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GUEST EDITOR'S NOTE: REGULATORY AFFAIRS

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CHANGE IS A GOOD thing. What would life be without change? Perhaps that is why I have made a career of regulatory affairs. In the corner of my bookcase sits my first New Drug Application, barely five volumes in total. It is quite a contrast to the image of pallets being loaded in the present. What has brought about this change, for the most part, is an explosion of scientific knowledge that requires validation and engagement by regulators.

Changes in the rules of our trade should be science-based and rely on real and quantitative risks, not hypothetical or perceived risk. Unfortunately, 40 years after the Kefauver-Harris amendment, we do not have a workable equation for the risk management of drugs. We are getting closer.

No adequate or accepted guidelines exist for the risk management of pharmaceutical products. There are variations in approaches across products. Some tools do exist: preapproval trials can identify risk at the level of 1/1000, epidemiology studies contribute disease incidence rates, observational studies further our understanding of product safety profiles, targeted postapproval trials can provide hypothesis testing and risk clarification, and spontaneous reports are useful in rare event identification.

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Regulatory agencies have voiced their concerns as to the effectiveness of existing risk management tools as well, ranging from questions about the applicability of controlled studies with real-world experience, to the effectiveness of the label as a risk management tool, to the adequacy of risk management education for health care practitioners. The Food and Drug Administration (FDA) is moving forward with plans for a Drug Safety and Risk Management Advisory Committee to look at the effectiveness of risk management strategies. FDA is also extending risk management communication through an overhaul in pharmaceutical product labeling. There are plans for a patient safety task force, a drug label database project, and other private/public partnerships.

We in regulatory affairs need to ensure that specific risk management plans are developed for each new product. The risk management plan should start early in the drug development cycle. As part of the plan, we should review known disease epidemiology, and carry out appropriate incidence/prevalence studies. We must identify risk areas and assess clinical trial limitations, and supplement these with disease epidemiology. Additionally, postapproval observational studies, if indicated, should be contemplated as a confirmation of the safety profile. Simple rules should be established for spontaneous reporting. Unconfirmed adverse event reports should not be used to dictate further action. But confirmed reports without confounding factors such as disease state or concomitant

medications might suggest a legitimate hypothesis. Hypotheses then need appropriate testing.

The time is right for such advancement. With the era of the Internet has come a virtual approach to risk management. For example, adverse event reporting is real time, compared to 10 years ago when a paper trail took weeks to months to complete a cycle. As the paperless label database project progresses, we can foresee a time when we can communicate the detection and confirmation of a signal quickly and relay this to the patient point of contact within days or sooner.

Our vision should, therefore, be a risk management program that is rigorously supported by quantitative experience with hypothesis testing, so that the appropriate risk can be assigned. The management side of the equation should be equally quantitatively based so that a hierarchy of intervention can be appropriately applied and measured.

There is a loose translation of Buddha claiming to have once said, "Man must first direct the way he should go; only then can he instruct others." I believe you will agree that this special regulatory issue is a good start for the changes that lie ahead.