

**Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852**

**Comments to: Docket No. 2004D-0189,
Good Pharmacovigilance Practices and
Pharmacoepidemiologic Assessment;
69 Federal Register: Pgs 25130-25132**

From: Eli Lilly and Company

Eli Lilly and Company (Lilly) appreciates the opportunity to offer the following comments to FDA Docket No. 2004D-0189, Draft Guidance on Good Pharmacovigilance Practices and Pharmacoeconomic Assessment. Lilly agrees with and supports the comments submitted by the Pharmaceutical Research and Manufacturers of America. The few comments of ours that duplicate ones included in their comments are intended to reinforce their importance. Our comments consist of general comments on the guidance papers, followed by general and specific comments on the individual guidance paper.

Lilly compliments the FDA on:

1. Separating risk assessment and risk management
2. Recognizing that risk assessment is iterative throughout a product's life cycle
3. Focusing risk minimization efforts on known safety risks
4. Eliminating references to different "levels" of risk management interventions
5. Recognizing that for most products FDA-approved professional labeling will be sufficient for risk minimization. We suggest that Patient Package Information be explicitly included as a tool whose use would not be considered to constitute a RiskMAP.

Lilly would like to express the following general concerns and suggestions:

1. Please provide clearer guidance and criteria (a unifying concept) to help companies determine when a RiskMAP should be prepared and submitted. For example, a unifying concept could be expressed as "Consider using more than routine labeling and pharmacovigilance when the number or severity of a product's risks appears to undermine the magnitude of its benefits in an important segment of potential or actual users".
3. The guidances should explicitly state that the information concerning RiskMAP tools that is made publicly available will not divulge any company's proprietary information.
4. Although the target number or rate of occurrence of the risk that is attempting to be minimized, can, as an ideal, be set at the theoretical "zero", such an approach is neither

practical nor informative with regard to setting a threshold for subsequent action. The guidances should explicitly acknowledge this point and direct sponsors and regulators to engage in open dialogue to establish a realistic target value for the risks being minimized.

5. FDA authority to impose requirements in this area needs to be understood, particularly when imposing requirements (other than labeling) on products that otherwise meet the statutory standard of "safe" (for instance, a manufacturer is required to *verify* that patients obtain lab tests prior to using product).
6. The guidances should be explicit in stating that sponsors of generic products will be held to the same risk-management standards as sponsors of the innovator product. This should be applied to both risk management elements that are contained in the label (and thus generic should be required to copy) as well as risk management elements (including RiskMAPs) that go beyond labeling.

General comments for Docket No. 2004D-0189, Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

1. We compliment FDA for providing clear descriptions of the components involved in identifying and describing safety signals.
2. An explicit cross reference to ICH E2E: Pharmacovigilance Planning in section VII would help clarify how the requirements in this ICH guidance could be incorporated into a RiskMAP when a RiskMAP is needed, and how a pharmacovigilance plan could be developed and submitted in the absence of a RiskMAP.
3. Comments and guidance are needed on the use of traditional methods for signal detection. For example, the use of cumulative number of cases, increased frequency of reports over time (simple trend analysis), a single report (or a few reports) of a designated medical event are still appropriate methods for signal detection which are complemented rather than supplanted by newer methods.

Line specific comments for Docket No. 2004D-0189, Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

1. Line 201 The reporting of medication errors and the use of the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) taxonomy tool implies that there are specific regulatory reporting requirements. To date the most specific guidance regarding medication error reporting from the Agency was in the Tome draft. Will the Tome precede the final rule on this guidance? If the Tome precedes this guidance, will it contain specific reporting requirements? If not, more clarity is needed on what to report and when to report medication errors.
2. Line 252 The text affirms that it is difficult to assess relatedness with a "high level of certainty" and that there are "no internationally agreed upon standards or criteria for assessing causality". Further it states that the FDA does not recommend any specific categorization of causality, but does list the World Health Organization terms. Would it not

be valuable for the Agency to focus on one set of criteria to help standardize assessments? It does seem contradictory to not recommend any categorization but list one as an example.

3. Line 316 Data mining is NOT a technique that can be used to make causal attributions between products and adverse events. As stated in the sentence preceding line 316, data mining may be able to identify unusual or unexpected product-event combinations warranting further investigations. Data mining is a signal generating tool, not a technique for attributing causality. Please delete the sentence in line 316-317 since it implies that data mining can be used to make causal attributions.
4. Line 325 The statistical validity of the available data mining tools has not yet been established. The draft guidance documents make reference to thresholds, sensitivity and specificity; this is overstating the capabilities of these tools at the current time. Additional developmental work is needed on these tools.
5. Line 410 Will the request to perform analyses using data (adverse event and patient exposure) obtained only in the US preclude an FDA interest in analyses involving global data? Sponsors frequently perform their analyses of safety using fully integrated global datasets. Performing region-specific analyses will add a layer of complexity to these analyses and open up the possibility for having discrepant results. Selective reporting of region-specific analyses also adds a layer of complexity to the preparation of regulatory reports and opens the possibility of different regulatory agencies receiving differing views of the safety of a product.
6. Line 412 While we agree that, ideally, a direct estimate of the number of patients exposed should be used as the denominator when calculating reporting rates we are aware that patient-level data are often not available outside of the US. In such instances it is necessary to use prescription-level data and number of pills or kilograms sold to derive estimates of the number of patients exposed. In addition, there are circumstances in which the duration of a patient's exposure must also be taken into account when evaluating a signal. In this latter circumstance data on prescriptions written, amount of product sold and defined daily dose can be used to derive patient \times duration estimates. These approaches should be recognized as legitimate.
7. Line 463 Lilly strongly supports the use of pharmacoepidemiologic "nonrandomized observational studies of patients in the real world" to characterize, clarify or validate safety signals for pre- and/or post-marketed drug products. However, the regulatory reporting of adverse events reported in these types of studies is unclear, specifically, expedited and/or periodic adverse event reporting. The draft E2D and Tome, and CIOMS V documents, seem to imply that any organized attempt to collect drug data in the post-marketing environment should be categorized as "solicited data". Is it correct to assume that these data would be categorized as solicited, but be reported according to post-marketing expedited and periodic reporting rules? If this is not a correct assumption, then would these data be categorized and processed according to clinical trial reporting rules? Would these data then be included in an IND Annual Report? Regardless of how these data are reported, should they be segregated from mainstream pre- and post-marketing periodic reports?

8. Line 476 Systematic reviews and natural history studies are important in risk management, especially when they are initiated prior to marketing. It is inappropriate to characterize their usefulness as “on rare occasions”.
9. Line 522 Traditional literature reviews may generate a biased result. We suggest that in some instances a systematic review may be more appropriate than a critical review of the literature.
10. Line 553 Lilly supports the position that diagnostic findings in a claims database need to be validated and agree with the idea that “review of at least a sample of medical records“ be used because a review all medical records would present a extreme challenge to the conduct of these studies. It would be useful to have an FDA-industry consensus opinion on the appropriate sample size, or percentage, of medical records needed to be reviewed for purposes of validating of a claims database.
11. Line 562 Lilly is requesting similar clarifications and questions for Registries as stated in the item for line 463.

Regards,

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