

Co-evolution: Innovation and Regulation of Medical Products

**Regulatory Affairs Professionals Society
And
Institute for Alternative Futures
Rockville, Maryland
June 8, 2001**

OVERVIEW

A group of leaders from regulation and industry met to explore the future environment for the innovation and regulation of medical products. They identified opportunities to accelerate and improve the contribution innovation and regulation can make to health gains.

Participants used a series of thirteen forecasts for the next decade to stimulate thinking. These forecasts helped meeting participants recognize both probable and preferable developments for the future. Using this exploration of the future, participants identified and then ranked five opportunities to accelerate progress toward the most promising of future developments.

1. Anticipate and ensure that the emerging electronic medical record and related infrastructure can facilitate better study designs for new medical products.
2. Accelerate the development and deployment of biomarkers as surrogates for disease endpoints through coordination of industry, regulators, and other stakeholders.
3. Develop the capacity to learn from the collective experience of companies, including both successful and failed clinical trials through a “secure data mart.”
4. Enhance “grass roots international cooperation” between regulators, industry and other stakeholders, particularly through international meetings focused on high-level concerns.
5. Encourage public education/public discussion on the nature of risks to support appropriate expectations for new medical products.

The meeting will lead to subsequent steps following further discussion prompted by this report. As co-sponsors, RAPS and IAF will confer over specific steps including proposals directed toward the specific opportunities listed above. A follow-on meeting will be planned and announced shortly.

INTRODUCTION

On June 8, 2001, the Regulatory Affairs Professionals Society and the Institute for Alternative Futures led a forum to discuss the co-evolution of innovation and regulation of medical products. The meeting was designed to gather ideas to advance the ability of industry and regulatory agencies to channel health-enhancing products to the public. By recognizing advancements in medicine and science, the regulatory community can strengthen their role in the development of medical products. A wide variety of top leaders in innovation and regulation from the pharmaceutical, biotechnology and device industries joined with senior FDA scientists and others whose expertise added to the meeting (see Appendix 1).

This report highlights the key opportunities for steps that can be taken now that emerged from discussions exploring the future co-evolution of innovation and regulation.

OBJECTIVES

The aim of the meeting was to investigate the future in order to identify ways to advance innovation and regulation of medical devices, drugs and biologics. As the future brings changes to science, regulatory concerns must also evolve appropriately. The following meeting objectives were formally agreed upon:

- **Discuss selected forecasts for the development and regulation of new medical products**
- **Identify probable and preferable forecasts that matter the most for health and innovation**
- **Find opportunities to accelerate the co-evolution of innovation and regulation of medical products**
- **Explore the value of and approaches for continued exploration**

PROBABLE FORECASTS

IAF had developed thirteen forecasts for key areas affecting regulation and innovation for medicines and devices (see Appendix 2). Participants discussed and ranked these forecasts according to their importance in shaping the future of regulation and innovation. This exchange of views created a common set of assumptions about likely developments. Furthermore, this discussion led to subsequent agreements over which opportunities to act on. The forecasts that the group determined to be most important and likely were:

- **Ability to predict disease susceptibility**
- **Increased role of genetic factors and molecular basis in defining diseases**
- **Emergence of electronic medical records used to enhance health and care**
- **Localized treatment of diseases in body due to a marriage between drugs and devices**
- **Use of distributed intelligence such as telemedicine and embedded sensors**
- **Growth of computational modeling to detect biomarkers as surrogates**

PREFERRED FORECASTS

Having considered what is most likely to be important, participants in turn discussed what they would most prefer to see for the co-evolution between innovation and regulation. Preference was based on the mission for innovation and regulation that IAF proposed: “to improve the quality of life worldwide by developing knowledge and products that reduce suffering and enhance human potential.” The most important preferred forecasts include:

- **Molecular understanding of diseases**
- **Emergence of electronic medical records used to enhance health and care**
- **Shift in intellectual property paradigm to promote industry information sharing**

- **Use of technology and tailoring of drugs to overcome access problem**
- **Increased use of biomarkers as surrogate endpoints to study genetic diseases and adverse drug effects**
- **Continued use of genetic language to describe disease**

KEY OPPORTUNITIES

Given the likely forces and the preferred forecasts, participants identified opportunities to accelerate the co-evolution of innovation and regulation. Having considered a range of opportunities that arose in a brainstorming session, participants selected five as particularly worth pursuing.

- 1. Design post-marketing approaches for the emerging electronic infrastructure so that improvements in the study of new medical products can be facilitated by: fast feedback loops to clinicians; networks linking patients, providers and payers; and new methodologies suited to a computerized environment.**

Participants discussed the need for, design of, and impact from an electronic infrastructure to enhance R&D, especially clinical processes. An electronic data-sharing age will allow health care to become global. Patients, for instance, are likely to access their medical records confidentially from anywhere on the globe. The capacity for collection and communication will include technology as simple as phone wires and as advanced as supercomputers. As the future of the electronic infrastructure unfolds, many elements of collection and protection of information must first be thoughtfully considered. Large numbers of patients will have electronic medical records and will use more sophisticated biomarkers and biomonitoring devices to evaluate health status. By identifying which measures and variables will be the most meaningful when biomonitors come online, we can explore new research designs suited to an online environment.

Better electronic feedback will not only enhance patient medical care, but also allow health product companies to increase the number of potential research subjects for clinical trials. The electronic medical records (EMRs) could aid in the patient recruitment and screening process and in turn be used to support the creation of groups for clinical trials. After the clinical trial stage, EMR's will provide a resource for obtaining data in the post marketing setting. Whereas both industry and regulators learn a great deal about a drug, biological product or device prior to marketing through controlled studies, far less is learned once a product is marketed due to the limited available tools to assess products when used in the non-

controlled environment of the “real world.” This post-marketing data could provide a better understanding of effectiveness in a real world setting, including populations who were not evaluated during clinical investigations. Post-marketing studies in an electronic environment may also help companies and regulators gain a more complete understanding of the safety profile of the products by identifying patients with elevated risk levels.

In addition, the future electronic infrastructure will foster a greater role for computational modeling. Combining the use of telemedicine and new sensors, (including those embedded in clothing or in the body) researchers will gain insight into aspects of short- and longer-term adverse effects caused by interactions among drugs, medical devices, biological products, foods, supplements, physiological processes, and genetic variations. To better prevent adverse effects, wireless monitoring can be used to provide quicker detection. For example, with continuous monitoring of a patient’s blood pressure levels, the variable effects of a medication may be better studied.

Better post-marketing surveillance could provide more confidence for approvals that were based upon smaller studies. While controlled trials will continue to be necessary, confidence that rare effects will be found through post-market studies could lower the pressure for ever-larger studies. Furthermore, wireless monitoring of clinical trial patients increases information gained from trials, thereby giving more evidence of efficacy and effectiveness of the product. This increased amount of information will likely be processed through networks offering distributed computing capabilities in a growing electronic infrastructure.

One caveat is that increased information will not necessarily mean increased certainty. Thus the demand for more information can create a large increase in research costs without a commensurate benefit. The ability to gather data can race ahead of the capacity to ask the right questions. So it will be important for both regulators and industry to identify appropriate designs and constraints for post-marketing studies in an electronic environment. Otherwise, data collection, storage and analysis could be far more abundant, but not more useful when decisions need to be made.

2. Create a coordinated “biomarker to surrogate” policy function with mediated integration of industry, NIH, FDA, and HCFA views. The goal is to develop the understanding of biomarkers as surrogates and their implications for funding, personnel, priorities in research, and access to innovative products.

Meeting participants saw the need for a process through which new knowledge about biomarkers can be shared and ratified by industry, NIH, FDA, and HCFA, to speed innovation and increase public access to improved medical products. Intermediates such as the Institute of Medicine could play a vital role working across the diverse cultures of scientific discovery, regulation, and health-care finance to resolve future issues more quickly. Biomarkers that can serve as surrogates for disease processes or adverse events will present a pivotal set of issues touching all of the interests of the public and private medical institutions that define innovation, regulation and payment.

A process that begins with shared aspirations and fosters collaboration could accelerate the sharing of knowledge. In order to move forward on this opportunity, a trusted facilitator who shares common interests--yet is independent of industry or government agencies--needs to be identified and recruited. NIH will also need to play a more defined role as an intermediate between industry and the FDA in determining the status of biomarkers. The need for the proposed process will be contingent upon the ability to find genes and proteins that have predictive power.

In discussing biomarkers, it is important to clarify terms and recognize different perspectives. A large number of biomarkers are useful during the discovery process, but far fewer are accepted as valid for clinical medicine or reimbursement. Those biomarkers that will likely be accepted as biological surrogates in the future might be the focus of federal research. Corporations will then be able to better identify molecules or devices addressing these surrogates.

There may be problems with surrogates gaining acceptance before a consensus among scientists has fully characterized their utility. For example, a biomarker such as QT prolongation¹ could lead innovators and regulators to abandon promising projects or remove drugs from the market when a fuller understanding would reveal that safety issues could be surmounted. Pharma R&D now has a tremendous and growing capacity to generate potentially negative data about a compound's activity prior to learning the full clinical significance of such data. Clinical 'validation' of the endpoint or biomarker, however, can be an arduous activity as we have seen with QT interval assays. With an increasingly molecular view of disease developing, there could be exponential growth in the number of

potential biomarkers that signal abnormal development or disease. The scientific task ahead is therefore enormous. Because the potential of biomarkers includes both new understanding and misleading conclusions, the importance of bringing different perspectives to determine when and how surrogates should be used is that much greater.

3. Create a secured “data mart” for industry to pool data from toxicology as well as both failed and successful clinical studies.

Health product companies can benefit from a consortium that pools and protects clinical trial data to enable faster and cheaper R&D. Molecular understanding of diseases provides growing opportunities to develop and test new health products. In turn, the demand for more trials is greater as are expenses for industry. Pooled data could help eliminate waste, enhance trial design, and improve early “go, no-go” decisions about products in development.

For a consortium to succeed and secure support from competing companies, an economic model must first be developed to assure that incentives promote information sharing. Security systems must also protect patient privacy and intellectual property, while providing access to information that helps participating companies speed up their projects and cut inefficiencies in clinical trials. A high volume of data exchange will be created, which must be justified economically and secured technically.

Similar to a stock exchange, this data mart is anticipated to benefit participants whether they contribute data or mine it for insights. Companies that reap benefits from the data will pay royalties to those providing valuable information. Thus, companies that currently gain nothing from a failed trial could receive payments based upon data that was useful to another company. In a time of increasing drug development costs, the consortium could provide a new means to extract value from a resource that is currently underutilized by companies.

4. Support greater “grass roots international cooperation” among regulatory agencies, companies, and other stakeholders to determine what future information should be gathered and how it should be communicated.

Ongoing discussions about evolving scientific and regulatory practices can support better understanding of how public health and safety can be improved. By strengthening lines of communication across international boundaries, the discussions can advance efforts to make more products affordable to the developing world as well as the wealthy countries affording rigorous regulation. Global cooperation that speeds access to new products, increases understanding of the regulatory role, and

strengthens public health and safety could benefit all countries as well as industry.

5. Engage the public in risk-education dialogs and consider new interactive regulatory processes that allow earlier access to promising but unapproved products while maintaining minimum safeguards.

Public information through the Internet creates great potential for both good and harm. As the desire of educated patients to control their own level of risk and access grows, more research subjects may gain access to unapproved drugs and devices. Issues such as informed consent and conflicts of interest must be addressed, often in populations with very different education levels and cultural perspectives. An effort to engage groups in risk dialogs that support the evolution of innovation and regulation should receive industry and government support.

NEXT STEPS

IAF agreed to prepare this report and confer with RAPS and interested participants to determine support for specific action items. The following specific commitments were made prior to participants receiving this report. First is the agreement to hold a follow-up forum to report on activities and plans initiated subsequent to the June 8 meeting. RAPS will host this meeting. Second is an agreement to link up with industry associations who have an interest in the findings of the meeting. Third is a proposal to add the regulatory issues that arose in the meeting to an international ethics conference that will focus on the developing world. Finally, it was agreed that IAF will take this report to the Institute of Medicine and solicit letters of support from companies and associations who support the effort to accelerate the co-evolution of innovation and regulation of medical products.

APPENDIX 1: PARTICIPANTS

John Ameling
Section Head RA
The Procter & Gamble Company

Frank Navran
Ethicist
Ethics Resource Center

Clem Bezold
President
Institute for Alternative Futures

Richard Pazdur
Director for Oncology
CDER, FDA

Joy Cavagnaro
President
Access Bio

Jonathan Peck
Vice President
Institute for Alternative Futures

Willard Dere
Exec. Director,
Global Clinical Research
Eli Lilly & Company

Mary Pendergast
Executive VP, Government Affairs
Elan Pharmaceuticals

Neal Fearnot
President
MED Institute

Kristan Phillips
Regulatory Project Director
Medimmune Incorporated

Gio Gutierrez
Futurist
Institute for Alternative Futures

Jack Reynolds
Senior VP, Worldwide Toxicology
Pfizer, Incorporated

William Herman
Director
Division of Physical Sciences
CDRH, FDA

Cyndy Rosso
Vice President, Communications
Regulatory Affairs Professionals Society

Linda Horton
Director International Agreements
Office of the Commissioner, FDA

Lucian Russell
Chief of Data & Knowledge
Management Practice
Dynacorp

Sherry Keramidas
Executive Director
Regulatory Affairs Professionals Society

Jeffrey Shuren
Medical Officer
Office of the Commissioner, FDA

Alison Lawton
Senior Vice President RA
Genzyme Corporation

Laurie Smaldone
Senior VP Worldwide Regulatory Affairs
Bristol-Myers Squibb Company

Ellen Strahlman-Vogel
President
Rogellen Partners, Incorporated

Robert Temple
Director of Medical Policy
CDER, FDA

Gregory Szpunar
Senior Vice President, Product
Development
Pharmacia Corporation

Donna-Bea Tillman
Deputy Division Director, Cardiovascular
and Respiratory Devices
CDRH, FDA

Linda Temple
Vice President
Education & Knowledge Services
Regulatory Affairs Professionals Society

Melissa Walker
Vice President RA, Quality & Clinical
Stereotaxis

Roger Williams
Executive Director
US Pharmacopeia

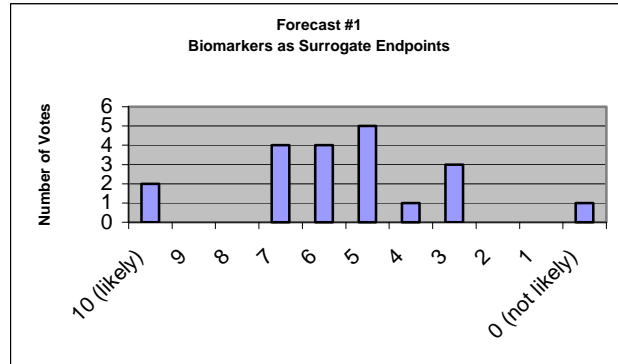
APPENDIX 2: IAF FORECASTS AND PARTICIPANT ASSESSMENTS OF LIKELIHOOD

Participants were asked to evaluate the following forecasts. Each forecast was voted on its likelihood to occur in the future on a scale of 0 to 10, where 0 means impossible and 10 means absolutely certain. The results of the survey are below.

Forecast #1: Biomarkers as surrogate endpoints

By 2005 regulatory agencies will accept the use of a substantially larger number of biomarkers as surrogate endpoints in the drug approval process.²

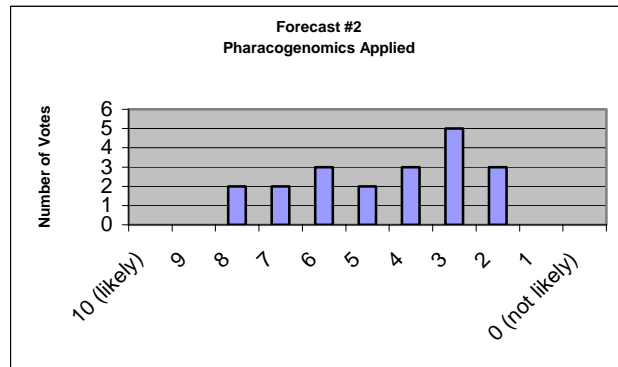
Mean: 5.50



Forecast #2: Pharmacogenomics applied

By 2005 it will be common for patients to take genetic tests before their doctors decide which drug, or what dose, to prescribe for them.³

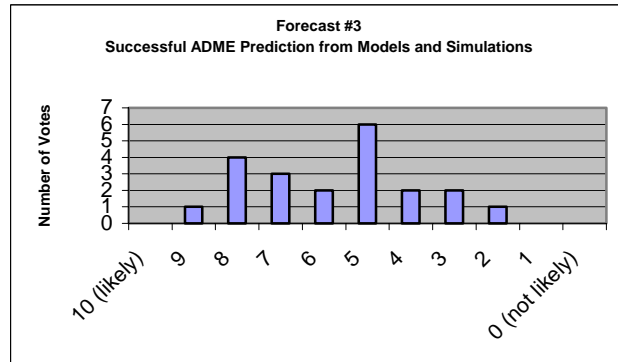
Mean: 4.55



Forecast #3: Successful ADME⁴ prediction from models and simulations

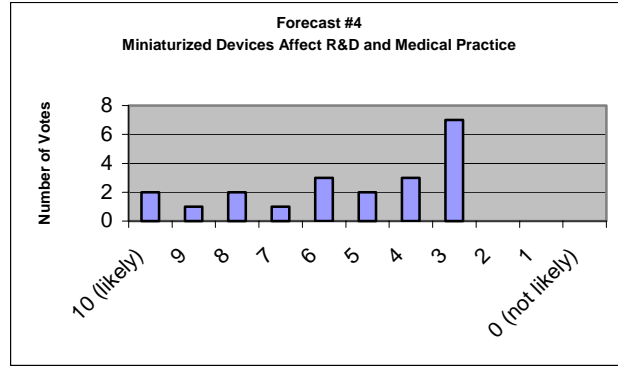
By 2005 models and simulations (M&S) will be used in preclinical research to screen compounds and provide accurate prediction of ADME characteristics prior to clinical studies.

Mean: 5.71



Forecast #4: Miniaturized devices affect R&D and medical practice

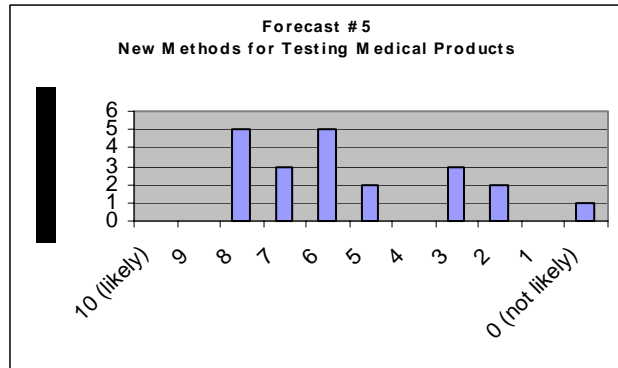
By 2005 BIOMEMS (MEMS are microelectromechanical devices) will be approved for uses in surgical procedures, monitoring of health status and therapeutic drug levels on a 24/7 basis.



Mean: 5.30

Forecast #5: New methods for testing medical products

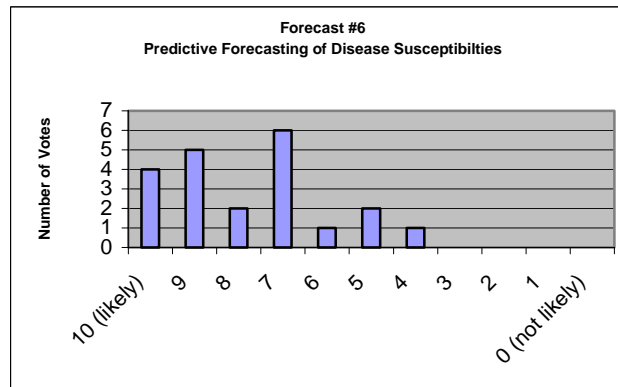
By 2005 a number of alternative study designs will be used to complement and extend the double-blind, random selection trials that are most commonly used today.⁵



Mean: 5.43

Forecast #6: Predictive forecasting of disease susceptibilities

“By the year 2010, it is expected that predictive genetic tests will be available for as many as a dozen common conditions, allowing individuals who wish to know this information the ability to learn their individual susceptibilities and to take steps to reduce those risks for which interventions are or will be available.”⁶

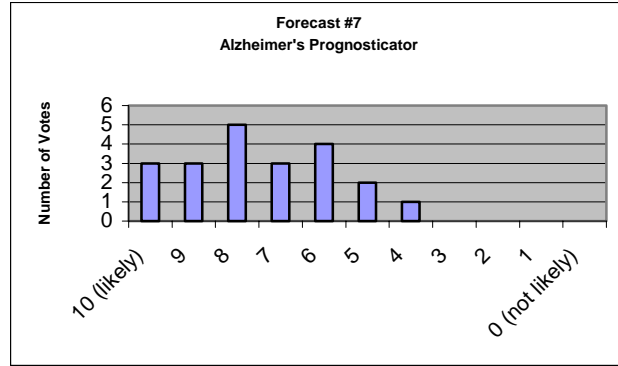


Mean: 7.76

Forecast #7: Alzheimer's prognosticator

By 2010 there will be a preclinical biomarker that forecasts Alzheimer's disease approximately 20 years in advance of clinical symptoms.

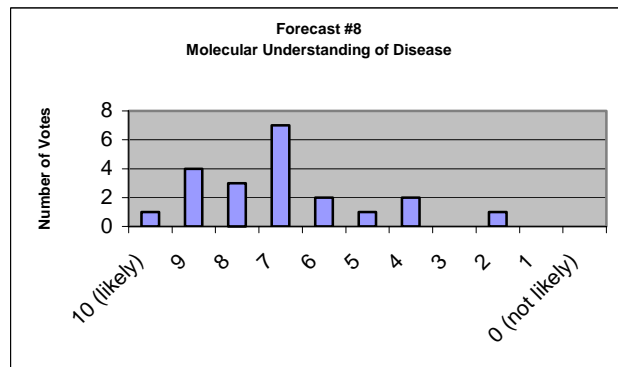
Mean: 7.43



Forecast #8: Molecular understanding of disease

By 2010, "The increasing understanding of molecular medicine will shift clinical practice from empirical treatment to therapy-based on a molecular taxonomy of disease. Physicians will be prescribing rationally designed drugs that have increased efficacy and reduced toxicity."⁷

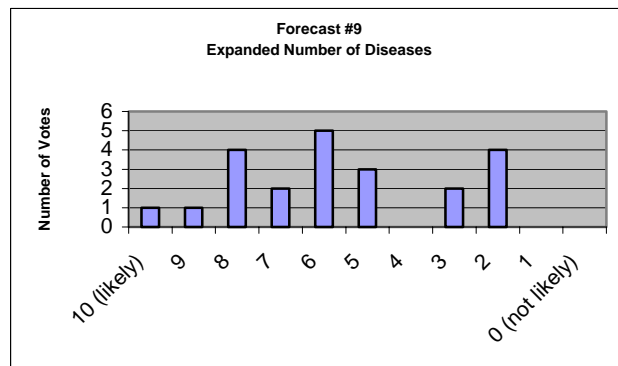
Mean : 6.95



Forecast #9: Expanded number of diseases

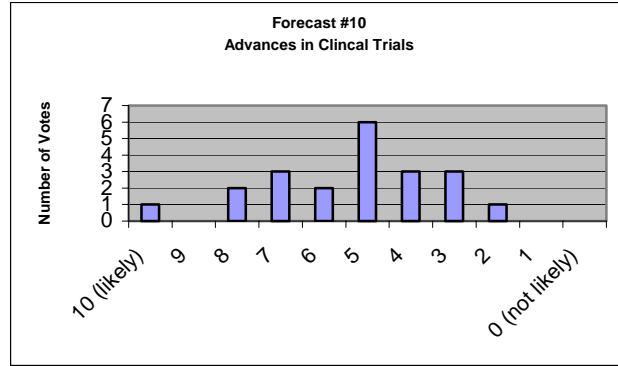
By 2010 the ICD-11 code will classify over 20,000 diseases based upon molecular understanding of illnesses, and there will be a corresponding increase in the number of diagnostics and new treatments available.⁸

Mean: 5.64



Forecast #10: Advances in clinical trials

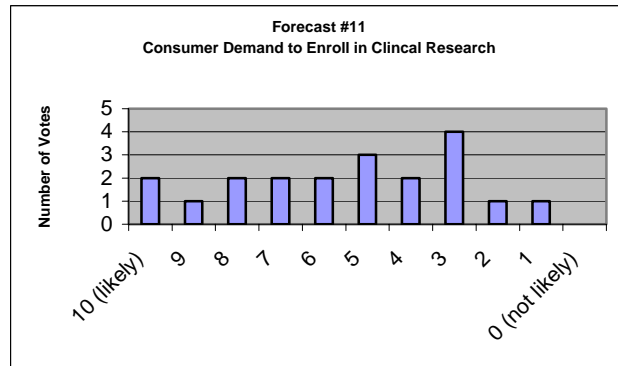
By 2010 95% of clinical trials are conducted using Internet II, which is constantly integrating data from monitors embedded in clothing, appliances and bodies.



Mean: 5.33

Forecast #11: Consumer demand to enroll in clinical research

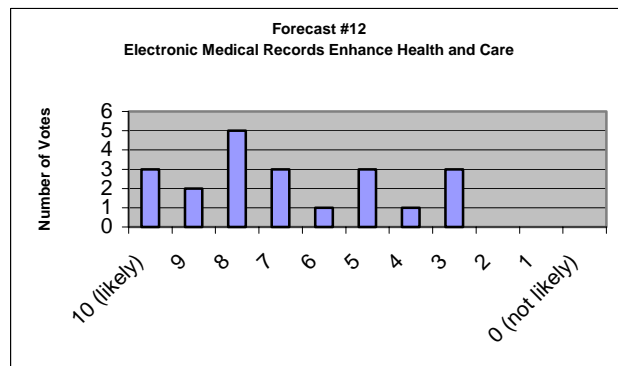
By 2010 a large pool (100 million or more) of consumers will routinely seek out drug development projects to get access to experimental medicines, providing both a larger pool of research subjects and a difficult set of demands for those designing studies.



Mean: 5.45

Forecast #12: Electronic medical records enhance health and care

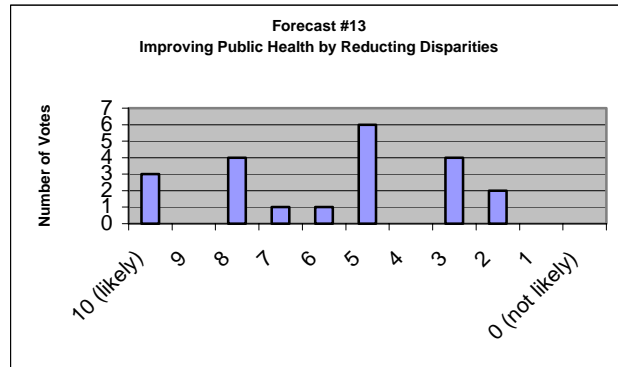
By 2010 the “vast majority of individuals have an EMR with standardized, secure data” that serves as “an enabling tool” for meeting health goals and aids customization of care through “significant subgrouping of patient populations.”⁹



Mean: 6.81

Forecast #13: Improving public health by reducing disparities

By 2010 growing disparities in access to innovation leads to changes in drug and device regulation that offer accelerated approvals of products that can thereby reduce such disparities.



Mean: 5.76

¹ QT prolongation occurs when the QT interval seen on an electrocardiogram (EKG) is lengthened resulting in a potential lethal heart arrhythmia. Qtdrugs.org.

² Forecasts are taken from IAF unless another source is noted.

³ Taken from *The Washington Post*, June 24, 2000.

⁴ ADME stands for absorption, distribution, metabolism and excretion, which all address the pharmacokinetic properties of drugs.

⁵ Examples of methods from an IAF Foresight Seminar include: patient outcome questionnaires, epidemiological data bases from electronic medical records; the Institute of Medicine also lists such methods as meta-analysis and sequential measurement using predesigned specifications (see <http://www.iom.edu/IOM/IOMHome.nsf/Pages/smalln+intro> for description)

⁶ Francis Collins & Victor McKusick, "Implications of the Human Genome Project for Medical Science" in *JAMA*, February 7, 2001, p.543.

⁷ Todd Golub, M.D., "Genome-Wide Views of Cancer," guest editorial in *NEJM*, February 22, 2001, p. 601. IAF assigned 2010 as year for forecast.

⁸ THE ICD-10 code has about 8,000 disease classifications, while the iCD-9 code had only about 5,000 according to *National Vital Statistics Reports*, Vol. 49, Number 2, May 18, 2001.

⁹ Taken from extrapolative and visionary forecasts developed for the Cancer Surveillance Futures Project facilitated by the Institute for Alternative Futures with the American Cancer Society, Centers for Disease Control, and the National Cancer Institute, April 2001.