Accelerating the Development of Biomarkers for Drug Safety: Workshop Summary

Steve Olson, Sally Robinson, and Robert Giffin, Rapporteurs; Forum on Drug Discovery, Development, and Translation; Institute of Medicine

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Accelerating the Development of Biomarkers for Drug Safety

Workshop Summary

Steve Olson, Sally Robinson, and Robert Giffin, Rapporteurs

Forum on Drug Discovery, Development, and Translation
Board on Health Sciences Policy

INSTITUTE OF MEDICINE
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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the final draft of the report before its release. The review of this report was overseen by **Dr. Johanna T. Dwyer,** Tufts University School of Medicine & Friedman School of Nutrition Science & Policy, Frances Stern Nutrition Center, Tufts-

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New England Medical Center. Appointed by the Institute of Medicine, she was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authors and the institution.

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Preface

Biomarkers are central to the future of medicine. By providing a measure of a biological state, they can indicate normal biological processes, pathogenic processes, or responses to an intervention or perturbation in the environment. They can be used to monitor the on-target and off-target effects of medical interventions, including treatments for disease; they can be used in diagnostic and prognostic tests; and they can define the individuals and populations most likely to respond to therapy. At the broadest level, they can provide insight into biological pathways and networks.

It is also important to recognize that biomarkers have limitations. In isolation, they reveal just one aspect of complex biological systems. Therefore, they may or may not be correlated with clinical outcomes, since other biological systems may override the particular marker being measured. The work needed to understand the relation of a biomarker to either a clinical outcome or a biological system can be enormous. Yet biomarkers are most powerful when they are linked with knowledge about biological systems, with empirical data about diagnostic and therapeutic trials, or with clinical outcomes derived from large populations. The power of modern biology comes from the ability to integrate disparate bases of knowledge, leading to better decisions.

As the cost of developing drugs has risen and the number of new drugs approved for use has fallen, many people have looked to the development of biomarkers as a way to cut costs, enhance safety, and provide a more focused and rational pathway to drug development. Accordingly, greater regulatory emphasis has been placed on the development and use of biomarkers in drug development, which has increased the urgency of accel-

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erating preclinical and clinical research on these markers and establishing evidentiary standards for their use. Biomarker advocates tend to emphasize the progress that has been made, while many drug development teams and experts in clinical effectiveness are skeptical. In fact, both perspectives have merit, and the workshop summarized in this report provided some reassurance that biomarkers, placed in proper perspective, will advance both biomedical science and the pragmatic science of developing drugs that improve human health. At the same time, the workshop also demonstrated the inability of current biomarkers to substitute fully for actual measurement of the risks and benefits of interventions since multiple biological networks and pathways are always in play.

The workshop's final sessions considered the increased complexity of validating and qualifying multimarker panels of biomarkers. Until recently, biomarkers had been developed one at a time. But the advent of large-scale genomic, proteomic, metabolomic, and advanced imaging technologies is changing the environment in which biomarkers are identified and assessed. In the final session, speakers explored the potential for applying cutting-edge scientific technologies to enhance the prediction and detection of drug-induced toxicity, discussed the integration of systems biology and computational biology into toxicity assessments early in drug development, and considered the regulatory and scientific challenges involved in the development and use of multimarker panels.

The workshop was not designed to produce consensus on future steps that should be taken, but in the course of the discussion, numerous ideas arose that can provide insight into measures that might be useful. The workshop challenged participants to consider how each individual and group might contribute to advancing this work, and the workshop organizers hope that this publication will do the same for a broader group of readers.

Robert Califf
Chair

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Contents

1 INTRODUCTION 1
Workshop Purpose, Scope, and Objectives, 2
Crosscutting Issues, 3
Organization of the Report, 5
References, 5

2 OVERVIEW OF KEY ISSUES 6
Predictions Based on Biomarkers, 9
Validation vs. Qualification, 10
Mechanisms vs. Patterns, 11
Regulatory Approval of Biomarkers, 12
Regulation of Single Biomarkers vs. Panels of Biomarkers, 13
Measures of Success, 13
An Example: Biomarkers for Toxicity of Psychiatric Drugs, 14
References, 16

3 CARDIAC SAFETY BIOMARKERS 17
The Regulatory Response, 19
Responses of Drug Developers, 20
Effects on Physician Decision Making, 21
Other Cardiac Safety Biomarkers, 22
The Cardiac Safety Research Consortium, 24
Lessons Learned, 26
Highlights of the Breakout Discussion, 26
References, 28

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Accelerating the Development of Biomarkers for Drug Safety: Workshop Summary
http://www.nap.edu/catalog/12587.html

4 ASSESSING AND PREDICTING KIDNEY SAFETY 29
The Current State, 30
A Vision of the Future, 37
Highlights of the Breakout Discussion, 39
References, 41

5 BIOMARKERS OF ACUTE IDIOSYNCRATIC HEPATOCELLULAR INJURY IN CLINICAL TRIALS 42
Acute Idiosyncratic Hepatocellular Injury (AIHI), 43
Current State of Biomarkers for AIHI, 45
Potential New Biomarkers for AIHI, 50
Highlights of the Breakout Discussion, 52
References, 55

6 FUTURE CONSIDERATIONS 58
Creating Incentives for Collaboration, 58
Moving Forward Without Understanding Mechanisms, 61
Dealing with Different Levels of Risk, 63
References, 64

APPENDIXES

A Workshop Agenda 65
B Speaker Biographies 71

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Tables, Figures, and Boxes

TABLES

3-1 Strengths and Weakness of the QTc Interval as a Safety Biomarker, 18

4-1 Promising Translational Biomarkers of Acute Kidney Injuries, 32
4-2 Current Deficiencies, Needs, and Proposals to Address Kidney Safety Issues in Early Drug Development, 38

5-1 Regulatory Actions on Approved Drugs Due to Hepatotoxicity, 1995–2008, 44

FIGURES

2-1 The number of new molecular entities (NMEs) submitted to the FDA has fallen since the mid-1990s, 8

5-1 Acute idiosyncratic hepatocellular injury, 44

BOXES

2-1 The Toll of Mental Illness, 15

4-1 Initiatives to Advance Understanding of Kidney Safety Biomarkers, 33

6-1 Systems Biology and Biomarker Development, 62

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1

Introduction

Biomarkers are biological substances, characteristics, or images that provide an indication of the biological state of an organism.[1] Biomarkers can include physiological indicators, such as blood pressure; molecular markers, such as liver enzymes and prostate-specific antigen; and imaging biomarkers, such as those derived from magnetic resonance imaging and angiography. In the research context, biomarkers can provide indications of both the potential effectiveness and the potential hazards associated with a therapeutic intervention. They can be used to understand the mechanism by which a drug works, to make decisions about whether to develop a drug, to screen compounds for toxicity before they enter clinical trials, to monitor the development of toxicity during clinical trials, and to forecast adverse events resulting from wider exposure. Thus biomarkers can potentially reduce the costs of developing drugs, enhance the safety of drugs, and speed the movement of drugs to market.

The use of biomarkers in drug development raises a number of issues. As a measure of biological function, a biomarker can help unravel a mechanism or biological pathway, or it can serve as a predictor of the future course of health or disease. As biomedical science evolves and becomes increasingly computational and probabilistic, the tools for understanding the predictive value of biomarkers are changing, as are the criteria used

[1]A National Institutes of Health (NIH) working group has defined a biological marker or biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to therapeutic intervention" (Biomarkers Definitions Working Group, 2001).

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for assessing them—for example, sensitivity, specificity, reliability, and discrimination. Since biomarkers typically quantify physiological states or therapeutic responses, choosing the values in decision rules—for example, "cutoff points"—becomes very important and difficult, as different values can yield quite different perspectives. In the familiar examples of creatinine for kidney injury, troponin for cardiac injury, and alanine aminotransferase (ALT) for liver injury, the higher is the value, the higher is the probability of true injury, yet low values may signal the early phase of damage.

The use of biomarkers often involves a trade-off between sensitivity, or the proportion of positive responses that a biomarker correctly identifies as positive, and specificity, or the proportion of negative responses that a biomarker correctly identifies as negative. Different degrees of sensitivity and specificity are needed in different circumstances, and will be dependent upon the intended use of the biomarker.

Individual biomarkers differ in the extent to which they reflect a known biological mechanism. Greater understanding of mechanism can be extremely helpful in such tasks as comparing the action of related drugs or gauging the relevance of animal findings to humans. However, biomarkers can provide useful information even when a detailed understanding of mechanism is lacking.

No one biomarker is likely to have all of the characteristics necessary to provide a robust understanding of response As a result, future use of combinations of multiple biomarkers to enable improved prediction of drug efficacy and safety is likely. Yet the use of such combinations of biomarkers may introduce its own challenges, including technical issues of how to combine results, how to control quality, and how to interpret results in different clinical contexts.

The improper use or interpretation of biomarkers can be detrimental in both clinical and research settings by misdirecting therapy or research activities. If biomarkers are to be used properly, there needs to be an understanding of their sensitivity and specificity, how and in what contexts to use them, how to interpret them in those various contexts, and how to properly validate them.

WORKSHOP PURPOSE, SCOPE, AND OBJECTIVES

To better understand the current state of the art in the development of biomarkers, consider the issues involved in their development and use, and discuss their future development, the Institute of Medicine's (IOM's) Forum on Drug Discovery, Development, and Translation held a 1-day workshop on October 24, 2008, on "Assessing and Accelerating the Development of Biomarkers for Drug Safety." Participants included experts from academia, government, and industry. To ensure a manageable range of content, the

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workshop was limited in two ways. First, it focused on biomarkers used to determine safety; biomarkers used to determine efficacy were not considered. Second, consideration of safety biomarkers was limited to those associated with three organ systems: cardiac, kidney, and liver. These three were chosen because they represent a large proportion of toxicity problems related to drug development, they include a diverse range of biomarker types, and they are associated with varying degrees of success in biomarker development.

The workshop had three main objectives:

- To assess the current state of the art for screening technologies to find off-target effects early in drug development
- To compile a list of questions to address remaining obstacles to the development of biomarkers for drug safety
- To discuss how to accelerate the development of biomarkers through public and private means

The workshop benefited from three white papers on the state of biomarker development and use for the above three organ systems. Using these papers as a starting point, three breakout groups each focused on one of these systems, producing a host of observations and insights relevant to the three objectives of the workshop.

CROSSCUTTING ISSUES

During the course of the workshop, three major issues emerged that affect the development and use of biomarkers to detect toxicity across the three organ systems.

Incentives

The development of needed information about biomarkers is thought by most to be beyond the scope of an individual company or academic institution. Furthermore, the Food and Drug Administration (FDA) is neither equipped nor funded to conduct such research. Accordingly, incentives are needed to encourage research groups to overcome traditional barriers of secrecy and protection of intellectual property. Incentives could be helpful in translating the results of basic research into biomarker applications that have an impact on health care. In particular, incentives that promote collaboration among industry, the FDA, the National Institutes of Health (NIH), and academic researchers could yield much more rapid progress in the development of biomarkers. Clear agreement on the data that need to be submitted to regulatory authorities would reduce industry-perceived

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constraints on generating some forms of data. Collaborations also could lead to the establishment of standards for submission databases, review databases, and electronic medical records. Successful partnerships depend on finding common ground among partners and taking into account the varying interests of different groups.

Understanding Mechanisms of Action

Although a biomarker can provide predictive information based solely on the association between its intensity and organ toxicity or other outcomes, biomarkers have their greatest value when they unveil a mechanism that can be understood so the drug can be altered to avoid the toxicity. The same is true when biomarkers reveal mechanisms of benefit. Yet regardless of whether such mechanistic insights are gained, reliable information that can distinguish who is at risk and who will benefit is valuable. And the discovery of a predictive biomarker can lead to further research on the association between that biomarker and an outcome.

Benefit/Risk Balance

Ultimately, the goal of drug development is to optimize the balance of benefit and risk when a drug is used, and then to provide accurate information for patients, physicians, payers, and ultimately society about the balance that will be observed when that drug is used by patients. In the past, these estimates of benefit/risk balance have come from projections from mechanistic reasoning, often without empirical data, or from average population outcomes from clinical trials. The identification of biomarkers that can distinguish patients particularly susceptible to risk or suggest an enhanced likelihood of benefit could make these calculations more accurate, and enable decisions to be tailored to the characteristics of individual patients. This capability forms the basis for the concept of personalized medicine, which employs biomarkers to stratify populations into smaller groups according to such differences in benefit and risk.

Realizing this capability is one potential outcome of the "learning healthcare system" that has been described by IOM (2007). In such a system, patients will be more likely to participate actively in research programs, knowing that their participation will contribute to a broader understanding not only of their condition, but also of the particular risks and benefits they face as individuals.

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ORGANIZATION OF THE REPORT

The remainder of this report provides a comprehensive summary of the presentations and discussions that occurred during the workshop. Chapter 2 provides an overview of key issues in the use of biomarkers in drug development. Chapters 3, 4, and 5 present final versions of the white papers prepared for the workshop on cardiac, kidney, and liver safety biomarkers, respectively. In addition, the final section of each of those chapters summarizes the discussions that occurred during breakout sessions that followed the presentations in these areas. Chapter 6 summarizes future actions suggested by workshop participants to further the use of biomarkers in drug development.

It should be noted that while the IOM Forum on Drug Discovery, Development, and Translation introduced the idea for this workshop, its planning was the responsibility of an independently appointed committee. That committee's role was limited to advance planning; this summary was prepared by an independent rapporteur, with the assistance of forum staff, as a factual summary of what occurred at the workshop.

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IOM (Institute of Medicine). 2007. *The learning healthcare system: Workshop summary*. Washington, DC: The National Academies Press.

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2

Overview of Key Issues[1]

As indicators of biological function or state, biomarkers have many potential applications in research and medicine: they can provide information useful for the diagnosis, treatment, and prognosis of disease; they can indicate whether a drug is having an effect in an individual and whether side effects can be anticipated; and they can be used to screen populations for particular biological characteristics or environmental exposures. Biomarkers also have many potential applications in the development of drugs. As Janet Woodcock of the FDA pointed out, they can improve the predictability of drug development, and increase the value of preventative and therapeutic interventions by targeting individuals with a high probability of benefit and screening out those at high risk of side effects. Biomarkers can be used to screen compounds for toxicity before they enter clinical trials, to inform decisions about whether to develop a drug, to monitor the development of toxicity, to forecast adverse events given wider exposure, or to understand the mechanism by which a drug works.

Tests to assess the variability of a patient's drug-metabolizing enzymes are already being used to adjust doses in individuals. Other biomarker-based tests are being used to determine whether an individual is at increased risk of having an adverse reaction to certain compounds, and to avoid treatment if the balance of benefit and risk is unacceptable. These kinds of applications can be expected to multiply rapidly.

[1]This chapter is based on the remarks of Janet Woodcock, Director of the FDA's Center for Drug Evaluation and Research; Alastair Wood, Managing Director of Symphony Capital, LLC; and Thomas Insel, Director of the National Institute of Mental Health.

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Biomarkers can take many different forms. In preclinical screening, for example, they may entail studies of gene expression or cell systems. Animal studies can make use of genomic and proteomic techniques, thereby increasing the probability that initial administration to humans will be safe, or help establish the relevance of animal findings to humans. Biomarker findings in clinical trials and postmarket data also can provide information about mechanisms of drug toxicity or benefit and suggest the need for additional nonclinical studies to fully elucidate the relevant mechanisms. In a clinical setting, such information can be used, for example, to monitor reactions to drugs in individuals or to deselect individuals from trials who may be at risk from a treatment.

In considering the use of biomarkers for drug development, additional issues arise, said Alastair Wood of Symphony Capital, LLC. To be useful, a biomarker for toxicity found to be elevated by an investigational drug in preclinical studies must provide some level of confidence that carrying such a drug forward into clinical trials will produce toxicity in a proportion of patients. This proportion must be significant enough to alter decision making about developing the drug, to point to a different course of action in patient selection for clinical trials, or to necessitate more detailed studies prior to marketing so that safety signals can be assessed. Conversely, the absence of elevation of a biomarker should imply confidence that a safety problem will not occur in more than a known (low) proportion of patients. In this way, the use of a biomarker can provide risk assessment and risk mitigation, both to patients who are likely to receive the drug clinically and to the development program carrying that drug forward.

Beyond these broad considerations lie more detailed questions. If a biomarker is elevated in a small number of people in early clinical studies, what is the overall risk to any given individual or to a population? If the absolute degree of elevation is small, does this mean that the likely toxicity will be mild when the drug is given to a large population of patients, and/or does it mean that only a small proportion of patients will develop severe toxicity? Unfortunately, the answers to these questions are seldom known with any degree of certainty. Does the absence of a biomarker signal necessarily predict long-term safety?

The use of biomarkers potentially could address several major problems associated with drug development. The costs of new drug development have risen rapidly even as the number of new molecular entities (NMEs) submitted to the FDA has fallen (Figure 2-1). In addition, a number of drugs have been withdrawn from the market because of safety concerns. By enhancing the ability to assess whether drug candidates are promising early in development, biomarkers could reduce the costs of developing drugs and bringing them to the market, enhance the safety of new drugs, and improve

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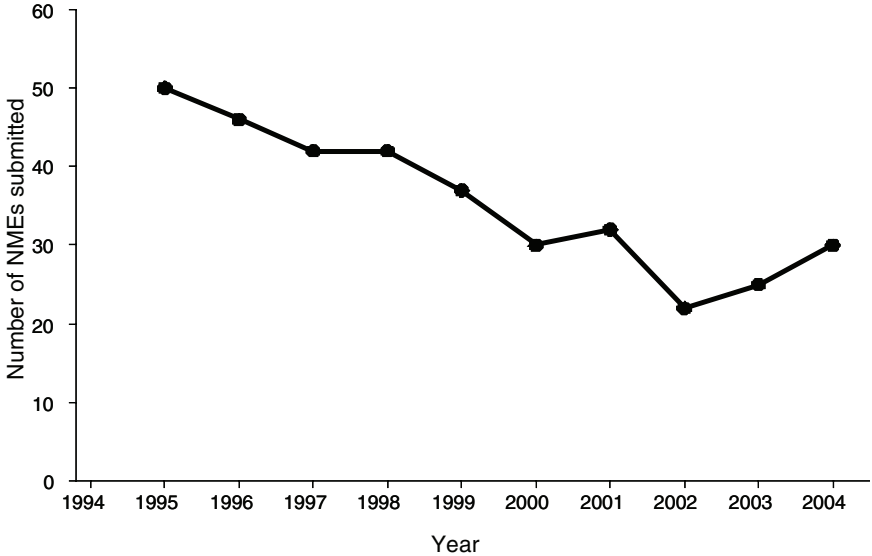

FIGURE 2-1 The number of new molecular entities (NMEs) submitted to the FDA has fallen since the mid-1990s.
SOURCE: Frantz, 2004.

the cost-effectiveness of drugs by targeting treatment to those patients with the best balance of risk and benefit.

A particularly valuable use of biomarkers would be to help bridge the gap between the preclinical and clinical development of new drugs. For example, a preclinical biomarker that produces similar results in tissue cultures or model organisms and in clinical use in humans might reliably predict human responses to a compound. Or a bridging biomarker might predict toxicity very early in humans—before harm occurs—and at very low doses. As the FDA white paper *Innovation or Stagnation: Challenges and Opportunity on the Critical Path to New Medical Projects* states, "A new product development toolkit—containing powerful new scientific and technical methods such as animal or computer-based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques—is urgently needed to improve predictability and efficiency along the critical path from laboratory concept to commercial product" (FDA, 2005, p. ii).

The remainder of this chapter reviews several important issues involved in the use of biomarkers in drug development: predictions based on bio-

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markers, validation vs. qualification, mechanisms vs. patterns, regulatory approval of biomarkers, regulation of single biomarkers vs. panels of biomarkers, and measures of success. It concludes with a specific example: the use of biomarkers to improve the treatment of mental illness.

PREDICTIONS BASED ON BIOMARKERS

One critical issue involved in assessing the utility of biomarkers is how well they predict relevant outcomes. Measures of the performance of biomarkers include sensitivity, specificity, calibration, discrimination, and reclassification:

- Sensitivity represents the proportion of truly affected cases (persons) in a screened population who are identified as being diseased by the test, and is a measure of the probability of correctly diagnosing a condition.
- Specificity is the proportion of truly nondiseased persons who are identified as such by the screening test. For example, if a biomarker has high sensitivity but low specificity, most of the truly at-risk cases will be correctly identified, but many of the not-at-risk cases will also be identified as at-risk.
- Calibration refers to the agreement between the predicted probability of an outcome and the actual probability when measured in a population.
- Discrimination refers to the ability of a biomarker to distinguish those with a disease or event from those without. A biomarker could have excellent calibration with poor discrimination and vice versa.
- Reclassification has become a critical issue in assessing biomarkers. It refers to the ability of a biomarker measurement to move the probability of an outcome beyond a threshold that leads to a different diagnosis, prediction of outcome, or clinical decision than would have been made based on prior information.

The synthesis of these measures is complex since biomarkers can be excellent for some purposes and mediocre for others, thereby complicating their use for decision making. One of the greatest challenges to the application of biomarkers in drug development is that numerous and conflicting arguments can be made for placing greater emphasis on specificity than sensitivity or vice versa. For example, one could argue that a biomarker that yields a high number of false negatives may fail in preclinical studies to detect problems with drugs that go on to produce toxicity in clinical studies. This lack of sensitivity not only puts patients at risk but also may result in

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the waste of future development costs. On the other hand, false positives can be equally damaging by causing large numbers of potentially successful and safe drugs to be lost during development. Thus if sensitivity is too high at the expense of specificity, false positives will result in denying patients access to useful therapies. This complexity can be greatly exacerbated by the simultaneous use of multiple biomarkers in screening. For example, if every drug must be screened using 50 safety biomarkers, and if each biomarker has a false positive rate of 1 percent, up to half of all useful drugs will be wrongly eliminated during an early stage of development.

The acceptable sensitivity and specificity will vary from drug to drug and from indication to indication. For example, the safety requirements differ between a therapy for nasal allergy and a cancer drug. Wood stressed that a nuanced approach is needed to answer specific questions.

A major potential use of biomarkers is to predict and monitor the toxicity of a drug in a clinical trial. In these cases, an important issue is the extent to which a negative or a positive test has predictive value. In other words, if a person shows elevation of a biomarker and is deselected from a trial, how likely was that person to have actually experienced a clinically significant adverse event? Often the answer remains unknown, even when a drug is on the market, because the only way to fully articulate the performance of a biomarker is to measure the outcomes of the relevant population with an adequate sample size to generate reliable probability estimates.

Assays that can make such determinations may already be on the market with another indication or may need to be codeveloped with a drug. An example is the drug abacavir, whose use is limited by a significant incidence of adverse events. A randomized controlled trial demonstrated risk reduction with the use of a human leucocyte antigen (HLA) region marker for risk (HLA-B*5701), and this marker was recommended for use in a black box on the drug's label. This diagnostic test had been well established because HLA markers are used for tissue typing.

With safety markers for new drugs, ethical considerations dictate ascertainment of the value of a test as early as possible in drug development. Explicit study designs are needed to answer safety questions, such as when to stop enrolling patients who test positive or to discontinue treatment in those with an elevated biomarker. It is critical to obtain definitive answers about safety while keeping participants in a trial as safe as possible.

VALIDATION VS. QUALIFICATION

Currently, there is a lack of clarity regarding several terms commonly used in the discussion of biomarkers. In particular, Woodcock urged that standard definitions be adopted for the terms "validation" and "qualification." Validation, she said, should be used for analytic validation, which is

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a measure of how well a test detects or quantifies an analyte under various conditions. Validation thus would require demonstration of the performance characteristics of an assay. In contrast, qualification is a measure of the use of a biomarker in a specific context. That context may be selecting or deselecting people for a clinical trial, monitoring drug-induced toxicity, or some other purpose. The amount of evidence needed to qualify a biomarker for a given purpose is related to the consequences of using the result to make decisions, such as whether to pursue the development of a drug or whether to withhold a drug from individuals in a clinical trial.

Analytic validation is necessary but generally not sufficient for a biomarker. It requires a stable platform and the establishment of standards that facilitate the linking of results across laboratories. Validation also requires study of variability among users and among laboratories. In addition, validation requires an understanding of the potential for drugs or other conditions to interfere with results. These are not the kinds of activities that generally earn tenure for faculty members, Woodcock observed, but they are critically important to understanding the performance of an assay. In contrast, qualification requires context-specific measurement of the performance of the biomarker in relation to an outcome or outcomes of interest.

MECHANISMS VS. PATTERNS

Another important issue for the development of biomarkers is the distinction between mechanistic understanding and pattern recognition. For some biomarkers, there may be a detailed understanding of the mechanism that links the use of a drug to the elevation of a biomarker and thence to the development of clinical toxicity. In other cases, a drug may produce an effect pattern—such as a pattern of gene activity on a microarray—but the mechanism linking the use of the drug to the change in the array and thence to an adverse clinical effect is either unknown or poorly understood. In these cases, decisions may have to be made on the basis of pattern recognition without a clear understanding of the mechanistic link.

When a mechanism is unknown, considerable work is required to define the level of specificity needed to influence decisions. Drug developers may not know what preclinical signals of toxicity to look for until clinical toxicity has been observed late in drug development or even in clinical use. For example, many kinase inhibitors now used clinically in oncology produce cardiac toxicity, perhaps because they inhibit a specific kinase in the heart. Without knowing whether that is indeed the mechanism or which specific cardiac kinase is responsible, however, mechanism-based biomarkers cannot be used to screen for this toxicity in preclinical studies. If the relevant kinase were discovered, a biomarker assay for that mechanism

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would enable rapid screening of drugs for toxicity. Therefore, understanding of the mechanisms of toxicity offers the best chance of both developing safer drugs lacking that toxicity and defining useful biomarkers to detect toxicity early in drug development, while purely empirical assessment of biomarkers requires much larger samples with greater uncertainty.

An understanding of mechanism also can be critical in gauging the relevance of animal findings to humans. Many drugs are lost from development because of toxicity findings in animals that are seen infrequently or not at all in humans. Because the mechanism often is not understood, however, it is difficult to predict whether the same toxicity will occur in humans since there is no way to determine, other than by empirical observation in large numbers, whether the same systems are at play in human biology.

REGULATORY APPROVAL OF BIOMARKERS

Biomarkers being developed for commercial uses have several paths toward regulatory approval, each of which requires a different level of evidentiary data. For novel diagnostics, a premarket approval (PMA) application must be submitted, although the FDA can assign a "de novo classification" to a diagnostic test that streamlines the approval process. Other biomarkers used as in vitro diagnostics reach the market through a 510(k) application, which demonstrates that a product is "substantially equivalent" to some previous device. An important distinction between these mechanisms is that a PMA application must include data showing that the device is safe and effective, whereas a 510(k) application need only include data supporting the performance standards and validity of the device's intended use. A third category of biomarkers reach the market as laboratory-developed tests that are not submitted to the FDA for approval but are marketed by laboratories overseen by the Clinical Laboratory Improvement Amendments (CLIA) program. Most commercially available genetic tests fall into this category.

If a biomarker or panel of markers is to be used to justify regulatory decision making, the assay used to measure that marker(s) must demonstrate validity and clinical utility. According to the FDA's pharmacogenomic guidance document (FDA, 2005, p. 4), a valid biomarker is "a biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of test results."

For in vitro diagnostics requiring a PMA, clinical utility must be demonstrated along with validity. Clinical utility could be demonstrated, for example, by adequate detection of an analyte if a clinical link is well-established in the literature. It also could be established through other

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means, such as the analysis of stored specimens. Again, the burden of proof is proportional to the risk; thus, for example, prognostic claims for a test in the absence of a specific critical decision directly linked to the test result have less of a burden than other claims.

REGULATION OF SINGLE BIOMARKERS VS. PANELS OF BIOMARKERS

Marketing standards are the same whether a diagnostic is a single assay, a set of assays, or a panel of biomarkers. For example, in vitro diagnostic multivariate index assays (IVDMIAs) use the results from multiple analytes to create an "index," "score," or other measure. The method used to derive a score is often algorithmic and not clinically transparent. This is typical of several new technologies, such as the use of genomic or proteomic screens to produce a result.

The FDA has proposed a regulatory framework for IVDMIAs that involves submission to and review by the agency. Technical issues are often significant for an IVDMIA because of decisions about which analytes to include, how to weight those analytes, what cutoff values to use, how to handle changes to a test once it has been developed, and what quality control methods to apply. The FDA proposal has been controversial because of the conflict between the need for FDA review and the rapid evolution of the industry.

Multiplexed assays raise issues of effectiveness in addition to safety. For example, the National Cancer Institute is planning a prospective randomized trial for treatment or nontreatment of early-stage cancer based on a gene expression panel. In such cases, efficacy must be definitively tested in the intended population, and several trial designs for this purpose have been proposed in the literature.

MEASURES OF SUCCESS

A general issue in the use of safety biomarkers is how success should be defined. In the broadest possible terms, success is measured by improvement in the clinical safety of drugs being developed. As there is no way of preventing every drug that proves to have a toxic effect from proceeding into clinical trials, however, definitions and measures of safety must be established.

An unintended consequence of biomarker development may be a decrease in the number of available drugs. Once a biomarker has been developed and marketed, it may inhibit the development of drugs if it generates a positive signal that indicates potential future problems. Many companies would hesitate to proceed with the development of such a biomarker, even if there were a poor correlation between the biomarker and

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toxicity. One way to help establish definitions of success would be to look back at drugs that have shown toxicity and identify which biomarkers were elevated in preclinical models. Such an approach would require that companies share compounds for study after clinical development or marketing has ended. This retrospective approach would be valuable as there is substantial knowledge of actual clinical experience with such drugs. In contrast, when elevation of a biomarker results in a company's preemptive termination of development, there is limited evidence to evaluate.

Much of the publicity regarding drug safety has focused on the detection of events that are rare, such as acute hepatic failure, which recently was a cause for concern with the drug troglitazone. But a bigger problem, according to Wood, is the drug that produces an increased incidence of a frequent event, such as the Cox-2 inhibitors, which caused an increase in myocardial infarctions. A substantial increase in the rate of myocardial infarction with a drug could produce hundreds of thousands of cases, yet it could be difficult to detect the problem in preclinical work, especially if a mechanistic hypothesis were not available. In addition, the postmarket reporting system is ill qualified to detect an increased frequency of such events that are common in the background population.

The challenge, Wood concluded, is to develop safety markers that are reliable and validated across drugs and across companies, both prospectively and retrospectively. Regardless of whether the mechanism of action is known or unknown, it is necessary to develop systematic methods for exploring the biological and clinical implications. Thus, improved understanding of biomarkers must be coupled with improved epidemiological surveillance methods and randomized trials, when needed to elucidate modest differential effects of a drug on common outcomes. Meeting these needs will allow for the development of increasing numbers of drugs that are safer and less expensive to bring to market.

AN EXAMPLE: BIOMARKERS FOR TOXICITY OF PSYCHIATRIC DRUGS

Thomas Insel of the National Institute of Mental Health discussed the use of biomarkers in addressing a major problem in the United Stats, as well as globally—mental illness (see Box 2-1). Responses to both drugs and other types of therapy used to treat mental illness vary greatly. Today, there is no way to determine, a priori, which patients will respond well to which treatments or will experience adverse side effects with medication. The hope is that biomarkers will provide guidance for interventions at all stages of a mental illness. Biomarkers may even make it possible to predict future problems arising from mental illnesses such as schizophrenia and to use medications preemptively.

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BOX 2-1
The Toll of Mental Illness

Mental illness is the leading cause of medical disability for people between the ages of 15 and 44. Mental illness is often chronic, can start early in life, is highly prevalent, and may be severely disabling.

More than 30,000 suicides occur each year in the United States. By comparison, only three forms of cancer kill more than 30,000 people per year, and homicides and AIDS kill 18,000 and 20,000 people, respectively. Life expectancy for people with major mental illnesses is only 56 years, more than a quarter century less than the average. Most of this excess mortality is not due to suicide, but to general medical disorders that are secondary to the mental illness, such as pulmonary and liver disease. According to one estimate, for example, 44 percent of all cigarettes are smoked by people with mental illness.

Although medications are widely used to treat mental illness—more than 200 million prescriptions per year are written for antidepressants, more than for any other class of drugs—currently available drug therapies are much less effective than desired. The total direct and indirect costs of mental illness in the United States are estimated at more than $300 billion, or more than $1,000 per American, yet only about $5 per American is spent on efforts to understand the causes, treatment, and potential preventive measures for these conditions. If these heterogeneous problems could be better understood and classified using biomarkers, substantial impact on mortality and morbidity in the U.S. population might be realized.

SOURCE: Insel, 2008. Data: WHO, 2002.

A major emphasis in recent years has been pharmacogenomics—the use of high-throughput resequencing to associate particular genetic variants with responses to medications. For example, variants in a protein that transports compounds across the blood–brain barrier can influence whether a medicine will be effective. Similarly, variants in neurotransmitter receptors can predict some of the variation in response. Thus far, however, the observed effects of genetic variants have been relatively small. In addition, the predictive power of genomics is limited by the heterogeneity of the disorders being treated and by individual variations in choice of treatment, response, toxicity, and adherence to a therapeutic regime.

A key problem has been predicting adverse effects in patients treated with psychiatric drugs. In a study involving 1,742 patients, 120 developed suicidal ideation while receiving antidepressants. Variants in two receptor genes were associated with increased thoughts of suicide, but these findings need to be replicated and extended.

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While an individual marker may be informative, a combination of several markers related to different parts of a pathway could be far more useful. Some of these markers may not be genetic—they may be "downstream markers" such as protein or metabolite levels in cells or the blood, or imaging of active brain regions. For example, imaging of a region of the brain known as "area 25" has revealed that it is overly active before treatment for depression and less active after treatment. This is the case whether the treatment consists of medication, cognitive-behavioral therapy, or even placebo. Conversely, in those who do not respond to an intervention, activity in this area does not decrease. This decrease in activity in area 25 thus appears to be necessary, and possibly sufficient, for the antidepressant response. Perhaps by combining a better understanding of brain circuitry from imaging with genetic and proteomic data, a panel of diverse biomarkers could be developed that would predict responses.

NIH supports research to discover potential biomarkers using a variety of approaches. The development and use of biomarkers can contribute to what Insel called the 3D pathway, which stands for discovery, development, and dissemination. Once potential indicators of clinical response or toxicity have been identified, these predictors need to be studied through prospective development studies. Finally, predictors need to be cost-effective so that they will be adopted and change the standard of care. Too often, powerful evidence-based interventions are neglected in medical practice because they either are not reimbursed or are not well understood.

Insel noted that, while biomarkers could have an enormous impact on the prevention, diagnosis, and treatment of mental illness, their benefits and costs need to be carefully weighed. The emphasis today is on making health care more efficient and less expensive, not more high-tech and more expensive.

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3

Cardiac Safety Biomarkers[1]

In the 1990s, reports of potentially fatal cardiac arrhythmias in adverse event data focused attention on the potential of several drugs to cause cardiac toxicity. One effect of these drugs was to prolong the interval between the onset of the Q wave and the conclusion of the T wave in the heart's electrical cycle—which is known as QTc when corrected for heart rate. This association with QTc prolongation and cardiac arrhythmias led to the removal of a series of drugs from the market, including terfenadine in 1998, astemazole and grepafloxacin in 1999, and cisapride in 2000. QTc is one of the oldest and best-known safety biomarkers used throughout drug development. The effect of a drug on QTc is an important input to regulatory decision making and has a major impact on how pharmaceutical companies design and prioritize drug development programs.

Compared with the newer safety biomarkers discussed later in this chapter, QTc has a number of strengths and weaknesses (Table 3-1). Among its strengths are that the technology needed to measure it is established and nearly universally available; a great deal is known about the molecular mechanisms of the ion channels that affect ventricular repolarization; a number of well-established in vitro and in vivo models exist; there is substantial clinical experience with patients who have a congenital prolonged QT (LQT) syndrome; and a wide array of stakeholders are interested in advancing the understanding and use of this biomarker.

[1]This chapter is based on the remarks of Janet Woodcock, Director of the FDA's Center for Drug Evaluation and Research; Alastair Wood, Managing Director of Symphony Capital, LLC; and Thomas Insel, Director of the National Institute of Mental Health.

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TABLE 3-1 Strengths and Weaknesses of the QTc Interval as a Safety Biomarker

Area	Strengths	Weaknesses
Biology	• Knowledge of molecular mechanisms and ion channels • Cellular models • In vivo models	• Weak links between experimental models and clinical events
Clinical experience and relevance	• Genetic syndromes (LQT), documented clinical events	• Rare clinical events, multifactorial etiologies, unpredictability • Insufficient data available to close gap between signal and rare events
Measurable biomarker	• Old technology, universally available	• Low-frequency and low-amplitude signal, resulting in difficult measurement and poor signal-to-noise ratio • Numerous methods of measurement • Measured in static condition
Multisector involvement	• Interest from academia, clinical medicine, industry (technology, diagnostics, pharma), regulatory agencies	• Lack of harmonization among stakeholders • Lack of infrastructure for a coordinated collaborative effort (now addressed by Cardiac Safety Research Consortium)

Despite these strengths, however, QTc also has several weaknesses as a biomarker for safety. First, there is no consensus on the optimal method of acquiring, measuring, and analyzing the QTc interval. This is due in part to the nature of the signal, which has low frequency and low amplitude, has a poor signal-to-noise ratio, is intrinsically variable, and is affected by a number of important confounding factors. Second, the link between the experimental models of QTc and the occurrence of rare and unpredictable clinical events is weak, in part because insufficient data have been collected to close this gap. Specifically, clinical epidemiology data have not been collected that would define the probability of an episode of the ventricular tachycardia known as torsade de pointes based on the QTc interval.

It should be noted that, while many biomarkers are used to understand a wide range of cardiovascular conditions—such as hyperlipidemia, inflammation, and ischemia—the scope of the discussion in this session of the workshop was limited to biomarkers of electrophysiologic toxicity, in particular, those related to QT interval prolongation.

This chapter begins by describing the regulatory response to the recognition that cardiac events were resulting from adverse reactions to drugs,

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the responses of drug developers, and effects on physician decision making. This is followed by a review of issues related to the development of potential cardiac safety biomarkers other than QTc, with a particular focus on troponin, and the possible contributions to this work of the Cardiac Safety Research Consortium (CSRC). Some lessons learned from experience to date with the development of cardiac safety biomarkers are then summarized. The chapter ends with highlights from the breakout discussion of key steps necessary for further progress.

THE REGULATORY RESPONSE

The recognition that cardiac events were being caused by adverse reactions to drugs led to a variety of regulatory responses. In 1997, the FDA and the International Conference on Harmonisation (ICH) issued *Guidance for Industry: S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (FDA, 1997). This was followed in 2001 by *Guidance for Industry: S7A Safety Pharmacology Studies for Human Pharmaceuticals* (FDA, 2001). Both of these documents stated that cardiovascular safety testing should be performed on new drugs, but provided no specific guidance on how this testing should be conducted. In 2001, the FDA announced that in fall 2002, it would begin collecting raw electrocardiogram (ECG) data from sponsors, and in 2002 a "points to consider" document was jointly authored by the FDA and Health Canada (FDA, 2002). This was followed by FDA/ICH guidance documents providing more specific recommendations regarding clinical (E14) (FDA, 2005a) and preclinical (S7B) (FDA, 2005b) testing approaches. The E14 guidance called for "thorough QT" (TQT) studies of new drugs to assess their potential for causing torsade de pointes. Even prolongation of QTc by just a few percent was considered to be clinically relevant. The FDA then established an interdisciplinary team to handle the review of QTc-related protocols and studies, to ensure a uniform response, and to accumulate experience in this area.

As the regulatory response was being crafted, the FDA made a public appeal for the development of standards for digital ECG data. This action was based on the idea that it will be critical to review the ECGs from TQT studies. Such a data standard was developed in 2002 and formally adopted by the Health Level 7 (HL7) standards organization in early 2003.[2]

As the data standard was being finalized, the FDA entered into a Cooperative Research and Development Agreement with Mortara Instruments

[2]See http://www.hl7.org/search/viewSearchResult.cfm?search_id=17061&search_result_url=%2FLibrary%2FCommittees%2Frcrim%2Fannecg%2FaECG%20Release%201%20Schema%20and%20Example%2Ezip.

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to develop a web-accessible repository for conforming digital ECG data. This repository came online in 2005 and now hosts more than 2.5 million digital ECGs collected from more than 150 clinical studies.

RESPONSES OF DRUG DEVELOPERS

As the ICH S7B and E14 guidance documents were being developed, responses from the pharmaceutical industry were mixed. In general, industry appreciated clarification of the standards for preclinical and clinical assessments of the effects of a drug on ventricular repolarization. In particular, industry was pleased that E14 created a clear definition of a compound with no QTc risk and made it clear that no further evaluation of QTc would be necessary for these compounds.

However, industry representatives raised two concerns related to the E14 guidance. First, E14 specified that every systemically available small molecule would require a clinical TQT study even if the results of the extensive preclinical studies related to ventricular repolarization outlined in S7B were completely normal. Second, E14 set an extremely high bar for declaring that a compound posed no QTc risk: at supratherapeutic exposures, a compound had to demonstrate an increase in QTc of less than 5 milliseconds (ms) (mean) or 10 ms (upper confidence limit) in a study that demonstrated assay sensitivity by detecting an increase in QTc of a similar magnitude with a positive control (usually moxifloxacin).

These two concerns were focused primarily on a fear that very small signals in QTc would be identified in compounds when there was no theoretical risk, when no preclinical evidence suggested future problems, and when early clinical evidence showed no signs of QTc prolongation. The initial lack of understanding of what it means when a compound demonstrates a 5–10 ms increase in QTc generated considerable uncertainty in drug development. In particular, drug developers asked questions such as the following:

- What was the clinical significance of such a small increase in QTc?
- What additional studies would be necessary in later phases of drug development to clarify the clinical significance of an increase in QTc of this magnitude?
- How would these additional studies affect the timelines and costs of drug development?
- What is the likelihood that these additional data would be able to offset the perceived risk associated with a small but clearly documented increase in QTc from a TQT study?
- How should a company weigh this potential increase in risk against the potential benefits of a drug?

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- How would these issues be described on the drug label?

Because of the uncertainty surrounding these questions, some pharmaceutical and biotechnology companies avoided developing compounds with any potential for this liability. In the process of prioritizing compounds in a portfolio, companies began looking for ways to kill compounds with any potential QTc liability. Any increase in QTc in preclinical studies generated the perception that the compound would face enormous hurdles in drug development. Some companies began to discontinue compounds in development solely because of in vitro studies demonstrating an interaction with the hERG channel (a potassium ion channel involved in ventricular repolarization), even in the absence of evidence of prolonged QTc during in vivo animal studies. In addition, as compounds advanced through development, companies feared being penalized for evaluating supratherapeutic exposures and attempted to minimize this risk by limiting the maximum doses studied.

With regard to drug development, the ultimate success of the E14 and S7B guidance documents will be realized when there is a shared understanding between pharmaceutical companies and regulatory agencies of the clinical significance of a small increase in QTc interval in the context of the possible benefits of a new molecular entity. Excessive focus on this biomarker in the absence of true clinical risk could stifle innovation and lead to an unfortunate decision to discontinue the development of a drug that could offer patients benefits outweighing the actual risk.

One solution to this potential conundrum is to create an environment in which regulatory agencies, academics, and industry scientists can collaborate to better understand the link between the safety biomarker (in this case QTc) and the event it is intended to predict (in this case torsade de pointes). All parties involved would benefit from improved clinical epidemiology and greater understanding of how to measure and use this safety biomarker. If successful, this type of collaboration would likely result in better decision making that would place the risks of a drug in the context of its benefits. The potential of this approach is demonstrated by the CSRC, discussed later in this chapter.

EFFECTS ON PHYSICIAN DECISION MAKING

The regulatory guidance discussed above has important effects on physician behavior and decision making. The provision of information to physicians on a product insert or label regarding how a drug might affect the QTc interval raises a number of important questions:

- How do physicians use the information on the label?

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- How successful are physicians in measuring the QTc interval when instructed to do so by the label?
- How do physicians make risk/benefit decisions for an individual patient?
- Are physicians avoiding potentially beneficial medications because of the fear of a small increase in QTc?
- What is the impact of including new warnings on the labels of drugs that have been used for a long period of time (e.g., methadone)?

OTHER CARDIAC SAFETY BIOMARKERS

The recent developments related to QTc provide insight into the complexity facing the development of other cardiac safety biomarkers. Some examples of biomarkers that might merit further attention because of their link to cardiac morbidity and mortality include

- heart rate,
- blood pressure,
- lipids,
- troponin,
- C-reactive protein (CRP),
- brain or B-type natriuretic peptide (BNP),
- ex vivo platelet aggregation, and
- imaging biomarkers (cardiac magnetic resonance imaging).

It is beyond the scope of this chapter to discuss all of these potential cardiac safety biomarkers in any depth. However, examination of one example highlights both the challenges involved and the potential path forward.

Troponin is a protein complex involved in contraction in cardiac muscle. Subtypes of troponin can be sensitive indicators of damage to heart muscle caused by myocardial infarction or other cardiovascular conditions, and these uses are well established and supported by considerable research. Cardiac troponin also has been recognized as a potential biochemical marker of subclinical myocardial injury. Much less is known, however, about the use of troponin to identify drug-induced cardiotoxicity. For example, troponin has been studied as a potential biomarker of cardiotoxicity associated with two chemotherapeutic agents—the anthracycline doxorubicin and the humanized monoclonal antibody trastuzumab. Since the toxicity associated with anthracyclines varies considerably among individuals, the use of cardiac troponin has been suggested as potentially important in planning and monitoring treatment to allow maximum anthracycline dosages without causing severe cardiac damage, and in developing preventative

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strategies to limit cardiomyopathy in later life. A complicating finding is that the early left ventricular dysfunction associated with doxorubicin may be reversible in the short term, even though clinical heart failure may not appear until much later.

Trastuzumab is an example of a drug whose use could be optimized by employing an appropriate biomarker. Trastuzumab has been used to prolong the lives of women with advanced breast carcinoma who have overexpression of the HER2 oncogene. Preclinical animal studies on mice and monkeys did not reveal cardiac toxicity for this drug; however, subsequent clinical trials demonstrated an unexpectedly high incidence of such toxicity. Despite the reversibility of trastuzumab-induced cardiac changes in most cases, this toxicity frequently leads to discontinuation of antibody therapy. If cardiac troponin were shown to be a reliable biomarker of patients at risk for this toxicity, it could help optimize the use of trastuzumab.

A number of important questions are raised by this approach:

- When should cardiac troponin be measured, and how should it be quantified?
- Which cardiac troponin assay should be used?
- What is the appropriate threshold to establish that an increase in cardiac troponin will be clinically significant?
- How will that threshold be determined in the context of the potential benefits of the drug?
- What should be done about events that are biochemically detectable but below that threshold and therefore may be clinically insignificant?
- How should investigators manage elevations in troponin in clinical studies?
- Which compounds need to undergo a cardiac troponin evaluation preclinically?
- Are the preclinical models sufficiently predictive? If not, which compounds warrant a cardiac troponin evaluation in clinical studies?
- How can a negative cardiac troponin evaluation be defined? Will a positive control be necessary to determine assay sensitivity? How would a positive control be used?

To examine the potential of QTc and other cardiac safety biomarkers, the Health and Environmental Sciences Institute (HESI), the FDA, and the CSRC hosted an open think tank forum on October 6–7, 2008, titled "Integrating Preclinical and Clinical Issues in Cardiac Safety: Translational Medicine Meets the Critical Path." Experts from academia, industry, and the FDA gathered to discuss key topics in cardiac safety assessment, with

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a particular focus on the translational gaps between the preclinical and clinical perspectives.

Plenary presentations titled "Collaboration, Critical Path, and Cardiac Safety: The FDA View" and "How Can Collaborations in Cardiac Safety Efforts Best Impact the Regulatory Landscape?" set the stage for examining the value of the collaborations promoted by the HESI and CSRC consortia. Organizational updates from HESI and CSRC summarized the challenges of and solutions to data-sharing processes, and presented the first proof-of-concept report illustrating the sharing of data from a number of companies in the ECG warehouse. The forum's agenda encompassed the exploration of a number of potential biomarkers in addition to QTc, and included discussion of the following questions:

- Cardiotoxicity and troponin: Where do they fit in drug development?
- Preclinical and clinical testing for QTc proarrhythmia: How do they relate to one another and to the risk of life-threatening arrhythmic events?
- QTc evaluation of non-QTc proarrhythmia: What is appropriate preclinical and clinical testing?
- Biologics and large molecules: How should proarrhythmia and myotoxicity be evaluated?
- Risks and benefits of developing drugs with safety signals: What are the challenges?
- New horizons for cardiac safety programs: Do we need "thorough" blood pressure, heart rate, platelet, and lipid studies?

THE CARDIAC SAFETY RESEARCH CONSORTIUM

As the ECG warehouse was coming online, the FDA and the Duke Clinical Research Institute initiated the CSRC, a public–private partnership, to "advance scientific knowledge on cardiac safety for new and existing medical products by building a collaborative environment based upon the principles of the FDA's *Critical Path Initiative* as well as other public health priorities."[3] This initiative brought together pharmaceutical companies, clinical research organizations, and academic partners in an effort to leverage the ECG warehouse and associated clinical data for mutual benefit.

The implementation of the CSRC has faced many challenges related to governance, infrastructure, resources (both funds and staff time), intellectual property, antitrust and other legal issues, and how to get companies to share data in a collaborative environment. Many of these challenges

[3]See http://www.cardiac-safety.org/about_us.

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have been or are being overcome. Companies have begun to share data, and CSRC research teams—including industry scientists, academics, and regulators—have begun to make progress on a number of projects.

An important accomplishment of the CSRC has been enhancing communication and education by promoting dialogue among scientists from the pharmaceutical industry, academia, and regulatory agencies. The CSRC has established common ground and an environment in which difficult issues can be discussed outside of formal regulatory channels. These discussions have included methods for evaluating the effects of chemotherapeutic agents and large molecules (antibodies and biologics) on QTc, as well as different statistical approaches to evaluating the effect of a drug on QTc, including concentration–response (PK-QTc) modeling. Recently, a number of pharmaceutical companies agreed to allow the FDA to share data from the ECG warehouse to create a meaningful data set that will enable companies and scientists to enhance the use of old measurements of QTc and develop new measurements of ventricular repolarization. This data set will also provide the opportunity to gain insight into the effect of moxifloxacin (the most commonly used positive control in TQT studies), including a better understanding of outliers and nonresponders. The potential will exist for informative studies in pharmacogenomics that might not be possible in a single company.

Combined with the technological and regulatory advances that have been achieved over the past few years, the CSRC has the potential to generate significant improvements in the utility of QTc as a safety biomarker. But it is not clear at this time whether the CSRC will be able to generate the clinical epidemiology studies and data necessary to provide a more refined link between drug-induced QTc prolongation and the risk of developing torsade de pointes. The next few years will determine whether the collaborations within the CSRC will generate the data sets necessary to provide meaningful and relevant answers to questions that limit the use of QTc as a safety biomarker.

The CSRC also hopes to foster collaborations among industry, academia, and regulatory agencies to further the development of new cardiac safety biomarkers. These advances in biomarker development will require investments in basic science to better elucidate the molecular mechanisms of cardiac toxicity and in preclinical models and clinical data to allow evaluation of the use of biomarkers. A coordinated approach to this effort is important to ensure that scientific issues are addressed appropriately, that regulatory strategies are crafted, that an infrastructure is developed to collect industrywide experience, and that the proper public–private partnerships are forged to profit from the aggregate experience.

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LESSONS LEARNED

A number of important lessons that may be applicable to the development of other safety biomarkers have been learned from the development of regulatory guidance on evaluating the potential of drugs to prolong QTc; the technological advances that enabled the formation of the ECG warehouse; and the healthy dialogue that has taken place among the pharmaceutical industry, academia, and regulatory agencies through the CSRC. This series of events has yielded a fairly complete (but still evolving) system for addressing a public health issue through regulatory and technical developments. The historical account makes the endeavor look like a coordinated response, but that is an inaccurate perception. Rather, individuals who recognized what needed to be done next made sure those steps were taken. The original "points to consider" document had its roots in a document authored by Health Canada's Collette Strnad. The effort to develop a digital ECG data standard, which involved a team of people from pharmaceutical companies, clinical research organizations, device manufacturers, and academia, was initiated and managed by Scott Getzin of Eli Lilly. The CSRC came into being largely through the efforts of Christopher Cabell, then at the Duke Clinical Research Institute. Had any of these individuals failed to become involved when and to the extent that they did, the result would most likely have been significant delay and a suboptimal response. There is a pressing need to develop a quality-assured response to other perceived biomarker-based health risks.

HIGHLIGHTS OF THE BREAKOUT DISCUSSION

The breakout group on cardiac toxicity identified several key steps necessary for progress on both the enhanced use of QTc as a biomarker and other biomarkers that can supplement the information provided by QTc. In the plenary session following the breakout, Alastair Wood described the group's main conclusions.

Standardization

The collection, annotation, curation, and submission of data need to be standardized across the entire research spectrum, including NIH, the FDA, and academia. Annotation and curation of data are especially important so that data will be usable, standardized, and accessible.

Without standardization, it is impossible to look across databases or even different studies and make comparisons or compare outcomes against biomarkers. In addition, patient data need unique identifiers, since frequently it is difficult to identify a patient who took part in more than one

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study or developed toxicity after an event. Even drug names need to be better identified, since the trade names of drugs can change.

Identifying Mechanisms

It is important to relate biomarkers to mechanisms of toxicity. Mechanistic understanding can be used to generate hypotheses that can then be tested experimentally. Identifying a biomarker can help clarify a mechanism and vice versa. And understanding mechanism can provide information on long-term clinical outcomes and on biomarkers that do and do not correlate with these outcomes.

Access to Data

Access to data held by the FDA and by private companies would be valuable for those involved in the development of biomarkers. For example, noncompetitive access to old drug data would benefit multiple stakeholders. Removing restrictions on access to FDA data would require legislation.

In general, broader access to compounds and past data associated with those compounds could improve productivity. For example, compounds that were abandoned because of toxicity concerns could yield data that relate to potential biomarkers currently being studied. Such data could reveal correlations or their lack and would allow for comparisons across studies.

Responsibilities for Future Actions

A variety of organizations need to assume or be assigned responsibility for bringing stakeholders together and arranging for funding to advance the development of cardiac safety biomarkers. Among the issues that need to be resolved is who will support the needed research, what mechanisms will drive the research, and what is the proper balance of incentives and requirements to foster participation.

As part of this allocation of responsibilities, NIH's role in biomarker development needs to be rethought and redefined. If NIH interprets its role too narrowly, it may not be willing to support clinical research that can have a major impact on patient outcomes. One option would be to convene a standing group including representatives of the National Heart, Lung, and Blood Institute, the FDA, industry, and academia to identify and prioritize high-impact opportunities in terms of public health and to recommend specific targets for research funding. Topics that NIH should consider include technology and animal model development aimed at translation to human studies; development of biomarkers through detailed studies of human

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genomics, proteomics, and metabolomics; human studies to validate biomarkers in adequately sized longitudinal studies; and definition of appropriate institutional roles in the development of standards. Such initiatives are beyond the capability of either the FDA or most private companies unless they work together within a collaborative framework.

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4

Assessing and Predicting Kidney Safety[1]

One of the primary reasons for the attrition of promising therapeutic agents from the drug development pipeline is the observation of treatment-related histologic injury to the kidney in animal toxicology studies. At the same time, the ability to recognize when a therapeutic intervention is damaging the kidneys in humans and to predict when removal of that agent would arrest further deterioration is severely limited. Progress in identifying, evaluating, and qualifying biomarkers of kidney injury would therefore yield great benefits in drug development.

This chapter describes the current state of biomarker use and development in four specific areas: (1) the qualification of new kidney safety biomarkers to bridge the gap between preclinical animal toxicology testing and early human clinical investigations; (2) the flawed gold standard (serum creatinine and blood urea nitrogen [BUN]) that plagues the assessment of new kidney safety biomarkers; (3) collaborations among drug developers, regulatory authorities, funding agencies, and investigators; and (4) the development of in vitro and other screening model systems that could identify lead candidates for drug development. In each of these areas, the major questions that need to be answered and the hurdles that need to be

[1]This chapter is derived from a white paper prepared by Frank D. Sistare, Merck and Co., Inc., and Prasad Devarajan, Cincinnati Children's Hospital Medical Center, University of Cincinnati, with additional input from workshop discussions. Panelists contributing to the paper were Joseph Bonventre, Harvard Medical School, Brigham and Women's Hospital; Frank Dieterle, Novartis Pharma; Robert Star, National Institute of Diabetes Digestive and Kidney Diseases, NIH; and David Warnock, University of Alabama at Birmingham. Melanie Blank, FDA, participated in the panel.

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overcome are presented. The chapter then describes a vision for the future development and use of kidney safety biomarkers in drug development. The workshop's breakout session on kidney safety biomarkers, summarized at the end of the chapter, focused on what needs to be done to achieve this vision.

THE CURRENT STATE

The current state of kidney drug development is characterized by several notable deficiencies: a limited ability to screen compounds to predict kidney toxicities; problems in identifying agents that would result in human kidney toxicity; difficulties in confirming that in some instances, kidney toxicities are specific for the tested animal species and are not necessarily relevant to humans; and a limited ability to monitor kidney damage associated with drugs that have been approved for use in humans despite their potential for nephrotoxicity because they provide health benefits or address unmet medical needs. Current approaches to toxicity testing and decision making can waste time and resources and may not identify or support development of the best lead candidates for human use.

The kidney is a major site of drug metabolism and elimination, so it is not surprising that toxicologic findings are more common in the kidney than in most other organs. Merck has reported that renal injury is the second-leading cause of drug attrition, after liver toxicity (Merck, unpublished findings). Indeed, commercially marketed drugs with known nephrotoxic potential are contributing factors in at least 25 percent of acute kidney injury in critically ill humans, causing significant increases in mortality, morbidity, and health care costs (Pannu and Nadim, 2008).

As noted, the current biomarker gold standard for kidney toxicity is levels of serum creatinine and BUN. These measures of kidney function are not sensitive indicators of structural injury, however, in part because of the excess capacity—or "renal reserve"—of the kidneys (Ferguson et al., 2008; Parikh and Devarajan, 2008). In the absence of more sensitive biomarkers to detect acute changes in renal damage, early indications of kidney injury cannot be monitored without histologic examination.

Histology provides accurate detection of kidney injury in preclinical animal studies. However, the current standard of care for evaluation of potentially nephrotoxic agents in human studies does not extend to surveillance with renal biopsies. As a result of this inability to monitor for early indications of kidney injury in human subjects, the development of compounds found to cause kidney damage in preclinical animal studies may be suspended, even when the relevance of the findings to humans has not been established. Drug toxicities seen in animal studies account for more than 30 percent of the attrition of compounds from drug development (Kola and

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Landis, 2004). It is important to note that adverse findings from one species in animal toxicology studies are not always seen in other species, and only 40 to 60 percent of such findings are predictive of toxicities in human trials (Olson et al., 2000; Knight, 2008). Thus, promising compounds are dropped from the development pipeline even though adverse kidney effects in humans might not ever occur or might be manageable through monitoring with sensitive biomarker tests.

Qualification of Kidney Safety Biomarkers

As novel renal biomarkers for clinical use are developed to detect early indications of nephrotoxicity, more reliance will be placed on these biomarkers in making critical drug development decisions than is currently placed on the results of animal studies (which as noted often are not accurately predictive of human toxicity). It may be hoped that this will both improve the safety of drugs and decrease the need to conduct exhaustive preclinical studies (Sistare and DeGeorge, 2007).

Novel renal biomarkers may also ultimately play a role as surrogate markers of drug efficacy. Many companies are working to develop new drugs for treating diabetes, hypertension, obesity, heart failure, hyperlipidemia, and transplant rejection, conditions in which the possibility of kidney injury is an ever-present risk. Since current biomarkers of kidney injury and function lack sensitivity and specificity, it is difficult to properly assess kidney status at baseline or after treatment. New drugs might actually be ameliorating or slowing the progression of kidney diseases, but without sensitive and specific measures of clinically meaningful renal injury and/or function, improvements during treatment of these diseases is extremely difficult to assess. At this time, improvements in renal function can be assessed only by conducting large and lengthy clinical trials (using doubling of serum creatinine as the efficacy endpoint). Once it has been established that novel renal biomarkers are predictive of future renal morbidity, they will likely be accepted as surrogate markers of clinically meaningful renal disease and be relied upon to assess renal benefits during drug development.

Biomarkers have already been developed as surrogates in other areas. For example, large-scale trials have shown that statins reduce the risk of adverse cardiovascular outcomes, and the reduction they cause in serum low-density lipoprotein (LDL) levels is predictive of this effect. LDL cholesterol is now accepted as a surrogate endpoint for regulatory marketing approval. But examples of such biomarkers remain rare, and the burden of proof for marketing approval is high.

Table 4-1 lists several promising translational biomarkers of acute kidney injury that have been proposed in published studies (Dieterle et al., 2008; Ferguson et al., 2008; Parikh and Devarajan, 2008). A number of

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TABLE 4-1 Promising Translational Biomarkers of Acute Kidney Injuries

Urinary or Serum Biomarker	Proposed Structural/Functional Interpretations
Urine Albumin	Biomarker for glomerular and tubular epithelium functional change
Urine α-GST	Tubular epithelium cell membrane disruption and cytosol leakage
Urine KIM-1	Proximal tubule epithelium dedifferentiation and regenerative repair response
Urine NGAL	Distal tubule and collecting duct rescue signal to bind deleterious substances, limit damage, and promote survival and proliferation
Urine TFF3	Decrease in concentration removes cellular maturation signaling, allowing dedifferentiation
Serum Cystatin C	Functional measure of glomerular filtration
Urine Cystatin C	Biomarker for glomerular alterations or tubular damage that interferes with efficient proximal tubular protein reabsorption
Urine β2-Microglobulin	Biomarker for glomerular alterations or tubular damage that interferes with efficient proximal tubular protein reabsorption
Urine Protein	Biomarker for glomerular and tubular epithelium functional change
Urine L-FABP	Biomarker of anoxia/ischemia signal in tubular epithelium and potential oxidative damage signal
Urine Clusterin	Biomarker for tubular epithelium regenerative repair response
Urine NAG	Biomarker for proximal tubule lysosomal enzyme release and proximal tubular damage
Urine IL-18	Tubular epithelium protein reflecting initiation of apoptotic cascades
Urine GGT	Tubular epithelium cell membrane disruption

NOTE: α-GST = glutathione-s-transferase alpha; KIM-1 = kidney injury molecule-1; NGAL = neutrophil gelatinase associated lipocalin; TFF3 = trefoil factor-3; L-FABP = liver type fatty acid binding protein; NAG = n-acetyl glucosaminadase; IL-18 = interleukin-18; GGT = gamma glutamyl transferase.

groups are collaborating to advance understanding of these biomarkers for specific uses (Box 4-1), some of which involve early drug development. Many of these biomarkers could contribute unique and specific information to an overall assessment of the state of kidney function, structural perturbation of the kidneys, and the healing response. A prospectively defined and systematically collected data set could allow some of these biomarkers to gain broad acceptance and qualification for monitoring renal safety in early clinical human registration trials.

Key questions that need to be addressed include the following:

- Qualification of a biomarker as fit-for-purpose for safety monitoring is an antecedent to qualification of that biomarker as fit-for-purpose for an efficacy outcome. Some biomarkers may be ideally suited to safety monitoring and early detection of kidney injury but

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BOX 4-1
Initiatives to Advance Understanding of Kidney Safety Biomarkers

AKIN: The Acute Kidney Injury Network was formed in 2004 as a multidisciplinary collaborative network of members representing about 20 key societies in nephrology and critical care, with additional experts in adult and pediatric acute kidney injury. AKIN has promoted the definition of acute kidney injury and has developed a research agenda to test the AKIN diagnostic and staging criteria for predicting patient outcomes in clinical settings.

C-Path PSTC NWG: The Critical Path Institute's Predictive Safety Testing Consortium Nephrotoxicity Working Group was formed in 2006. It includes representatives of 16 companies working with academic advisors, the FDA, and the European Medicines Evaluation Agency (EMEA) to establish and qualify translational bridging biomarkers for use in monitoring drug-induced kidney injury for regulatory decision-making purposes in both animal toxicology studies and early clinical trials.

ILSI/HESI Kidney Biomarker Committee: The Kidney Biomarker Committee of the International Life Sciences Institute/Health and Environmental Sciences Institute consists of 10 companies collaborating to evaluate promising accessible biomarkers of drug-induced kidney toxicity in animals.

IMI: The Innovative Medicines Initiative is a European-based public–private partnership between the pharmaceutical industry, represented by the European Federation of Pharmaceutical Industries and Associations, and the European Communities, represented by the European Commission. Its goal is to remove research bottlenecks in the current drug development process. The first round of projects, which start in 2009, includes one consortium that is investigating mechanisms of drug-induced hepatotoxicity and nephrotoxicity and defining safety biomarkers in different animal species, and a second consortium aimed at the clinical qualification of safety biomarkers for monitoring drug-induced kidney, liver, and vascular injury in humans.

Extramural NIH Studies: Examples include the Acute Kidney Injury Natural History Cohort consortium, the Translational Research Investigating Biomarker Endpoints in Acute Kidney Injury (TRIBE-AKI) consortium, the University of Alabama-Birmingham/University of California-San Diego O'Brien Kidney Research Core Center, the Chronic Kidney Disease Biomarkers Consortium, and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Workshop on Assessment of Kidney Function and Damage. Academic biomarker development projects include those at Harvard University, the University of Cincinnati, and the University of Colorado.

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may not be appropriate as surrogate endpoints of clinical efficacy. Which data are critical for establishing that a specific biomarker is fit-for-purpose (Wagner et al., 2007)?

- How can existing data sets from animal and human studies be used most effectively to support qualification of safety biomarkers?
- How can diverse stakeholders best collaborate and set reasonable expectations and evidentiary standards for fit-for-purpose qualification of candidate safety biomarkers and generate any needed new data?
- How can the decision-making processes be made transparent to all stakeholders?

There are a number of opportunities for answering these questions:

- Biomarkers that appear to outperform changes in serum creatinine measurements in animal toxicology studies need to be identified, and a harmonized lexicon needs to be established for histopathology as the gold standard for these preclinical studies.
- A critical review of published studies needs to be conducted to identify the most promising new renal biomarkers. If possible, data from these studies should be collected into a usable shared database.
- Standardized methodologies need to be used for preclinical and clinical data collection, sample collection, histopathology interpretation, biomarker measurements, and data interpretation. These methodologies should reflect the collaborative efforts of experts and vested stakeholders, including sponsors, investigators, and regulatory scientists.
- Biomarker studies are needed to better understand such biological processes as the anatomical region and cell types perturbed in kidney injuries, the functions perturbed, and the recovery response.
- Tissue sample and biomarker banks need to be created. The use of both fresh samples and archived, frozen, or formalin-fixed samples should be optimized to minimize the drain on resources and maximize the knowledge gained from such studies.
- Prospective outcome-based human clinical trials need to be conducted to assess the relative performance of biomarkers in real time; the temporal profiles of changes in biomarkers relative to changes in renal function should be assessed by more traditional methods.
- Collaboration needs to be improved across groups that have common interests in the development of kidney safety biomarkers to foster common goals and shared access to critical samples, assays, data, and funding.

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- Funding needs to be optimized through partnering with NIH.
- Biomarker thresholds need to be established. Normal ranges based on variance and intervention thresholds need to be determined based on medical experiences with a variety of study populations.
- The output from diverse work streams needs to be directed to key regulatory decision and policy makers at the same time that drug developers are kept fully informed through written communications and regular meetings that include all interested stakeholders.
- Issues surrounding the commercial development of biomarker assay panels for use in human and animal studies need to be considered, including technical and fiscal issues surrounding the identification, validation, commercial development, and acceptance of multimarker panels.

The Flawed Gold Standard

When comparing the sensitivity and specificity of two or more tests, it is important to have a standard against which to make the comparison. Otherwise, one can see only how two measures correlate with one another, and comparison of the sensitivity and specificity of new biomarkers to creatinine or other more traditional biomarkers of kidney function and injury in the clinical setting is difficult. For ethical reasons, kidney biopsy—which would be an ideal standard for assessment of the performance of new biomarkers when nephrotoxicity is suspected in the clinical setting—is not possible. Unfortunately, as discussed above, the current gold standard of serum creatinine and BUN is seriously flawed.

There are several major research opportunities for developing an improved standard:

- Conduct studies to explore the utility of adjudication committees or more complex algorithms of renal dysfunction as better gold standards. Consider the value of incorporating other measurements, such as casts or fractional excretion of sodium, into the gold standard.
- Conduct preclinical studies to explore the best fit between other laboratory variables (aside from novel renal biomarkers) and histopathology changes.
- Explore through further discussion whether measuring the time lag between early alterations in biomarkers and subsequent persistent serum creatinine elevations and/or other traditionally used biomarker changes (perhaps in a patient population with no renal reserve) might be an adequate way to qualify renal biomarkers for use in Phase 1 clinical trials.

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- Establish the relationship among novel biomarkers, kidney damage, and serum creatinine by analyzing ongoing studies in which human biopsy samples are available. Examples include protocol transplant biopsies and biopsies of patients with hematuria or proteinuria in whom serum creatinine may still be normal despite kidney injury as reflected by histopathology.

While the initial focus must necessarily be on safety monitoring, the ultimate application of these endpoint considerations to efficacy trials should be kept in mind. To this end, it will be necessary to establish the relationships between biomarker elevation and appropriate short-, intermediate-, and long-term clinical outcome measures, such as dialysis, death, and hospitalization days; repeated hospitalization, infections, or resource utilization; or progression to chronic kidney disease, end-stage renal disease, or cardiovascular disease.

Collaborations Among Drug Developers, Regulatory Authorities, Funding Agencies, and Investigators

Many stakeholders share an interest in defining the appropriate use of new kidney safety biomarkers. An efficient approach to assessing the performance of emerging biomarkers, as well as gathering control patient data on new biomarkers, would be to add such measurements to ongoing animal and clinical trials. However, there currently are few incentives and many disincentives to adding measurements from unqualified exploratory safety biomarkers to such regulated studies (Sistare and DeGeorge, 2008). Key questions that must be addressed include the following:

- How can regulatory authorities establish and communicate an official regulatory policy to support the innovative development of safety biomarkers within the context of product development?
- Can regulatory authorities provide encouragement or support to advance the evaluation of a declared set of safety biomarkers using samples from ongoing registration studies?
- Can other, nonregulatory federal agencies provide access to samples from clinical trial sample sets that would allow a prioritized list of new safety biomarkers to be developed?

Major opportunities exist for answering these questions:

- Transparent and realistic communications need to occur between regulatory authorities and drug development scientists.

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- Disincentives under the current drug development framework need to be removed.
- Issues of patient consent in clinical trials pertaining to testing of novel biomarkers need to be resolved.
- Exploratory studies and studies of negative controls are needed.
- A role for NIH-sponsored clinical natural history studies and clinical trials in this overall process needs to be identified.
- Roles for public–private partnerships and patient advocacy groups need to be identified.
- FDA–industry–NIH partnerships for monitoring drug safety and toxicity and providing broad access to study samples need to be explored.

Development of in Vitro and Other Screening Model Systems

In vitro and other screening model systems that could definitively rule out human kidney toxicity caused by test compounds and identify specific kidney toxicities in animal test species would be exceedingly helpful in drug development. Key questions in this area include the following:

- Are such systems viable and close to being established?
- How can their evolution be fostered, and how can they be efficiently validated?

There are several major opportunities for answering these questions:

- Studying the role and limitations of current primary cell cultures and of embryonic stem cells for assessing new biomarkers.
- Studying the utility of other in vitro model systems of nephrotoxicity (e.g., in zebrafish).
- Creating partnerships among academia, the pharmaceutical industry, NIH, industry technology providers, and advocacy groups to explore the advancement of in vitro and other model systems for early drug toxicity screening.

A VISION OF THE FUTURE

Table 4-2 summarizes a vision of the future for avoiding and addressing kidney safety issues in early drug development. The main features of such a vision are as follows:

- In vitro test systems would be available to predict the risk of kidney toxicity, including glomerular and tubule cell injury and functional

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TABLE 4-2 Current Deficiencies, Needs, and Proposals to Address Kidney Safety Issues in Early Drug Development

Concept	Current Needs	Future Availability
Improved kidney injury biomarkers and kidney toxicity screening systems would help optimize the selection of leading candidates for development and provide for better drug development animal toxicology studies.	• Qualified biomarkers and screening test systems for identifying human-relevant kidney toxicities • Qualified biomarkers to monitor kidney toxicity in animals noninvasively	• In vitro and other screening model systems that can predict kidney toxicity, injury, and functional changes in preclinical and clinical studies • Expedited resource-sparing study designs incorporating readily available commercial multiplexed assays and tissue biomarkers that report/predict kidney toxicity in animals
Biomarkers that enable early detection and monitoring of toxicity and structural and functional changes in humans would enable safety monitoring of both early and later phases of clinical drug development.	• Qualified biomarkers of acute kidney toxicity to translate from animals to humans that outperform currently employed functional measures • Once safety biomarkers have been established, qualified biomarkers for kidney toxicity in humans that can predict clinical outcomes, could be used for individual patient dose setting, and could be relied on for assessing the efficacy of interventions • Qualified biomarkers for assessing improvements in kidney involvement as a known comorbidity of underlying disease processes	• Translational qualified biomarkers for monitoring kidney safety in animal toxicology studies and early human clinical trials • Translational qualified predictive biomarkers for kidney toxicity in humans that outperform currently employed functional measures for safety monitoring in humans • Qualified kidney safety biomarkers to demonstrate benefits of agents directed against other diseases with kidney comorbidities

changes, and to assess whether the toxicity is species-specific or is relevant to all species, including humans.

- A limited number of rodent and nonrodent model systems would be available for short-term toxicology testing using a validated, easily accessible biomarker or multiple biomarkers that might include a combination of tissue and accessible biomarkers (e.g., genomic, metabolomic, protein, or imaging biomarkers). These biomarkers

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would predict dose-dependent acute kidney injury in terms of dysfunction, anatomic alteration, or structural damage.

- Readily available qualified human biomarkers would be available to diagnose or rule out the involvement of specific anatomic regions, to assess the severity of an injury, to signal the need for early intervention, and to monitor the reversibility of injury-associated processes.
- Sponsors and investigators would be encouraged by regulatory authorities to demonstrate that a compound lacks the potential to injure the kidney or that kidney toxicity can be monitored and managed using qualified safety biomarkers that bridge the gap between preclinical animal studies and early human clinical trials.
- Qualified predictive biomarkers for kidney toxicity in humans would be available that would outperform functional measures currently employed to predict important clinical outcomes and the efficacy of intervention strategies. These biomarkers would be defined according to their applicability to patients with chronic kidney disease, as well as those with no known kidney disease.
- Where kidney involvement is a known comorbidity of disease, qualified biomarkers would be available to assess the effects of a drug on kidney processes in Phase II and III trials.
- Qualified biomarkers for kidney injuries would be used to diagnose and stage kidney diseases with pathologies related to kidney toxicities.

HIGHLIGHTS OF THE BREAKOUT DISCUSSION

The breakout group that discussed biomarkers for kidney toxicity focused on prioritizing what needs to be done to achieve the future vision outlined above. Participants discussed the most critical obstacles and data gaps that need to be addressed in the four areas reviewed in the above section on the current state of renal biomarker development. In the plenary session following the breakout, Prasad Devarajan of the Cincinnati Children's Hospital Medical Center, University of Cincinnati, presented the group's main conclusions:

- **Greater understanding of biomarkers**—The group concluded that new biomarkers should outperform those already available. The current gold standard for preclinical biomarker discovery is animal toxicity studies based on histopathology, and the use of that standard should continue. Also needed are biomarkers that indicate the anatomic site of kidney injury in animal studies because different agents can affect different nephron segments, and biomarkers

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should provide temporally ordered information regarding the stage of kidney injury. Needed as well is greater understanding of what biomarker combinations reveal about the stage of kidney injury or repair.

- **Collection and analysis of data**—Mechanisms for accumulating standardized preclinical data and for sharing and interpreting the data should be established through rules set by consortia. For example, assessments of histopathology need to be harmonized among the many groups working on kidney safety issues. Because data on long-term clinical outcomes can take many years to gather, it is important that short-term outcomes—including serum creatinine, dialysis requirements, and mortality—be correlated with biomarkers.
- **Correlations with biopsies**—Efforts should be made to correlate human biopsy histopathology with biomarkers. While not all patients with nephrotoxicity are biopsied, more can be learned from the biopsies that are being done, such as the protocol kidney transplant biopsies that are frequently performed in many institutions. Biopsies of patients with blood in the urine and glomerular disease should be simultaneously correlated with noninvasive biomarkers.
- **National biorepositories**—Standardized national biorepositories need to be established to enable comparison of biomarkers from ongoing clinical trials. Researchers should have access to de-identified samples, and it should be possible to share data generated from these samples. NIH has a public–private partnership office that could coordinate this cooperation. In addition, a system is needed for sharing clinical data, including data gathered by industry.
- **Incentives, dialogue, and partnerships**—Incentives could be structured to promote investigations of new safety biomarkers in regulated studies that support new product development. Incentives also need to be considered for exploratory studies and negative controls. An open dialogue between industry and regulatory agencies could identify and refine such incentives. In addition, an FDA–NIH partnership could consider funding research on biomarker development for monitoring drug safety and toxicity, making the FDA a funding as well as a regulatory agency.
- **Preclinical model systems**—In vitro and other screening models need to be developed for detecting nephrotoxicity. Clinical and animal studies are expensive. Cell culture systems have not been very reliable, but new systems, such as embryonic stem cells and zebrafish models, are promising, and additional models may emerge. A partnership between industry and NIH could accelerate

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the development of these in vitro and other systems for detecting a compound's nephrotoxicity potential.

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5

Biomarkers of Acute Idiosyncratic Hepatocellular Injury in Clinical Trials[1]

Hepatotoxicity is the adverse event that most frequently leads to regulatory action on drugs, including failure to approve, postmarketing warnings added to the label, and withdrawal from the market (Temple, 2001). Among research priorities in adverse drug events, hepatotoxicity was ranked first in a 2006 survey of pharmaceutical companies (Holden, 2008). Because most events are inaccurately classified (Aithal et al., 1999), the population incidence of drug-induced liver injury is unknown. Yet drugs are the most frequent cause of acute liver failure among those under consideration for liver transplantation in the United States (Lee, 2003).

Animal studies in rodents, dogs, and monkeys detect approximately half of compounds exhibiting hepatotoxicity in humans (Olson et al., 2000). In vitro human hepatocyte testing similarly detects 50–60 percent of drugs that can cause severe liver injury in humans, including some not detected in animal testing (Xu et al., 2008). However, no currently available preclinical tests detect the potential for serious human hepatotoxicity with both high sensitivity and high specificity.

A recent example reveals some of the issues involved in drug safety testing. A major pharmaceutical company submitted a new drug application for treatment of a chronic disease. The FDA agreed with the sponsor's efficacy data. However, it was noted that among approximately 4,000 treated patients in clinical trials, two developed elevations in both serum alanine

[1]This chapter is based on the remarks of Janet Woodcock, Director of the FDA's Center for Drug Evaluation and Research; Alastair Wood, Managing Director of Symphony Capital, LLC; and Thomas Insel, Director of the National Institute of Mental Health.

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aminotransferase (ALT) and bilirubin. As a prerequisite for approval, the company was told to conduct a new safety study of 10,000 patients treated with the drug for 1 year, and to include an additional 10,000 subjects receiving comparator treatment for 1 year to exclude an unacceptable level of risk for clinically serious acute idiosyncratic hepatocellular injury (AIHI).[2] The delay and additional investment required to bring such drugs to market can be detrimental not only to their manufacturers, but also to patients with unmet medical needs.

This chapter begins with an overview of AIHI. It then describes the current state of biomarkers for AIHI and reviews potential new biomarkers now emerging from various lines of investigation. The chapter ends with highlights of the breakout session on liver safety biomarkers.

ACUTE IDIOSYNCRATIC HEPATOCELLULAR INJURY (AIHI)

The clinical and histologic presentation of drug-induced liver injury can take many forms, mimicking most types of liver disease. AIHI is of greatest concern in drug development because of its potential rapidity of development and high morbidity and mortality (Andrade et al., 2005; Bjornsson and Olsson, 2005). Table 5-1 lists marketed drugs that have been subject to regulatory actions since 1995 because of liver safety concerns. All of the drugs listed can cause AIHI, with the exception of terbenafine (mixed hepatocellular/cholestatic injury), valproate (microvesicular steatosis), and acetaminophen (hepatocellular injury, but without the characteristics of AIHI discussed below). The discussion at the workshop focused exclusively on AIHI and not on other forms of drug-induced liver injury.

Figure 5-1 shows a typical presentation of AIHI. The patient exhibited normal liver chemistries at baseline and for several weeks while receiving treatment, but then developed serious liver injury with loss of overall liver function, manifested as a rise in serum bilirubin and ultimately death.

During AIHI, if treatment is not withdrawn promptly, and in some cases even with prompt discontinuation, the progressive loss of hepatocytes leads to liver dysfunction and ultimately death (absent liver transplant). The event is frequently termed "idiosyncratic" because the majority of treated patients are able to take the drug safely at the recommended dose range; the affected individuals are different from the majority in ways that make them susceptible to injury or less able to recover from injury. With most of the drugs listed in Table 5-1, fatal AIHI typically occurs in 1 in every 10,000 to 100,000 treated patients. It is rare for fatal AIHI to occur in preapproval clinical trials, in part because most such trials involve insufficient numbers

[2]This chapter uses the term "AIHI" to refer specifically to acute and idiosyncratic hepatocellular injury that can progress to liver failure.

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TABLE 5-1 Regulatory Actions on Approved Drugs Due to Hepatotoxicity, 1995–2008

Withdrawals	Second Line	Warnings
• bromfenac • troglitazone • pemoline	• felbamate • tolcapone • trovafloxacin	• acetaminophen • atomoxetine • leflunomide • bosentan • nefazodone • infliximab • nevirapine • saquinavir • pyrazinamide/rifampin • interferon 1β 1β • terbinafine • telithromycin • valproic acid (kava, lipokinex) • zifirlukast

SOURCE: Guo et al., 2008.

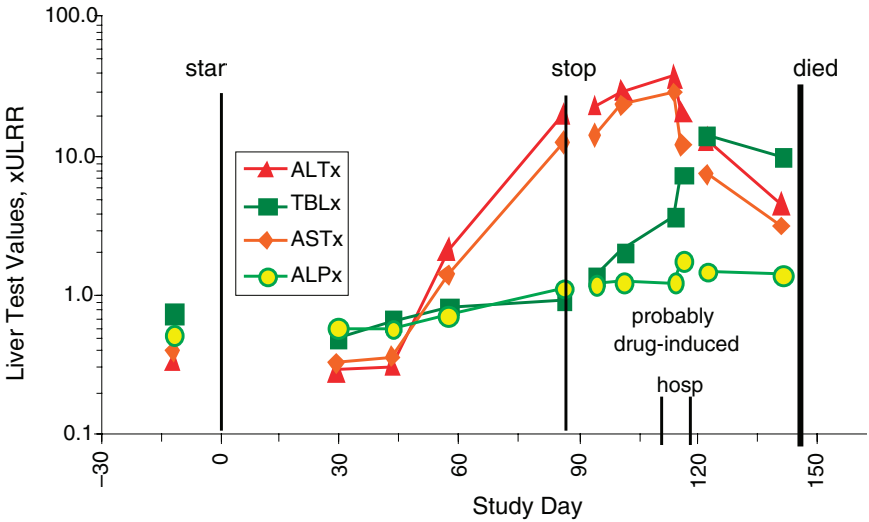

FIGURE 5-1 Acute idiosyncratic hepatocellular injury. An 80-year-old man who experienced acute idiosyncratic hepatocellular injury exhibited marked increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) starting about 45 days after treatment began. Total bilirubin (TLB) rose dramatically before death, while alkaline phosphatase (ALP) increased less markedly. Measures are compared with the upper limit of the reference range (ULRR).
SOURCE: Watkins slide presentation.

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of patients treated for long enough to have a high likelihood of identifying such rare individuals.

CURRENT STATE OF BIOMARKERS FOR AIHI

The primary biomarkers discussed at the workshop were those that detect a drug's potential to cause AIHI in a preapproval clinical trial. Biomarkers to identify individual susceptibility to a drug with established AIHI potential were discussed to the extent that they were relevant in this context. Other types of biomarkers, such as those that may aid in causality assessment, were not discussed.

Serum ALT activity is the biomarker used most frequently to detect hepatocellular injury in clinical trials and is more liver-specific than aspartate aminotransferase (AST) (Green and Flamm, 2002). Serum ALT can increase, even markedly (for example, to levels exceeding 20 times the upper limits of normal [ULN]), as a result of events other than hepatocyte necrosis, including hepatocyte autophagy in anorexia nervosa (Rautou et al., 2008) or hepatic glycogen accumulation in uncontrolled type 1 diabetes (Olsson et al., 1989; Sayuk et al., 2007). Lesser ALT elevations are observed with hepatic steatosis (Browning et al., 2004). Activation of ALT gene transcription can occur in response to Peroxisome proliferators activated receptors (PPAR) agonists in cell culture (Thulin et al., 2008). In addition, it is theoretically possible that drugs could interfere with ALT degradation or blood clearance. However, no published data support transcriptional or clearance-related ALT increases due to these events occurring in humans.

Drugs recognized to cause AIHI have demonstrated an increased incidence of ALT elevations of more than three times ULN relative to placebo or controls in preapproval clinical trials (Temple, 2001). However, ALT elevations have a limited specificity to predict AIHI. Even frequent and fairly high ALT elevations do not reliably predict the potential to cause AIHI in clinical trials, as evidenced by tacrine. In clinical trials, about 25 percent of Alzheimer's disease patients receiving tacrine developed ALT elevations of greater than three times ULN, and 2 percent exhibited ALT elevations of greater than 20 times ULN (Watkins et al., 1994). However, tacrine exhibits a very low risk of causing AIHI. Similarly, although statins have demonstrated up to a 3 percent incidence of ALT of greater than three times ULN in clinical trials relative to placebo or controls, statin use has not been associated with an increased risk of acute liver failure (Kaplowitz, 2005). Heparins also can cause ALT elevations but pose a very low or zero risk of causing AIHI. Drugs such as tacrine, heparins, and statins generally exhibit transient, self-limited liver injury that resolves with continued treatment in a process termed "adaptation." Adaptation is observed not only with drugs that pose a low risk of causing AIHI but also in many or

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most patients who experience ALT elevations while receiving drugs that can cause AIHI, such as troglitazone (Watkins, 1998) and isoniazid (Mitchell et al., 1975).

Common pathways likely underlie initial injury, regardless of whether the injury progresses or resolves with continued treatment. These pathways include those that determine the intracellular "dose" of hepatotoxic metabolites or bile acids (for example, cellular transporters, Phase 1 and 2 drug metabolism, and concomitant medications) and the production of hepatocyte injury (for example, oxidative stress or mitochondrial impairment), as well as regenerative or hepatoprotective abilities (including hepatic glutathione redox status, Nrf2 activation of cell defense systems, and liver regeneration). All of these pathways may be influenced by genetic (Larrey, 2002; Daly et al., 2007; Kindmark et al., 2007; Wilke et al., 2007), epigenetic (Murata et al., 2007), demographic (Kaplowitz, 2005; Uetrecht, 2007), infectious/inflammatory (Roth et al., 2003), and environmental factors (Larrey, 2002; Kaplowitz, 2005).

A popular theory is that progressive liver injury occurs in those individuals who fail to adapt to the initial insult. However, data to support this theory are sparse. It has been claimed that with drugs capable of causing AIHI, such as isoniazid, troglitazone, and ximelagatran, the AIHI events typically occur with a latency similar to that of the more frequent ALT elevations observed in clinical trials (personal communication, D. Larrey, J. Uetrecht, P. Watkins), a view consistent with a mechanistic link between isolated ALT elevations and AIHI events. The temporal relationship between ALT elevations observed in clinical trials and postmarketing AIHI events has not been systematically examined.

A logical conclusion would be that drugs that cause ALT elevations can be placed along a spectrum. On one end are drugs causing ALT elevations that may reflect liver injury but never cause AIHI. On the other end are drugs that cause liver injury that progresses to AIHI with relatively high frequency (perhaps 1 in 10 subjects with ALT elevations who are continued on treatment). While ALT is a sensitive biomarker for liver injury, it alone cannot differentiate between drugs at opposite ends of this spectrum.

Drug-Induced Liver Injury with Jaundice: The Current Gold Standard Biomarker for AIHI Potential

Hy Zimmerman (1968) first noted that a patient who presented with drug-induced hepatocellular injury with jaundice had at least a 10 percent chance of dying from liver failure (before liver transplantation was available). In hepatocellular injury, a rise in total and direct bilirubin reflects a substantial risk because it indicates a major loss of functioning hepatocytes (when other causes for increased bilirubin are excluded). The approxi-

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mately 10 percent mortality or transplant rate for drug-induced hepatocellular jaundice—known as "Hy's Law"—has been confirmed in recent reports from Sweden and Spain (Andrade et al., 2005; Bjornsson and Olsson, 2005).

FDA draft guidance for evaluating liver safety in a clinical trial defines "Hy's Law cases" as subjects in a clinical trial who experience ALT elevations of more than three times ULN and total bilirubin of more than two times ULN and satisfy the following three criteria: (1) the liver injury should be hepatocellular in nature, and there should not be a prominent cholestatic component (e.g., serum alkaline phosphatase of more than two times ULN); (2) there should be no more likely alternative cause than drug-induced liver injury, such as acute viral hepatitis A or B or C, preexisting or other acute liver disease, or another drug capable of causing the observed injury; and (3) there should be evidence that the drug causes more frequent but less severe hepatocellular injury as shown by more frequent ALT elevations of greater than three times ULN in the treated group relative to the control group (FDA, 2007). The FDA has placed great confidence in the specificity of Hy's Law cases as a biomarker for identifying drugs capable of inducing serious AIHI, reporting, "We are not aware of false positive Hy's Law findings" (FDA, 2007).

Hy's Law cases are, however, a specific but imperfect biomarker for drugs capable of causing AIHI. In an FDA review of 26 new drug applications (13 of the drugs were known to be "hepatotoxic"), Hy's Law events were seldom observed in the clinical trials, even with compounds later demonstrated to be capable of causing severe AIHI (Pauls, 2004). This is not surprising since the rarity of susceptible individuals and the delayed appearance of the event generally would require very large and prolonged clinical trials for detection. Also, clinical protocols usually mandate frequent monitoring of and strict stopping rules based on serum ALT, especially once a liver safety issue has been established for a drug in development. Stopping treatment at a low level of liver injury may allow a patient susceptible to AIHI to recover without demonstrating a rise in serum bilirubin. The only way to determine whether a patient with ALT elevation will adapt or progress is to continue treatment and observe the patient closely, with frequent monitoring of liver chemistries. The draft FDA guidance on liver safety (FDA, 2007) suggests that continued treatment may be considered in subjects with asymptomatic ALT elevations exceeding three times ULN. This practice may place these study subjects at greater health risk than subjects without ALT elevations, which raises ethical concerns.

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Do Better Biomarkers Than Hy's Law Cases Exist?

The ideal biomarker would not require placing patients at significant risk in the course of distinguishing between drugs capable of causing AIHI and drugs, such as heparin and statins, that do not appear to cause AIHI. The ideal biomarker also would be able to make this distinction in a relatively small clinical trial of short duration. The plausibility of such a biomarker rests on the mechanistic differences between drugs that have the potential to cause AIHI and those that cause only reversible ALT elevations. At least two possibilities exist:

- The mechanisms that distinguish AIHI are many, complex, and agent-specific, to the extent that identifying a manageable number of predictive markers applicable to most drugs capable of causing severe AIHI is impractical or impossible.
- Common mechanisms for AIHI exist and can be translated to a manageable number of validated biomarkers that could be applied to better understand the hepatic safety of candidate drugs in both the preregistration and postmarketing settings.

The first of these possibilities suggests the need for drug-specific biomarkers for those agents whose risk/benefit balance warrants continued marketing (as when agent-specific markers for patients at risk are available) when the incidence of liver safety events is high enough to characterize premarketing development. The existence of a small group of markers that, in the aggregate, have predictive value for AIHI in many or most cases relies on the second possibility being correct. What follows are three lines of thought regarding the pathogenesis of AIHI that can be used to examine possible biomarkers.

Cumulative Injury Theory

Cumulative injury theory maintains that drugs capable of causing AIHI induce progressive impairment of critical functions of hepatocytes that may start soon after the initiation of treatment but is not detected by elevation in serum ALT. An example is progressive mitochondrial injury (for example, as demonstrated for fialuridine and in cell culture for other drugs, such as nefazadone and troglitazone) where adenosine triphosphate (ATP) generation is progressively compromised over a period of weeks or months during treatment (McKenzie et al., 1995; Dykens et al., 2008; Xu et al., 2008). When mitochondrial function deteriorates to a critical level, hepatocellular necrosis may ensue, releasing or recruiting injury-propagating factors and/

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or increasing metabolic demands on neighboring hepatocytes, which may progress to liver failure.

Some recent data suggest that a small number of critical pathways may compromise hepatocyte function to produce AIHI. In a recent study, fluorescent imaging of human hepatocytes was used to examine the effects of 300 hepatotoxins and nonhepatotoxins on mitochondrial damage, oxidative stress, and intracellular glutathione. These in vitro studies predicted approximately 60 percent of drugs capable of causing AIHI (many of which had not been detected in preclinical testing) with a high specificity (a false positive rate of 0–5 percent) (Xu et al., 2008). Because mitochondrial damage, oxidative stress, or depletion of intracellular glutathione may be downstream of molecule-specific events, such as reactive metabolite accumulation, a drug capable of causing severe AIHI could induce characteristic changes in the serum proteome or metabolome or in the urinary metabolome that would not be present in patients treated with drugs incapable of causing AIHI.

Immune Response Theory

Another mechanism proposed to account for the temporal delay in the onset and progression of liver injury is the production of reactive metabolites resulting in immune activation (Uetrecht, 2007). Within the hepatocyte, a drug is bioactivated to a reactive metabolite that binds to and modifies hepatocellular proteins. When this modified protein or hapten is presented by antigen-presenting cells to T cells, they transform to cytotoxic T cells and antibody-producing B cells (Kaplowitz, 2005; Park et al., 2005). Such drug-induced immune reactions typically occur within the first month of treatment and more rapidly with rechallenge (Kaplowitz, 2005), as seen with halothane (Mushin et al., 1971), and may be accompanied by clinical signs of hypersensitivity, such as fever, rash, and eosinophilia. The role of a specific hepatotoxin/metabolite in this immune response can be assessed in some cases by the lymphocyte stimulation test (Kaplowitz, 2005; Sanderson et al., 2006). These immune responses may be enhanced by acute inflammation or circulating lipopolysaccharide in rodents (Roth et al., 2003), and may explain why immunoallergic hepatotoxicity is more common in AIDS patients (Kaplowitz, 2005). It is quite probable that many AIHI cases result from episodic environmental/infectious/inflammatory changes that occur during drug therapy and that affect susceptibility or directly trigger a toxic interaction with a drug.

A variety of data suggest that immune mechanisms may underlie AIHI even when there are no clinical signs of hypersensitivity; an example is a report of human leukocyte antigen (HLA) associations with zimelagatran

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hepatotoxicity (Kindmark et al., 2007). It is possible that biomarkers of immune activation could be useful in distinguishing benign ALT elevations from those that can portend AIHI. In support of this concept, ALT elevations accompanied by hepatitis symptoms (fatigue, nausea, right upper quadrant pain) appear to be more predictive of AIHI potential than are asymptomatic ALT elevations (Nolan et al., 1999). These symptoms may be mediated by cytokines or other endogenous proteins, which may be detectable long before symptoms appear.

Failure of Adaptation

If the critical issue in AIHI is failure to adapt to the initial injury, there may be biomarkers that could identify patients likely to adapt—and, conversely, those likely to progress to severe liver injury—at a very early stage in the injury process.

POTENTIAL NEW BIOMARKERS FOR AIHI

Sources of Candidate Biomarkers

Candidate biomarkers for AIHI are emerging from many lines of investigation, including extensive transcriptomic profiling of rats treated with a variety of hepatotoxic drugs. In the Liver Toxicity Biomarker Study (LTBS), pangenomic approaches are being used in rats to identify biomarkers capable of distinguishing pairs of drugs that are structurally and pharmacologically similar but differ in that one is capable of causing AIHI and the other is not. The Predictive Safety Testing Consortium has been identifying potential liver safety biomarkers but has not yet focused on detecting those for AIHI.

Another path to identifying potential biomarkers for AIHI is the ongoing effort to study patients who have actually experienced the condition. The Severe Adverse Event Consortium (SAEC) (Holden, 2008) has begun whole-genome single nucleotide polymorphism (SNP) analysis on germ-line DNA from patients who have experienced varying degrees of drug-induced liver injury, including AIHI. The expanding U.S.-based Drug Induced Liver Injury Network (DILIN) (Hoofnagle, 2004) will begin genetic analysis on a similar cohort and has the advantage of maintaining identity links to the participants so that additional phenotyping studies can be performed. Because subjects are enrolled in these registries only after a diagnosis of drug-induced liver injury has been made, it is generally not possible to obtain blood or urine early in the course of or prior to the injury.

One research priority will be to generate hypotheses that can be tested in gene banks and in the DILIN subjects themselves. International drug-

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induced liver injury registries in the United States, the United Kingdom, Japan, Spain, Sweden, and Denmark now contain thousands of expert-adjudicated cases, which can be combined and analyzed for risk factors predicting progression to AIHI. Mining of large postmarketing adverse event databases also may suggest drug–environment susceptibility factors that could lead to testable hypotheses or be used to provide supportive data for genetic associations observed in these networks. In addition, analysis of blood/urine samples obtained in clinical trials of drugs known to cause AIHI may be useful in identifying biomarkers, especially when compared with blood/urine samples obtained in clinical trials of drugs that cause ALT elevations but do not have the potential to cause AIHI. A large prospective trial in isoniazid-treated patients has been proposed for this purpose (Watkins et al., 2008). Studying differences in susceptibility to hepatotoxicity across panels of inbred strains of mice and performing quantitative trait loci mapping may be a promising approach to generating hypotheses that would be testable in relatively small numbers of human subjects. Recent models have emerged in which drugs that cause AIHI in humans also cause liver injury in animals. It may be productive to explore biomarkers in these animal models, especially for biomarkers that are related to injury progression and adaptation and that predict serious downstream injury. In choosing drugs for study, consideration should be given to AIHI-associated drugs having a negative comparator in the same pharmacologic/structural class that is devoid of an equivalent degree of AIHI liability (e.g., trovafloxacin-levofloxacin).

Finally, the FDA has sponsored a cooperative research and development agreement to develop a computer-based model for understanding and predicting drugs capable of causing AIHI.[3] The goal of this effort is to incorporate current mechanistic knowledge, as well as data and insights gained from ongoing efforts such as the SAEC and DILIN analyses. This evolving model could suggest novel biomarkers and provide a biological rationale for biomarkers discovered by other means.

Validation of Candidate Biomarkers

Biomarkers that are predictive in small clinical trials of short duration would be extremely useful. Potential biomarkers could be tested by administering examples of drugs both with and without AIHI liability to small groups of closely monitored patients or healthy volunteers and analyzing prospectively collected blood/urine samples. For example, the first pair of drugs studied in the LTBS were tolcapone (whose use is restricted because of

[3]More information about this agreement can be found at http://www.entelos.com/newsReleases.php?ID=press101.

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liver toxicity) and entacapone. Since both drugs are in clinical use, it should be possible to test candidate biomarkers that emerge from the LTBS effort in patients or possibly healthy volunteers treated with these drugs. Short-term studies of this design with healthy volunteers may be ethical since the onset of liver injury is typically delayed weeks or months with tolcapone (Olanow and Watkins, 2007). However, it is possible that drugs capable of causing AIHI will be distinguishable only once liver injury has begun as signaled by ALT elevations, so that longer-term treatment would be required to evoke the phenotype. In this case, blood/urine samples would have to be obtained from patients with ALT elevations induced by drugs capable of causing AIHI and then compared with blood/urine samples obtained from patients with ALT elevations induced by drugs that do not cause AIHI. If (for at least some drugs) human AIHI occurs via interaction with an acute inflammatory stress, then plasma biomarkers based on this mode of action can be examined. For example, prolonged elevation of plasma cytokines, hemostatic biomarkers, and/or markers of neutrophil activation, when used in conjunction with traditional biomarkers such as ALT, might prove predictive. Generally, biomarkers with mechanistic/mode-of-action underpinnings are likely to be the most consistent predictors of AIHI.

True validation of biomarkers will ultimately require large numbers of samples obtained from individuals with well-known phenotypes, including both healthy and diseased populations, as well as populations treated with many different drugs. One path would be to institute protocols for standard data and blood/urine collection once ALT elevations have been observed in a clinical trial. An example of a liver safety data management system is eDish (Guo et al., 2008). This or a similar format could be directly linked to the sample bank, and would allow immediate identification of individuals of interest and immediate access to all pertinent clinical and laboratory data for those patients for detailed evaluation. Because the true potential of a drug to cause AIHI may not be evident preapproval, the blood/urine samples and data bank would need to be maintained for some time postmarketing. It would obviously be ideal if scientists had access to samples and clinical data from the clinical trials of many of the drugs listed in Table 5-1.

HIGHLIGHTS OF THE BREAKOUT DISCUSSION

In plenary session, John Bloom of Eli Lilly presented the main conclusions of participants in the breakout session on biomarkers for liver toxicity. Discussants in the breakout session observed that candidate AIHI biomarkers are best identified and validated in three relevant human populations: Hy's Law cases; subjects in prospective, controlled clinical trials with established and well-characterized AIHI agents, including isoniazid;

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and subjects in clinical trials who receive a drug known to cause ALT elevations but not yet known to cause AIHI. Some data suggest that subpopulations of these groups may exhibit changes that share common mechanisms with those associated with AIHI. Discussants identified the following six priority research efforts.

Accessing and Characterizing Hy's Law Cases

The first priority is to develop methods for overcoming key barriers to accessing clinical information and biospecimens from Hy's Law cases, which arguably constitute the most relevant population to study. This priority need raises several important questions. How can these rare cases be better accessed and characterized? How can well-annotated specimens be obtained, including specimens from matched controls? Can ongoing initiatives such as those of SAEC, DILIN, and other partnerships be integrated more effectively? How can electronic health records and large databases, such as those from the U.S. Department of Veterans Affairs or private insurers, be better leveraged? Can a warehouse for data be established? Could such an effort be integrated into the FDA's Sentinel Initiative?

Developing and Implementing Protocols for Specimen and Data Collection in Clinical Trials of Specific Marketed Drugs Known to Either Cause or Not Cause AIHI

A second priority is to develop and implement protocols for specimen and data collection in prospective clinical trials of isoniazid and other drugs known to cause AIHI or known to cause ALT elevations but not AIHI. A number of key questions need to be addressed. What would a protocol look like in terms of the subjects who are enrolled and controls for concomitant treatments and diseases? Are there markers that can be used to enrich this patient population? Can signals or markers for adaptation and severity of liver injury be differentiated and stratified? Are there markers that can predict, rather than simply demonstrate, the effect of the disorder? What other agents should be considered for prospective trials? To what extent will the identified markers be agent-specific and therefore not more broadly applicable? How can this kind of study be sponsored or funded, and can it be coupled with ongoing studies?

Investigating ALT Signals in Clinical Trials during Drug Development

A third need is to develop and implement protocols for standardized data and biospecimen collection in clinical trials when an ALT signal is identified. Important questions include the following: What should be the

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trigger for collection, and which specimens should be collected? How can standardization of specimens and data be achieved, including ascertainment as well as phenotyping? What should be the role of regulators? Should access to specimens and data be restricted? How can the risk for the sponsor be managed in such a situation?

Making Use of Existing Databases

A fourth priority is to conduct a thorough examination of existing FDA liver safety databases from Phase III clinical trials, and perhaps from the Adverse Event Reporting System database, to test hypotheses for the more frequent benign ALT elevations. An important hypothesis is that such elevations in this population, or more likely a subset of these patients, are mechanistically linked to AIHI, and that this link could be validated or at least corroborated. How can these data be mined? How can privacy issues be addressed? How can alignment among regulatory agencies and private companies be achieved? What are the incentives for alignment? What resources and oversight are needed? Can this research be decoupled from regulatory decision making?

Prioritizing Biomarker Discovery

A fifth research need is to prioritize biomarker discovery options using the data and biospecimens from the three populations described above. This work will require answers to a number of questions. How should the right specimens be collected when candidate markers are not known? How should options be kept open? Should candidate biomarker domains be prioritized according to established and emerging hypotheses? For instance, if a toxic metabolite or other form of injury leads to subsequent immune responses, there are pathways from which one can derive biomarkers for these responses. Should biomarker discovery searches be prioritized along the lines of these hypotheses or enabling technology platforms? Should this guide which specimens are collected?

Identifying and Prioritizing Nonclinical Research Options

Finally, there is a need to identify and prioritize nonclinical research options for generating biomarker hypotheses for testing in clinical specimen banks. Can animal models enable method development? If relevant models are identified, can they provide information on progression factors, reversibility, the kinetics of biomarker changes, and other questions enabled by tightly controlled conditions? Can nonclinical studies be linked to clinical studies to inform biomarker identification? Are there surrogate

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in vivo or in silico models that can suggest new candidate biomarkers for human studies?

Next Steps

The questions identified by the discussants in each of the above six areas attest to the complexity and challenges of implementing such a multidisciplinary and interinstitutional endeavor. Many additional questions remain regarding coordination, oversight, and sponsorship of efforts in these areas. Breakout session participants discussed potential roles for the IOM in facilitating efforts of the research community in addressing these questions. One suggested approach would be for the IOM to convene and facilitate working groups in each of the six priority research areas.

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6

Future Considerations

Over the course of the workshop, several panel presentations concluded with general discussions of the major issues affecting the development and use of biomarkers. These discussions focused on three main issues: creating incentives for organizations to collaborate, moving forward even when a thorough understanding of biological mechanisms is lacking, and dealing with different levels of risk in biomarker development.

CREATING INCENTIVES FOR COLLABORATION

Janet Woodcock noted that approximately half a million reports of drug-induced injuries are submitted to the Adverse Event Reporting System annually. These injuries represent both a major public health problem and substantial health care costs. At the same time, observed Daniel Bloomfield, the expectations for safety and the amount of research needed to get a drug approved have increased, even though the typical commercial life of a drug has not changed. Given the reduced returns from drug development, fewer companies are pursuing difficult projects with the potential to reduce the toll of drug-induced injuries.

Woodcock emphasized that investing millions of dollars in basic research and hoping that the resulting knowledge will automatically become available for use in human populations may be insufficient. Instead, special initiatives often are necessary to translate new knowledge into results that can have an impact on health care. Woodcock cited two such projects that have been supported by the Foundation for the National Institutes of Health (FNIH). One is the Alzheimer's Disease Neuroimaging Initiative,

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which also has been supported by NIH and industry and in which the FDA participates. Another is the Osteoarthritis Initiative, a prospective investigation of a large number of potential biomarkers. In addition, Woodcock noted that the FNIH helped establish the Biomarker Consortium, a major public–private biomedical research partnership with participation from a broad and diverse group of stakeholders, including government, industry, academia, and patient advocacy and other nonprofit private-sector organizations. The goal of the Biomarker Consortium is to collaborate in rapidly identifying, developing, and qualifying potential high-impact biomarkers.

Many workshop participants stressed that such collaboration among industry, the FDA, and academic researchers could yield much more rapid progress in the development of biomarkers. The question then becomes whether incentives could be established to promote such collaboration.

One important set of incentives, according to Frank Sistare, would be clear agreement on the data that could be generated in regulated phases of drug development that would not need to be submitted to regulatory authorities. When drug development is in its earliest stages, companies need freedom to operate without worrying about having to submit all such data to regulators, who may then decide that the development process should be slowed so that certain concerns can be probed more thoroughly. The FDA has offered guidance on these decisions, and there is an ongoing dialogue with the agency to clarify the issues involved. But the current lack of clarity continues to inhibit industry from generating data that could be extremely useful for fear that the data could be used to slow drug development.

Government and industry need to be creative in implementing incentives and removing disincentives, Sistare continued. For example, could a company be offered a reduction in user fees for the submission of data related to the discovery or development of safety biomarkers deemed critically important by regulatory authorities, or could it gain a period of added exclusivity for a product? Although both of these steps would require legislation, they represent the kind of out-of-the-box thinking that is needed.

James Stevens of Eli Lilly suggested that incentives might include staggered goals for what can be done in 1 year, 3 years, and 5 years. Some research projects take relatively long to complete, and potential partners in collaboration may be unwilling to participate unless they know when particular goals should be achieved.

Other workshop participants questioned the practicality of establishing new financial incentives to foster partnerships. Given the many financial demands on the federal government, said Alastair Wood, incentives that require additional funding probably will not succeed. Unless collaborations have realistic objectives and expectations, the potential to make progress through cooperation may be forfeited. Wood also questioned why incentives are necessary if a partnership results in drugs being developed more

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quickly and with less investment of resources. If a given partnership makes sense, why are incentives needed to foster it?

According to Robert Califf of the Duke University Medical Center, multi-institutional partnerships and collaborations with industry will be necessary for substantial progress to occur. This requires both "big science," characterized by extensive cutting-edge technologies, and "big populations," where associations can be detected and refined. An undertaking of this magnitude, Califf observed, is too big for individual companies, even large multinationals, no matter how global they are. The same is true for individual academic centers, even those with broad, interdisciplinary skills and knowledge. Califf described his own experience with the recently launched David Murdock Research Institute as an example of the type of partnerships that will be required in the future. Created by a major philanthropic gift, the Institute is a collaboration among Duke University, the University of North Carolina (UNC) system, and Dole Foods. The Institute also has links to universities and industries throughout the United States, and partnerships with organizations in India and Singapore. Substantial funding has enabled the Institute to combine large-scale biobanking and state-of-the-art technology with support for manufacturing and commercialization. Califf characterizes the Institute's approach as a "factory approach to biomarkers development."

Califf further observed that existing public–private partnerships have been inhibited by uncertainty about how to manage conflicts of interest when public entities and for-profit corporations work together. A lack of clarity about the terms of engagement can stifle creative solutions.

Interests and incentives will vary even from one federal agency to another. For example, NIH has taken on important responsibilities, such as the Drug Induced Liver Injury Network (DILIN) and the Biomarker Consortium, that differ from the responsibilities of the FDA. Yet interagency collaborations have already begun to emerge, as exemplified by FDA and NIH interactions with respect to the DILIN initiative and the Biomarker Consortium. Successful partnerships hinge on finding common ground among agencies and between the federal government and industry. If important tasks are being overlooked within the federal government, it may be necessary to develop a new infrastructure within a federal agency to carry out those tasks. For example, a new, independent, cross-agency institute may be needed to foster biomarker development, suggested Richard Paules of the National Institute of Environmental Health Sciences.

John Bloom pointed out that partnerships could help establish standards for submission databases, review databases, and electronic medical records. Greater standardization throughout the biomarkers field also would encourage more sophisticated approaches to informatics. Bloom expressed the opinion that biomarker development faces no insurmount-

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able barriers that cannot be overcome through a coordinated effort. But opportunities need to be seen as worthy of the attention and resources of institutions.

Wood also noted that many stages of biomarker development lend themselves to a noncompetitive structure. The more information that is shared among companies, the more productive research will be. Many companies see secrecy as essential to gaining an advantage, but secrecy also works in reverse. For example, other companies may have information about problems with another drug in the same class as the drug under development. A drug that proves to have problems early in the development process often is not extensively discussed outside the company that is developing it. Sharing such information could reduce the costs of research without compromising competitive positions.

Concluding the discussion, William Mattes of the Critical Path Institute suggested that any incentives put in place need to be carefully considered and structured so they do not create the appearance of favoring individual stakeholders. Incentives will be successful if they account for the varying interests of different groups. For example, academic researchers are rewarded for publishing their work and are unlikely to share information extensively before publication. Similarly, a company has incentives to work on its own compounds rather than in partnership with other companies on projects that are not directly product related.

MOVING FORWARD WITHOUT UNDERSTANDING MECHANISMS

As Califf pointed out, it is possible to make predictions with biomarkers that are probabilistically quite accurate without knowing much if anything about the mechanisms behind those biomarkers or the biological processes they reflect. This is already the case with cancer treatment, with physicians and patients being able to purchase multiple prognostic tests, each based on somewhat different arrays of biomarkers. While such options are available, however, it is always preferable to understand the mechanism involved because of the possibility of developing new targets for treatment or redesigning molecules to avoid toxicity by not engaging the mechanism.

Ravi Iyengar of Mount Sinai School of Medicine, whose workshop presentation addressed the role of systems biology in biomarker development (see Box 6-1), put the issue in a different context. Often a general mechanism is apparent for 90 percent of the cases of a disease or adverse drug reaction, and most of the other cases can be accounted for by using more tests and statistical associations. But 1 percent of cases may remain mysterious unless a biological mechanism is understood extremely well. If a signature for these outliers exists, Stevens asked, will clinicians be com-

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BOX 6-1
Systems Biology and Biomarker Development

In his presentation, Ravi Iyengar described the challenges facing systems biology, as well as the potential of this new perspective on biological processes to aid in the development of biomarkers. There are several definitions of systems biology. In the context of biomarker discovery, Iyengar described systems biology as the use of computational approaches to drive understanding. Network and statistical models that are implemented computationally are used to probe how the parts of a biological system function together. An understanding can be gained of how and why a complex biological function occurs as it does, although detailed mechanistic understanding of a molecular interaction may require different kinds of studies.

Biological systems exist at different levels—from the organ level, to tissues and cells, to intracellular networks, to the molecular level. Many of the actual physiological measures in medicine are made at the level of clinical analysis and indicators. Systems biology models can often relate events at a lower level to clinical outcomes. A great challenge for systems biology, said Iyengar, is to integrate understanding of these different levels vertically.

As an example of a correlation without detailed understanding, Iyengar cited an FDA-approved breast cancer diagnostic that is based on 70 genes, while an alternative diagnostic is based on 76 genes. Yet the two sets have only three genes in common, which raises the question of how the sets are related. Research in Iyengar's laboratory has shown that both sets of genes are linked to overlapping sets of upstream transcription factors and signaling. In turn, transcription factor activity profiling and network analyses can help identify relationships between mutated disease genes and prognostic gene expression signatures. This is one way to connect events at different levels, enabling oncologists to use molecular markers in treatment decisions.

Iyengar's laboratory also has been looking at congenital and drug-induced arrhythmias. Using genes identified as being related to long-QT (LQT) syndrome, he and his colleagues built a disease gene network to see how the genes are related. From a very large network of 15,000 nodes and 70,000 interactions, they identified an LQT gene "neighborhood" of about 1,400 nodes. They found that unique networks can be constructed around genes involved in disease states, and the properties of these networks can help explain some of the characteristics of different states.

Iyengar said that these networks also can explain drug side effects because there is a relationship between the genomics and systems pharmacology of LQT syndrome. Networks of biomarkers are likely to perform better than single biomarkers for complex diseases because networks across genes integrate multiple sources of information. In this way, systems biology approaches can provide insight into the pathogenesis of adverse events and suggest alternative targets for treatment. It may even be possible to predict clinical outcomes 2–5 years into the future on the basis of information from cellular or molecular networks.

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fortable using it to make clinical decisions without knowing the mechanism behind a response?

Several workshop participants responded that biomarkers can provide valuable information even when biological mechanisms are largely unknown. At a fundamental level, Califf observed, many biological mechanisms remain at least partly unknown. Woodcock stated that medicine is conducted among many uncertainties, and reliable information that can distinguish who is and is not at risk is an advance beyond not having such information. Also, Woodcock pointed out that the discovery of predictive biomarkers can lead to research on their reliability and on their association with outcomes.

Bloom emphasized the importance of not interpreting the term "biomarker" too narrowly. A biomarker is a piece of information that can be used correctly or incorrectly in making a decision or seeking additional information. The term "biomarker" can even be misleading if it is interpreted as denoting a single measurement without a broader biological context.

DEALING WITH DIFFERENT LEVELS OF RISK

Bloomfield described a hypothetical scenario involving a drug that is effective at treating depression but causes a mean blood pressure rise of 2 millimeters (mm) of mercury in a test treatment population. Should such a drug be approved? The ultimate question in such cases, he said, is the level of risk that patients, physicians, and society are willing to accept.

Woodcock emphasized the complexity of this issue. The older antipsychotics, for example, posed major risks, but at one point they were the only available treatments, so they were widely used. Regulators know that a 2 mm rise in blood pressure will translate to a mortality difference if a drug that causes it is used long enough. In the past, calculations of risks and benefits were left largely to physicians and patients; today, other groups play a role in these calculations as well. This is one example of how biomarkers could be pivotal. If it were possible to identify subgroups who would experience the 2 mm rise in blood pressure or would have a good response to the antidepressant, the risk/benefit calculation would be easier to make.

Califf suggested that an effective drug for depression would save lives, and therefore should be available on the market. At the same time, however, an outcome study should be done to determine the true effect of the drug on the balance of risk and benefit. The more biomarkers that can be identified to gauge the effects of a drug, the stronger the signal will be as long as the research reflects an awareness of the complex methodology that must be applied to understand the joint effects of multiple markers. Iyengar

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pointed out that most predictions take the form of probabilities, which do not tell a patient or physician exactly what to do, and proper decisions will be more likely if all parties involved understand the role of probabilities in decision making.

Insel proposed a promising way to involve the public in the biomedical enterprise and inform them about its results. He suggested that every patient should become a partner in a research program addressing the condition affecting that patient. This has already happened in some areas, such as cystic fibrosis and particular kinds of childhood cancer. It could occur as well for much broader groups, such as everyone with cardiovascular disease.

Califf responded by saying that one of the most encouraging aspects of establishing the David Murdock Research Institute is that the organizers have been overwhelmed by calls from people in the surrounding region who want to be enrolled in epidemiological studies. Involving these volunteers in research will take careful planning, but they represent a largely untapped resource that could speed the pace of scientific progress.

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Appendix A

Workshop Agenda

ASSESSING AND ACCELERATING THE DEVELOPMENT OF BIOMARKERS FOR DRUG SAFETY

NAS Keck Center, Room 100
500 Fifth Street NW, Washington DC
October 24, 2008

Objectives: The primary goals of this workshop are

- to assess the current state of the art for screening technologies to find off-target effects early in drug development—what have we been able to accomplish, and what remains to be done;
- to develop a prioritized questions list to address remaining obstacles; and
- to discuss how to accelerate the efforts through public and private means.

8:00–8:15 WELCOME AND INTRODUCTION OF WORKSHOP OBJECTIVES

Robert Califf (*Forum Member*)
Duke University Medical Center

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8:15–10:15 MORNING SESSION—ASSESSING THE CURRENT STATE OF BIOMARKERS TO PREDICT DRUG-INDUCED TOXICITY.

- What is the current state of the art for screening technologies to find off-target effects early in development—what have we been able to accomplish, and what remains to be done?
- What are the obstacles impeding progress?
- How can these efforts be accelerated through public and private means?

Moderator: MIKHAIL GISHIZKY (*Forum Member*)
Entelos

8:15–8:30 **Overview**
ALASTAIR WOOD
Symphony Capital, LLC

8:30–8:45 **Cardiac Toxicity**
NORMAN STOCKBRIDGE
U.S. Food and Drug Administration

DANIEL BLOOMFIELD
Merck Research Laboratories

8:45–9:00 **Hepatotoxicity**
PAUL WATKINS
University of North Carolina at Chapel Hill

9:00–9:15 **Nephrotoxicity**
FRANK SISTARE
Merck Research Laboratories

9:15–10:10 Panel **Discussion**

10:10–10:15 **Charge to the Breakout Groups**
ROBERT CALIFF (*Forum Member*)
Duke University Medical Center

10:15–10:30 **BREAK**

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10:30–12:30 BREAKOUT SESSION 1—
PREDICTIVE BIOMARKERS FOR NEPHROTOXICITY
Room 206

Moderators: FRANK SISTARE
Merck Research Laboratories

PRASAD DEVARAJAN
Cincinnati Children's Hospital Medical Center, University of Cincinnati

Panelists: JOSEPH BONVENTRE
Harvard Medical School, Brigham and Women's Hospital

FRANK DIETERLE
Novartis Pharma

ROBERT STAR
National Institute of Diabetes and Digestive and Kidney Diseases

MELANIE BLANK
U.S. Food and Drug Administration

DAVID WARNOCK
University of Alabama at Birmingham

10:30–12:30 BREAKOUT SESSION 2—
PREDICTIVE BIOMARKERS FOR HEPATOTOXICITY
Room 201

Moderators: PAUL WATKINS
University of North Carolina at Chapel Hill

CHRISTINE HUNT
GlaxoSmithKline

Panelists: JOHN BLOOM
Eli Lilly and Company

MARK AVIGAN
U.S. Food and Drug Administration

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Leonard Seeff
National Institute of Diabetes and Digestive and Kidney Diseases

James Freston
University of Connecticut Health Center

10:30–12:30 BREAKOUT SESSION 3—PREDICTIVE BIOMARKERS FOR CARDIAC TOXICITY
Room 109

Moderator: Jay Mason
University of Utah

Panelists: Daniel Bloomfield
Merck Research Laboratories

Norman Stockbridge
U.S. Food and Drug Administration

Paul Eisenberg
Amgen

Michael Domanski
National Heart, Lung, and Blood Institute

12:30–1:45 LUNCH
Room 100

1:45–3:15 BREAKOUT SESSION REPORTS

Moderator: Robert Califf (*Forum Member*)
Duke University Medical Center

1:45–2:00 Nephrotoxicity Breakout Report
Prasad Devarajan
Cincinnati Children's Hospital Medical Center, University of Cincinnati

2:00–2:15 Hepatotoxicity Breakout Report
John Bloom
Eli Lilly and Company

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2:15 2:30 **Cardiac Toxicity Breakout Report**
ALASTAIR WOOD
Symphony Capital, LLC

2:30–3:15 **Panel Discussion**

3:15–3:30 **BREAK**

3:30–5:30 **AFTERNOON SESSION—
COPING WITH THE INCREASED COMPLEXITY
OF VALIDATING AND QUALIFYING
MULTIMARKER PANELS.**

Until recently biomarkers have been developed one at a time, and at times the scientific community has debated their utility. The advent of large-scale genomic, proteomic, metabolomic, and advanced imaging technologies is changing the environment in which biomarkers are identified and assessed. During this session speakers will: explore the potential of applying cutting-edge scientific technologies to enhance prediction and detection of drug-induced toxicity; discuss integration of systems biology and computational biology into toxicity assessment in early drug development; and consider the regulatory and scientific challenges involved in the validation and qualification of multimarker panels.

Moderator: ROBERT CALIFF (*Forum Member*)
Duke University Medical Center

3:30–3:45 **Regulatory considerations for validation and qualification of multimarker panels**
JANET WOODCOCK (*Forum Member*)
U.S. Food and Drug Administration

3:45–4:00 **Systems biology of biomarkers**
RAVI IYENGAR
Mount Sinai School of Medicine

4:00–4:15 **A future direction of drug safety assessment—
North Carolina Biomarker Factory Project**
ROBERT CALIFF (*Forum Member*)
Duke University Medical Center

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4:15–4:30 **Biomarkers for psychiatric drug toxicity: opportunities and challenges**
THOMAS INSEL
National Institute of Mental Health

4:30–5:30 **Panel Discussion—Integration of new science into drug safety prediction and assessment**

- How can we develop more efficient approaches to biomarker evaluation and qualification in animals and humans?
- What potential policies could be enacted to help guide this effort?
- How could these efforts be advanced through public or private means?

5:30 **Adjourn**

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Appendix B

Speaker Biographies

Mark Avigan, MDCM, obtained his BSc (1972) and MDCM (1977) degrees from McGill University in Montreal, Canada. He completed residency training in internal medicine at the VA Medical Center/Georgetown University in Washington, DC. Subsequently, he served as chief medical resident and completed a clinical GI/hepatology/nutrition fellowship. Dr. Avigan served as a staff fellow in the Liver unit of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in Bethesda, Maryland, where he participated in the clinical evaluation of new therapeutics for the treatment of viral hepatitis. He later moved to the National Cancer Institute (NCI), where he pursued studies in molecular and cellular mechanisms governing the dysfunctional expression of oncogenes during carcinogenesis. In 1990 he joined the faculty of the School of Medicine at Georgetown University. As an assistant and later associate professor, he attended patients on the GI/Liver service at the Georgetown University Medical Center, and served as a mentor of graduate students in the Department of Pathology and clinical fellows in the Division of Gastroenterology's clinical program. In addition, he was the principal investigator of National Institutes of Health (NIH)-funded R-29 and R0-1 grants that supported studies to elucidate transcriptional and post-transcriptional growth regulation pathways. After joining the Center for Drug Evaluation and Research (CDER) of the Food and Drug Administration (FDA) in 1999 as a medical officer in the Division of Gastrointestinal and Coagulation Drug Products, he developed a strong interest in drug-induced liver injury and the impact of pharmacogenomic analysis on evaluation of the risk associated with drug treatment. Since 2003 he has served as a division director in the Office of Surveillance and

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Epidemiology. He is currently a member of CDER's Drug Safety Oversight Board.

Melanie Blank, MD, is a nephrologist in the Division of Cardiovascular and Renal Products at the FDA. She is a member of the Biomarker Qualification Review Team. Prior to joining her current division, Dr. Blank was a medical officer in the Division of Medical Imaging. She performed her internal medicine residency at Lenox Hill Hospital in New York City and her nephrology fellowship at George Washington University Hospital. She was in private practice for 14 years prior to joining the FDA 4 years ago.

John C. Bloom, PhD, holds a BS degree in biology from the University of Pittsburgh and doctorates in veterinary medicine and experimental hematology from the University of Pennsylvania. He completed his postdoctoral training at Lankenau Hospital (Jefferson Medical College) in hematology/oncology and served on the faculty of the University of Pennsylvania School of Veterinary Medicine as chief, clinical laboratory medicine before joining Smith Kline & French Laboratories in 1981 as associate director of pathology. Dr. Bloom is a past president of the American Society for Veterinary Clinical Pathology and has been active in the fields of hematotoxicology, hepatotoxicology, and immunotoxicology within the pharmaceutical industry. He has authored several manuscripts, chapters, and reviews on these topics; edited texts on toxicology and clinical biomarkers in drug development; and served on several committees sponsored by the National Academy of Sciences, the Institute of Medicine (IOM), the Society of Toxicologic Pathology, and PhRMA. He joined Lilly Research Laboratories in 1989 as head, clinical pathology in the Toxicology Division, and in 1991 moved to the Medical Division, where he established the department of Clinical Laboratory Medicine, and later the departments of Experimental Medicine and Clinical Diagnostic Services. As distinguished medical fellow (executive director), diagnostic and experimental medicine, he is now responsible for routine laboratory, electrocardiogram (ECG), imaging, and specimen banking support for global clinical development, and novel clinical biomarker discovery, validation, and application in the Division of Translational Medicine and Pharmacogenomics. Dr. Bloom holds adjunct academic appointments at the University of Pennsylvania and Purdue University.

Daniel M. Bloomfield, MD, MPhil, FACC, currently works at Merck Research Laboratories as an executive director in clinical cardiovascular research and is responsible for drug development for hypertension, arrhythmias, and heart failure. After receiving a BA in chemistry at Haverford College, he studied social anthropology at Oxford University as a Rhodes Scholar. Upon returning to the United States, he attended Harvard Medical School, and then received

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http://www.nap.edu/catalog/12587.html

training in internal medicine and cardiology at Columbia before joining the faculty. As an associate professor of medicine in the Division of Cardiology, Dr. Bloomfield received grants supporting his academic research career from NIH, foundations, and industry, and developed expertise in syncope (fainting spells) and in identifying patients at risk for sudden cardiac death. His laboratory was also involved in studies related to T wave alternans, the autonomic modulation of cardiac repolarization, and characterization of U wave behavior in diverse autonomic states. Dr. Bloomfield joined Merck Research Laboratories in 2003 working in clinical pharmacology, and was involved in and co-chaired a number of early development teams. He has chaired the QT Task Force (a multifunctional group of more than 20 individuals involved in all aspects of Merck's response to the E14 guidance), and created the Integrated Preclinical and Clinical Cardiovascular Safety Team (CVST) and the Cardiac Safety Board. Dr. Bloomfield is currently co-chair of the Cardiac Safety Research Consortium, a public–private partnership among the FDA, academia, and industry devoted to advancing scientific knowledge on cardiac safety for new and existing medical products by building a collaborative environment based on the principles of the FDA's Critical Path Initiative, as well as other public health priorities.

Joseph Bonventre, MD, PhD, is Robert H. Ebert Professor of Medicine at Harvard Medical School and professor of health sciences and technology (HST) at Massachusetts Institute of Technology (MIT). He is also chief of the Renal Division of the Brigham and Women's Hospital (BWH); director of the BWH-HST Center for Biomedical Engineering at the BWH; co-director of the Brigham Research Institute Stem Cell, Regenerative Medicine and Tissue Engineering Center; and a faculty member of the Harvard Stem Cell Institute (HSCI). Dr. Bonventre received his BS with distinction from Cornell University in 1970 in engineering physics and MD and PhD degrees in biophysics from Harvard University in 1976 and 1979, respectively. He holds honorary doctorate degrees from Mount Saint Mary's College and from the Norwegian Institute of Science and Technology in Norway. His research focuses primarily on the study of kidney injury and repair and signal transduction, with a special emphasis on the role of inflammation, biomarkers, and stem cells. His work on biomarkers led to the discovery of a marker that is appropriate for identification of early kidney injury and kidney cancer in preclinical as well as clinical studies. Dr. Bonventre received a MERIT award from NIDDK. He has been elected to the American Society of Clinical Investigation, the Association of American Physicians, and the American Institute for Medical and Biological Engineering. Dr. Bonventre is a member of the Council of the American Society of Nephrology and future president of that organization. He chairs the Kidney Group of the Harvard Stem Cell Initiative

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http://www.nap.edu/catalog/12587.html

and is co-chair of the Technology in Medicine Initiative at the BWH. In addition, he is a member of the board of directors of the National Space Biology Research Institute and the board of advisors of the Norwegian Institute for Science and Technology.

Robert Califf, MD (***Forum member***), is currently vice chancellor for clinical research, director of the Duke Translational Medicine Institute, and professor of medicine in the Division of Cardiology at the Duke University Medical Center in Durham, North Carolina. For 10 years he was director of the Duke Clinical Research Institute (DCRI), the largest academic research organization in the world. He is editor-in-chief of Elsevier's *American Heart Journal*. He is the author or co-author of more than 650 peer-reviewed journal articles and is a contributing editor for www.theheart.org. Dr. Califf led DCRI for many of the best-known clinical trials in cardiovascular disease. In cooperation with his colleagues from the Duke Databank for Cardiovascular Disease, he has written extensively about the clinical and economic outcomes of chronic heart disease. He is considered an international leader in the fields of health outcomes, quality of care, and medical economics. He has served on the FDA's Cardiorenal Advisory Panel and the IOM's Pharmaceutical Roundtable. He served on the IOM committees that recommended Medicare coverage of clinical trials and the banning of ephedra, and he is currently serving on the IOM's Committee on Identifying and Preventing Medication Errors. He is director of the coordinating center for the Centers for Education and Research on Therapeutics, a public–private partnership among the Agency for Healthcare Research and Quality (AHRQ), the FDA, academia, the medical products industry, and consumer groups. Dr. Califf graduated from Duke University (summa cum laude) in 1973 and from Duke University Medical School in 1978. He performed his internship and residency at the University of California, San Francisco, and his fellowship in cardiology at Duke University. He is board certified in internal medicine and cardiology and is a fellow of the American College of Cardiology.

Prasad Devarajan, MD, is Williams Endowed Chair, professor of pediatrics and developmental biology, director of nephrology and hypertension, director of clinical laboratories, and CEO of the Dialysis Unit at Cincinnati Children's Hospital Medical Center and the University of Cincinnati. He serves on the editorial and review boards for more than 20 journals and on multiple NIH study sections. He has authored more than 120 peer-reviewed journal articles. His work has been continuously funded by NIH and several other foundations for 20 years. Dr. Devarajan's major research interests lie in the pathogenetic pathways, diagnostic biomarkers, and novel therapies of acute kidney injury.

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http://www.nap.edu/catalog/12587.html

Frank Dieterle, PhD, is head of External Affairs iTox in Novartis Pharma. He is responsible for safety biomarker strategies within Novartis from early development, to implementation, to clinical trials. This work includes the qualification of biomarkers for regulatory decision making together with health authorities and in cooperation with consortia. Dr. Dieterle is co-chair of the Nephrotoxicity Working Group of the Critical Path Institute's Predictive Safety Consortium, which performed the first qualification of safety biomarkers together with the European Medicines Evaluation Agency (EMEA) and the FDA. Before joining Novartis, he was responsible for the implementation of metabonomics at Roche. Dr. Dieterle holds a PhD in analytical chemistry from the University of Tübingen.

Michael J. Domanski, MD, is chief of the Atherothrombosis and Coronary Artery Disease Branch, National Heart, Lung and Blood Institute. He received his bachelor of aerospace engineering degree from the Georgia Institute of Technology and his MD degree from the University of Maryland. He has more than 15 years of experience in the performance of large randomized trials, related mainly to coronary disease, heart failure, and sudden cardiac death. Dr. Domanski serves on the FDA's Circulatory Devices Panel, the Department of Veterans Affairs (VA) Cooperative Studies Scientific Merit Review Board, the Engineering Advisory Committee of the Georgia Institute of Technology, and the board of directors of the Society of Geriatric Cardiology, and as a professor of internal medicine (cardiology) at the Uniformed Services Medical School. Dr. Domanski is American Board of Internal Medicine (ABIM) certified in internal medicine, cardiovascular diseases, and interventional cardiology and actively practices a wide range of invasive, noninvasive, and interventional cardiology. He has authored more than 200 publications, including textbooks on transesophageal echocardiography and randomized clinical trials (in press).

Paul Eisenberg, MD, MPH (*Forum member*), is senior vice president of global regulatory affairs and safety at Amgen, effective February 2008, after serving as vice president of global regulatory affairs and safety since January 2007 and vice president of global safety since December 2005. Prior to joining Amgen, he was vice president of Lilly Global Product Safety. At Lilly he also led clinical development teams in the cardiovascular, critical care, and inflammation therapeutic areas as vice president, internal medicine, and in discovery as executive director of cardiovascular research and clinical investigation. Dr. Eisenberg received his MD from New York Medical College and his MPH in tropical medicine from Tulane University School of Public Health. He was a professor of medicine at Washington University in St. Louis, where his academic career, over 18 years, was focused on basic and clinical research in cardiovascular disease and thrombosis. This

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work led to more than 100 publications in peer-reviewed journals and books. Dr. Eisenberg has been involved in the discovery and development of numerous new molecular entities (NMEs) in both his academic and industry careers. He has led the development and registration of multiple NMEs in cardiovascular and critical care. In addition, he has extensive experience in global safety and risk management for drug development programs and post-marketing in multiple therapeutic classes.

James Freston, MD, PhD, is professor of medicine emeritus and past Boehringer Ingelheim Chair of Clinical Pharmacology at the University of Connecticut Health Center. He served as chair of the Department of Medicine there for 17 years, a position he relinquished to direct the Health Center's clinical research programs, which include an NIH-sponsored General Clinical Research Center, a Clinical Trials Office, and investigator training and education services. Previously he was professor of medicine and pharmacology in the College of Medicine and professor of biochemical toxicology in the School of Pharmacy at the University of Utah, where he won the Outstanding Professor Award six times and directed the Gastroenterology and Clinical Pharmacology Divisions. He was founding chairman of the American Gastroenterological Association (AGA) Foundation and President of the AGA. He is past chairman of the American Digestive Health Foundation. He was consultant to the surgeon general for the gastrointestinal section of *The Health Consequences of Smoking* and a member of two FDA gastrointestinal Advisory Panels, as well as numerous NIH panels and committees. He currently serves on the NIH Council for NIDDK and as a co-investigator in the NIH-sponsored Drug Induced Liver Injury Network. He is internationally recognized for his expertise in the clinical pharmacology of gastrointestinal drugs and diseases, particularly drug safety aspects. He was founding Editor of the AGA's acclaimed Digestive Diseases Self-Education Program (DDSEP), a popular multimedia continuing medical education program that is in its fifth edition. He lectures worldwide and is the author of more than 140 journal articles and 40 books and chapters. Dr. Freston received the AGA's Mentor Honoree award in 2005; the Distinguished Alumnus Award from the University of Utah in 2006; and the AGA's Julius Freidenwald Medal in 2007, awarded for outstanding contributions to gastroenterology. In 2008 the AGA endowed an annual scientific conference in his name. Dr. Freston received his MD degree from the University of Utah and his PhD degree from the University of London. He is trained in clinical pharmacology, gastroenterology, hepatology, and aerospace medicine.

Mikhail Gishizky, PhD (*Forum member*), is chief scientific officer for Entelos, Inc. He has more than 25 years of experience in applied disease-

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Accelerating the Development of Biomarkers for Drug Safety: Workshop Summary
http://www.nap.edu/catalog/12587.html

related research. Prior to joining Entelos, Dr. Gishizky held positions of increasing scientific and management responsibility at Sugen-Pharmacia-Pfizer. His most recent position was research zone head, vice president of target discovery. Throughout his career, Dr. Gishizky has been responsible for implementing a broad range of discovery technology efforts in areas ranging from human genetics to bioinformatics. In addition, he has led discovery efforts in oncology, immunology, inflammation, and central nervous system (CNS) and metabolic diseases, establishing the critical link between preclinical/clinical research and early discovery. Dr. Gishizky received his doctorate training in endocrinology at the University of California, San Francisco, where his research focused on defining the molecular mechanisms responsible for the development and progression of diabetes mellitus. His postdoctoral training at the University of California, Los Angeles, focused on cancer biology and hematopoietic cell development. His research there was instrumental in demonstrating the causative role of the bcr/abl oncogene in the development of human chronic myeloid leukemia.

Christine M. Hunt, MD, FACP, is board certified in internal medicine and gastroenterology/hepatology, and is a fellow of the American College of Physicians and a member of the American Association of Liver Disease and the American Gastroenterological Association. She pursued basic and clinical hepatology-based research on the faculty of the Medical College of Virginia (1987–1988) and Duke University (1988–1996). In 1996, Dr. Hunt was recruited to join the global hepatitis and GI drug development team at GlaxoSmithKline (GSK). In 2005, she transitioned to chair the GSK Hepatotoxicity Board and co-chair the GSK Safety Biomarker Strategy Team. Dr. Hunt is vice president, GSK Clinical Safety Systems, building proactive safety systems to address the key toxicities affecting drug development. She represents GSK on the FDA Hepatotoxicity Special Interest Group and the Critical Path Translation Team on Predictive Biomarkers.

Thomas R. Insel, MD, is director of the National Institute of Mental Health (NIMH), the component of the National Institutes of Health charged with generating the knowledge needed to understand, treat, and prevent mental disorders. Immediately prior to his appointment as director, which marks his return to NIMH after an 8-year hiatus, Dr. Insel was professor of psychiatry at Emory University. There he was founding director of the Center for Behavioral Neuroscience, one of the largest science and technology centers funded by the National Science Foundation, and, concurrently, director of an NIH-funded Center for Autism Research. From 1994 to 1999, he was director of the Yerkes Regional Primate Research Center in Atlanta. While at Emory, Dr. Insel continued the line of research he had

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initiated at NIMH studying the neurobiology of complex social behaviors in animals. Early in his NIMH research career, which extended from 1979 to 1994, he conducted clinical research on obsessive-compulsive disorder (OCD), carrying out some of the first treatment trials for OCD using the selective serotonin reuptake inhibitor (SSRI) class of medications. Dr. Insel has published more than 200 scientific articles and four books, including *The Neurobiology of Parental Care* (with Michael Numan) in 2003. He has served on numerous academic, scientific, and professional committees, including 10 editorial boards. He is a member of the IOM, a fellow of the American College of Neuropsychopharmacology, and a recipient of several awards (the A. E. Bennett Award from the Society for Biological Psychiatry, the Curt Richter Prize from the International Society of Psychoneuroendocrinology, the Outstanding Service Award from the U.S. Public Health Service, and a Distinguished Investigator Award from the National Alliance for Research on Schizophrenia and Depression). Dr. Insel graduated from the combined BA–MD program at Boston University in 1974. He performed his internship at Berkshire Medical Center, Pittsfield, Massachusetts, and his residency at the Langley Porter Neuropsychiatric Institute at the University of California, San Francisco.

Ravi Iyengar, PhD, is Dorothy H. and Lewis Rosenstiel Professor and chair, Department of Pharmacology and Systems Therapeutics, Mount Sinai School of Medicine, New York. He received his PhD in biophysical sciences in 1977. He received his postdoctoral training at Baylor College of Medicine, and was a faculty member at Baylor before joining Mount Sinai in 1986. The Iyengar laboratory focuses on the systems biology of cellular regulatory networks, with special emphasis on signaling through G protein-coupled receptors (GPCRs) and heterotrimeric G proteins. The research projects in his laboratory converge on understanding how signals are routed and processed through cellular signaling networks. The laboratory is developing systems pharmacology to understand how diseased genes relate to drug targets in integrated networks and whether such networks can be used to predict side effects. Dr. Iyengar is a fellow of the American Association for the Advancement of Science and editor of the journal *Systems Biology* and serves on the editorial board of *Science Signaling*. He is director of the National Institute of General Medical Sciences (NIGMS)-funded Systems Biology Center of New York.

Jay W. Mason, MD, is an independent consultant in cardiac safety. He graduated from Princeton University and obtained his MD degree from the University of Pennsylvania. He trained in medicine and cardiovascular diseases at Stanford University, where he was a member of the faculty from 1975 to 1983 and served as director of the Cardiac Arrhythmia Service and

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Accelerating the Development of Biomarkers for Drug Safety: Workshop Summary
http://www.nap.edu/catalog/12587.html

co-director of the Cardiac Catheterization Laboratories. He became chief of cardiology at the University of Utah in 1983. In 1999 he was appointed chair of the Department of Medicine at the University of Kentucky. He remains a professor of medicine and cardiology at the latter two institutions. From 2003 to 2007 he served as medical director and director of R&D at Covance Cardiac Safety Services. At present he is chief medical officer (in a consultant role) at Oxford Biosignals, Inc. and Spaulding Clinical Research, LLC. His clinical, teaching, and research emphasis is in cardiac arrhythmias, electrocardiography, and electrophysiology. Dr. Mason has chaired the American College of Cardiology's electrocardiography educational committees for more than 20 years. He has been awarded more than $29 million in NIH support during his research career and is the author of more than 400 publications.

Leonard B. Seeff, MD, graduated in 1961 from the Medical School of the University of the Witwatersrand, Johannesburg, South Africa. He came to the United States in 1964 to work with Dr. Hyman J. Zimmerman, then chief of medicine at Mount Sinai Hospital in Chicago and one of the world's leading authorities in hepatotoxicity. A year later, he moved with Dr. Zimmerman to the VA Medical Center in Washington, DC, to complete his training in general medicine and his fellowship in GI/hepatology. Thereafter, he initiated and coordinated the first of what were to be four large-scale VA cooperative studies on post-transfusion hepatitis B and C, funded by the VA, the National Institute of Allergy and Infectious Disease (NIAID), the National Heart, Lung and Blood Institute (NHLBI), and NCI. Dr. Seeff moved to the VA Medical Center in Boston in 1968. He returned to the Washington VA Medical Center in 1971 as assistant chief of medicine for 8 years, followed by an appointment as chief of gastroenterology and hepatology in 1979. He continued his research in viral hepatitis and in 1984 was appointed professor of medicine at Georgetown University School of Medicine. In 1998, he joined NIDDK as senior scientist for hepatitis research, now senior scientific officer. He is a member of the American Association for the Study of Liver Disease (AASLD), where he served as councilor-at-large from 1997 to 2000. He is senior author of the AASLD guidelines for the treatment of hepatitis C, as well as other guidelines. Currently in the Liver Disease Research Branch of NIDDK, he helped design and oversee several large network studies, related mainly to viral hepatitis but also to the DILIN study. He has also coordinated several NIDDK meetings and workshops, including the Consensus Conference on Hepatitis C. His primary research interests are viral hepatitis and drug-induced liver injury. He has received numerous awards and has published more than 150 articles and 50 book chapters.

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Frank D. Sistare, PhD, has served since 2003 as executive director of the Department of Laboratory Sciences and Investigative Toxicology within Safety Assessment at Merck Research Laboratories. The department is responsible for genetic toxicology assessments and molecular carcinogenesis investigations; for bioanalytical toxicokinetic support; for the implementation of directed investigative toxicology research solutions and support for safety lead optimization; for the incorporation of new in vitro and in vivo model systems and technologies, including ion channel systems, genomics, proteomics, and metabonomics; and for the provision of clinical pathology, immunology, and biomarker development support to safety assessment. Dr. Sistare previously served for 15 years with the laboratory research component of the FDA's CDER, where he also served on or chaired numerous regulatory committees and working groups. Dr. Sistare is a retired captain with the Public Health Service (PHS) Commissioned Corps and has received several PHS Unit Commendations; PHS Meritorious Service, Commendation, and Achievement Awards; and CDER and FDA awards for excellence in laboratory research. He earned his BS in pharmacy from the University of Rhode Island and his PhD in pharmacology at the University of Virginia, and was awarded a postdoctoral Pharmacology Research Associate (PRAT) Fellowship at NIH.

Robert A. Star, MD, is director of the Division of Kidney, Urologic, and Hematologic Diseases at NIDDK. He is also a senior investigator and chief of the Renal Diagnostics and Therapeutics Unit at NIDDK. Dr. Star was a postdoctoral fellow at NIH in the mid-1980s before joining the faculty of the University of Texas Southwestern Medical Center in Dallas. In 1999, he returned to NIH to serve as a senior scientific advisor for kidney disease and to run a laboratory studying acute kidney injury. In 2002, he became senior advisor for clinical research in the NIH Office of Science Policy and Planning. There he worked on NIH Roadmap for Medical Research initiatives to reengineer the clinical research enterprise. The Roadmap aims to stimulate research and develop research resources for crosscutting, large, and complex projects with profound potential impact. Dr. Star also led training and career programs for clinical researchers and helped develop the clinical and translational science awards. Especially interested in translational research, Dr. Star's laboratory focuses on the early identification, prevention, and preemption of sepsis and acute kidney injury. Dr. Star's research has produced more than 100 published manuscripts, and he has written eight textbook chapters and holds several patents. He graduated summa cum laude in applied mathematics from Harvard College and cum laude from the Harvard Medical School–MIT Joint Program in Health Sciences and Technology. His internship and residency in internal medicine were performed at Michael Reese Hospital in Chicago. In addition, Dr. Star has

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received honorary awards and research support from NIH, the FDA, and the biotech industry, and the prestigious Young Investigator Award recognizing excellence in nephrology research, awarded jointly by the American Society of Nephrology and the American Heart Association.

Norman Stockbridge, MD, PhD, received his MD and PhD (physiology) degrees from Duke University. He performed basic science research before joining the FDA as a medical officer in 1991. Dr. Stockbridge is currently director of the Division of Cardiovascular and Renal Products in the FDA/CDER.

David G. Warnock, MD, is director of the Office of Human Research and Marie K. Ingalls Professor of Medicine at the University of Alabama at Birmingham (UAB). He graduated from the University of California, Berkeley, and received his MD degree from the University of California, San Francisco (USCF). His clinical training was completed at USCF, including a 1-year research fellowship with Isidore Edelman, MD, in the Cardiovascular Research Institute. Following a fellowship with Maurice Burg, MD, at NIH, Dr. Warnock returned to UCSF as a faculty member. He served as section chief at the San Francisco VA Medical Center during the last 5 years of his appointment at UCSF. Following a sabbatical with Bernard Rossier, MD, at the Institute of Pharmacology in Lausanne, Switzerland, Dr. Warnock was recruited to UAB as professor of medicine and director of nephrology in 1988, serving in that role until 2008. He was appointed director of the Office of Human Research at the University of Alabama in Birmingham in 2005. In 2006, he was named Marie S. Ingalls Professor of Medicine. During a sabbatical in 2008, he worked with Professor Frederic Jaisser at the College de France in Paris. Dr. Warnock's research interests include acid-base physiology, sodium transport mechanisms, chronic kidney disease, acute kidney injury, and inherited renal diseases. He is a member of the American Society for Clinical Investigation, the American Association of Physicians, the American Physiologic Society, the American Society of Nephrology (ASN), the National Kidney Foundation (NFK), and the International Society of Nephrology (ISN). He is currently immediate past president of the NKF and a founding member and member of the Executive Steering Committee of the Acute Kidney Injury Network.

Paul B. Watkins, MD, is Verne S. Caviness Distinguished Professor of Medicine, professor of pharmacology and experimental therapeutics, and professor of toxicology at the University of North Carolina, Chapel Hill (UNC-CH). He attended medical school at Cornell University and completed his internship and residency in internal medicine at New York Hospital–Cornell Medical Center. He received subspecialty training and

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http://www.nap.edu/catalog/12587.html

board certification in clinical gastroenterology and hepatology at the Medical College of Virginia. He was on the faculty at the University of Michigan from 1986 to 1999, when he moved to North Carolina. There he became director of the General Clinical Research Center and, more recently, director of the UNC Translational and Clinical Sciences (TraCS) Institute. In July 2008, Dr. Watkins became the director of a new Center for Drug Safety Sciences, a collaboration between UNC-CH and The Hamner Institutes. The Hamner Institutes is a not-for-profit organization based in Research Triangle Park (formerly called the Chemical Institute for Industrial Toxicology) and has a three-decades-long history of leading research on the health effects of environmental chemicals. Dr. Watkins is an accomplished basic and translational investigator in the fields of drug metabolism and hepatotoxicity. He is the recipient of numerous honors and awards, including the Therapeutic Frontiers Award from the American College of Pharmacy and election to the Association of American Physicians (AAP). He is one of the most frequently cited authors in the field of pharmacology according to www.ISIhighlycited.com. He serves as chair of both the steering committee for DILIN and the scientific advisory board for the Liver Toxicity Biomarker Study, an FDA Critical Path Initiative. He has served on multiple national advisory committees, including the FDA Clinical Pharmacology Advisory Committee. For the past two decades he has been a frequent consultant for both industry and government agencies on issues involving drug metabolism and hepatotoxicity.

Alastair J. J. Wood, MB, ChB, is managing director of Symphony Capital, LLC, a New York–based private equity company managing more than $300 million in investments in the clinical development of novel biopharmaceutical products. He received his medical degree from St. Andrew's University and Dundee Medical School in Scotland. He joined the Faculty at Vanderbilt University School of Medicine in 1978, where he became tenured professor of both medicine and pharmacology and attending physician at Vanderbilt Medical School. Dr. Wood was assistant vice chancellor for clinical research (1999–2004) and associate dean, Vanderbilt Medical School (2004–2006), before being appointed emeritus professor of medicine and emeritus professor of pharmacology in 2006. His current academic appointments are as professor of medicine and professor of pharmacology at Weill Cornell Medical College, New York. Dr. Wood is a member of many societies and has received numerous honors, notably election to membership in the IOM, the American Association of Physicians, and the American Society for Clinical Investigation; Honorary Fellow, American Gynecological and Obstetrical Society (AGOS); Fellowship of the American College of Physicians; Fellowship of the Royal College of Physicians of London; and Fellowship of the Royal College of Physicians of Edinburgh.

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He was the 2005 recipient of the Rawls-Palmer Award in recognition of "Drug investigation that brings the effects of modern drug research to the care of patients" from the American Society for Pharmacology and Therapeutics. Dr. Wood was a member of *The New England Journal of Medicine* editorial board (2004–2006), drug therapy editor of *The New England Journal of Medicine* (1985–2004), and a member of the editorial board of *Clinical Pharmacology and Therapeutics*. He previously served on the editorial boards of *The British Journal of Clinical Pharmacology* and *Biopharmaceutics and Drug Disposition*. He authored the chapter in *Harrison's Principles of Internal Medicine* on adverse drug reactions from the ninth through fifteenth editions. Dr. Wood was chair of the FDA's Nonprescription Drugs Advisory Committee until 2006 and chaired the 2005 FDA Advisory Committee on Cox-2 inhibitors. He previously served as a member of the FDA's Cardiovascular and Renal Advisory Committee and Nonprescription Drugs Advisory Committee. Dr. Wood has also been both a member and chair of NIH study sections, and has served in a similar capacity for various philanthropic grant-giving bodies. His research interests have been focused on understanding the mechanisms of interindividual variability in drug response, with a particular emphasis on the molecular genetics of adrenergic receptors, ethnic differences in drug response, vascular response, and the genetics of drug metabolism. His research has been continuously funded by NIH and has resulted in more than 300 articles, reviews, and editorials.

Janet Woodcock, MD (***Forum member***), is director of CDER at the FDA. She also served as CDER director from 1994 to 2005. Dr. Woodcock held various positions within the Office of the Commissioner, FDA, from October 2003 to April 2008. Prior to her 2008 reappointment to CDER, she served as deputy commissioner for operations and chief operating officer, responsible for overseeing agency operations and crosscutting regulatory and scientific processes. She previously served in other positions at the FDA, including director, Office of Therapeutics Research and Review, and acting deputy director, Center for Biologics Evaluation and Research. Dr. Woodcock received her MD from Northwestern Medical School, and completed further training and held teaching appointments at the Pennsylvania State University and the University of California, San Francisco. She joined the FDA in 1986.

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