve patient safety.

5. The Post-marketing 30-day Follow-up Report requirement for initial serious and unexpected SADR reports, always expedited reports, and medication error reports that do not contain a full data set [Proposed 310.305(c)(2)(vi), 314.80(c)(2)(vi), 600.80(c)(2)(vi); Preamble Section III.D.6.]

Under the proposed rule, in addition to the currently required 15-day follow-up reports of new information and required retention of records of unsuccessful attempts to seek new information, FDA would require a 30-day followup report for initial serious and unexpected SADR reports, always expedited reports, and medication error reports that do not contain a full data set. Because FDA provided no explanation of the risk management benefits anticipated as a result of this new requirement, neither the problem it is intended to address nor the likelihood of its success are clear. A requirement for all sponsors to submit 30-day follow-up reports routinely that outline futile attempts to obtain information appears to be a poor use of pharmacovigilance resources for summarizing follow-up data collection activities, constructing chronological narratives, quality controlling paper or electronic follow-up reports, and transmitting this information to FDA each time the effort to obtain follow-up information is unsuccessful. This proposal creates another administrative requirement that adds nothing to management of risk but provides a mandate against which applicants can be cited for non-compliance.

Recommendation: We recommend that the current system requiring the maintenance of records of investigative attempts to obtain additional information on reported events and making those records available to FDA upon request be retained. The proposed 30-day reporting requirement should be dropped from the final rule. We believe the 30-day report will be resource intensive for industry to prepare and for FDA to process and review while achieving no clear additional safety objective. We believe this 30-day report requirement is counter to the stated FDA goals in revising its safety reporting regulations, namely, to reduce the unnecessary resource expenditure by industry not in pursuit of needed information. Furthermore, the benefits of waiting for 30 calendar days are not readily obvious from a process perspective and actually create counter processes for global organizations that must ensure 15 day follow-up submission for all other regulatory agencies worldwide.

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[3] *Federal Register*, Vol. 68, No. 50, March 14, 2003, p. 12502.

In addition, the proposed rule states that any new safety information in the 30-day follow-up report must be highlighted. Applicants updating information electronically in accordance with the intent and spirit of the ICH E2B standard will not be able to highlight the new information electronically. We recommend that FDA reconsider the requirement for highlighting new information and, instead, endeavor to tailor its reporting requirements to ICH E2B standards unless there is a compelling need to depart therefrom. We also believe that many of the concerns outlined in the Proposed Rule can be addressed as part of Agency inspections.

6. <u>Incidental Findings</u>

During the course of follow-up data collection for a spontaneously reported adverse experience, medical concepts beyond the reporter's original verbatim adverse experience term(s) are often introduced to describe the patient's clinical course. These concepts, which are not the focus of the reporter's reason for contacting the Company and for which no causal association with the use of the drug or vaccine is stated or implied, have been described in CIOMS V as "incidental findings".

CIOMS V defines incidental findings as follows:

*An **incidental** event, adverse or otherwise, is one that satisfies the following criteria: although it occurs in reasonable clinical temporal association with the use of a drug product, it is not the intended subject of a spontaneous report (i.e., it did not prompt the contact with the pharmaceutical company or the regulator) and there is no implicit or explicit expression of possible drug causality by the reporter, other parties cited in the medical record, or the company's safety review staff.*

Companies are increasingly being asked by FDA to code all clinical events, including incidental findings abstracted from medical records, discharge summaries, and other sources which occur at any point after introduction of the suspect drug/vaccine. This practice decreases the ability to identify the reporter's focus of the report to the Company and increases the "noise" in the spontaneous reporting system. Furthermore, the Company's practice of medical review of all serious adverse experience reports permits a clinical judgment of each such event for possible relationship to the suspect therapy. It is only after such review that a finding is designated as "incidental."

Recommendation: We recommend that the CIOMS V definition of incidental findings be incorporated into the new safety reporting rule. We propose to exclude coding unrelated "incidental" adverse experiences that are identified in response to a request for follow-up information from Section G(8) of Form 3500A and item 7 of VAERS and CIOMS forms. We propose a description of the incidental findings in the narrative portion of the government forms, thus enabling an evaluation (Company or Agency) to discern the reporter's focus of the report versus incidental events. Recognizing that FDA believes that all events occurring after introduction of the suspect drug should be coded,

even if the reporter mentions them incidentally, we alternatively recommend that, with the adoption of ICH E2B/M2 standards for electronic reporting of individual case safety reports, FDA strongly consider use of the ICH E2B field B.2.i.3, "Term highlighted by the reporter." Adoption of this field would allow differentiation between the adverse reactions/events explicitly provided by the reporter versus incidental findings abstracted from follow-up information obtained by sponsors as part of efforts to obtain quality data.

7. The requirement for appendices to the ICH standard PSUR [Proposed 314.80(c)(3)(ii)(K), 600.80(c)(3)(ii)(K); Preamble section III.E.2.k]

Although we recognize that additional data may be requested by a regulator under the ICH E2C document, the objectives of the effort to harmonize will remain unrealized if all other regulatory agencies follow this example and impose their own set of requirements in addition to the core information described in ICH E2C.

Recommendation: Careful consideration should be given to imposing additional, country specific, reporting requirements beyond the ICH E2C recommendations which the FDA took part in formulating. Such additional requirements should only be imposed where the information is deemed to be truly important to continued, effective risk management.

Specific Comments

1. **Disclaimers [Proposed 310.305(h), 312.32(e), 314.80(i), 600.80(j); Preamble Section III.A.1.]**

The current safety reporting regulations state that a safety report or other information submitted to FDA by a manufacturer does not necessarily reflect a conclusion by the manufacturer or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse experience. In the proposed rule, FDA specifically sought comments on whether these "disclaimers" are sufficient to protect manufacturers, applicants and sponsors from the use of SADR reports in product liability actions. Merck believes that the current disclaimers are not sufficient protection in product liability litigation. Despite these disclaimers, some courts have allowed the use of SADR reports as part of the plaintiff's evidence to prove causation. In addition, even if the reports are not ultimately admitted into evidence, manufacturers must still spend significant sums of money producing SADR reports in product liability litigation (including, in some cases, downloading the company's entire adverse event database for specified products) and deposing and challenging experts who base their causation or other opinions on SADR reports.

Recommendation: Merck believes that FDA should adopt a stronger position in the new rule in order to prohibit the misuse of SADR reports in product liability actions. Merck would recommend that FDA clearly state that SADR reports are not admissible in any court of law for any reason. Such a rule would ensure that SADRs are not admissible to

prove causation and, further, would provide a disincentive for plaintiffs to request, and for manufacturers to produce, large numbers of SADR reports in product liability litigation.

2. SADR with Unknown Outcome [Proposed 310.305(a), 314.80(a), 600.80(a); Preamble Section III. A.3, C.5, E.4]

As described in the proposed rule, "outcome" refers to a determination of whether an event is serious or non-serious and sponsors must make such a determination within 45 days. A "serious SADR" is defined as *"any SADR that results in any of the following outcomes: Death, a life-threatening SADR, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious SADR when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition."*

In general, to satisfy current reporting requirements, if either the initial report or follow-up indicate that the patient did not seek medical care as a consequence of a reported event, the event is considered to be a non-serious event. The above definition, with its emphasis on "appropriate medical judgment," implies that events that did not result in consultation with a medical professional would continue to be appropriately categorized as non-serious.

Recommendation: Use of the term "outcome" to simply refer to the determination of whether an event is serious or not is confusing. "Outcome" has generally referred to patient outcome - that is, what happened to the patient. We recommend that the agency consider an alternative term such as "classification," "categorization," or "characterization" of the reported adverse event. We also think that discussion of criteria for characterizing events as non-serious in the absence of evidence of serious criteria (per regulatory definition) and of medical care would be helpful.

3. Spontaneous Report [Proposed 310.305(a), 314.80(a), and 600.80(a); Preamble Section III. A.7]

We believe that the definition of *spontaneous report* in the proposed rule, by excluding cases identified from pregnancy registries, will create inconsistency in the reporting of events related to exposures during pregnancy. The result is likely to be a reduction in both the number of 15-day reports and in the total number of reports submitted to the agency.

The proposed rule defines a *"spontaneous report"* as:

> *Spontaneous report means communication from an individual (e.g., health care professional, consumer) to a company or regulatory authority that describes an SADR or medication error.* ***It does not include cases identified from information solicited by the manufacturer or contractor****, such as individual case safety reports or findings derived from a study, company-sponsored patient support program, disease management program, patient registry, including* ***pregnancy registries****, or any organized data collection scheme. It also does not include information compiled in support of class action lawsuits (emphasis added).*

According to the preamble to the proposed rule (68 FR 12421), cases identified from information "solicited by companies," including pregnancy registries, would be handled according to the safety reporting requirements for a study.

This provision will create confusion and fragment the reporting of events related to exposure during pregnancy for a number of reasons.

1. The term *"pregnancy registry"* is undefined and, in current use, is loosely applied to any number of programs of varying levels of intensity and formality. At Merck, for example, we have voluntarily established pregnancy registries for several products. The labeling of these products includes a notice that Merck maintains a "registry to monitor the pregnancy outcomes of women exposed to..." the product while pregnant. A toll-free telephone number is provided to *encourage* healthcare providers to report prenatal exposure to these products via this mechanism. Experience has shown, however, that most contacts with the company are spontaneous requests for information related to the use of these products during pregnancy. Only a fraction of the contacts come to us via the designated toll-free number. Nonetheless, all reports of exposure are designated for follow-up. If efforts to obtain follow-up information following such initial contact constitute "information solicited by the manufacturer," and, therefore, disqualify these reports as "spontaneous reports," the only reports that would qualify as *spontaneous* under the definition are reports that provide complete information at the time of initial contact. If only reports received on the toll-free number constitute "solicited" reports, a dual reporting mechanism would be required to differentiate reports that are qualitatively identical.

2. Unless the definition is revised, reports of pregnancy exposure to some products would be handled as spontaneous reports while qualitatively identical reports on other products would be reported according to the requirements for a study. While Merck has established voluntary "registries" for certain products, we routinely follow-up reports of exposure during pregnancy on all of our products. Under FDA's proposed definition of *"spontaneous report,"* different reporting requirements would apply in the event of exposure to products for which specific registries have not been established. In addition, the same report may have to be changed from a study report to a spontaneous report if a patient declined to be

enrolled in the registry, or from a spontaneous report to a study report if new information was received which met enrollment criteria.

The pregnancy registries that have been voluntarily established at Merck and, we believe, are most commonly instituted by industry, are enhanced "surveillance programs" intended to provide both information from, and, ultimately, added protection to, a special population that is unlikely to have been exposed to products during clinical development. They are designed to collect and evaluate more formally data that originate as spontaneous reports. Most such programs do not remotely approach the level of "solicited information" or "organized data collection schemes" common to clinical studies, yet they can provide valuable information on rare adverse experiences and clarify the safety profile of marketed products. Requiring a different safety reporting mechanism for information gathered through such simple registry programs will add an additional and unnecessary resource cost that will discourage such efforts. More importantly, it seems likely to reduce rather than enhance the reporting of such information to the Agency.

Recommendation: The definition of *"spontaneous report"* should be revised to delete *"patient registry, including pregnancy registries"* as examples of the kinds of information not considered to be spontaneous reports. We believe that most such programs clearly do not constitute data collection that substantially differentiates them from spontaneous reports or that remotely resembles the level of data collection common to clinical studies. We recommend defining *"spontaneous report"* as:

> *Spontaneous report means communication from an individual (e.g., health care professional, consumer) to a company or regulatory authority that describes an SADR or medication error.* ***It does not include cases identified from information solicited by the manufacturer or contractor,*** *such as individual case safety reports or findings derived from a study, company-sponsored patient support program, disease management program, or any organized data collection scheme. It also does not include information compiled in support of class action lawsuits.*

4. Contractors, [Proposed 310.305(a), 314.80(a), 600.80(a), 310.305(c)(2)(xi)(A), 314.80(c)(2)(x)(A) and 600.80(c)(2)(x)(A); Preamble Section III. A.4, D.9]

The proposed rule states that *"Contractor means any person (e.g., manufacturer, joint manufacturer, packer, or distributor whether or not its name appears on the label of the product; licensee, contract research organization) that has entered into a contract with the applicant (includes participants involved in divided manufacturing) to manufacture, pack, sell, distribute, or develop the [drug or licensed biological product] or to maintain, create or submit records regarding SADRs or medication errors."* The proposed rule also indicates that contractors would be subject to complying with certain postmarketing safety reporting responsibilities. Specifically, under the proposed regulations, contractors would be required to submit safety reports of any SADRs or medication errors about the

applicant's product to the applicant within 5 calendar days of receipt of the report by the contractor.

In today's global marketplace, large companies who are the holders of approved new drug applications enter into contracts with business partners who market products and have regulatory reporting responsibilities stipulated in the contract. Generally, these contracts define specific time frames for exchange of serious and non-serious adverse event reports based on date first learned by the contractor (e.g., 5 to 8 calendar days for serious adverse experiences and 30 calendar days for non-serious AEs.

Recommendation:

(a) We recommend FDA adopt a flexible approach in its definition of contractor and in the timeframe stipulated for exchange of safety information. It should be recognized that in some cases it may be the contractor who is given reporting responsibilities. We recommend that the final rule clearly allows 5 calendar days to forward information to the party with reporting responsibility and that the party with reporting responsibility has 15 days to report to FDA. In addition, we recommend that a longer time frame for transmission of non-serious reports from the contractor to the applicant (e.g., 30 days) be permitted.

(b) We recommend that the definition of contractor be revised to specifically exclude healthcare organizations such as the Veterans Administration, Kaiser Permanente, and others, who enter into contractual arrangements with industry for formulary distribution purposes within their own healthcare systems.

(c) We recommend that any provisions regarding the exchange of adverse event information between contractors and applicants described in the final rule be applied prospectively.

5. Data Lock Point and International Birth Date [Proposed 314.80(a), 314.80(c), 600.80(a), 600.80(c); Preamble Section III.A.10]

We agree that a product's international birth date (IBD) determines all future data lock points for a drug or a biological product. As noted in ICH E2C, reporting harmonization is particularly important during the initial years of marketing.

Recommendation: We propose that FDA harmonize its postmarketing periodic safety reporting regulations with the recommendations in the Addendum to ICH E2C guidance which was recommended for adoption at step 4 of the ICH process on February 6, 2003 by the ICH Steering Committee. Specifically, the recommendations for the acceptance of supplemental line listings/summary tabulations, addendum reports, and summary bridging reports would provide the increased flexibility required to achieve worldwide harmonization of the data lock point and reporting frequency.

6. Determination of Outcome, Minimum Data Set and Full Data Set [Preamble Section III.C.5.]

Minimum Data Set [Proposed 310.305(a) and (c), 314.80(a) and (c), and 600.80(a) and (c)]

Merck commends FDA's efforts to distinguish, in the Post Marketing Regulations, adverse events that have less medical significance from those that have more medical significance by identifying the concept of required minimum data set and full data set. FDA defines minimum data set as "identifiable patient, identifiable reporter, suspect drug or biologic product and an SADR" and in the case of medication errors, "minimum information" may or may not include a patient or an SADR.

Merck agrees with FDA's proposal only to require manufacturers to obtain a minimum data set for non-serious SADRs and to further require that that all safety information that has been received by the manufacturer for these reports be submitted to FDA. This will allow manufacturers, in their efforts to enhance the quality of reports, to refocus and dedicate resources to obtain follow up for the more medically important SADRs.

Recommendation: We recommend including further information in the rule to clarify the kind and amount of information needed to meet the criteria for an "identifiable patient". For example, reference to "a patient," or to age, gender, date of birth, initials, or a patient identity number all individually constitute patient identifiers of varying specificity. Whether each of these alone would be sufficient under the proposed regulation to constitute an "identifiable patient" is not clear.

Full Data Set for Serious SADRs, Always Expedited Reports and Medication Errors [Proposed 310.305(c)(1)(iv), 314.80(c)(1)(iv), and 600.80(c)(1)(iv); 310.305(c)(2)(vi), 314.80(c)(2)(vi), and 600.80(c)(2)(vi)]

The proposed rule would require applicants to obtain a full data set using active query[4] and would require applicants to submit follow-up reports within 15 and 30 calendar days after the initial submission of the expedited report. If a full data set is still not obtainable, the 30-day follow-up report must contain the safety information obtained, the reasons for the inability to get a full data set, and a description of the unsuccessful steps taken to obtain the information (see General Comment #3 above).

Recommendation: We agree that, in the case of incomplete information in initial reports that qualify for expedited submission, a requirement for follow-up efforts to obtain additional information to complete the full data set is both reasonable and necessary. We recommend, however, that FDA allow applicants flexibility in choosing the most effective follow-up methodology on a case by case basis.

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[4] Active query is defined as direct verbal contact with the initial reporter of an SADR or a medication error by a health care professional representing the manufacturer.

In addition, there appears to be no risk-management benefit to the proposed requirement for routine 30-day follow-up reports for every applicant and every product for which efforts to obtain a full data set were unsuccessful. This, instead, appears to be a policing activity. Unless a clear public health benefit to this resource intensive requirement can be articulated, we recommend that instead of imposing a universal reporting requirement, FDA should revise its thinking and simply require companies to maintain records of their efforts to obtain a full data set. Such records would be made available to FDA upon request in the same manner that "waived" non-serious, expected AE reports are currently handled. This would provide FDA with a cost-effective enforcement tool that could be targeted to specific situations in which FDA suspects non-compliance with follow up reporting requirements instead of imposing a costly and unnecessary universal requirement on the entire industry.

7. Failure of expected pharmacologic action [Proposed 310.305(c), 314.80(c), 600.80(c); Preamble Section III.C.7, E.1.C., E.2.H., E.2.K.vi]

FDA's proposed definition of SADR no longer will include "any failure of expected pharmacologic action" and consequently the proposed regulation will not require that all reports of lack of efficacy be submitted to FDA as individual case reports. Instead, under the proposed regulations, lack of efficacy reports on products used in treating a life-threatening or serious disease must be expedited when they contain information that is identified by the manufacturer as sufficient to consider a product administration change. In addition, however, post-marketing periodic safety reports for all products (not just those for serious or life-threatening diseases) would be required under this proposal to include a discussion of "an assessment of whether it is believed that the frequency of lack of efficacy reports...is greater than would be predicted by the premarketing clinical trials for the drug product" [see Traditional Periodic Safety Reports (TPSRs) at 314.80(c)(3)(i)(A)(3) and 600.80(c)(3)(i)(A)(3) and Appendices to Periodic Safety Update Reports (PSURs) at 314.80(c)(3)(ii)(K)(6) and 600.80(c)(3)(ii)(K)(6)].

Recommendation: Merck believes that ICH E2C sufficiently covers the handling of medically relevant reports of lack of efficacy[5]. Clinically, "lack of expected drug effect" reports cannot be interpreted unless there is a specific marker for the response such as altered antibiotic sensitivity testing (e.g., strains of *E. coli* have been reported which no longer show sensitivity to XYZ-mycin). The risk management value of analysis in attempting to compare the incidence of lack of efficacy from post-marketing reports with pre-marketing clinical trial data to provide the proposed assessment is questionable. It is generally recognized that spontaneous report data are unsuitable for determining incidence rates because of both the lack of a denominator and the fact that reporting rates cannot be assumed to reflect incidence rates of the underlying events. Therefore, we recommend that this provision be deleted from the TPSR and PSUR requirements.

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[5] See ICH E2C, Section 2.8.1 "Efficacy-Related Information: For a product used to treat serious or life threatening diseases, medically relevant lack of efficacy reporting, which might represent a significant hazard to the treated population, should be described and explained."

8. Information Sufficient to Consider Product Administration Changes [Proposed 310.305(c)(2)(ii), 314.80(c)(2)(ii) and 600.80(c)(2)(ii); Preamble Section III.D.2.]

Merck's current practice is to review and conduct an ongoing assessment of all available safety information received from both foreign and domestic sources during our label review process. Any unanticipated safety finding from any source is considered and should information warrant a product administration change, this information would be submitted to FDA as a supplemental application for revision of the labeling, along with supporting documentation.

The proposed rule would require information sufficient to consider product administration changes that is received post-marketing to be submitted to FDA as an expedited report "as soon as possible, but in no case later than 15 calendar days after determination by the manufacturer that the information qualifies for expedited reporting." In the preamble to the proposed rule, the Agency notes that "this proposed requirement is consistent with the proposed revisions to the premarketing expedited safety reporting regulations at proposed section 312.32(c)(1)(ii)." Such information would include "...any significant unanticipated safety finding or data in the aggregate from an *in vitro*, animal, epidemiological, or clinical study...that suggests a significant human risk, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of a lack of efficacy with a drug product used in treating a life-threatening or serious disease."

Recommendation: While there is clearly value in reviewing and submitting these data in the pre-market arena to FDA, regulators, investigators, and IRBs, the value added in submitting data in 15 calendar days from the post market arena is not readily apparent. When data are determined to be sufficient to consider product administration changes Merck promptly submits a supplement containing the supporting information to FDA for label revision. Submitting those same data as an expedited report, post-marketing, would prove to be a redundant activity for industry and we urge FDA to reconsider this proposal in the post marketing regulations.

9. Unexpected SADRs with Unknown Outcome [Proposed 310.305(c)(2)(iii), 314.80(c)(2)(iii), and 600.80(c)(2)(iii); Preamble Section III.D.3.]

Under the proposed rule, unexpected SADRs for which sufficient information to determine whether the event is serious or non-serious has not been obtained must be reported as an "expedited report" within 45 calendar days after initial receipt of the minimum data set (identifiable patient, identifiable reporter, suspect drug, and an SADR).

The introduction of yet another reporting clock as proposed creates an additional tracking obligation for sponsors. In order to assure that unexpected SADRs with unknown outcome are reported within 45 days of the receipt of a minimum data set, current electronic tracking systems throughout the industry will have to be redesigned to accommodate this requirement. The result will be a significant initial resource cost to

industry merely to satisfy a newly imposed U.S. clock since the rest of the world does not operate on this time frame. The necessity of this requirement is particularly questionable given the fact that the reports to be submitted are, by definition, events for which insufficient information is available to allow meaningful evaluation.

In general, obtaining sufficient additional information to classify adverse events reported by health care providers as serious or non-serious can be accomplished through follow-up efforts. Obtaining additional clear and relevant information on reports from other sources, particularly reports initially submitted by consumers, is far more difficult. Accordingly, in following up consumer reported events we always ask whether the patient sought medical attention as a result of the event. We classify as non-serious those events for which medical attention was not sought by the patient.

Recommendation:

(a) Safety surveillance is a global activity and requires sensitivity to harmonization unless there is a clear and compelling reason for unique requirements. In the absence of worldwide consensus for a 45-calendar day reporting timeframe, we recommend against introducing this artificial requirement and focusing the resources on follow-up activity from healthcare providers.

(b) For consumer-reported events, we recommend that information confirming that the patient did not seek medical attention as a result of the event be considered sufficient to characterize the event as non-serious. We believe this is in keeping with the definition of "serious SADR" within the proposed rule which, in addition to death and life-threatening events, includes "important medical events" that "based upon appropriate medical judgment may jeopardize the patient or subject and may require medical or surgical intervention...."

10. Always Expedited Reports [Proposed 310.305(c)(2)(iv), 314.80(c)(2)(iv), and 600(80(c)(2)(iv); Preamble Section III.D.4.]

We note that item 19 on the "always expedited" list describes events that fulfill the ICH E2A definition of "serious" ("any other medically significant SADR that FDA determines to be the subject of an expedited report (i.e., may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject)").

The similarity of language between the ICH E2A definition of other medical events (OMEs) that should be considered serious and the explanation of other medically significant SADRs that FDA determines to be the subject of an expedited report creates the implication that any event that meets the ICH E2A definition qualifies for "always expedited reporting."

Recommendation:

(a) We believe that FDA should provide the corresponding MedDRA Preferred Terms for the list of always expedited terms. As currently written, it is not clear what level of specificity the "always expedited" terms list encompasses.

(b) We disagree with adding new SADRs to the always expedited reports list through the agency's current guidance for industry on post-marketing safety reporting for human drugs and biological products. It is illogical for certain SADRs to be subject to regulation and others subject to FDA guidance which, by definition, is not binding on either the Agency or the public.

11. Supporting Documentation [Proposed 310.305(c)(2)(viii)(A), 314.80(c)(2)(viii)(A), and 600.80(c)(2)(viii)(A); Preamble Section III. D.7]

The proposed regulations would require, in the case of a death, that the applicant submit to FDA a copy of the autopsy report or, if an autopsy report is not available, a copy of the death certificate. Active query would be required to obtain these documents and the documents would be required to be submitted as a 15-day follow-up report. The proposed regulation also requires that if these documents are not in English, the document must be accompanied by an English translation.

We believe that, in the event of a death in a hospital, it is reasonable to attempt to obtain an autopsy report or death certificate. However, in many states, manufacturers would need to obtain death certificates from a relative of the deceased since vital records are not public documents. This proposed requirement for a death certificate presents challenges particularly when communicating with a non- healthcare professional on such a sensitive issue as death.

In addition, the benefit of the requirement for these documents to be routinely submitted to the FDA is unclear other than to validate the accuracy of the applicant's report of the event. If this is the objective, it could be achieved by requesting that such information be submitted at FDA's request on a case by case basis.

Standard "good pharmacovigilance practices" entail the collection of a hospital discharge summary and the death certificate/autopsy report as appropriate. Merck subsidiaries translate all follow-up information into English locally and provide the information in English to the US either electronically or via a data collection form. Merck questions the value of obtaining a line-by-line translation for these documents, the contents of which already have been translated by the designated pharmacovigilance person prior to entry into the database. Line-by-line translation, if required, presents a dilemma to the applicant in meeting proposed time-frames since line-by-line translations for many languages by outside translation services often take up to three months.

Additionally, in mandating the collection and submission of these documents, FDA needs to appreciate the fact that in many countries, such documents are not always easily obtained and there are often local procedures and/or legal requirements in place,

particularly with regard to patient privacy, that limit their availability to industry. In many third world countries, poor health care system standards make it impossible to obtain supporting documentation such as autopsy reports. Also, in some countries, post-mortem examinations may not be done at all for religious reasons.

Recommendation:

(a) Mandating manufacturers to provide a death certificate if an autopsy report is not available for all reports of death should be reconsidered. Instead, we recommend that applicants should be required to seek an autopsy report or death certificate when the report appears to be a pharmacovigilance signal. Such reports, when obtained, should be reviewed by the company and maintained on file to be provided to FDA upon request. There is little justification in terms of public health or risk assessment benefit in routinely obtaining and providing death certificates for all reports of death.

(b) Merck recommends that the requirement for submission of line-by-line translations of hospital discharge records or autopsy/death certificates from foreign sources be omitted. We recommend that translations of these documents should be made available only upon request in those instances where a signal has been generated and the need for precise understanding of the medical data by all evaluators worldwide is critical to developing a risk management plan.

(c) The requirement for companies to provide in the expedited report narrative a list of all other relevant documents maintained by the applicant should be reconsidered in view of ICH E2B/M2. Since the ICH E2B/M2 specifications have fields which capture the specific types of source documents available, Merck recommends the Agency waive this requirement for companies transmitting expedited reports electronically to FDA.

12. Scientific Literature [Proposed 314.80(c)(2)(ix) and 600.80(c)(2)(ix); Preamble Section III.D.8.)

The proposed changes to the regulations remove the previous limitation that restricted 15-day reporting based on scientific literature to reports found in scientific and medical journals "either as case reports or as the result of a formal clinical trial." The explanation in the preamble to the proposed rule (68 FR 12434) states that, "all reports from the scientific literature including case reports, and results of a formal clinical trial, epidemiological study, in vitro study, or animal study, that qualify for expedited report" would be required for submission to FDA. Reference is also made to the statement that expedited reports must be accompanied by a copy of the published article.

Recommendation: Presumably by removing the phrase "either as case reports or as the result of a formal clinical trial" and stating "all reports from the literature, including...", the proposed revision would include review articles in the scientific or medical literature. We recommend further revision to specifically exclude review articles and epidemiological studies. Review articles and epidemiology studies are likely to provide

information that is less than a minimum data set (i.e., lack identifiable patients) and, depending on the case, may trigger active follow-up. In addition, it is likely that in many instances the events summarized in the review article will have already been reported via other mechanisms.

13. Electronic Communications with Applicants via the Internet [Proposed 310.305(b)(1), 314.80(b)(1) and 600.80 (b)(1); Preamble Section III.C.1., III.C.2.)

The proposed handling of Internet information is particularly troublesome in its implication. By restricting this as a source to sites sponsored by the company, some control is put on the process. However, making the company responsible for information on an Internet site that it does not sponsor is not reasonable. Information on non-sponsored sites is generally non-verifiable, not from a health care provider, and leaves the company open to tracking chat-rooms when one site refers to a second, third or fourth site. Moreover, usually neither the patient nor the reporter are identifiable. The manpower involved in tracking down and data-entering such reports is considerable and minimum data set information is unlikely to be available.

Recommendation: Information to be reported from Internet sources should be restricted to that from company-sponsored sites and include only reports where specific information permitting identification and verification of the reporter source is provided.

14. Contact Person for PSUR [Preamble Section III.E.1.h., III.E.2.K.xi.]

Merck understands the importance of medical review and evaluation of information contained in a Periodic Safety Report. Merck supports the concept that physicians be responsible for the ongoing review and evaluation of the safety profile of a marketed drug or biological product. However, Merck understands from several public meetings that FDA's position is that the contact person must be a physician with a license which is in active status. Most companies today are global and, as such, have physicians working in pharmacovigilance with medical licenses from other countries worldwide. Completion of medical training, as evidenced by a medical degree from an accredited university, not licensure to practice, is the relevant qualification for evaluation of safety reports. In addition from a practical standpoint, most physicians in industry are no longer "practicing", i.e., seeing patients, and, therefore, their licenses are routinely moved to "inactive" status.

Recommendation: Merck recommends that the Agency adopt a flexible position on the definition of the medical reviewer of an aggregate periodic report that would include physicians without regard to present licensure status, either in the U.S. or any other country.

15. Changes to CCSI [Proposed 314.80(c)(3)(ii)(D); 314.80(c)(iii)(D), 600.80(c)(3)(ii)(D) and 600.80(c)(iii)(D); Preamble Section III.E.2.d.]

Recommendation: Merck proposes that the recommendations in the Addendum to ICH E2C regarding the CCSI be incorporated into the final rule. Specifically, for 6-month and annual reports, the version of the CCSI in effect at the beginning of the period covered by the report should be used as the reference. For reports greater than 1 year duration, the version of the CCSI in effect at the end of the period covered by the report can be used as the reference. However, when listedness is assessed at the time of PSUR preparation after the data lock point, the current version of the CCSI can be used.

16. Worldwide Patient Exposure [Proposed 314.80(c)(3)(ii)(E); 314.80(c)(iii)(E), 600.80(c)(3)(ii)(E) and 600.80(c)(iii)(E); Preamble Section III.E.2.e.]

The Proposed Rule suggests that patient exposure information, when possible, should be broken down by gender and age (especially pediatric versus adult). Data for the pediatric population would be reported by age groups (if possible). If such data are not available, "an explanation for the lack of such information would be included".

Recommendation: Given the lack of readily available data, we recommend revision of the proposed rule to require only additional data analyses concerning patient exposure in the presence of a safety signal specific to a special population. If a signal is detected, then additional workup, including details by country or other segmentation are appropriate.

17. Semi-annual Submissions [Proposed 314.80(c)(3)(v) and 600.80(c)(3)(v); Preamble Section III.E.2.f.i., III.E.4]

Current postmarketing reporting regulations require applicants to submit to FDA all domestic adverse experience reports that have not been submitted as expedited reports. This includes all serious, expected events and all non-serious events whether expected or unexpected.

The proposed rule would revise the regulations to require semi-annual submissions that would include, in addition to the currently required domestic reports, serious, expected/listed SADRs from foreign sources. In the preamble to the proposed rule FDA states only that its proposal to require submission of serious expected/listed SADRs from foreign sources would provide the agency with "important information that the agency does not currently receive (e.g., reports from foreign countries in which the product is approved for more indications than in the United States or the product results in exposure to certain populations that are limited in the United States.)".

The requirement for submitting serious expected reports from foreign sources was deleted from the U.S. regulations in 1985 in the NDA re-write. We estimate that we would be required to submit approximately 800 non-U.S. serious, expected reports every 6 months if this rule goes into effect.

Companies are receiving and analyzing these reports currently, although the individual case safety reports are not submitted to the FDA. When a signal is detected, it is followed

up and submitted to the Agency in detail in the context of a labeling change. The routine inclusion of all such individual reports in semi-annual submissions is inconsistent with both the general recommendation in the ICH E2C Addendum[6] regarding individual case reports and the goal of minimizing duplication of effort to satisfy differing national regulatory requirements.

Recommendation: In the absence of a signal, the individual case reports of serious, listed SADRs from foreign sources are of little value in monitoring public health risk. Line listings and tabulations of such events as outlined in ICH E2C and its addendum are sufficient for this purpose. Merck also recommends reconsideration of the need to provide semi-annual submissions for these data beyond the first five years of market approval.

18. Appendices [Proposed 314.80(c)(3)(ii)(K), 314.80(c)(3)(iii)(J), 600.80(c)(3)(ii)(K), and 600.80(c)(3)(iii)(J); Preamble Section III.E.2.k.]

(a) General Comment on Appendices

The proposed rule calls for the inclusion of 11 appendices. Most of the proposed appendices are not addressed in the ICH E2C tripartite guidance. The proposed requirement to include numerous appendices specifically for a single regulatory authority does not serve the intended objective of a harmonized PSUR within the ICH regions. Harmonization of PSUR format, content, and reporting frequency is essential to eliminate unnecessary reporting burdens on industry so that companies can focus on the safety profiles of their products and not on the different reporting requirements of different regions.

Recommendation: In view of the international effort to harmonize both the information requirements and the format for PSURs, the necessity for each of the 11 appendices to the PSUR for U.S. regulatory authorities to adequately monitor product safety needs to be carefully and individually evaluated and justified before being adopted in the final rule.

(b) Comments on specific appendices

i. Company Core Data Sheet (CCDS)

The proposed rule would require the inclusion of the CCDS that was in effect at the beginning of the period covered by the PSUR plus the CCDS for the next

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[6] ICH E2C Addendum, Section 2.6; Presentation of Individual Case Histories: "There is no specific guidance in E2C on the presentation of individual case report narratives. As it is impractical to present all case reports for the reporting period in this section of the PSUR, a brief description of the criteria used to select cases for presentation should be given."

reporting period. At the time of PSUR preparation and/or distribution the CCDS for the next reporting period may not be available. In fact, more than 1 CCDS may have been issued during a PSUR reporting period.

Recommendation: The proposed requirement to attach the CCDS for the next reporting period should be deleted. We encourage adoption of the Addendum to ICH E2C which proposes that for 6-month and annual reports, the version of the CCDS in effect at the beginning of the period covered by the report should be used as the reference. For reports greater than 1 year duration, the version of the CCDS in effect at the end of the period covered by the report can be used as the reference. When listedness is assessed at the time of PSUR preparation, after the data lock point, the current version of the CCDS can be used.

ii. Spontaneous Reports Submitted to the Applicant by an Individual Other than a Health Care Professional

The proposed requirement to discuss the impact of spontaneous reports submitted to the applicant by a non-healthcare professional is not in accord with the ICH E2C guideline. The ICH E2C guidance states "medically unconfirmed reports should be submitted as addenda line listings and/or summary tabulations only when requested by regulatory authorities" and that "it is considered that such reports are not expected to be discussed within the PSUR itself". A requirement for the submission of unconfirmed reports is counter to the concept and spirit of the ICH E2C.

Recommendation: We agree with the philosophy expressed in the ICH E2C guidance and strongly recommend FDA to adhere to the ICH principles in finalizing the new safety reporting rule. Although ICH recommended submission of unconfirmed reports only upon the request of regulatory authorities, we don't believe that it intended such a request to become a permanent regulatory requirement applicable to all such reports on all products in any jurisdiction. The requirement for this appendix should be deleted.

iii. Class Action Lawsuits

We agree that individual case reports identified from class action lawsuits differ from true spontaneous reports and that information from such lawsuits should be presented in summary tabulations separate from the requirements for reporting of spontaneous reports. We believe, however, that this appendix should be expanded to include all multi-plaintiff litigation. The agency stated that its rationale for submitting information from class action lawsuits in summary tabulations is that it believes SADRs from class action lawsuits would be submitted to FDA from other sources (e.g., spontaneous reports) prior to the initiation of the class action lawsuits. This rationale applies equally to other multi-plaintiff litigation, even if that litigation does not get classified, for procedural reasons, as a class action.

Recommendation: Information from class action or other multi-plaintiff lawsuits should be provided in summary tabulations for all SADRs obtained or otherwise received during the reporting period by the applicant from class action or other multi-plaintiff lawsuits.

iv. Lack of Efficacy Reports

We agree with the intent of ICH E2C that evaluations of lack of efficacy reports should be focused on products used to treat serious or life-threatening diseases and medically relevant lack of efficacy reporting which might represent a significant hazard to the treated population. [See also item 7, page 19].

Recommendation: Information regarding lack of efficacy should be presented in section 2.8.1 (Efficacy-Related Information) of the PSUR. We recommend against requirement of a separate appendix for this purpose.

v. Information on Resistance to Antimicrobial Drug Products

Routine PSUR preparation and safety surveillance measures for antimicrobial products currently identify important new information on resistance to antimicrobial drug products. When identified, this information is presented within the PSUR (ICH E2C section 2.8.1 Efficacy-Related Information).

Recommendation: Preparation of this appendix is not warranted.

vi. U.S. Patient Exposure

This appendix would require an estimate of the U.S. patient exposure to the product covered by the PSUR. As a routine exercise for all products, regardless of the length of marketing experience or the presence of a safety signal, this effort appears to be without merit. The proposed regulation itself recognizes that measures of patient exposure are difficult if not impossible and may be meaningless[7]. No explanation of how FDA intends to use this "information" is provided in the proposed rule or the preamble to the proposed rule.

Recommendation: We recommend against requiring the routine submission of U.S. exposure information as described in the proposed rule. In the event of a safety signal that requires such estimates as part of a thorough risk assessment, patient exposure information should be requested on a case by case basis.

vii. Location of Safety Records

[7] See, for example, 68 FR 12483, proposed 314.81(c)(3)(iii)(K)(10); "If the patient exposure is impossible to estimate or is meaningless, an explanation of and justification for such conclusions must be provided."

The proposed regulation would require applicants to submit an appendix containing a list of the current addresses where all safety reports and other safety-related records for the products are maintained.

Recommendation: Specific FDA requests for additional information concerning safety issues should be directed to the designated contact person for pharmacovigilance activities whose job includes responding to such requests and who can provide the information to FDA in the most efficient and expedient manner. This appendix is unnecessary and may delay FDA's access to reports it needs in specific cases by inadvertently directing agency personnel to inappropriate sources of information.

viii. Contact person

Recommendation: The name of the contact person could be included in either a PSUR title page as described in the Addendum to ICH E2C or in the cover letter accompanying the PSUR. A separate appendix is unnecessary.

19. Interim Periodic Safety Reports [Proposed 314.80(c)(3)(iii) and 600.80(c)(3)(iii); Preamble Section III.E.3.]

FDA proposes a new type of report, the Interim Periodic Safety Report (IPSR), which is to be submitted 7.5 and 12.5 years following U.S. approval. The stated purpose of this report is to "provide the agency with an overview of the safety profile of a drug product containing a drug substance or biological product without requiring summary information on individual case safety reports". We disagree with the concept of and the need for IPSRs.

The proposal differs significantly from the intent of harmonized periodic safety update reporting in the ICH regions and places a significant and unnecessary burden on applicants. In the preamble to the proposed rule, FDA states that it is providing for the submission of TPSRs rather than PSURs for products approved prior to January 1, 1998, "because the agency recognizes that the most significant new safety information on a product is usually acquired in the first few years after it has been on the market". We agree with this assessment and, therefore, wonder why FDA deems it necessary to impose further reporting requirements this late in a product's life cycle.

Recommendation: Instead of the requirement for an IPSR for products approved in the U.S. after January 1, 1998, we propose that FDA harmonize its postmarketing periodic safety reporting regulations with the recommendations for summary bridging reports contained in the Addendum to ICH E2C guidance which was recommended for adoption at step 4 of the ICH process on February 6, 2003, by the ICH Steering Committee. Summary bridging reports provide an approach for satisfying longer reporting frequency requirements (i.e., 2.5 year) for applicants who prepare 6 month PSURs indefinitely.

Although we disagree with the concept of IPSRs, summary bridging reports provide a means of satisfying this requirement with a reduced impact on some applicants.

20. Reporting Requirements and Reporting Intervals [Proposed 314.80(c)(3)(i) and 314.80(c)(3)(ii); 600.80(c)(3)(i) and 600.80(c)(3)(ii); Preamble Section III.E.5]

We agree with the proposal to revise reporting requirements to be consistent with ICH E2C for the preparation of PSURs that are based upon data sets of 6 months or multiples thereof.

(a) For products approved in the U.S. before January 1, 1998, we agree with the reporting frequency of either a TPSUR or a PSUR every 5 years. Since some applicants may continue to prepare 6 month or annual PSURs for products approved before January 1, 1998, (because, for example, of long intervals between approvals in different regions), FDA should harmonize its postmarketing periodic safety reporting regulations with the recommendations for summary bridging reports contained in the Addendum to ICH E2C. Although, as stated above, we disagree with the concept of IPSRs in the proposed rule, summary bridging reports provide a means of satisfying this requirement with a reduced impact on applicants.

(b) For products approved in the U.S. after January 1, 1998, we agree with the proposed reporting frequency for PSURs during the first 5 years and the concept of 5 year reports thereafter. Once again, we propose that FDA harmonize its postmarketing periodic safety reporting regulations with the recommendations for summary bridging reports contained in the Addendum to ICH E2C Guidance.

(c) While we agree with the concept of an alternative reporting frequency if new safety concerns arise (e.g., approval of a new indication or dosage form for the product, approval for use of the product in a new population, new safety issues in individual case safety reports submitted to FDA for the product) we urge consideration of the proposal in the ICH E2C Guidance (Section 1.4.4.) that "the potential consequences on the safety profile raised by such new types and extent of population exposures should be discussed between regulatory authorities and MAH since they may influence the requirements for periodic reporting". We believe that a dialog between FDA and applicants is necessary prior to supplement approvals to ensure that the data support re-setting the reporting "clock" to 6 month or annual submissions. This philosophy is also reflected in the Addendum to ICH E2C Guidance (1.4.4.4.) which recommends that, with restarting the reporting clock, "the analyses in the PSUR should focus on the newly-indicated population by identifying and characterizing any differences from the established safety profile in the previously indicated populations".

Recommendation: We recommend FDA review of the ICH E2C Guidance and the Addendum to the ICH E2C Guidance to assure that the reporting interval requirements are consistent with the ICH recommendations.

21. Reporting Format for ICSRs [Proposed 314.80(c)(4) and 600.80(c)(4)]

The proposed regulation states that "Each completed FDA Form 3500A or CIOMS I form must include the name and telephone number (and fax number and e-mail address, if available) for the *licensed physician* responsible for the content...".

Recommendation: As noted in comment #14, page 24, Merck disagrees that the physicians involved in safety evaluation and reporting should be required to maintain active licenses to practice medicine. Accordingly, we recommend that 314.80(c)(4)(iv) and 600.80(c)(4)(iv) be revised to stipulate that the form must include "...the name and telephone number (and fax number and e-mail address, if available) for the *designated contact person for safety".*

22. Products with Approved Pediatric Use

The proposed rule would require applicants holding an approved pediatric use supplement to an approved application (i.e. a supplement for use of the human drug or biological product in the pediatric population) to re-set the reporting frequency "clock" for submission of PSURs and IPSRs with U.S. approval of the supplement.

Recommendation: We propose that FDA harmonize its postmarketing periodic safety reporting regulations with the recommendations in the Addendum to the ICH E2C guidance. Specifically, Section 1.4.4.4 of the Addendum recommends that for products in a long-term PSUR cycle, the return to 6-monthly or annual reporting could apply after important additions or changes in clinical use are first approved in an ICH region, such as a previously unapproved use in a special patient population, such as children. If the clock "restarts," the analyses in the PSUR should focus on the newly-indicated population by identifying and characterizing any differences from the established safety profile in the previously indicated populations.

23. Post-marketing Approved New Drug Application (NDA) and Biologics License Application (BLA) Annual Reports [Preamble Section III.J.]

Merck commends the Agency for proposing to eliminate areas of redundant safety reporting, i.e., revoking the requirement for safety-related information in post-marketing approved NDA and BLA annual reports and to remove the requirement to include the section on non-clinical laboratory studies in approved NDA annual reports.

24. Proposed Implementation Scheme

It is proposed that the final rule (excluding MedDRA implementation) would become effective 180 days after its date of publication in the *Federal Register.* We believe that 180 days is not a sufficient amount of time to implement the database changes that would be required to support the final rule.

If the proposed rule is adopted as currently drafted, it would require system modifications to identify a full data set, to track reporting for incomplete data sets and unknown outcome, to identify "always expedited" terms, to create a new environment for class action lawsuits, to flag actual and potential medication errors, to document active querying, to modify the tracking of periodic reports, and to develop new PSUR appendices.

We estimate that the changes noted above will require over 30 person-months of effort. This includes design, development, integration testing, user acceptance testing, and worldwide deployment. Because of the sequential nature of system development, additional resources will not necessarily shorten the development time, as the requirements have to be discussed before development starts, and development has to be completed before testing can begin. We believe it will take a minimum of three months to discuss the system design and write the required documentation, three months to program the system modifications and complete integration testing, and three months to conduct user acceptance testing and deploy the changes worldwide.

Recommendation: We recommend changing the proposed implementation scheme to make all proposals in the final rule effective one year after publication.

25. Time to Construct PSUR versus IPSR [Preamble Section V.D.1.b.vi.]

Based upon an internal review and analysis of PSUR preparation times, Merck estimates that the average times required to complete postmarketing periodic safety report submissions would be approximately 23 hours for submissions with no SADRs, 33 hours for submissions with a few episodes with SADRs (1 to 50), 57 hours for submissions with a moderate number of episodes with SADRs (51 to 250), and 104 hours for submissions with a large number of episodes with SADRs (> 250). The number of individual case reports can only be used as a general guide to generate estimates of PSUR preparation times since the times required to complete PSURs are also influenced by the complexity of the issues associated with a medicinal product, PSUR-specific regulatory authority requests, and the cumulative numbers of serious, unlisted SADR reports (ICH E2C section 1.4.2). Merck estimates that for companies who continually prepare 6-month PSURs the average times required to prepare summary bridging documents to satisfy the requirements for IPSRs would be 6 hours for a simple submission and 10 hours for a complex submission.

Recommendation: Based upon our experience, we believe that FDA's estimates for the average times required to prepare PSURs appear reasonable for those PSURs with either none or a few episodes with SADRs during an interval reporting period. In order to effectively manage those cases where the number of episodes that qualify for inclusion in a PSUR is extremely high, we recommend that FDA harmonize its postmarketing periodic safety reporting regulations with the recommendations in the Addendum to ICH E2C guidance that would permit a marketing authorization holder to make a special request to the Regulatory Authority for 30 additional calendar days to submit a PSUR

(Section 1.4.4.5). This would provide the increased flexibility required to prepare PSURs that satisfy the goals of summarizing interval safety data, conducting systematic analyses of safety data, and preparing overall safety evaluations that will serve to protect the public health. Although we object to the requirement for IPSRs, we do believe that FDA's estimates for the time required to prepare IPSRs will be reasonable assuming FDA harmonizes its postmarketing periodic safety reporting regulations with the recommendations for summary bridging reports contained in the Addendum to ICH E2C guidance. Summary bridging reports provide an approach for satisfying longer reporting frequency requirements (i.e., 2.5 year) for applicants who prepare short duration PSURs indefinitely.

26. Analysis of Impacts [Preamble Section V.]

FDA notes that, "Because the rule may impose a mandate on the private sector that will result in a 1-year expenditure of $110 million or more (the current inflation adjusted threshold), FDA has conducted a cost-benefit analysis according to the Unfunded Mandates Reform Act. The premise for FDA's analysis is that the submission of more complete safety information (68 FR 12449) and more timely safety assessments (68 FR 12451) would reduce the number and duration of hospitalizations due to SADRs. Based on a number of assumptions, the analysis concludes that "if the proposed rule reduced the incidence of SADR-related hospitalizations by 2 percent, these annual savings could be $368.5 million." FDA also concluded that a reduction of 0.85% would outweigh the annualized projected industry costs.

Irrespective of whether one agrees with the magnitude of FDA's projected costs and savings, the validity of the expectation that the proposed regulatory changes in adverse drug experience reporting is likely to have any effect on hospitalizations or extensions of hospitalizations related to the adverse effects of drugs should be explained. In general, the proposed rule alters the way post-marketing reports of SADRs are submitted to the Agency. Hospitalization or extension of hospital stay reasonably associated with administration of a drug product meets the definition of "serious" in current regulations. The proposed rule does not mandate a shorter time frame for reporting serious events to the FDA. Applicants would still be required to submit such reports as 15-day expedited reports. Under the current safety reporting rule, applicants are required to "promptly investigate all adverse drug experiences that are the subject of these postmarketing 15-day Alert reports" and to "submit followup reports within 15 calendar days of receipt of new information or as requested by FDA." The proposed rule would mandate *the way in which follow-up is conducted* (Active Query), would require submission of a 15 day follow-up report of any new information received "or otherwise obtained," and submission of an additional report within 30 calendar days of the initial report (whether or not additional information was obtained). Clearly, the proposed rule will not lead to more timely submission of serious reports, that is, reports of the kinds of experiences that result in hospitalization, and there is no reason to expect that "active query" will yield more complete information compared to the information obtained using the variety of information collection practices currently employed. Therefore, the premise upon which

the economic impact analysis is based appears to be flawed. If so, none of the savings projected by the Agency will be realized.

One further premise in the analysis of impacts is worthy of note. FDA states that "the full benefits of this proposed rule will accrue when international regulatory inconsistencies are addressed, safety reporting submission requirements are harmonized internationally, and electronic information exchange is uniform and compatible for the major participants involved in monitoring drug safety." The agency also notes, "...as the international community harmonizes, companies would achieve efficiencies..." (68 FR 12453), and "The agency contracted with the Eastern Research Group, Inc., (EFG), an economics consulting firm, to estimate the potential benefits that would accrue to drug and biologics companies in the long run, *as international harmonization efforts align and generate cost savings*." (Emphasis added) (68 FR 12449). As noted in a number of our preceding comments, many of the requirements in the proposed rule do not conform to the harmonization recommendations of the ICH. It appears, therefore, that the agency expects the international community to harmonize with FDA's requirements rather than drafting regulations that take advantage of all the harmonizing steps that have been agreed upon internationally.

Recommendation:

(a) Because the economic analysis depends so heavily on the assumption described above, its validity demands justification before the specific dollar costs and savings can be considered.

(b) Product safety is a global issue that requires international cooperation; therefore, we recommend against codifying differences from ICH recommendations into the final rule with the expectation that the international community will follow.

FDA's Specific Requests for Comments

In the preamble to the proposed rule, FDA specifically sought comment on the following issues.

68 *FR*, p. 12409 (col. 2): re: ICH E2C and ICH V1[8] draft guidance
FDA is interested in comment from the public on whether the agency should implement these recommendations (e.g., permit use of summary bridging reports, include an executive summary in PSURs, permit use of different versions of reference safety information within a reporting interval or use of the version in effect at the end of the reporting interval).

We propose that FDA harmonize its postmarketing periodic safety reporting regulations with the recommendations in the Addendum to ICH E2C guidance which was

[8] "ICH V1" was the former designation of the ICH E2C Addendum

recommended for adoption at step 4 of the ICH process on February 6, 2003 by the ICH Steering Committee. Specifically, the recommendations for the acceptance of supplemental line listings/summary tabulations, addendum reports, summary bridging reports, and special requests for 30 additional calendar days to submit a PSUR, would provide the increased flexibility required to meet FDA's expectations and to achieve worldwide harmonization for periodic safety update reporting.

68 *FR*, p. 12413 (col. 1): re: MedDRA
The agency invites comment on the unintended potential impact of this proposed rule on those parties not subject to FDA's safety reporting requirements [i.e., HCPs]. The agency also invites comment on the potential strategies and approaches for facilitating seamless cross-standard communications, such as mapping between alternative terminologies and MedDRA.

We do not believe the use of MedDRA will impose any additional burden on health care providers. We fully support FDA's choice of MedDRA for reporting of safety information by the industry when the new safety reporting rule is finalized.

68 *FR*, p. 12417 (col. 3): re: SADR
FDA seeks comment as to whether use of the proposed or alternative definition of SADR would lead to significant increases in reporting to the agency beyond what FDA has identified in the following paragraphs. FDA is particularly interested in learning of examples of events beyond those identified by the agency that are not currently reported to FDA but would be required to be reported under these definitions.

See our General Comment 1 (page 2).

68 *FR*, p. 12419 (col. 1): re: Disclaimers
FDA seeks comment as to whether these "disclaimers" are sufficient to protect manufacturers, applicants, and sponsors from the use of SADR reports in product liability actions. For instance, perhaps the agency should consider also prohibiting use of SADR reports the agency receives in product liability actions. Accordingly, FDA seeks comment on the need for any further action to promote submission of SADR reports to the agency and guard against their misuse, as well as FDA's legal authority to take any such action.

See our Specific Comment 1 (page 13).

68 *FR*, p. 12421 (col. 1): re: Follow Up Information
FDA seeks comment as to whether the agency should permit written requests for follow up information and, if so, in which situations should these requests be permitted.

As we noted in our general comments (see general comment #3, page 7), Merck supports the objective of obtaining complete, accurate, timely information on serious SADRs, always expedited reports, and medication errors. We do not support *mandated*, direct

verbal contact with the reporter to obtain follow-up information as the only means of data collection. We reiterate our firm recommendation against imposing a regulatory directive on the manner in which follow-up information must be obtained. It is sufficient for FDA to define the information necessary to complete a full data set and to stipulate the time frames for reporting. Mandating the manner in which such information must be obtained unreasonably limits options and will lead to unintended effects on spontaneous reporting that should not be underestimated.

68 *FR*, p. 12443 (col. 1): re: Changes to current reporting requirements for SADRs
FDA seeks comment on these proposed changes. [1) different reporting frequencies (i.e., semi-annually vs. quarterly or annually), 2) receipt of spontaneously reported serious, expected SADRs from foreign sources and 3) submission of nonserious, expected SADRs in a summary tabulation instead of as individual case safety reports for drugs and biological products that are not vaccines.]

In response to the second issue identified in this request for specific comment, we refer back to Section III.E.4 of the preamble to the proposed rule (page 12442). FDA comments in the above section that "the semi-annual submission from applicants that submit PSURs for a drug product containing a drug substance or licensed biological product would include an individual case safety report for each **serious, listed** SADR whether domestic or foreign ...". "The Agency's proposal to require submission of spontaneously reported serious expected/listed SADRs from foreign sources would provide FDA with important information that the Agency currently does not receive (e.g., reports from foreign countries in which the product is approved for more indications than in the United States or the product results in exposure to certain populations that are limited in the United States)".

In the absence of a safety signal and in the spirit of harmonization of the PSUR content, Merck believes that sufficient information is currently provided to the Agency in line listings and body system tabulations which include serious, listed reports from **all** sources, both foreign and domestic. Accepting the Agency's need to review individual case safety reports for serious, listed reports from foreign sources that would be summarized in a PSUR, Merck questions the selection criteria for these individual case safety reports as defined in the Preamble of the Proposed SADR Rule. Specifically, at the time of receipt of a serious adverse drug experience report, the sponsor assesses the reported adverse experience for expectedness/unexpectedness using the US package circular. Those foreign reports which contain serious, unexpected adverse experiences are sent to FDA as 15-day reports.

The reports which were determined to be "expected" using the US package circular would be held for submission semi-annually. However, if a sponsor is planning to submit a PSUR for the product involved, individual reports previously assessed as "expected" using the US package circular will often be considered "unlisted" when assessed using the Company Core Safety Information (CCSI) as required per PSUR requirements. Serious, unlisted reports would not be included in semi-annual submissions. Hence, the

current requirements as described in the Proposed SADR Rule do not fulfill the need stated by the Agency to obtain "important information that the Agency currently does not receive". In fact, only a small subset of individual case reports from foreign sources would be provided to the Agency in semi-annual submissions.

In the absence of FDA accepting the PSUR reporting requirements of line listings and tabulations for serious, listed individual foreign reports from foreign sources, Merck recommends the Agency re-evaluate the selection criteria to be used for individual foreign reports included in semi-annual submissions of individual case safety reports for licensed drugs and biological products.

68 *FR*, p. 12448 (col. 2): re: *In vivo* Bioavailability and Bioequivalence Studies
FDA believes that this new proposed safety reporting requirement [i.e., submit expedited safety reports to FDA for BA/BE studies that are not subject to an IND] will result in submission of minimal reports to the agency (~200/year). FDA seeks comment on the reasonableness of this estimate and requests that comments provide information to support any alternative estimates.

We do not have sufficient familiarity with the history of the number of BA/BE studies conducted annually that are not subject to an IND. Therefore, we cannot assess the accuracy of FDA's estimate of the number of reports likely to be generated from this source.

68 *FR*, p. 12463 (col. 3): re: Paperwork Reduction Act/Collection of Information
FDA invites comment on: (1) whether the proposed collection of information is necessary for proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

While we fully support FDA's public health objective to achieve maximum benefit from pharmaceuticals through effective assessment, management, and minimization of risk, we believe that the points outlined in our "General Comments" warrant further consideration by the Agency if the objective of a risk-based approach to pharmacovigilance is to be realized. We believe that FDA underestimates the burden of the proposed changes to the safety reporting requirement.

Conclusion

In conclusion, Merck fully supports FDA's public health objective to achieve maximum benefit from pharmaceutical and biologic products through effective assessment, management and minimization of risk. However, as described above in our comments,

we believe that certain unintended consequences that will defeat the Agency's stated objectives will result from the revisions to the current safety reporting regulations described in the proposed rule.

We recommend, therefore, that the proposal be revised in light of our comments and we welcome the opportunity to discuss our comments before the Final Rule is issued.

Sincerely,

Thomas H. Marshall

for David W. Blois, Ph.D.
Senior Vice President
Office of Policy