Highlights of the Society for Medicines Research symposium held September 18, 2003, in London, United Kingdom.

Trends in Early Drug Safety

by Richard E. Armer and Ian D. Morris

Summary

Successful introduction of a new drug to the market is not only an extremely costly and complicated process, but also fraught with a substantial risk of failure. The number of new drugs launched each year from 1990 to 2000 has stayed relatively constant, while the cost of pharmaceutical research and development has risen by almost 2.5-fold over the same period. What is not revealed by these figures is that the chance of success for a drug candidate passing through the various hurdles in pharmaceutical development is at best 1 in 10 and has barely changed despite advancing technology in other areas of research and development. While we expect high failure rates in drug discovery, it is of substantial concern that most candidates in development on which large investments have already been made are probably not going to make any return. A major stumbling block is the absorption, distribution, metabolism, excretion and toxicology profile of drug candidates. These issues were discussed at the Society for Medicines Research symposium held September 18, 2003, in London, United Kingdom. Recent SMR symposia have focused on the ADME and pharmacokinetic aspects of drug discovery and development. Indeed, it is now uncommon for drug discovery projects not to address these issues early in their lifetimes. Although it is less common to address drug safety early in a project, it is being utilized more frequently to help select the best clinical candidates for further development. This meeting report summarizes some of the key aspects of early drug safety issues facing the drug discoverer today. Classical approaches to toxicology, P450-mediated safety, cardiovascular safety, "omics" approaches and their impact upon clinical safety will be discussed.

Drug safety is an essential and integral component of the preclinical development of any new medicine. Recent high-profile withdrawals of drugs from the market place, such as cerivastatin, and the continued loss of development compounds for toxicology reasons have highlighted the need to address drug safety earlier and more effectively in the discovery and development timeline.

On September 18, 2003, the Society for Medicines Research held a one-day meeting in London entitled *Trends in Early Drug Safety.* The meeting brought together speakers from the United Kingdom representing both academia and industry and provided an overview of the latest trends in the application of safety studies within pharmaceutical research and development. The three main themes of the meeting were: 1) general safety and P450-mediated safety issues; 2) new opportunities in drug safety; and 3) clinical and regulatory aspects.

Toxicology in drug safety

Dr. Mark Graham (Safety Assessment, AstraZeneca R&D Charnwood, Loughborough, U.K.) gave an overview and examples of the current application of drug safety studies within early research at AstraZeneca. Usually, the toxicologist will first engage in a new drug discovery project at a relatively early stage (e.g., during the lead identification phase), and the project team will then have toxicology input throughout the discovery and development processes to life-cycle management. The basic aim of the "discovery toxicologist" is to provide a "package" of *in vitro* and *in vivo* data, which is designed to evaluate the risk of exposing people to the compound under development. This package contains information on the potential target-organ toxicities, the reversibility of the lesions, the characteristics of the dose-response curves and, consequently, sensible plasma exposure levels to aim for in the clinic. If the risk is considered acceptable, the compound will

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progress into the clinical stages of development, but the fact that roughly 40% of new drug candidates fail at the preclinical stage illustrates that toxicological evaluation is a significant factor in drug development. Given that drug development becomes exponentially more expensive as the project progresses, there is obviously an urgent need for reliable, predictive safety screens that can be applied early during the drug discovery process. A wide variety of information is currently available, including *in silico* databases, structure–activity screens, specific *in vitro* screens (e.g., for genetic toxicity and safety pharmacology parameters), and *ex vivo* and *in vivo* assays, but the very fact that so much attrition still occurs suggests that there is considerable room for improvement.

There is substantial regulatory guidance as to what preclinical studies are required to support the various stages of clinical development, but there is also leeway for the toxicologist to design studies appropriate for the project in question. Typically, prior to first dose to man, which is often in volunteers, cardiovascular, CNS and respiratory safety pharmacology studies, *in vitro* and *in vivo* genetic toxicology, acute toxicity studies in rats and mice, and subacute (up to 1 month duration) toxicity studies in a rodent and a nonrodent species will have been completed. Where possible, the proposed clinical route and schedule of administration will be taken into account in the study design. For example, if the new drug is intended principally for intravenous use, an appropriate formulation by the intravenous route must be developed. As clinical trials progress to longer-term studies, the toxicology studies required to support them are also of longer duration, such that by registration, studies of 6 months duration in rats, 9 or 12 months in dogs and lifetime carcinogenicity studies in rats and mice will have been completed. A program of reproduction toxicology is also included to support later clinical trials and registration.

Role of P450s in drug safety—Drug–drug interactions and variable metabolism: Inhibition, induction and polymorphisms

Dr. Nick Plant (Molecular Toxicology, School of Biomedical and Molecular Sciences, University of Surrey, Guildford, U.K.) comprehensively reviewed the cytochrome P450 enzymes and their role in drug safety. It is well established that there exists interindividual variation in the expression of all 50 or so CYP proteins within the human body. Whereas such variation provides us with our uniqueness, it also presents a potential problem for the development and administration of therapeutic compounds: if everyone is different then how do you develop a drug that is safe in everyone?

In addition to this inherited variation, it is also clear that drugs themselves may alter the levels of enzymes within the body, causing either induction or inhibition of drug-metabolizing enzymes. However, in situations in which individuals are exposed to multiple inducing compounds, be they pharmaceutical drugs, "consumer drugs" or environmental agents, the potential for drug–drug interactions arises. Induction/inhibition of drug metabolizing enzymes by one drug may alter the effects of a second, potentially leading to loss of efficacy or increased adverse side effects.

To study the role of both genetic and environmental factors in determining cytochrome P450 levels in an individual, two examples of CYPs involved in the metabolism of therapeutic compounds were described: CYP2D6 and CYP3A4. Both enzymes are susceptible to induction/inhibition of activity by drugs, and this can result in clinically significant drug–drug interactions. CYP2D6 activity also has a clearly defined genetic component, with approximately 7–10% of Caucasians being classed as "poor metabolizers." Such an established effect clearly demonstrates the need to incorporate this into the safety assessment of novel compounds. In contrast, CYP3A activity levels show a marked interindividual variability, yet no polymorphisms within the *CYP3A4* gene have been identified that could account for the majority of this variability. The role of polymorphisms in other CYP3A enzymes and the transcription factors that control *CYP3A4* expression may, however, shed some light on the observed interindividual variation. Either through the expression of enzymes with similar metabolic capacities (e.g., CYP3A5) or through changes in the transcription factor network that mediate *CYP3A4* gene expression, the observed interindividual variation in CYP3A activity may be achieved.

Drug discoverer's guide to avoiding P450 pitfalls

Dr. Barry Jones (Pharmacokinetics Dynamics and Metabolism, Pfizer Global Research and Development, Sandwich, U.K.) outlined the characteristics of the cytochrome p450 enzymes and their structure activity relationships. The major human CYPs can be characterized in terms of their substrate selectiveness as:

- CYP1A2: Neutral or basic lipophilic planar molecules with at least one putative H-bond donating site. A good example of a xenobiotic substrate is theophylline.

- CYP2D6: Aryl-alkyl-amines (basic) with site of oxidation a discrete distance from protonated nitrogen. Substrates are lipophilic, particularly when measured or calculated for the neutral form. Principal substrates are β-adrenoceptor blockers, and class I antiarrhythmic and tricyclic antidepressants. Often hydroxylation occurs in an aromatic ring or an accompanying short alkyl side chain.

- CYP2C9: Neutral or acidic molecules with site of oxidation a discrete distance from H-bond donor or possibly anionic heteroatom. Molecules tend to be amphipathic, with a region of lipophilicity at the site of hydroxylation and an area of hydrophobi-

city around the H-bond–forming region. Principal substrates are nonsteroidal antiinflammatory agents. Oxidation often occurs in an aromatic ring or an accompanying short alkyl side chain.

- CYP3A4: Lipophilic, neutral or basic molecules with site of oxidation, often nitrogen (N-dealkylation) or allylic positions. This CYP metabolizes a wide range of substrates covering all types of pharmaceuticals.

- CYP2E1: Small (molecular weight of 200 daltons or less), normally lipophilic linear and cyclic molecules. Volatile anesthetics are a good example of this isozyme.

It is noteworthy, however, that there are many exceptions to these broad rules, and CYPs represent the ultimate in promiscuous enzymes.

Inhibition of human P450 isoforms can cause issues for compounds during development. By definition, all substrates of P450 have the ability to act as competitive inhibitors. Some compounds are activated to meta-stable or stable complexes during metabolism and become irreversible or slowly reversible inhibitors. These compounds are known as "mechanism-based inhibitors." Very potent inhibitors of P450 often include a nitrogen-containing heterocycle (pyridine, imidazole or triazole) capable of forming a lone-pair ligand interaction with the heme of P450. The ligand interaction contributes some 6 Kcal of binding energy to the interaction (3 order-of-magnitude increase in potency as an inhibitor). Although such heterocycles are essential for the activity of certain drugs (azole antifungals: 14-α demethylase inhibitors), their incorporation into molecules is commonplace to increase solubility by replacing (for instance) a phenyl group.

Medicinal chemists have responded to metabolism by CYPs in a variety of ways. Overall reduction of lipophilicity is one such tactic. In some cases, the P450 involved is partially selective and metabolizes compounds in a discrete region. Stable functionality can be incorporated in this region to attenuate or block metabolism. Examples of stable functionality include halogens, cyclopropyl groups, and primary or secondary amines (compared with tertiary amines).

QT prolongation: Identifying risk and potential impact on drug development

Prolongation of the QT interval measured on the electrocardiogram is associated with life-threatening arrhythmias. The risk of QT prolongation by new therapeutic entities is of particular interest to regulators worldwide and was discussed by Dr. Leslie Patmore (Vice President, Preclinical Safety and Efficacy, Quintiles Ltd, Heriot Watt University Research Park, Edinburgh, U.K.). QT prolongation has contributed to the withdrawal of drugs from the market (e.g., terfenadine, cisapride, terodiline) or labeling restrictions imposed on current products (e.g., pimozide), which has considerable pharmacoeconomic consequences. The European Medicines Evaluation Agency introduced a "Points to Consider" document, CPMP 986/96, which indicated that more in-depth testing of cardiac toxicity should be conducted before clinical trials. Currently, it is a special International Conference on Harmonisation (ICH) topic, with the guidance document ICHS7B at a late-draft stage. The current version indicates that the risk of QT prolongation in new therapeutic entities should be evaluated on four different levels:

- Theoretical assessment based on pharmacological/chemical class
- Interactions with IKr or HERG channel
- Repolarization assay (e.g., Purkinje fiber)
- QT measurement *in vivo*

The predictivity of these assays is a point of interest and has resulted in some contention in finalization of the ICHS7B guidance.

Quintiles has developed considerable experience in performing these assays, particularly rapid HERG screening, by investing in the latest technology amenable to HTS (fluorescence and Rb flux) and automated patch clamping. Repolarization assays also present issues, for example, differences in species sensitivity to IKr blockers as well as sex differences. What may not be forthcoming after these assays is a correlation of *in vitro* (e.g., HERG block) and *in vivo* (QTc) assays. Predictions are not easy. What is clear is that compounds that block HERG do not necessarily prolong action potential or QT, and compounds that do not block HERG can prolong cardiac action potential. Some HERG blockers shorten the action potential. Quintiles is using these methods to support the development of new drugs and to assist in candidate selections. It has established a considerable database on the outcome of these studies.

In an overview of industry practice, a 2002 survey of emerging practices in safety pharmacology showed that from 33 responding companies, most included HERG, repolarization and *in vivo* QT studies. This indicates that the ICHS7B guidelines are being adopted ahead of finalization of the document.

Toxicogenomics—The future of early drug safety?

Dr. Jonathan Tugwood (Molecular Toxicology Group, Safety Assessment Dept., AstraZeneca Pharmaceuticals, Macclesfield, U.K.) introduced a new approach to early identification of toxic potential of compounds using gene chip technology. In an attempt to address compound failure due to safety issues, drug developers are now starting to "front-load" toxicology into the drug discovery process, and genomics technology, specifically transcript profiling, is playing an important part in this initiative. In this regard there are two main applications of this toxicogenomic technology: 1) to assist with mechanistic investigations of drug toxicity ("problem solving"); and 2) the construction of gene expression databases as a means of developing poten-

tial predictive tools that can be used to assist compound selection decisions early in the discovery process.

The development and application of gene "arrays," comprising large collections of genes from a number of species, has facilitated experimental effort in both these areas. The presentation focused on array technology and provided illustrative examples of applications using the rat Affymetrix chips, which can provide information on more than 25,000 genes. Specifically, investigative work aimed at understanding the corneal toxic effects of a class of novel anticancer agents (epidermal growth factor receptor-tyrosine kinase [EGFR TK] inhibitors) was discussed. Studies using phospho-specific antibodies demonstrated that the toxicity was unlikely to be due to inhibition of EGFR TK in the cornea. It was suggested (not proved) that kinases compensating for the inhibition of EGFR TK may also be inhibited, causing the toxicity. This approach allowed the identification of gene clusters specially associated with the pharmacology or toxicology of the compounds under development. Interestingly, these clusters were not necessarily consistent between the different chemical groupings. This approach is expensive and has led to a multicompany collaborative strategy toward developing a rat toxicity transcript profile database. The results from 225 studies using 10,000 gene chips providing 260 million data points are now available to this group, information that hopefully will lead to predictive *in vivo*, drug-induced toxicology.

Metabonomics—A new approach to early toxicology

Dr. Elaine Holmes (Biomedical Sciences, Imperial College London, U.K.) presented the evolving area of metabonomics and its potential application to study human toxicological events. Metabonomics provides a non-invasive system approach to measuring dynamic biochemical responses of organisms to pathological stimuli or genetic modification and operates by profiling the metabolic responses of key intermediary biochemical pathways. Metabonomic technology, coupling sophisticated analytical methods such as high-resolution ^{1}H NMR spectroscopy or mass spectrometry with appropriate chemometric strategies, enables simultaneous measurement of a wide range of metabolites in biofluids or tissues in a dynamic manner. Such analysis has been shown to be of considerable value in providing detailed information regarding the metabolic status of an organism and in characterizing and predicting a wide range of pathological conditions. Models of site- or mechanism-specific toxicity can be constructed and combined to form predictive expert systems for toxicity screening. The complexity and interactive nature of biological systems introduce confounding variation into the metabonomic data. Various chemometric and bioinformatic strategies for optimizing the characterization and prediction of pathological conditions can be adopted to increase the sensitivity of metabonomic analysis by reducing the influence of confounding random and systematic noise, accommodating the presence of large dynamic range in the measurement variables and/or incorporating the temporal dependence of pathological lesions. Using such sensitive technology, it is often possible to improve the efficiency of drug toxicity screening and lead candidate selection.

Clinical safety—How predictive are animal safety models?: Maximizing information and speed in early human trials

Dr. Paul Rolan (Medeval, Manchester Science Park, Manchester, U.K.) gave an eloquent overview of the options to be considered to ensure a first safe entry of a drug into humans. The safety of a drug can be defined as the difference between the dose-concentration-response relationships for target pharmacology and toxicology or nontarget pharmacology. In his view, proving drug safety is like proving innocence. It is often retrospective and evidence-based, requiring a large data set, and as such is not really an objective of first-in-human studies. Maximum tolerated doses (MTDs) are often sought in first-in-human studies but this can often be inappropriate (e.g. with anticoagulants, insulin), and as the MTD may be orders of magnitude higher than the effective dose, safety/efficacy biomarkers may replace it as an end point. The "safety" of a study is defined as achieving the study objectives with minimum likelihood of clinically important adverse events, and in human trials this relies on prediction from preclinical information and the clinician being expectant of the unexpected. Key predictive methods include the use of animal data, tests on human material *in vitro*, observation of desired pharmacological effect, effects of other similar compounds and any natural or unnatural phenotypes that may be available.

The basic premise behind animal safety studies is that large doses of drug given to small numbers of animals will predict likely human toxicities. Undoubtedly, these studies have prevented some toxic drugs or doses being given to humans. However, with an increasing proportion of potential new medicines coming from biotechnology, such a scientific premise is unlikely to be correct. For example, humanized antibodies may be immunogenic in animals but not humans, or animals may lack the target antigen and hence show little response. Similarly, the long-term biological consequences of potential therapies such as DNA vaccines, cellular (e.g., stem cell) therapeutics and immune modifiers may be uniquely human.

Even for conventional small molecules, many problems can occur. Species variability can cause several issues such as variation in receptor affinity/action, metabolic differences and the fact that effector and control systems may vary from animal to humans (e.g., triptans appear toxic in dogs but are safe in humans). Population homogeneity may also hinder prediction of toxicity; for example, inbred lines of laboratory rats can give very specific responses that are not representative of the general species.

Limited sample sizes and the fact that nonphysiological bolus dosing is often employed alongside histological rather than functional end points can lead to misinterpretation of data. For some types of organ toxicities (e.g., behavioral toxicities such as cognitive or perceptual impairment), it may be difficult to detect effects in animals, and sometimes the desired pharmacology may mask any toxic event, for example, in neuromuscular blockade. Prediction of hepatotoxicity is notoriously poor from animal studies, and this can be compounded by unhelpful human data, such as the significant elevation of liver enzyme activity (e.g., transaminase), that have been reported in placebo groups during phase I trials.

A unique solution for all these problems is unlikely, but the appropriate solution will come from the type of problem. For uniquely human biologicals, toxicity is likely to be an exaggeration of the primary pharmacology, and a mechanistic understanding of the drug's action will assist prediction, and hence early detection and management, of toxicity.

It is more difficult to be confident of detecting toxicities not associated with the primary pharmacology. Traditionally, we have sought clear end points such as histological damage. However, such damage is at the end of a spectrum of drug effects, and it is often difficult to make predictions about the safety of low doses in humans on the basis of toxicity in a few animals at high doses.

Noninvasive biomarkers that could detect early drug-related injury predictive of clinical toxicity would be of great interest. Such biomarkers are likely to be system- rather than drug-specific. This makes their development unattractive to the pharmaceutical industry (potential risk to a compound's commercial success, fear of regulators requiring the data) and incompatible with the therapeutic area specialization and preclinical/clinical separation. Although there is cross-company collaboration in the validation of biomarkers for efficacy (e.g., Osteoporosis Consortium), there is less effort with potential safety biomarkers. An example of the potential use of this approach was given in which preclinical data suggested vascular inflammation as the limiting toxicity. It would be hard to detect this effect clinically in mild or early stages, so a panel of incompletely validated biomarkers (vWF, E-selectin, CRP) of inflammation were successfully used in first-in-human studies but not defined as stopping rules. Similarly, peak saccadic velocity was effectively employed in first-in-human studies as a safety biomarker for a suspected sedative compound.

Hence, the best current practice is for the clinical pharmacologist to be closely involved with the preclinical program. This includes assisting with the interpretation of potentially toxic effects and suggesting the incorporation of noninvasive tests that could be used in humans to confidently and rapidly commence early human evaluation and to assist the decision on when to stop. The final advice given to best ensure a first early safety clinical evaluation was to review desired/undesired pharmacology and analyze by concentration; review toxicity and analyze by concentration; ask yourself how relevant the animals are likely to be with current knowledge; examine effects of other drugs in class; consider experiments of nature to predict safety; ask which biomarkers might give a subclinical signal of an important effect and incorporate into preclinical studies; and to consider in advance when to stop.

To generate a good investigator's brochure, ensure that desired and undesired effects are related to concentration; use all sources of prior knowledge; increase use of biomarkers; don't always seek a MTD; observe carefully; and most importantly, think clearly.

P450-mediated metabolism and early drug safety: A regulatory perspective

Dr. Rashmi Shah (Medicines and Healthcare products Regulatory Agency, Nine London, U.K.) completed the symposium with a personal view of some of the issues that face regulatory authorities today. The key questions the regulator asks of a new drug are (1) does it work; and (2) is it safe, the overall aims being to improve public health. Evaluation of these points involves a measure of the risk/benefit profile of any drug dependent on dose, potential co-medication interactions and effects based on the ethnicity or genotype of the patient. Between 1990 and 2001 in the United Kingdom, 23 drugs were withdrawn—five for hepatotoxicity, seven for QT prolongation, one for drug–drug interactions, two for a combination of QT prolongation and drug–drug interactions, and eight for other reasons. Interestingly, between 1960 and 1999, of 87 out of 121 drug withdrawals, 31% occurred within 2 years of launch and 50% within 5 years. Analysis of the average lifetime of any drug also paints a worrying picture with the average drug lifetime being 12.3 years in the 1970s, 6.6 years in the 1980s and only 2.6 years in the 1990s. Similarly, safety-related label changes to lower the maximum dose followed this trend with 58 U.S. FDA-enforced actions between 1980 and 1999.

The withdrawal of cerivastatin, an effective and clinically popular HMG-CoA reductase inhibitor, from the market because of rhabdomyolysis (31 fatal cases reported to date) associated with its use highlights the perils of drug–drug interactions that afflict many drugs during their routine clinical use. First approved in the United States and the European Union in 1997, the drug was withdrawn from the market worldwide in August 2001, after a market life of just over 4 years. Cerivastatin represents the most recent example in a long list of many valuable drugs that have been lost because of their drug interaction potential. Other drugs withdrawn from the market since 1993 because of drug interactions observed during their routine clinical use include sorivudine (1993), terfenadine (1998), mibefradil (1998), astemizole (1999), cisapride (2000) and levacetylmethadol (2001).

In the current context of P450-mediated metabolism and early drug safety, regulatory interest focuses on genetic modulation of these important drug-metabolizing enzymes with consequences for dose-response studies, drug interactions and extrapolation of data from one population to another.

Dose-response studies are critical to selecting the doses for pivotal efficacy studies. However, it is becoming apparent that dose requirements may be substantially different depending on the genetically determined metabolic capacity of patients. Nortriptyline and perhexiline are good examples of this, with poor metabolizers of CYP2D6 requiring about 5–15 % of the doses required in extensive metabolizers. Not surprisingly, a significant proportion of drugs require postapproval safety-motivated downward amendments to their dose. The International Conference on Harmonisation guideline on "Dose-Response Information to Support Drug Registration" refers to the role of polymorphic metabolism and pharmacological targets in determining dose-response. Of particular regulatory concern is the fact that many new chemical entities are often poorly characterized during their preapproval phase for their interaction potential. Cerivastatin was thought to be primarily metabolized by CYP3A4 with minor contribution from other CYP isoforms. Since there were no interactions with inhibitors or substrates of CYP3A4 and CYP2C19, it was prescribed widely, very often concurrently with gemfibrozil. The dominant role of CYP2C8 in the metabolism of cerivastatin and its inhibition by gemfibrozil was not uncovered until after its withdrawal. Apart from characterization of all P450 isoforms involved in the metabolism of any new drug, it is important that suspected interactions are either confirmed or excluded in adequately designed *in vivo* studies. Since poor metabolizers are not expected to display an interaction, all subjects in early studies should be appropriately genotyped. Regulatory authorities in all the three ICH regions (E.U., U.S.A. and Japan) have issued guidance notes to address all these concerns. Increasing globalization of drug development programs makes a compelling case for early characterization of any metabolic differences between the population investigated and the one targeted. Formal therapeutic studies may well be necessary if it is anticipated from early bridging studies that dose-response relationships in the two populations may be sufficiently different as to be of clinical relevance. The principles are detailed in the ICH Note for Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data.

Conclusions

Drug safety will always play a key role in the development of any new drug. The improved understanding of toxicological and other safety mechanisms coupled with advances in the application of new technologies will allow the pharmaceutical industry to evaluate drug safety issues much earlier in the drug's lifetime, which will provide benefits to both the industry and the patient.

This meeting provided a timely overview of the issues and opportunities facing today's drug discoverer, with opinions from early in the drug discovery process right through to the regulatory process.

Dr. Ian D. Morris, Professor of Pharmacology and Physiology, The Hull York Medical School, University of York, York, U.K., and Dr. Richard E. Armer, Head of Chemistry, Oxagen Ltd., Oxon, U.K., are members of The SMR Committee, which organizes conferences on behalf of the Society for Medicines Research four times a year. These one-day conferences are of a multidisciplinary nature, therapeutically focused and normally staged in or around London. Details about forthcoming meetings can be obtained from: SMR Secretariat, Triangle House, Broomhill Road, London, SW18 4HX, U.K. Tel: +44 (0)20 8875-2431, Fax: +44 (0)20 8875-2424; E-mail: secretariat@socmr.org; URL: http://www.socmr.org.

YAMANOUCHI AND FUJISAWA ANNOUNCE AGREEMENT TO MERGE IN 2005

The Japanese pharmaceutical companies Yamanouchi Pharmaceutical Co., Ltd. and Fujisawa Pharmaceutical Co., Ltd. announced February 24, 2004, that they have entered into a basic agreement to merge on April 1, 2005. This merger will result in a pharmaceutical company ranked number one in the Japanese pharmaceutical market, and 17th in the global pharmaceutical market, with sales of about 800 billion Japanese yen. It is expected that the merger will enhance research and development and marketing capabilities, domestic sales and global operations. Board meetings for the approval and signing of the basic agreement were held today, and meetings for the approval and signing of the final merger agreement are scheduled for May 2004. Shareholder meetings to approve the merger will be held in late June 2004, and the merger will go into effect April 1, 2005. The name of the resulting company is yet to be determined.