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Executive Summary

The bulleted items below generally form the basis of work we note as "foundational" to the efforts of Accelerate Progress. We have focused on systems-analysis work to identify areas of critical inefficiencies throughout the drug-to-patient system and also to recommend key improvements that would increase efficiency throughout that same system. The major areas to be covered in this report are listed below. Each will be covered briefly within the report and additional supporting materials and referenced articles are footnoted and attached.

Summary List of Recommendations:

- **Move more promptly to human testing**
- **Make more appropriate use of the Accelerated Approval mechanism**
- **Define approval criteria for new therapeutics by a favorable benefit to risk assessment**
- **Expand support for innovative and efficient programs such as RAID and Quick Trials**
- **Reposition FDA and NCI in audit and oversight capacity for the Comprehensive Cancer Centers to speed initiation of clinical trials (reference *Natural Clinical Practice Oncology* December 2008 editorial by Dr. Vincent DeVita on the "800 days" problem)**
- **Implement a meaningful Conditional or Provisional Approval mechanism for therapeutics against life-threatening diseases**
- **Move to modernize the regulatory review process to increase agency understanding of and use of scientific tools of the 21st century**
- **Focus on increasing transparency in regulatory decision-making**
- **Focus on increasing transparency in development**
- **Set appropriate incentives and processes to drive development of genomic-based tests to improve diagnostics capabilities and drive better drug labeling**

Accelerate Progress' Recommendations for Improving Health Policy and FDA Focus

- ✓ **Move more promptly to human testing**

"Despite the elegance of the science, the only data that count for the cancer patient are those derived from the relevant species (humans), and we need to focus our attention on how we can obtain these data efficiently and, of course, ethically."[1] This is a quote from Dr. Schein's piece on the barriers to efficient development issues and I think captures the salient point well. The FDA whitepaper on Innovation or Stagnation referenced later also acknowledges that most tools for toxicology and human safety testing are decades old, while noting that traditional animal toxicology work is highly labor-intensive, time-consuming, requires a large amount of product, all of which would be fine but for the final note, that these studies very often fails to provide predictive information. Some piloted programs, including some from FDA, to move more quickly to rational proof-of-concept studies to choose drug candidates and dosing schedules, like those in the Exploratory IND program, should be expanded and studied for broader application.

- ✓ **Make more appropriate use of the Accelerated Approval mechanism**

"We believe that the benefits derived from the broad application of the accelerated approval mechanism for cancer therapies with promising activity, based on early efficacy data, outweigh potential risks. This is especially the case in settings where therapeutic options are limited and/or long-term, disease-free survival is not a realistic goal with available treatments."[2] Again, a direct quote from Dr. Schein and we agree wholeheartedly. As we move towards increasing personalization of therapeutic approach and evolve our knowledge to inform that a single cancer (say lung cancer) is not, in fact, a single cancer but rather may be made up of dozens or even hundreds of types of cancer cells and driven by multiple genetic or biologic pathways, we need an ever-increasing number of approved options to select from in order for doctors to be able to put together a combination to attack a specific patient's cancer or disease.

This also means our system must increasingly deal with smaller and more targeted trials as we more effectively assess who may benefit most from a particular therapeutic and this contrasts markedly with recent FDA moves to increase the size of patient populations under a process informed by our approach when all therapeutics against cancer where relative versions of a poison that worked in varying degrees across all patients, rather than more modern techniques that tend to provide stark and binary treatment effects (i.e.

[1] "Barriers to Efficient Development of Cancer Therapeutics", Schein and Scheffler, *Clin Cancer Res* 3243 2006;12(11) June 1, 2006

[2] "Barriers to Efficient Development of Cancer Therapeutics", Schein and Scheffler, *Clin Cancer Res* 3243 2006;12(11) June 1, 2006

they work or do not) in a given individual and are not well-suited to broad population studies as currently structured and guided by FDA.

- ✓ **Approval Criteria Should Be Defined by a Favorable Benefit to Risk Assessment**

Although much discussion and many public releases from the agency pointed to the 2005 creation of FDA's Clinical Endpoints document, and although we respect the efforts of those involved, as Schein and Scheffler note, and Accelerate Progress echoes, "…we remain frustrated by the rate of progress and, as an extension, believe that there is a responsibility to assess continuously the evolving dogma to see if we can do better."[3]

We at Accelerate Progress continue to ask the question whether these endpoints are realistic and appropriate given the nature of these life threatening diseases and the lack of options for many patients to use in their fight for quality and duration of life? Is a 'one-size-fits-all' regulatory approach really the best one to accommodate the complete spectrum of individual risk tolerances of patients fighting life-threatening diseases, some of whom might appropriately believe that they can tolerate more risk than a patient trying the next generation antihistamine but who are relegated the same criteria for access to a new option as those antihistamine patients? Do we not need to more overtly consider that the primary "clear and present danger" to a patient fighting, for instance, late stage pancreatic cancer is death from their disease and that tolerating some side effects like elevated liver enzymes or chills might well be reasonable and rationale choices for those patients in return for access to an option that is reasonably expected to offer additional months of life and time for those patients?

Schein and Scheffler go on to correctly document that FDA hasn't always looked at approvals in this way, but that:

> "In the mid-1980s, the FDA changed its policies to require demonstration of survival benefit, typically in two controlled randomized trials, based on statistical criteria, sometimes over clinical judgment…This has resulted in the need for very large trials with long periods of follow-up. Moreover, it should be noted that sample sizes needed to assure sufficient power to detect differences as statistically significant are only as accurate as the historical data from which they are estimated. Accruals for other than the most prevalent tumors types are often difficult to achieve. With more targeted therapies, the patient pool may be further limited. "[4]

This focus on two large trials using an arbitrary Type I error rate of 5% (which itself is derived from work of Sir Ronald Fisher almost ninety years ago) should be examined in light of our understanding that learning about and informing a therapeutics place on the

[3] "Barriers to Efficient Development of Cancer Therapeutics", Schein and Scheffler, *Clin Cancer Res* 3243 2006;12(11) June 1, 2006
[4] "Barriers to Efficient Development of Cancer Therapeutics", Schein and Scheffler, *Clin Cancer Res* 3243 2006;12(11) June 1, 2006

benefit to risk continuum continues throughout the development process, through approval, and, in fact, is accelerated when that therapeutic is placed in the hands of the physician community to use in an informed manner with their patients. It is not a binary event wherein we suddenly learn, at the moment of approval, that a drug has materialized before us as safe and effective for use. Considerations should also be expanded to include data from well-defined and medically plausible subset analyses as a basis for approval.

We ought to be focusing on putting in place strong systems to monitor these therapeutics post-approval, not just to detect early safety signals, which is an appropriate goal in itself, but also to detect and communicate early efficacy signals in new patient populations or additional efficacy when used in combination or at different dosing schedule. These high-level, well-trained and well-networked physician communities are well positioned to communicate and monitor such data and use it to inform the treatment of their next patients.

- ✓ **Expand support for innovative and efficient programs such as RAID and Quick Trials**

Accelerate Progress recognizes that there is no single way to go about making faster progress while maintaining appropriate scientific and ethical rigor. We support many different approaches, such as RAID and Quick Trials, as long as the job is getting done in an efficient manner and that the information derived from such work is disseminated quickly to others working on similar problems. The guideposts for all such efforts should be innovation, initiative, and an appropriate sense of urgency that reflects the needs of patients fighting life-threatening diseases.

> "Translational research, the clinical validation of a laboratory observation, is only now receiving the attention it deserves. The initial stages of clinical testing have unique requirements, including dedicated personnel and laboratory support. The introduction of a new chemical or biologic agent into a human subject is an exercise in ethics and scientific discipline, optimally carried out by well-trained investigators with substantial experience, as well as knowledge of the unique pharmacologic features of the new therapeutic."[5]

The Rapid Access to Interventional Development, or RAID, concept introduced by NCI mirrors the broader concepts advocated by Accelerate Progress, that it is, the critical importance of eliminating or at least reducing rate-limiting barriers that slow progress. In the specific instance of the RAID program, the focus is to reduce those barriers that:

> "…typically delay the clinical validation of a new therapeutic in an academic setting including the following: the scale-up of production, the development of suitable formulations for oral or intravenous administration, the development of

[5] "The Case for a New National Program For the Development of Cancer Therapeutics", Schein, *Journal of Clinical Oncology*, Vol 19, No 12 (June 15), 2001: pp 3142-3153

analytic methods required for assaying bulk substances, stability testing, animal toxicology, and planning for clinical trials and IND (investigational new drug) filing. These are routine facets of a development program within the pharmaceutical industry, but they may be quite foreign to an academic center…The concept is sound. Many potentially important therapeutic discoveries made in academic laboratories languish for years because of the inability of the inventor to attract the attention of the pharmaceutical industry. There is the distinct possibility that important treatments have died for lack of appropriate stewardship or sponsorship."[6]

Of course there are issues to deal with to appropriately expand and enhance the effectiveness of programs like RAID. One particular issue as regards RAID and as noted by Schein and Scheffler is that the program was set up to benefit and accelerate progress within academia but did not allow for direct participation by other groups, including small biotechs, that often collaborate with academia and might well benefit from such intervention. These companies are often strong in drug discovery but much weaker in regulatory expertise and other technical or regulatory experience that would allow them to efficiently or effectively accelerate development of a new product candidate through completion. However, for the overall benefit to the public health, we must not continue to incent and support regulatory expertise over drug discovery expertise.

- ✓ **Reposition FDA and NCI in audit and oversight capacity for the Comprehensive Cancer Centers in program to speed initiation of clinical trials (reference editorial by Dr. Vincent DeVita on the "800 days" problem)**

The attached editorial from Dr. Vincent DeVita should make every reader cringe and then hopefully angry, because as Dr. DeVita writes, "our clinical trials system is broken" and nobody appears to have noticed! At Accelerate Progress, however, we've noticed and will continue to work on better policy to support improved systems of clinical trial protocol review and approval. The process he suggests, which would move FDA and NCI to a more appropriate role as auditors and providers of something akin to the Underwriters Lab (UL) seal of approval for quality, which they already do in certifying NCI's Comprehensive Cancer Centers (CCCs), would certainly help place the decisions and responsibilities in the hands of the local experts seemingly best equipped to deal with such quickly advancing issues. Having surveyed several CCC Directors ourselves, we can say that such a change would be welcomed and readily accepted and seen as a very positive step for change and reduction in bureaucracy with a strong net increase in efficiency.

Dr. DeVita also references a second point about our systemic inability or unwillingness to allow for more adaptive trial design protocols which would allow us to take into account more real-time learnings as we approach the start of a trial and then continue into the trial itself. Again, given the way scientists learn, we believe adding more adaptive trial

[6] "The Case for a New National Program For the Development of Cancer Therapeutics", Schein, *Journal of Clinical Oncology*, Vol 19, No 12 (June 15), 2001: pp 3142-3153

protocols and increasing the use of Bayesian statistical analysis plans would be a substantial benefit to the speed of learning about new therapeutics while maintaining, and in some cases, enhancing the level of scientific rigor within a trial.

- ✓ **Implement a meaningful Conditional or Provisional Approval mechanism for therapeutics against life-threatening diseases**

EMEA has recently implemented a "Conditional Approval" which they use to denote an approval which is renewable in one-year increments as the sponsor demonstrates progress against the goal of full approval but which allows patients who could most benefit from a new option against an unmet or dire need to gain access to a therapeutic appropriately promising and with a sufficient probability of benefit over risk, when including risk from disease in the analysis. The FDA's 2007 Science Board Report also makes such a recommendation for what it called "Provisional Approval" in an Appendix to the Report, differentiating this type of approval from the already in use Accelerated Approval or Fast Track programs.

There are several different and promising ways to approach this issue, but all recognize that we must be more proactive in looking for probabilities of benefit, more open to the idea that learning about new therapeutics is an ever-evolving process and not simply step-wise, and that the most pressing danger to a patient is often from their disease, so that 'saving' them from the possible future risks from a new therapeutic is, in reality, allowing them to die from their disease without access to an option that might have defended them from that deadly disease. As noted earlier, supportive data for a conditional or provisional approval should also be expanded to include data from well-defined and medically plausible subset analyses.

- ✓ **Move to modernize the regulatory review process to increase agency understanding of and use of scientific tools of the 21st century**

These tools and considerations include Bayesian analysis, adaptive clinical trial designs, biomarkers and diagnostics for such, surrogate endpoint validation. This will also mean creating better processes to rely on outside expertise where appropriate, in collaboration with internal agency resources.

The background for this bullet is well laid-out in Scott Gottlieb's attached piece "Improving Access to Life-Saving Medicines through Modernization of the Regulatory Review Process" delivered at a recent Food and Drug Law Institute Colloquium.

Dr. Gottlieb's work and Accelerate Progress' approach look at FDA today and see the:

> "…Fundamental tradeoff that preoccupies the agency. It relates directly to the question of how FDA believes patients are best served in the long run: through earlier access to promising new medicines, even if early access could compromise

> the ability to conduct very formal and rigorous clinical studies, or through more rigorous evaluations that might forestall early access but preserve the ability to enable larger, placebo-controlled trials that will surface higher-quality clinical data that can guide future decision making. FDA is increasingly opting for more rigorous trials, willing to sacrifice early access for better information."[7]

We believe, and concur with Dr. Gottlieb here, that this tradeoff is not the black or white choice it initially appears, particularly when one is informed by modern scientific tools. The tools and methods facilitate more timely access to new drugs while, at the same time, allowing for the collection of rigorous scientific information "to demonstrate effectiveness and guide medical decision-making." Our goal should undoubtedly be to maintain and enhance scientific rigor and provide opportunities for future learning while expanding current patient access to promising and potentially life-saving new therapies.

As Dr. Gottlieb writes, however:

> "…in recent years, this goal has been stymied by the agency's inability to advance scientific principles that would enable faster approvals, including the validation of good surrogates for effectiveness and development of more adaptive approaches to designing clinical trials. Better scientific approaches could enable FDA to simultaneously achieve the dual objectives of facilitating early access while collecting reliable information about effectiveness."[8]

We must increase our use of and knowledge of these modern scientific approaches and technologies lest we continue to suffer from unnecessary inefficiency that results daily in unacceptable patient suffering and death.

- ✓ **Focus on increasing transparency in regulatory decision-making**

Outside of the most sensitive of proprietary documents, sunlight is sorely needed throughout FDA's review process. Non-public "regulatory briefings", non-public FDA decisions overruling public advisory committee meetings, etc. are a hindrance to public acceptance of the fairness and appropriateness of such a process. We must build broader public and private confidence in the strength of our development and review processes and adding transparency is undoubtedly a strong step in that direction. Having a process that is 75% public and 25% private but where all critical decision-making, guidance, etc. are given in the private 25% and are unavailable for public review or peer-comment is an unacceptable and inefficient decision-making process because it fails to inform broadly learnings from each review process and each participant or constituent is largely forced to 'learn it new' each time, driving hugely inefficient resource use and direction. Proposals

[7] "Improving Access to Life-Saving Medicines through Modernization of the Regulatory Review Process" Food and Drug Law Institute Colloquium on Access to Unapproved Drugs
[8] "Improving Access to Life-Saving Medicines through Modernization of the Regulatory Review Process" Food and Drug Law Institute Colloquium on Access to Unapproved Drugs

to increase objectivity of and transparency around Advisory Committee meetings are particularly important and merited here.

- ✓ **Focus on increasing transparency in development**

Too much efficiency is lost in the system because of the lack of either appropriate incentives or outlets for publishing what has commonly been known as 'failed' research. As anyone who has studied the process of learning knows, it is a highly iterative process, continuing in a perpetual feedback loop, always increasing understanding of the present 'what we know' to further inform the 'what we want to know' in research. Unfortunately, our current system essentially looks at learning as a series of long, step-like advances, i.e. we can't 'know' anything until this study is fully complete, even if that is seven years from now. When that time arrives, we will 'learn' what the trial told us and consider how to take our next step forward. This is highly inefficient of itself (see adaptive trial design need) but also, if the research turned out not to meet the initial hypothesis, the study may well go unpublished for the reasons mentioned above. This is highly inefficient, as unintended redundancy in research is one particularly inane use of resources.

It's one thing to repeat a study because one wants to test the repeatability of findings, it's another to do a study thinking you're the first to ever do it and be unaware of what might have been appropriate considerations to help inform perhaps a change in dosing schedule or administration technique or delivery mechanism, etc. in the trial, or even just a change in expectations of historical controls against which powering assumptions for the trial are made. We must continue to push incentives for both academia and industry to publish this 'dark' research because it contains within it vast public health good and efficiency for learning if made broadly publicly available. If done via a peer-reviewed outlet and properly lauded as contributing to scientific progress, this outlet would meet the need of academics in need of publication and also the need of the scientific community to be informed of such materials. Industry incentives are somewhat different because reasons for non-publication of industry-sponsored trials are different, but again, incentives can be created to support a push for industry to more fully publish these findings as well and increase the size and effectiveness of our public database of learning. At Accelerate Progress, we're working on the underpinnings for such an Open, peer-reviewed Journal of Progress, but there are many such forms this Journal could take, the important thing is to get it out there and get as many constituencies to contribute as fully as possible.

- ✓ **Set appropriate incentives and processes to drive development of genomic-based tests to improve diagnostics capabilities and drive better drug labeling**

Build off the language in then-Senator Obama's "Genomics and Personalized Medicine Act" , which created a system of "biobanks" for patient blood and tumor samples with the express purpose of accelerating "the development of genomic-based tests" to enable FDA to re-label drugs to more accurately reflect patient populations that could benefit from the therapeutic. It is crucial to appropriate incentives and processes that the language and intent from Senator Obama's bill denoting the requirement for such diagnostics to have been established "in practice", as opposed to via prospective clinical trials as is desired by current FDA, be the integral component of such policy.

Developing biobanks to store biological materials that would later be available for analysis and testing against results of drug trials and patient/doctor use is an key element of enhancing diagnostics development. As Dr. Scott Gottlieb, former Deputy Commissioner of FDA notes:

> "These tissue samples are preserved from drug trials precisely because the blood or tumor markers that can guide development of diagnostics are often discovered long after a new drug reaches the market."

We would recommend the strengthening of the current Clinical Laboratory Improvement Act (CLIA) to support development of these diagnostics and expand their use and coverage within the Medicare and Medicaid services. We must continue to push hard to incent development and expand use of these tests by creating appropriate guidelines specific to the issues involved in diagnostics development and use as opposed to trying to shoehorn drug development regulation into this field. It is a different field with different economics and different risks (far less direct to patient risk exists, for instance, because the diagnostic is just one of many tools a clinician would use to inform treatment regime). These tests may help us reduce use of drugs in patients who would not benefit from them and improve our ability to develop and deliver truly "personalized" medicine for the benefit of patients and public health.

Accelerate Progress' Coalition for Faster Progress Issue Identification and Elaboration

What follows here is a summary of common barriers that we have identified via the ongoing formation and expansion of our "Coalition for Faster Progress", a growing group of foundations and other interested groups or individuals that recognize a set of common systemic barriers to progress across disease and are committed to supporting better policy and better science to help all researchers overcome these issues.

We have identified the following common issues via survey and discussion with disease researchers across a number of private foundations, including a need for:

- ✓ Standardized and centralized tissue and data collection and support for broad access to such data when it does exist
- ✓ Increases in the knowledge base around appropriate use of advanced scientific protocols like adaptive trial design, Bayesian analyses, etc. to help accelerate learning loop within current and planned research efforts
- ✓ Further development and characterization of high-quality validated model systems for many diseases and pathways
- ✓ Dealing with many political and economic realities that drive incentive alignment problems hindering interaction among institutions and between multiple constituencies
- ✓ Creation of an international system to assess and communicate clinical responses tied to molecular diagnostics
- ✓ Focus on biomarker identification and validation and improvement in diagnostic assays for use of such

Elaboration on above:

1. Tissue and related data collection issues: (Specimen availability and quality) Not only do we need a network of surgeons willing to capture the sometimes rare tumors (and matching plasma, saliva and normal tissue), we also need more highly qualified pathologists to diagnose and handle the specimens as well as more motivated medical oncologists to update the patient histories, all who understand their role in the greater development and regulatory pathways supported and overseen by HHS/FDA/NCI.

2. Development and characterization of models issues: (Model availability and quality) Researchers need validated and well-characterized cell lines and xenograft models of tumors to conduct both basic and translational studies. Continued development is taking place in many broadly occuring cancers, but a strong effort to oversee prompt validation of such models that show the most promise must be undertaken. Additionally, the few models that exist for rare cancers often are contaminated or incorrectly identified. Broadly, developers of models receive too little recognition and compensation for their crucial contributions, and may be beaten to publication if they share their models too quickly, an incentive issue that must be recognized and overcome to maximize progress.

3. Research silos - Many researchers are expert in one technological platform (resequencing, proteomics, high-throughput screening, RNAi, microRNA, etc.) but do not have a holistic view of a particular disease. Focused coordination is necessary across the various silos to shepherd the same high-quality specimens and models through the panoply of technological platforms. This issue is further exacerbated in the instances where multiple institutions are involved, each of which may have slightly different standards for such silos.

4. Bioinformatics - Not only is it important to generate and make widely available the data from many technological platforms, it is also crucial to merge those stand-alone data sets to glean the most information possible. Bioinformatic efforts to tease out complicated biological relationships are generally underdeveloped and unable to access the larger datasets necessary to be effective. Creating an umbrella 'network' of data that establishes common data elements to be collected and shared and then 'plugging in' disease-specific databases as they come online would be helpful for expanding the total dataset and in so doing, enhancing the utility of bioinformatics efforts.

5. Statistical Significance – We need to more explicitly recognize that learning about a new cancer drug's benefits and risks is not, in fact, a binary event. It is not that we suddenly, at regulatory approval, learn that this is a fully effective and safe drug for patient use. We are informed, over time, as to the relative probabilities of a drug's effectiveness and safety and that learning is often accelerated after a drug is available for more broad use among heterogeneous populations and/or in combination with other therapies. The highly statistically significant risks to patients from their diseases must be strongly considered and weighed against the probability for benefit from a new therapy in order to provide meaningful patient access to such potentially life-saving or life-improving new therapies while they still hold promise for current patients. For rare disease studies, it may not be possible to reach the levels of statistical significance often reached in studies of common diseases. Sample sizes are simply too small. So raising the power of a study from 0% to 50% in a rare cancer may be just as significant as a study raising the power from 98% to 99% in a common cancer.

Science and Technology Board Report (December 2007) Summary and Comment from Accelerate Progress:

From the FDA's Science Board Report (2007), in boxes on relevant pages, are two summary sections that get at exactly the issues that drive too many Type II errors in regulatory decision making. The first deals with the issue about the science of the 21st century being very different than the science that drove the original FDA processes and procedures still used to evaluate safety and efficacy today. Page 7 of the Report (underlining/bolding is mine):

> **"FDA's inability to keep up with scientific advances means that American lives are at risk**. While the world of drug discovery and development has undergone revolutionary change — shifting from cellular to molecular and gene-based approaches — **FDA's evaluation methods have remained largely unchanged over the last half century**. Likewise, evaluation methods have not kept pace with major advances in medical devices and use of products in combination. "

The second key box section we reference deals with what may lie partially at the heart of the increase in delay choices as well as the increasing number of decisions later shown to be incorrect on either approvals or disapprovals. This is particularly important for all those who have historically suggested that it's inappropriate to question an FDA decision on efficacy matters which has supported continued poor decision-making without oversight or peer review. The Science Board Report underscores just how appropriate and important it is for the scientific community to be able to question and discuss these important issues. Further, we believe it highlights the need for greater transparency when the FDA chooses to ignore the opinion of its expert advisory committees which would seem to place the decision at much greater risk for error.

> "FDA's failure to retain and motivate its workforce puts FDA's mission at risk. Inadequately trained scientists are generally risk-averse, and tend to give no decision, a slow decision or, **even worse, the wrong decision on regulatory approval or disapproval.** "

Section 1.3 "Summary Statement and Recommendations" repeats themes raised by previous committee reports to the FDA but goes further, noting:

> **"In contrast to previous reviews that warned crises would arise...recent events and our findings indicate that some of those crises are now realities and American lives are at risk."**

Section 2.2 "The Criticality of Science" ends with this summary:

> "In summary, **getting the science right is critical** to FDA's ability to fulfill its mission. Decisions...must be based on understanding of contemporary and emerging science within the context of the risk analysis paradigm. Indeed, it will also increasingly be true of **assessing efficacy**, particularly as we move into the era of the personalization of medicine."

Section 3.1.2 which certainly includes new immunotherapies recently delayed in likely examples of Type II errors is titled "Finding: The development of medical products based on 'new science' cannot be adequately regulated by the FDA" and notes:

> "**The FDA lacks sufficient expertise** to understand the impact of product use, to maintain ongoing currency with their evolution or **to evaluate the sophisticated products produced**."
>
> "**The mission of getting safe and effective drugs to patients in a timely manner is currently threatened by inadequate expertise and capabilities**..."

Clearly, those quotes and sections sum up the urgency of the health crisis cancer patients are facing today. The Science Board Report of 2007 should be appropriately read against the background of FDA's own "Innovation or Stagnation" Critical Path document from March of 2004 to see that many of these issues have persisted despite initiation of the Critical Path project at FDA. It is clear to us that Critical Path is one very important initiative, though it needs to be broadly expanded through more robust funding and be driven by change-minded and forward-thinking leadership, with buy-in from the many constituencies involved in the systems addressed by Critical Path and FDA.

From the Innovation or Stagnation Document with Comment from Accelerate progress:

(http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html)

The language below from FDA's own 2004 whitepaper assessing the slowdown in innovation and decreases in effectiveness translating clinical progress into patient benefits largely stands on its own, but we have added emphasis or additional notes to a few key sections of the summary below. The entire whitepaper is worth the read, however, as it informs history at FDA well and should serve to inform future policymakers who do not want to repeat the mistakes of the past. Bold, underling, italics, etc. are our own.

> "This report provides the Food and Drug Administration's (FDA's) analysis of the pipeline problem -- the recent slowdown, instead of the expected acceleration, in innovative medical therapies reaching patients.
>
> Today's revolution in biomedical science has raised new hope for the prevention, treatment, and cure of serious illnesses. However, there is growing concern that many of the new basic science discoveries made in recent years may not quickly yield more effective, more affordable, and safe medical products for patients. This is because the current medical product[1] development path is becoming increasingly challenging, inefficient, and costly. (SR: ***recent data suggests that the length of clinical trials has increased almost 70% in recent years, owing largely to FDA demands for larger and longer clinical trials***)
>
> Developing products targeted for important public health needs (e.g., counterterrorism), less common diseases, prevalent third world diseases, prevention indications, or individualized therapy is becoming increasingly challenging (SR: ***see our notes within the Coalition for Faster Progress document for issues relating to more rare disease focus too***)… If the costs and difficulties of medical product development continue to grow, innovation will continue to stagnate or decline, and the biomedical revolution may not deliver on its promise of better health.
>
> What is the problem? In FDA's view, the applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic sciences. The new science is not being used to guide the technology development process in the same way that it is accelerating the technology discovery process (SR: ***and, per our other areas of discussion, the 'new' science is not being used enough in the regulatory review process nor within guidance for industry provided by regulatory bodies on whom some efficiencies in the discovery, development and translational processes rely***). For medical technology, performance is measured in terms of product safety and effectiveness. Not enough applied scientific work has been done to create new tools to get

fundamentally better answers about how the safety and effectiveness of new products can be demonstrated, in faster time frames, with more certainty, and at lower costs. In many cases, developers have no choice but to use the tools and concepts of the last century to assess this century's candidates. As a result, the vast majority of investigational products that enter clinical trials fail. Often, product development programs must be abandoned after extensive investment of time and resources. This high failure rate drives up costs, and developers are forced to use the profits from a decreasing number of successful products to subsidize a growing number of expensive failures (SR: ***this points again to the need to better use modern scientific approaches like Bayesian analyses and adaptive trial designs to jettison failures more quickly but also to inform where development might focus within a patient population for expected efficacy and benefit***). Finally, the path to market even for successful candidates is long, costly, and inefficient, due in large part to the current reliance on cumbersome assessment methods. (SR: ***We agree wholeheartedly. Even the strongest of candidates seems to run up against this inefficient process and take, on average, 12-15 years to navigate its path from discovery to bedside and cost in excess of $1billion. This can not, and has not, fostered the sorts of rational pricing decisions that would allow better and more effective use of public funds in healthcare).***

A new product development (SR: ***and, we'd argue, regulatory assessment***) 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. We need superior product development science to address these challenges -- to ensure that basic discoveries turn into new and better medical treatments. We need to make the effort required to create better tools for developing medical technologies. And <u>we need a knowledge base built not just on ideas from biomedical research, but also on reliable insights into the **pathway to patients.**</u>

Because FDA's standards are often used to guide development programs, we need to make sure that our standard-setting process is informed by the best science, with the goal of promoting efficient development of safe and effective new medical treatments. (SR: *This is exactly why it's so important that FDA, HHS, and related entities like NIH/NCI possess strong internal resources as well as a strong process for recognizing and collaborating with external leaders in their fields to inform and accelerate adoption of better processes, better standards, and better science.)*

Through scientific research focused on these challenges, we can improve the process for getting new and better treatments to patients. Directing research not only to new medical breakthroughs, but also to breakthrough tools for developing new treatments, is an essential step in providing patients with more timely,

affordable, and predictable access to new therapies. We are confident that, with effective collaboration among government, academia, and the private sector, these goals can be achieved.

Although necessary for product development, even [exemplary models of] translational research efforts will not yield the hoped-for results without an analogous focus on downstream development concerns. As one group has observed, "Massive investments in one part of the network are likely to be at least partly wasted unless the other links are strengthened as well." A third type of scientific research is urgently needed, one that is complementary to basic and translational research, but focuses on providing new tools and concepts for the medical product development process -- the steps that must be taken to get from selection of a laboratory prototype to delivery of an effective treatment to patients. We call this highly targeted and pragmatic research critical path research because it directly supports the critical path for product development success." (SR: ***Again, this returns to the point about why improvement must be driven by a systems-analysis as opposed to a silo-focus or component-driven initiative, because care must be given to assess flow of feature changes throughout the system and thought must be given to bottleneck areas in need of most immediate attention for improvement throughout the system. The issue of approving clinical trial protocols referenced in Dr. DeVita's attached editorial is one such example of a critical bottleneck.)***

Conclusions from Accelerate Progress

There are many hard-working, thoughtful people who have been involved in policy and regulatory decision making over the years. We respect the work and good intentions of those individuals and groups without whom what progress we have made against these difficult diseases would have been impossible.

We provide these policy recommendations and insights as part of our contribution to accelerating progress against disease because we believe that by stepping back and assessing the systems that discover, translate, develop, regulate, and govern use of new therapeutics against disease, particularly life-threatening diseases, it is hard not to see many opportunities for improvement and too many patients suffering and dying while awaiting those improvements. We have worked with urgency and diligence to bring together many constituencies involved with or affected by these systems, including those with experience in academia, industry, regulatory or other governmental bodies of FDA and NCI, physicians who treat patients for a living, physicians who research for a living, patients themselves, advocates, and other thoughtful and concerned groups, while ensuring that we remain beholden to none of these individual constituencies, thus maintaining our independence and credibility to accelerate progress.

We thank you for your review and consideration of our materials and welcome continued dialogue on these issues as it informs future positive action.

Sincerely,

Scott D. Riccio
Executive Director
Accelerate Progress