[S1-2] [10/10/2003(Fri) 10:10-10:50/ Grand Ballroom 102]

Balancing Benefit-Risk in Drug Evaluation

Chang H. Ahn

Chairman/CEO
Rexahn Corporation, Rockville, Maryland, USA

There have been remarkable medical advances, largely as the result of improved understanding of disease mechanisms and of advances in human genetics at the individual level. Subsequently, remarkable effective medicines continue to be discovered at an increasing rate. Development of these medicines become increasingly complex, accompanied by globalization and global standards, requiring ever higher standards of efficacy, safety and quality. Regardless of newly-marketed or long-established, Careful, diligent monitoring of the safety of all drugs are embodied principles of FDA regulations and pharmaceutical industry practice. In practice, any medical intervention is entirely risk-free. No medicine is risk-free or can be made completely safe. Efforts to identify all risks prior to regulatory approval may not be feasible without significant delays in drug development and ensuing costs.

Evaluation of benefits-risks of medicines is done during research and development on new medical products or by FDA, or by a physician on behalf of a patient or even by the patient. Although FDA and pharmaceutical industry routinely make decisions based on benefit-risk balance, there are no generally agreed procedures or regulatory guidelines for conducting and action upon benefit-risk assessment. Benefit-risk assessment can be made during the development of new medicines. Unfortunately, very limited approaches have been suggested for marketed medicines, despite much greater immediate consequences for the public health than medicines under development.

Here, basic principles and methodologies regarding benefit estimation, risk estimation and benefit-risk evaluation will be discussed. For benefit evaluation, information on target disease, intended outcome of the medicine, evidence for benefit (both in clinical trials and post-marketing), and alternative therapies should be obtained, analyzed and evaluated.

For risk evaluation, thorough review of the evidence including history and description of specific adverse drug reactions prompting the benefit-risk evaluation, predictability/preventability/

reversibility of the adverse drug reaction, overall risk profiles (e.g., common structure, estimated frequency of occurrence, qualitative reporting pattern, and comparisons for different drugs), risk weighing for individual adverse drug reactions, quantification of risk (e.g., incidence, existence of any high risk groups, drug-attributable incidence, incidence relative to alternative therapies, weighing adverse reactions using selected markers for comparison such as duration, severity and consequences of different reactions and quality of life, and estimation of total drug risk and sensitivity of the risk estimation.

For benefit-risk evaluation, adverse reactions are characterized by their seriousness, duration and incidence. Benefits may be described for a target disease in relation to seriousness, chronicity and extent of control or cure. To clarify benefit and risk properties, a classification descriptive grid can be used to describe the disease (seriousness, duration) under treatment or an adverse reaction (seriousness, duration, incidence) in terms of high, medium and low. When sufficient data on both benefits and risks are available, quantitative approaches of the descriptive grid technique may be more useful to calculate benefit-risk ratio by using the mean of all adverse reaction scores.