

**WORKSHOP ON BIO-MEDICAL AND ORGANIZATIONAL
INNOVATIONS IN A COST-CONSCIOUS ENVIRONMENT**

Comments on Manuscripts by Professors Samuel O. Thier and Ezekiel J. Emanuel

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The current “Workshop on Bio-Medical and Organizational Innovations in a Cost-Conscious Environment” is part of the FRESH-Thinking: Focused Research on Efficient, Secure Healthcare, a special project of the Center for Advanced Study in the Behavioral Sciences. The underlying belief of the Center is that the American health care system is seriously flawed, inefficient, inequitable, and increasingly unsustainable. This is the fundamental problem we are to address through the Center’s think tank. The Center further believes that achieving the three main goals of reform of the health care system – access, cost control, and quality, to attain cost-effective care, can only occur with comprehensive reform. While comprehensive reform is not imminent, the Center believes it will ultimately occur. The need for, and methods to accomplish this reform continue to be a critical issues for American society and popular topics for at least some of the Presidential candidates heading into the 2008 Presidential election.

The objective of FRESH-Thinking is to develop critical analyses that can inform all comprehensive reform proposals at the state or federal level. The FRESH-Thinking organization has emphasized that all health care reform proposals will need to confront multiple complex challenges, including: defining more explicitly the vision, near- and long-term goals of such reform, critical success factors to achieve them, including existing or new innovations or technologies, organizations, infrastructures to the delivery of care, payment to providers, structure of health plan competition, funding of health care for all Americans, legal and regulatory reform, and transitions and implementation issues, all in a cost-constrained environment. Many of these topics have already been covered during earlier workshops. The current workshop will focus on the role of innovation, or biomedical innovation, in achieving comprehensive health care reform.

Since it is unlikely that any comprehensive reform model will be able to anticipate all important variables, it will be important to build in plans to measure and assess outcomes to ensure the model is robust, valid, flexible to incorporate changes where appropriate, and allows for necessary course-corrections. Ultimately, prospectively defined measures of success will be required to support objective assessments to confirm that the unmet needs of Americans are being met by the reforms enacted. The FRESH-Thinking project addresses the details of policy options essential to all health care reform proposals.

The objective of my commentary is two-fold. First, I will provide feedback on the papers developed by Professors Samuel Thier and Ezekiel Emanuel and hope to stimulate further dialogue during the two-day meeting and beyond. Second, I will provide additional views regarding how biomedical innovation can potentially contribute to comprehensive health care reform, using the biotechnology, pharmaceutical, and device industry as an example of innovation (in search of innovative medicines) in the technology sector. I hope to translate my experience in the discovery, development, and/or approval of many successful medicines in the biotechnology, pharmaceutical, and medical/pharmaceutical device arenas to help us consider how biomedical innovation can be encouraged, rewarded, and linked to our goal of improving our health care system through meaningful reform.

COMMENTS ON PAPER PREPARED BY PROFESSOR SAMUEL O. THIER

Professor Thier presents a rigorous analysis of health care reform and biomedical innovation that addresses a wide-range of key topics. He begins by providing a definition of innovation, which forms a cornerstone for his paper defining the development and execution of strategies and operational plans to achieving biomedical innovation in connection with

significant health care reform. His definition of innovation, adding something new and valuable, will be clear to some, but may be ambiguous to others. Something new and valuable is subject to interpretation, especially when we consider the many stakeholders and interests that will be impacted by the decisions taken. For example, in the biotechnology, pharmaceutical, and device industry, where the focus is on innovative new products, what is new and valuable is highly subjective even within a given company. In these industries, the measure that is widely used to define innovation and an innovative product is the target product profile (TPP). Even the TPP can be contentious and often undergoes re-definition over time. The TPP incorporates scientific, medical, quality, cost, value, commercial (e.g., differentiation) and other objectively measurable endpoints that a project team will use as criteria for judging whether their proposed product meets the definition of being innovative.

Thier emphasizes the need for setting a new bar from which improvement can proceed and requires an implementation plan in addition to the fundamental idea. This can begin with the creation of a new vision, fueled by new knowledge. He recommends that this new vision should direct organizational change, the way we approach problems and educate health professionals, and address issues of reimbursement, which should facilitate reform. Thier further emphasizes that during the period of innovation and change, we must ensure that the public continues to receive an acceptable level of care, highlighting the importance of a safe, effective transition period. He acknowledges that increased value may be a subjective concept because of potentially competing interests but I believe that this needs to be emphasized further. This latter challenge highlights the importance of the process for inclusion in decision-making leading to reform. He emphasizes the need to attack the problem at the system level focused first on the

design and less on the policies to get us there. One fundamental challenge is the demographic and geographic variation in this country, which will require differing opinions.

Thier raises the notion of solutions that are national, with standards of access and performance agreed but allowing for variations in structure and financing. I would like to come back to Thier's underlying definition of innovation, which is at the heart of his paper. As I mentioned previously, while I support his definition of innovation in principle, stakeholders, depending on their or their industry's perceived or actual conflicts of interest, will likely attack it. Within the biotechnology, pharmaceutical, and device industries, the definition of an innovative product is highly contentious and often ambiguous. What can be a breakthrough product in one company can be a "me-too" product for another. Those responsible for reimbursement must also judge whether a new medicine or device is innovative or a "me too" product and that can have profound implications on the success of the product. Some companies in this sector claim they don't work on "me-too" products, yet many examples can be found to challenge their claims. Often, a product is considered to be innovative if it has the potential to reach the marketplace and generate significant revenue, rather strictly defining a product as being innovative on the basis of its effectiveness, safety profile, and a product that is a first-in-class on the basis of the product's putative mechanism of action. For some, a "me-too" product, one that is not innovative, refers to a second, third, or fourth generation drug, which is in the same chemical or biological class. Are drugs that are 2nd or 3rd to market really "me-too" and not innovative? Is this always true, false, or is there a way to have objective criteria? Can we distinguish between products on the basis of quality, cost and value objectively? Do we have criteria that will allow us to do so? Cost certainly may be simple, but quality and value may be more difficult. Even small chemical changes in a drug or binding affinities can lead to profound

differences in desirable and/or undesirable drug effects, yet these may be referred as non innovative products. However, if one looks at the differences from the standpoint of meeting unmet medical needs, or an improved therapeutic index, the differences may be clinically significant and may reflect true innovation. It is often impossible to accurately measure whether a 2nd or 3rd entry is innovative enough until it is evaluated in large-scale studies or in widespread use in disease populations, which occurs in the post-marketing period. This has been shown to be true for both small molecule therapeutic drugs and products coming from biotechnology (e.g., proteins, antibodies, etc.). For example, Atorvastatin (Lipitor) was the 4th HMG-CoA-reductase inhibitor that was approved by the FDA in the U.S. to lower LDL cholesterol. Is Lipitor an innovative drug or a “me too” drug? It was several times more potent than the 1st drug in its class, lovastatin (Mevacor). It became and still is the most widely prescribed drug in the world. Is it a “me-too” drug or an innovative drug because it is the best selling drug? It certainly is innovative in the sense that it achieves outstanding efficacy and is well tolerated by most patients. Its clinical pharmacology, pharmacokinetic, and drug-drug interaction profile is different from some other statins but it is not necessarily the most potent statin available today. There are many statins available. Are many of them non-innovative? That depends on whom you ask. The best measure of innovation is that measured by the patients that use the drug and physicians who prescribe it.

Another example is the monoclonal antibody field. There are currently three distinct TNF α blockers (e.g., Enbrel, Remicade, and Humira, in order of market entry) in the marketplace for the treatment of serious immune-based diseases. Are the latter two “me-too” or innovative products, like the first? On the surface, they look very similar based on their putative MOA, yet at the molecular level they are very different based on binding to cells, tissues,

receptors, and in their potential immunogenicity, based on one being a “fully humanized” antibody, while the other two are not fully human derived antibodies. A similar example could be given in the drug-coated stent field. Cypher, Taxus, and Endeavor (listed in order of entry into the marketplace) are used to prevent or reduce the likelihood of re-stenosis following angioplasty, yet the drug used to coat each stent varies. Are the 2nd and 3rd entries not innovative? Do they have similar effects on quality, cost and value? One could argue in either direction. They may all be innovative for different reasons. I want to reinforce the importance of having an agreement on the definition to drive measures of performance and metrics of success as we consider reforming the health care system. All may not agree with the definition, but at least one can build models based on the definition, which will be transparent and open to support, or criticism. Will we ever get to a definition that all stakeholders will endorse? I am skeptical this will be achieved in the biotechnology, pharmaceutical and device world.

Thier proposes that the three areas for focus should be clinical quality, patient-centeredness, and efficiency, and his “modest” proposal states that our system of care should maintain and/or restore health for as large a proportion of our population as possible. If it can’t accomplish this goal, it should at least protect functional autonomy and relieve suffering. His proposal increases the importance of preventive services as well as of long-term care. He recognizes the need for performance standards that address the concerns of the key stakeholders, including patients, providers, policymakers, and payers; all of whom will have different priorities and value judgements. His thesis is that we lack agreement on the goals of the system and as such we cannot begin the debate around how to organize to meet these goals. I fully agree with this critical assumption. Thier focuses our attention on how a new and improved health care system would differ from the present one, whether innovation could help us move towards the

preferred system, who would best lead this endeavor, and how best to catalyze and gain wide spread support for such innovation. What is not explicitly stated but is implied is that forces will undoubtedly push back those driving change. Again using the biotechnology, pharmaceutical and device industries as an example, virtually all of the top 10 companies in each sector have reorganized their leadership and infrastructure in order to increase innovation and add significant value to their customers (e.g., patients and physicians) and shareholders. If one measures the level of satisfaction at least by shareholders for these companies, the majority of companies in this sector would not fare well, based on the fact that their stock prices have not grown and in many cases have fallen or remained flat in many if not most cases. This is largely due to a lack of innovation, innovative products, or poor overall productivity of these companies as measured by the lack of new product approvals and launches. As a result of this lack of innovation, more and more of these companies are looking to smaller biotechnology companies or start-ups as sources of innovation, new targets, or new products to fuel large Biotechnology and Pharmaceuticals pipelines. Interestingly, the huge demand but relative paucity of early stage products with a high confidence in rationale has driven up the prices of licensing and acquisitions when they do occur, reflecting the value being placed on potentially innovative new products. This has also prompted entities to seek for new product innovation in this sector in Israel, India, China, to name but a few. I believe there are many lessons here that may apply to our goal of significant health care reform.

Thier reviews the various international models of health care and points to some of their strengths and weaknesses. Interestingly, primary care seems most important in these countries' systems but is actually in short supply in the U.S. where it is common to not be able to hire or make an appointment with a primary care physician. It is well known that there is an enormous

shortfall of primary care physicians in the U.S. I will leave it to others more knowledgeable than I to describe the root cause for this problem. Similarly, information technology infrastructure is more widely available in Europe than in the U.S. Thier goes on to evaluate the models in the U.S. at the federal and state levels and points to potential limitations or uncertainties and concerns associated with expanding extant systems serving sub-populations (VA health system, military health care, Medicare) to the broader U.S. population. In addition, he goes on to consider other non-federal models, including public state and private group health models (e.g., Group Health of Puget Sound, Kaiser, Partners Healthcare in Boston) but raises the question about whether some or all of these work best at a regional level.

Thier proposes that the Commonwealth Fund's Task Force (CFTF) on a High Performance Health System may provide an excellent step toward a system redesign. Their broadly based and accepted definition of a health system along with metrics for evaluating the level of performance of countries and states may be an opportunity worth serious consideration. This approach has been described in the Fund's first report entitled "Why not the Best?" The five critical descriptors of a high performance system include: 1) automatic affordable coverage for all; 2) aligned incentives for high value care; 3) accountable coordinated care; 4) aiming higher for quality and efficiency; and 5) accountable leadership. Thier points out that in a subsequent publication the CFTF points out the challenges and deficiencies state by state and interestingly those states with the largest deficiencies have been most responsive in seeking ways to improve their performance. This approach could become the basis for health care reform if it will continue to be supported by the various stakeholders and if the critical performance standards will be accepted widely.

Thier believes that innovation will be generated at the regional, state, or city level, not at the national level. He points out that the stimulus for innovation at the system level will be the need to improve efficiency and effectiveness, as has been observed in several successful models such as Kaiser or the VA, both of which operate within fixed budgets. Is there a paucity of acceptable models because there is no currently acceptable means by which we can bring all players into the process? Is the Commonwealth Fund approach a good model for doing so? What are the barriers to expanding this approach to a larger national system level? He points out that while there are aspects of health system reform that reside at the federal or national level, we don't necessarily have well defined means of evaluating procedures, nor have we done well in determining comparative efficacy between drugs, devices, and procedures. I agree with this position. These comparative evaluations and measurements of cost effectiveness are essential in reforming the system. One can draw parallels with the Biotechnology, Pharmaceutical, and Device sectors in comparing globally run versus locally run organizations. Genentech for example is a locally run Biotechnology company that is majority owned by Roche, but is run as a separate independent legal entity. It is generally recognized that virtually none of the mergers and acquisitions in the Pharmaceutical industry have led to increased innovation or greater value. In fact the evidence is to the contrary. The only exception is the Roche "acquisition" of Genentech. Most industry experts would agree that this acquisition was a successful one for Roche because they provide Genentech with virtually complete freedom to operate independently. The same is not true for other targets of acquisitions like Agouron, Warner-Lambert, and Pharmacia (all by Pfizer), Centocor, ALZA and Scios (all by Johnson & Johnson), and Chiron (Novartis), to name a few. There are similarly no real examples of large federal health care systems expanding and taking over small entities leading to expanded innovation and

value. Once again, as pointed out by Thier, the best examples of innovation in health care have been by local or regional entities, typically in the private sector. Again can we use the example in the biotechnology and pharmaceutical sector where becoming larger and larger and centralizing thinking, operations, and strategies tends to decrease innovation and productivity? Will models that work well locally continue to succeed and be innovative if we broaden their scope and geography? I also believe that real innovation is likely to be created, nurtured and sustained at the local and state level, and much less so at the federal level.

Thier points to the fact that there have been numerous failures at the federal level and growing numbers of exciting experiments at the state and local level, suggesting that the latter are the likely sites for innovation and progress. What is required still is general agreement on acceptable standards for the system and what should stimulate investment investment in innovation is the potential clinical and financial value of such reorganization. The challenge is to overcome all of the barriers to organizational change.

He has intriguing views on the importance of research, especially creative research, its relationship to science and its application, and why the public supports it. He emphasizes that scientific research is one of the key drivers of innovation. He then links discussions of science and health in relation to an expanded view of the sciences of health. He argues that over the past century, biology has assumed the primacy in the sciences of health, but is concerned that this may have created too narrow a view on the importance of other areas of science, such as mathematics, chemistry, computer science, neuroscience, nutrition, behavioral sciences, international health, and management sciences. While this may true, it does not in my view reduce the importance of biology as the driver for greater knowledge in health. I would rather say that we should use the term disease biology as the cornerstone for definitional purposes.

Disease biology certainly will include all aspects of biology, molecular biology, biochemistry, pathology, pathophysiology, and other key basic sciences. Pathology, for example, is a science that brings together all findings in a disease to forensically understand the underlying basis of disease, whether it is due to natural disease, or iatrogenic causes. Often, findings in pathology lead to fundamental understandings, which drive new discoveries around treatments, cures, and new products. It also leads to new innovative products or procedures with true societal and financial returns on investment. I agree with Thier about the need to be more inclusive in relation to disciplines. As with translational medicine, more information rather than less, leads to a clearer understanding of systems, processes, and disease pathways, ultimately leading to more focus on disease mechanisms, potential targets for medicines, etc.

Thier emphasizes the importance of the relationship between the university-industry partnerships that have kept us in the lead in the generation of new intellectual property (IP). He recognizes the dilemma between the fact that many of our health-based research industries like pharmaceutical, biotechnology, and device industries are driven by innovation, but generating new knowledge and getting return on investment (ROI) is getting progressively more complex. This is a very important concept and the more we understand why this is true, the more likely we can continue to develop strategies and technologies that will lead to further innovation.

This is why there is a growing tendency for these industries to work with academic researchers in search of innovative ideas at earlier stages than was true in the past. While the U.S. has been leading in this area historically, much smaller countries like Israel and India have demonstrated a high degree of success in translating innovation into new IP and products, but not necessarily linking these to clear impact on health care as the primary driver. However, truly disruptive technologies have the potential to change how medicine is practiced and how patients

are diagnosed and treated. For example, Israeli inventors discovered the technology whereby a patient swallows a camera/capsule that takes pictures throughout the gastrointestinal tract as an alternative, at least in some patients, for endoscopic procedures, including colonoscopy. While this procedure is still experimental, in some countries this technique is replacing routine use of colonoscopies. Other types of imaging are currently being applied in highly innovative ways to detect breast and other cancers and may change the practice of medicine, ultimately with the potential to impact on costs to society.

Thier points to some interesting differences between academia and industry related to bringing an idea to a product. He recognizes that the post-marketing phase is an especially important period for innovation, since it is during this time that physicians and patients recognize innovative new uses of medicines or devices. It is interesting to note that approximately 40% of revenue generated for medicines used in the U.S. comes from uses (FDA-approved and non FDA-approved) not originally the basis for the original approval. Another interesting point is the recognition that as the cost of research continues to increase, so does the pressure of enhanced research productivity. As the need increases to focus on areas of greatest unmet medical need, as opposed to commercial opportunity, this has the potential to create a chasm between competing interests. I could posit that more often than not what constitutes a commercial and financial opportunity will be in synchrony with real unmet medical need. For example, backers fund start-up biotechnology or pharmaceutical companies if their idea has potentially innovative technology or product opportunities. Typically, these companies get started where there is high unmet medical need, such as oncology, cardiovascular, endocrine-metabolic, pain, or other important diseases. Again, there is a lot that is subject to opinion. In the area of pain, for example, there is a clear consensus that we lack breakthrough medicines for mild, moderate or

severe pain that are non addictive. Yet there has been very little innovation in the last twenty years in this field, in spite of the progress with COX-2 inhibitors (e.g., Celebrex), which turn out to be at best only marginally superior to non-steroidal anti-inflammatory agents (e.g., Naproxen). The real dilemma is the lack of innovative, clinically proven targets for pain therapy, albeit many trials and failures. Similarly hypertension and adult onset diabetes mellitus, both common, chronic polygenic diseases, are still often under treated, require poly-pharmacy, and often result in debatable benefit, as was recently published by the journal *Science* (2008).

Another key area by Thier is education of the professions. This is crucial for several reasons, including the importance of stewardship and preparation for the next generation of professionals. He appropriately emphasizes the notion that education must continue over a career. This is, however, a real challenge. For example, genomic sciences have exploded in the last five to ten years, impacting the diagnosis, treatment, and care of patients across a host of diseases, but cancer has been one of the most affected. In spite of the fact that oncologists are generally highly experimental and research oriented, few are prepared to deal with the explosion of technologies, approaches, science and claims, leading to uneven use of this information and often restricted to key opinion leaders or academic medical centers. One of the key reasons for this dilemma is the fact that physicians don't have the time to receive training in these emerging sciences and thereby forfeit the opportunity to incorporate much of these learnings into their practices. Professor Samuel Silverstein at Columbia University Medical School has pointed out that physicians in practice often don't understand genomic sciences sufficiently to use cutting-edge techniques in their everyday practice. As a result, medical schools for example must be looking into the future to prepare their students to deal with the emergence of new medically

relevant sciences and encourage ongoing training in what inevitably be radical changes in biomedical sciences over the next ten years or more.

The last topic covered by Thier is finance. He points to better efforts at coordination of care as opportunities to approach in health care financing. He cites some very interesting examples of how small investments based on good science can catalyze innovation and lead to significant ROI. This has been especially noteworthy in the area of translational medicine. There are examples where resources have been limited but drove significant innovation and creativity, or faced the prospect of shut-down in patient services driven by the need for traumatic cost containment efforts. This leads to the notion of cost-consciousness, which has implications in all aspects of health care reform, including those associated with the use of drugs, devices, diagnostic techniques and technologies. Thier distinguishes between research support for innovative or creative research, clinical research, and high-risk research. Interestingly, NIH supported R01 grants typically favor research grants that pursue high significance and impact, demonstrate high levels of creativity and innovation, often involving high-risk research. Clearly Thier recognizes the critical importance of innovation impacting on and driving important changes in health care reform. I would maintain that this is a synergistic and iterative interaction, rather than a serial one. Just as drugs are discovered in the clinic during testing in patients, often for diseases they were not originally intended, so will innovation and health care reform fuel needed thinking and catalyze breakthroughs that will contribute to the needs of society and continue to drive our ability to lead innovation around the world, as we do in many areas of science in technology. Our challenge is to inspire and inform health care reform to become best practice around the world. Something we are far from today.

Thier importantly concludes by reminding us yet again we must begin by first defining the performance standards that will define success. Focusing on these at the front end will mitigate against the possibility of building something that does not address the real unmet medical and health reform needs.

COMMENTS ON PAPER BY PROFESSOR EZEKIEL J. EMANUEL

Professor Emanuel lays the foundation for his paper on the thesis that sustainable, comprehensive health care reform will have to address inflation and control costs, which have increased at a rate of 2.8% per year over the last three decades and he proposes that the target for annual increasing growth in costs should not be zero but between 0 and 1%. It would be worthwhile for Emanuel to explain what the basis is for this proposal. He indicates that the major drivers for increasing health care costs are increases in technology spending, including drugs, devices, surgical procedures, and other interventions. He recognizes that the costs associated with these newer technologies can grow substantially, especially when physicians that apply them to patients beyond those originally demonstrated to derive benefit from the technology adopt them. He provided persuasive examples, like drug eluting versus bare stainless steel stents in patients outside of the groups studied that led to their approval and launch in the marketplace. I fully agree with Emanuel that control of health care costs in comprehensive reform must focus not just on cost, but more importantly on cost-effectiveness and reduced costs overall. All medical procedures and technologies should be held to that standard in order to ensure that we make the best treatment decisions.

I agree that ideally technology driven costs will need to be owned by some type of technology assessment organization. I further agree that ideally such an organization should be

empowered to include costs in explicit cost-effective determinations and should have the authority needed and linked in some way to reimbursement decisions. It will be crucial to decide on the model used, whether it is advisory, deterministic, or otherwise. This is a very important decision and can have profound implications, as in Britain and in Israel. One might ask whether such strong links have had a positive or negative effect on innovation in these countries.

Emanuel compares and contrasts three mechanisms to create interventions to control technology-driven costs. In the insurance benefit redesign model, he uses an interesting example of options that could be provided in the treatment of prostate cancer and the level of expense that might be covered by insurance versus options for additional spending by patients. I suspect that those who can afford the more expensive procedures because of perceived benefits will opt for the more costly approach in this reference pricing approach. In the provider reimbursement model, and with a focus on pay for performance, it may be possible to reward providers for complying with guideline requirements in each disease category, based on expert opinion or standards established for appropriate treatment, and importantly linked to improved outcomes.

Another interesting proposal is bundling of payments. This theoretically would encourage integration of care among physicians and hospitals and create appropriate incentives to look at outcomes beyond the acute situation, and focus on the extended period following episodes of disease. Another interesting option could be one which shifts more of the risk to providers. Emanuel postulates that this might give providers an incentive to use lower cost, high value services and discourage wasteful “let’s try anything” approaches. A final approach might pay providers for patient care based on actuarial determinations of optimal care. It would be

important to further evaluate each of these options in relation to the cost to in deciding which option is preferred in the context of health care reform.

He goes on to review another approach employing disease management strategies. The foundation of this strategy is to optimize medications, keep patients taking their medications, and ensure patients adhere to their diets, exercise programs, etc. This approach seeks to prevent acute care hospitalizations, in part by substituting less costly approaches including education, visiting nurses, etc. Unfortunately, as we all know, the lack of good data precludes conclusive assessment of whether these approaches will be successful, especially on an expanded basis.

The next part of Emanuel's paper seeks to understand the impact of cost control strategies on biomedical innovation, with the assumption that cost controls aim to constrain the use of marginal value, and do not produce added benefits worth the incremental costs. The questions are 1) whether these cost controls will affect the development of new biomedical technologies; 2) whether they reduce the influx of funds supporting new biomedical technology companies; 3) whether they will reduce the amount of research and development conducted by biomedical technology companies; or 4) impact on more visionary pursuits, such as personalized medicine or the search for blockbuster drugs. These are difficult questions to answer explicitly. In my view, cost control strategies should focus on defining unmet medical needs and expect developers of new technology to incorporate cost-effectiveness as part of their focus when they are developing target product profiles. This will automatically focus attention on current medical practice, the need and demand for superior products, the competitive environment, and reimbursement issues.

In the U.S., and many other countries, new technologies are started by entrepreneurs who live or die by the quality of the ideas that drive the creation of innovative new products. If they are able to develop a clear business plan that lays out the unmet medical need and how and why their technology will be successful in the marketplace, they may be able to generate funding from angel investors, venture capitalists, or others to get to their first key milestones. There are numerous examples where this approach has been successful or has failed.

Emanuel next looks at the drug development process as a metaphor for new technology, understanding key decision-points, and how this current process might be altered by the various cost control strategies being discussed. He lays out a solid case that cost control strategies are unlikely to affect basic biomedical research, which is generally funded by NIH and predominantly occurs at universities, medical schools and other institutes. I agree that because basic research is primarily driven by creative and innovative scientists driven by the desire to focus on problems which have high significance and impact, changes at the federal level, like NIH funding, are likely to have the most profound effect on biomedical innovation.

He next explores the effect of cost controls on translational research, which also primarily occurs in universities, medical schools, private institutes, as well as biotechnology and pharmaceutical companies. I agree that cost control is again unlikely to impact on translational research per se. He postulates that these controls may influence which diseases are studied at universities, medical schools, etc. and speculates that controls would lead to a shift in focus to more common diseases, diseases with big unmet health needs, and diseases in which costs are high even if few interventions exist. However, while this may be intuitively correct, no data evidence is presented to support this hypothesis. He recognizes that the size of the beneficiaries of a new intervention may not translate into highly reimbursed interventions in a cost controlled

environment. His example of hypertension and the unlikely possibility that a new antihypertensive would command a premium price may or may not be valid. I would maintain that the key issue is whether the new drug or treatment addresses a clear unmet medical need. Recently, Gilead gained approval and launched a product that treated patients with primary pulmonary hypertension. I believe this product has been successful because it targets a specific hypertensive population for which effective treatment was not available and where cost-effectiveness could be persuasively argued to those responsible for reimbursement. If a new medicine to treat hypertension were only marginally better than already prescribed treatments and was not well differentiated, it would probably not be developed, would not likely be accepted by the medical community, and reimbursement would likely be a key issue. The critical issue would be differentiation on the basis of efficacy, safety, drug-drug interactions, or some other measurable and demonstrable criteria.

In my opinion, the biotechnology, pharmaceutical, and device industry spends an enormous amount of time making these assessments, irrespective of cost controls, with a heavy emphasis on differentiation, especially if the new drug is going to be competing with a like product. Commercial and medical groups typically base the decisions theoretically on thorough analysis. Having said that, the competitive environment can change rapidly and unexpectedly, leading to an erosion of confidence in a medicine if it was believed to be addressing high-unmet medical need. This may be driven by new findings undermining the confidence in rational or safety of a target. A recent example is torcetrapib by Pfizer, terminated just prior to FDA submission when it was discovered that in large-scale Phase III trials, mortality was actually increased, driven by increases in blood pressure in treated patients. Several large clinical trials have demonstrated that mortality is increased in cardiovascular patients with increasing mean

arterial blood pressure. What was more surprising was the hoped-for reduction in intimal wall thickening observed in atherosclerosis, that was expected to be reduced with medicine that led to increasing HDL cholesterol, was not observed, in spite of the observations that HDL was in fact elevated as a result of treatment. This undermined the CETP inhibition theory and has had a profound impact on the research programs at many other pharmaceutical companies in this field, many of whom have now dropped this therapeutic approach. In contrast, at least one company continues to believe in the CETP mechanism believing that the issue with torcetrapib was the structure-based, rather than mechanism-based, toxicity/mortality. This underscores the concept that the primary driver for decision-making in drug development is not cost control. Rather it is evidence-based data and science driving key medical, scientific and business decisions. On the other hand, when mechanisms of action are proven to be clinically relevant, as has been shown for several indications for Avastin, most recently for breast cancer, this then catalyzes further interest in the medicine acting by a presumed mechanism of action.

Emanuel describes the lead identification and lead optimization stages of drug discovery and development. What should be stressed is the radical difference in approach and methodology, and challenges depending on whether the product is a small molecule (e.g., typically a molecular weight of 250 – 500) or a biotechnology product (e.g., an antibody with molecular weight orders greater than a small molecule). Typically, 10's of 1000's of small molecules are made and screened before selecting a few for evaluation. This is very different from antibody approaches. Again, I would agree that cost controls would not have an impact on the LI and LO stages. However, I will discuss this issue in more detail later in my analysis of innovation in the pharmaceutical industry. It is important to emphasize to the group that Biotechnology drugs are almost always very different products that typical small molecule

products and as such we cannot generalize about drug development and innovation between these two areas of R & D easily.

Emanuel goes on to describe the clinical candidate selection stage and, like the preceding stages, I agree that cost controls would not impact on innovation or investments. These decisions are driven by the confidence in the rationale of the target, the confidence in the safety of the structural class and specific compounds being evaluated, and assessing the margin of safety of specific compounds in the context of the unmet medical need, competition, disease severity, and alternatives available. Similarly, Phase 0, which actually involves the performance and completion of regulatory toxicology studies to estimate safety margins in rodent and larger animal species (e.g., dog), are primarily focused on establishing an understanding of potential target organs for toxicity, and safety margins. Cost controls are not likely to influence decisions.

He explains the process of gathering input from the commercial organization to determine whether to pursue further investment and take the potential medicine into the clinic to evaluate safety, pharmacokinetics, and safety generally first in healthy subjects. While I agree with much of what Emanuel has written regarding the important medical and commercial analyses that are performed prior to entering Phase I, there is a lot of variability between companies as to when such information is gathered and factored into key organizational decisions. This can, and has, led to significant variability in the decision-making process, which ultimately leads to variability in productivity and the number of medicines reaching patients. In many of the best biotechnology and pharmaceutical companies, analysis to estimate the commercial value of the product is made very early on and scoring in this area is often a key variable about whether to give a high or low priority score to a discovery project and the prioritization of such a project in relation to others. This is not to suggest that these estimates are

usually accurate. Very often they can be significant under-estimations. This reinforces the notion that the value of a medicine may not be fully appreciated until it has been used widely in various patient populations.

I don't necessarily agree with the basis for decisions proposed by Emanuel during the clinical development stage. These decisions are taken earlier and will often have a profound impact on which projects continue and which terminate. This mostly revolves around the estimated NPV. As was suggested by Emanuel earlier, this may have little to do with the number of patients that might benefit from a new drug. It may have more to do with the estimated price that may be garnered by the company for the product even though the number of patients annually may be low. This has been a key strategy for larger Biotechnology companies and smaller ones where a premium price could be obtained because of the high cost of cost, innovativeness and differentiation of the product, etc. Emanuel postulates that cost controls may impact the number of drugs taken to the IND stage, and that those that do go to Phase I are more likely to succeed. This reasoning may be incorrect both for drugs targeting clinically proven, as well, as novel targets. In the former case, the number of drugs going to the clinic will depend on how important that therapeutic area is to the company, the importance of succeeding in that franchise, and the threat of large imminent revenue gaps, potentially because of drugs going off patent.

I agree with Emanuel's alternative hypothesis that a cost conscious environment will force sponsors of research to better understand the risk of failure, the confidence in the target, and as a result carefully balance their portfolio so as not to be carrying a pipeline that is overly weighted to a high probability of failure. Emanuel proposes that one way to encourage introduction of more drugs and other technologies into clinical trials is to reduce the risks of a

negative trial. He proposes that one important way to do so is to diversify the portfolio of the company. This may or may not be possible. It may be better to focus on getting a drug that is effective against HIV. This may entail some combination of a few drugs being tested that work through differing mechanisms of action, each of which may be innovative, or many drugs acting by a few, but well preceded, mechanisms. What is key in the latter case is that while the probability of efficacy may be high because a drug acting by the same mechanism of action may already be approved for use, it may be harder to convince the medical and commercial people of the drug's merits unless one can prove that the TPP defined earlier can and will be met. As he states, the government can even get involved in clinical trials and has in some areas (e.g., oncology).

A trials network can be a very effective means to test new drugs and has led to some breakthrough medicines. Interestingly, there is currently no clear incentive to develop or use clinical trial networks, although Emanuel points out some discreet advantages, including the potential for government requiring lower prices or a share in the profits in exchange for more direct financial support of the clinical trials phase of research. I agree this could be beneficial by spreading the risk and allow companies to lower the threshold for likelihood of effect and effect size. This is an approach that can succeed as shown by clinical trials sponsored by NIH.

Emanuel used drug development as the model for his paper and posits how innovation in drug development might be affected by cost controls. He hypothesizes that the model may be extended to innovation in other areas such as devices, imaging equipment, diagnostic tests, surgical innovations, etc. I do have some concerns about this proposition, as we need to look hard at that sector to see if it has been as innovative and productive as it should be. I would also like to clarify some of the costs. Emanuel states that typically the cost of clinical trials to bring a

new medicine to the market can be about \$500 million. This is potentially misleading. Some have even stated that it may cost as much as \$1.5 billion to bring a new medicine to market. In reality, this reflects largely the accumulated failures prior to finding the drug that finally succeeded. The actual cost of clinical trials depends on the disease, the length of the clinical trial, and the size needed. It is typically far less than \$500 million. This then leads to my analysis of the pharmaceutical industry in relation to the discovery of innovative new medicines, the future opportunities for innovation, and critical challenges in controlling cost, and increasing success. Before I do so, I would also like to address the current state of genomic, genetic and other technologies that are driving the notion of personalized medicine. This is a very confusing and complex area but is being pushed by some because it may represent scientific breakthroughs as well as financial rewards. As with many evolving technologies, personalized medicine is a very attractive concept and will be developing in an evolutionary way, one disease and one victory at a time. While the practice of personalized medicine may be best practiced today in oncology, it is still in its infancy. There are enormous scientific, medical, philosophical, and other challenges that will have to be addressed. At least for now, few companies can actually claim they have medicines that can be used as part of a personalized medicine strategy. This field is linked to an enormously important area called biomarkers, which will facilitate our goal of achieving personalized medicine. As with the term innovation, personalized medicine has many meanings and is subject to interpretation.

A MODEL PROPOSAL FOR ENHANCING INNOVATION AND PRODUCTIVITY

Over the last three decades, the pharmaceutical industry has been tremendously successful. The efforts of the biotechnology and pharmaceutical industry have yielded scores of new therapies that effectively treat most of the diseases that afflicted people in mid-life and led

to early deaths. As a result of these efforts, conditions such as hypertension and atherosclerosis have been significantly blunted and delayed as causes of death. Osteoporosis and prostatic hypertrophy are now preventable or treatable. Common inflammatory illnesses are much more manageable. Serious inflammatory diseases like Crohn's are significantly improved in a significant percentage of patients; something unheard of 10 years ago. Transplantation of organs has become common in large part because of better organ availability and primarily because of the discovery of anti-rejection medicines that are reasonably tolerated by many patients. Psychosis, depression, and anxiety can often be improved in a subset of patients in each disease allowing patients in many cases to lead reasonably normal lives. Many bacterial, fungal, and viral illnesses are treatable and in some cases curable. Certainly, HIV and HCV, both scourges and virtual death sentences even 10-15 years ago, can be controlled with medicines today leading to significant prolongation of life, often with good quality of life. These are just a few examples of the fruits of pharmaceutical research and development in the last three decades. In connection with of these important medical achievements in the pursuit of medical treatments has come powerful profitability in the pharmaceutical sector.

The successes of the previous decades have become progressively more difficult to replicate. Much of the "low-hanging fruit" has been harvested. Diseases requiring new treatments are often more complex than those which have been successfully treated. When breakthrough drugs are created, they relatively rapidly become the targets for competitors' fast-follower compounds with incremental improvements. This then triggers potential price pressures and the need for more intensive marketing and sales. In addition, the high costs of health care generally have brought across-the-board price pressures, as hospital formularies, third party payers, and eventually the government push for lower prices. For many of the major illnesses,

highly effective generic medicines are now available, as the fruits of previous successes have reached patent expiry. All these pressures increase the tension between profitability and expenditures in R & D. The time and expense required to discover and develop drugs have also increased for many indications, as more characterization of compounds for safety and comparative efficacy are needed. All these factors converge to compress the historic commercial successes and life span of drugs. For example, if the life span of a medicine is roughly seven years after launch, sustained success requires the generation of about 15 to 20% new sales each year. This has led many to argue that the model of growth fueled by internal R & D innovation and productivity is not sustainable. Many companies have "put their money where their mouth is" and tried to stave off the eventual slowing of growth by merger and acquisition and consolidation or by acquiring individual compounds from sources such as the biotechnology sector, some would say at high prices. In this potential future, the larger pharmaceutical companies become reduced to late stage development and commercialization houses and start-up biotechnology becomes the engine of innovation in which most fail and some are generously rewarded. The distribution of profits in this model becomes different, with substantial leakage from the coffers of large pharma into the coffers of venture backers of these biotech efforts. Whether or not this new model is sustainable is a matter of some doubt. Currently, large pharma is flush with cash from previous successes and repatriation, but this situation is not likely to be sustained. Start-up and established biotechnology companies are somewhat distressed from a series of leaner years in the sector. Already, earlier compounds in preclinical development and early clinical development are being bought at rising prices. More and more pharmaceutical and biotechnology companies are also looking to other regions like India, China, Israel and others as a source of new innovation in this sector. In addition to unprecedented up-front payments for

early development compounds, most of these acquired compounds are burdened with steep milestone payments and royalties often near 20%. Highly speculative technologies such as siRNA are being grabbed at high entry prices.

Is the pharmaceutical, biotechnology and device industry doomed to scour start-up companies and academic medical institutions to replenish its development pipelines, becoming a less profitable sector focused on late-stage development and commercialization? This is one, but not the only, option. There may be a far better way that can be realized today and serve as a model for increasing innovation and productivity, and this may also serve as a model that could be applied to reforming the health care sector.

An attractive alternative involves optimizing early development strategies that may make it possible to significantly increase value creation per dollar invested in R & D, or return on investment. An analyses that I, along with my colleagues, have performed, analyzing differing strategies for optimizing the breadth and depth of pharmaceutical R & D, resulted in surprising results. We evaluated the results of differing strategic alternatives using a predictive model that we developed for this purpose. These alternatives are often debated within pharmaceutical R & D organizations with little consensus on how to proceed. There are features of pharmaceutical R & D that serve as the context for such debates. Although there is a degree of variation from company to company, for newly established drug discovery programs, arriving at the first developable compound (i.e., a compound satisfying criteria to enter into pre-clinical development) takes about three years and costs between \$35 MM and \$50 MM (ca. 150 FTE-years). This includes all the efforts to come up to speed in the biological / pharmacological aspects of a novel target, to acquire or create the requisite tools (reagents, assays, and models), and the costs of lead identification and optimization. After the first compound is identified, there

is the opportunity to much more quickly and less expensively identify additional compounds for development directed against the specific target. For additional chemical analogues of the first compound moved into development, the incremental cost per compound may be about \$5 MM or less, requiring 6 months or less to identify after the first compound enters pre-clinical development. To identify additional compounds suitable for development from a second, chemically divergent lead series is only slightly more expensive for the first such compound (maybe an incremental \$10 MM and 6 - 12 months), after which the incremental costs are again about \$5 MM and 6 months per compound suitable to develop. R & D organizations often consider whether or not back up compounds should be sought, whether or not they should be moved forward into development, and when and how far they should be advanced. Should they come from the same or chemically diverse pharmacophores? Should they be moved forward as quickly as they can be identified, or should they be held to see what the fate of the compounds that they are backing up fail? How many should be advanced per target? Should they be parked at some point and, if so, at what point? Should all early development programs look the same or are there variants that are more suited to different kinds of programs, e.g., programs based on newly identified and less "validated" targets versus programs based on "validated" targets, such as fast follower compounds for which others may have already demonstrated clinical proof of concept or encouraging Phase IIb data? Do clinical "probe of concept" studies have to provide perfect information to be of value? Must such studies be powered to detect results with statistical significance ($p < 0.05$) or are imperfect answers achieved quickly and cost-effectively capable of enhancing value creation? Are there circumstances in which it makes sense to cut corners to get rapid clinical feedback on compounds and targets, accepting that this corner cutting carries with it the potential need to accept delays or additional costs for those programs

that show promising probe of concept results? Are there circumstances in which it makes more sense to jump the gun on frontloading expenditures and activities? I believe that the model developed with my colleagues, which we have used to approach these and related questions, have been constructed using assumptions that reasonably reflect the conditions and practices within the pharmaceutical sector. Based on experience and anecdotes, we believed that the one-size-fits-all full development with sparse and delayed backups was unlikely to be optimal for all programs within a portfolio. We have described results that powerfully support this belief. Even we are surprised by the magnitude of additional value creation that could be achieved without increasing expenditures. This could either allow much more effective value creation at the same levels of R & D expenditure or perhaps similar levels of productivity for lower expenditures. Using these approaches to shaping pharmaceutical development portfolios could go a long way to filling in the "productivity gap" that has currently sent companies into a frenzied search for compounds in the biotech sector.

Could this same approach be used in other technology areas focused on ways to increase productivity and innovation? Innovation continues to be defined by a TPP that addresses unmet medical needs first, and other key factors second. This concept is similar in principle to other models that begin with the notion of having fixed resources and defining strategies and processes to create new products that address unmet needs. I would propose that a similar approach should be part of our thinking as we approach ways to significantly improve our seriously flawed health care system. Innovation, creativity, and significance need to be the driving force. Let's use our entrepreneurial spirit and history in the U.S. to encourage creative people to seek creative and innovative solutions to our problems, and reward people for working collaboratively across lines to seek solutions that will be durable and sustainable, while recognizing our need to control cost.

Let us encourage those that will invent biomedical innovations and products that truly address unmet medical need and let cost-effectiveness be the real judge driving technology assessment and reimbursement decisions. It is very likely that the next 10-20 years will bring profound insights into the basis of disease, disease biology, pathways, new targets for medicines, and new concepts for new therapies. We must strive to develop reform that will encourage and support evolving science and technology that can be flexible enough to adapt to new knowledge and where incentives will drive further innovation in biomedical technology and products. Let's not send a message to inventors that we want to limit new innovation in this country. If we do so we will simply be encouraging more and more innovation to go off shore and thereby decrease our competitive edge in the world.

SUMMARY OF PAPERS BY PROFESSORS THIER AND EMANUEL

Each of the authors approached the question of biomedical innovation and health care reform in very different ways. Each recognized the conflict between these two potentially disparate objectives. Thier focused a lot of attention on developing a system that would address the major challenges of addressing unmet medical needs first by driving toward acceptance of performance standards, an enormous challenge. Emanuel started from the position that we must control cost and cost increases, as the historic increases are unsustainable and likely to put more pressure on the system because of the continuing trend to introduce more and innovative technologies, using drug development as a metaphor. While both approaches lead to the identification of many of the critical issues that will challenge the development of health care reform, I am optimistic that biomedical innovations will continue to yield major breakthroughs that will address unmet need and simultaneously force us to consider how to make choices since we will not be able to afford many of these.