International Society for Pharmacoepidemiology (ISPE)

Statement on Regulatory Systems to Improve Pharmaceutical Safety

INTRODUCTION

The public, some researchers, individual regulators and policymakers have recently voiced important concerns about the adequacy of existing regulatory systems for assuring the safety of drugs, biological products, and medical devices, hereinafter referred to as *pharmaceutical products* or *pharmaceuticals*.

Pharmacoepidemiology is the study of the use and effects of pharmaceuticals in populations, and is the scientific discipline underlying drug safety surveillance. The International Society for Pharmacoepidemiology (ISPE) is a global organization of over 800 professionals interested in pharmacoepidemiology, pharmaceutical safety surveillance, and therapeutic risk management. As such, ISPE feels a responsibility to offer its views on existing systems for assuring pharmaceutical safety to interested policymakers, members of the public and others. This *Statement*, having been ratified by ISPE's Board of Directors, represents the consensus views of this society. Because there is considerable similarity and indeed harmonization across national systems for assuring pharmaceutical safety, and because ISPE is interested in pharmaceutical safety worldwide, ISPE intends this *Statement* to be broadly applicable across international boundaries.

A. EXISTING REGULATORY SYSTEMS TO ASSURE PHARMACEUTICAL SAFETY

1. Pharmaceutical products are tested extensively in animal and other non-human (pre-clinical) studies before been administered to humans in clinical trials. Experimental clinical (i.e., human) trials are then performed in a highly rigorous and regulated manner. This rigorous process of pre-clinical and clinical testing demonstrates efficacy and eliminates many pharmaceuticals with unacceptable risks. After experimental clinical testing, the resultant data are submitted to regulatory bodies, often together with data from other countries in which the drug

has been marketed previously. Regulatory agencies then review the available data and decide if acceptable safety and efficacy have been demonstrated within the context that the drug is to be used. If these conditions are met, package information (labeling) is developed in conjunction with the manufacturer to provide healthcare practitioners with a summary of the safety and efficacy data, dosing information, indications for use, and other information.

2. Despite the strengths of the pre-marketing development and approval processes, they do not and cannot assure that products that are free from risk or from uncertainty about undiscovered risks. All pharmaceuticals are associated with risks, and new knowledge about those risks frequently comes to light after they are approved. Nevertheless, based on the information available at the time of approval, the benefits of a pharmaceutical product, when used as directed, are believed to outweigh the known risks in populations like those studied prior to approval. Clinical trials, combined with data from pre-clinical studies, are the accepted approach to demonstrating efficacy and safety prior to marketing. However clinical trials are not without limitations; in particular, there are important safety questions that cannot be answered by conventional clinical trials due to the following limitations:

    a. Size: The number of subjects studied in clinical trials is limited by availability of patient volunteers and investigators, as well as by cost and other constraints. Clinical trial programs typically include several thousand patients and are designed to evaluate efficacy and common adverse drug events. However, such programs are too small to measure with adequate precision elevations in uncommon risks that occur in the range of an excess of 1 per 100 patients to 1 per 1,000 patients or even lower risks. This is particularly true for adverse drug events that represent an increase in the background rate of an event that is expected in the population taking that drug, such as increases in the risk of heart attack in elderly patients. Even though pre-marketing clinical trial programs are typically too small to detect increases in small risks, serious adverse drug events that occur as in fewer than 1 per 10,000 patients can result in a product withdrawal.

    b. Patient population: Clinical trials cannot realistically include enough subtypes of patients to allow for their results to be applicable to all types of patients who will use the product once it is marketed. This is particularly true for special populations, such as children and pregnant women, who are often excluded from trials of pharmaceuticals that will ultimately be used in those groups. Further, pharmaceuticals are often used in patients with concomitant conditions that would have rendered those patients ineligible for pre-approval trials.

c. Duration of treatment: Trials usually evaluate drug treatment for up to a few months, and uncommonly up to 24 months, even for drugs that in clinical practice may be used for much longer periods. Consequently, clinical trials generally cannot rule out latent drug effects.

d. Prescribing patterns: The pattern of use of a new drug in trials may not reflect how the drug will be prescribed and monitored in actual practice after it is approved. For example, drugs are often used in patients receiving concomitant medications that would have rendered them ineligible for pre-approval trials.

3. Because of the limitations of the clinical trial process, there is a compelling need to study drug effects after approval using approaches complementary to those of clinical trials. Several key methods for such post-marketing surveillance and study include:

   a. Collection and analysis of individual case reports of possible adverse drug events,

   b. Conduct of observational pharmacoepidemiologic studies, and

   c. Use of post-approval trials.

4. Recognition of potential adverse drug events by astute clinicians is a powerful and crucial means by which many drug safety problems are initially identified. Adverse drug event surveillance systems use case reports submitted by manufacturers, healthcare professionals, and consumers. Despite their principal strength of allowing early identification of potential adverse drug events, such systems have important limitations. For example, they do not capture all true adverse drug events. In fact, reporting of all potential adverse drug events would be counter-productive, since most reported adverse drug events are already well-described, and complete reporting would overwhelm existing surveillance systems. A second limitation of surveillance systems is that not all reported cases are truly caused by the suspected drug, and it is usually impossible to determine with certainty which events were caused by the suspected drug and which were not. Thus, surveillance systems are very useful for identifying hypotheses about new and important adverse drug events that deserve to be examined by pharmacoepidemiologic studies and other means. In addition, absence of available data from formal pharmacoepidemiologic studies sometimes necessitates reliance upon adverse drug event reports as the primary basis for regulatory action.

5. Methods for conducting pharmacoepidemiologic studies are well developed, and methodologic advancements continue to be made in the field. Pharmaco-epidemiologic studies include follow-up studies and case-control studies, and can involve use of administrative databases, ad-hoc data collection, and other means

to identify study subjects. Pharmacoepidemiologic studies are designed so that inferences can be drawn with scientific rigor about a product's risk relative to alternative or no treatments. Manufacturers are often responsible for funding or conducting pharmacoepidemiologic studies examining the products that they produce.

6. Some national regulatory agencies lack adequate authority to ensure that manufacturers conduct post-marketing safety studies, including those promised as a condition of drug approval, as well as those necessary to address potential safety issues that emerge post-approval.

B. KEY ISSUES AND SUGGESTED ACTIONS

1. Although approval of pharmaceuticals alone will never be sufficient to entirely ensure patient safety, there are efforts worldwide to improve the safety information gathered during trials. Regulatory and non-regulatory bodies (e.g., International Council on Harmonization) have recently proposed expansion to the collection of safety data . ISPE supports such efforts. Even with the implementation of such recommendations the inherent limitations of the clinical trial process will remain so that many new risks will predictably become known only after approval. Therefore, it should be understood that identification of new safety information after a drug's approval does not necessarily represent a failure of the approval process.

2. Recognition of potential adverse drug events by astute clinicians is a powerful and crucial means by which many drug safety problems are initially identified. Therefore, post-marketing monitoring of individual case reports of adverse drug events is an important activity, and must be supported by manufacturers and regulatory bodies. Innovative ways to stimulate reporting by health care professionals of new, serious events should be developed.

3. When there are suggestions of important potential safety problems, either before or after a pharmaceutical is approved, the rapid conduct of pharmacoepidemiologic studies or expanded trials to understand the potential risks should be undertaken. Decisions about the conduct of such studies may often involve requests by regulatory agencies to manufacturers. In some countries, there is a need to increase the authority of regulatory agencies to require manufacturers to conduct such studies in a timely manner, if feasible.

4. Most of the data needed for approval of a drug derives from randomized trials of comparing the drug of interest to a comparator, often a placebo. Identifying, assessing, and quantifying post-marketing risk often requires different data sources and methods, particularly those of pharmacoepidemiology. Pharmacoepidemiology focuses on risk following "natural" exposures rather than assigned exposures in randomized trials. Therefore, knowledge gained through pharmacoepidemiologic studies complements that gained through randomized trials. Other uses of pharmacoepidemiologic study designs are important to

pharmaceutical safety. For example, the patterns of the disease being treated by a new pharmaceutical should be well understood before efficacy trials are performed. Epidemiologic studies of the disease of interest promote such understanding, and can thus lead to better trials. In general, throughout the drug development and marketing process, more emphasis should be given to pharmacoepidemiologic principles and practices as a way to improve drug safety, and thus the public's health.

C. OTHER SUGGESTED ACTIONS

1. Clinical trials are planned, conducted and analyzed by groups in industry and in regulatory bodies that often are administratively separate from those who monitor post-marketing safety and conduct epidemiological studies. Improved coordination and cooperation and balanced resourcing between these groups should be fostered. This is particularly true in the pre-approval and post-marketing assessment of risk and the identification of needed prevention activities and when product package labeling information is modified.

2. Increase surveillance subsequent to drug approval. Since most drug safety crises occur in the first several years after approval, ISPE favors enhanced surveillance and cautious promotion of products during this initial interval. It may be appropriate to restrict direct-to-consumer advertising for many products until safety in actual use has been adequately shown.

3. Increase funding for training and research in pharmacoepidemiology. Current funding for pharmacoepidemiologic research and training provided by governmental bodies worldwide is very limited. Increases are badly needed. Such funding could be channeled through regulatory bodies, national research councils, or through other mechanisms.

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