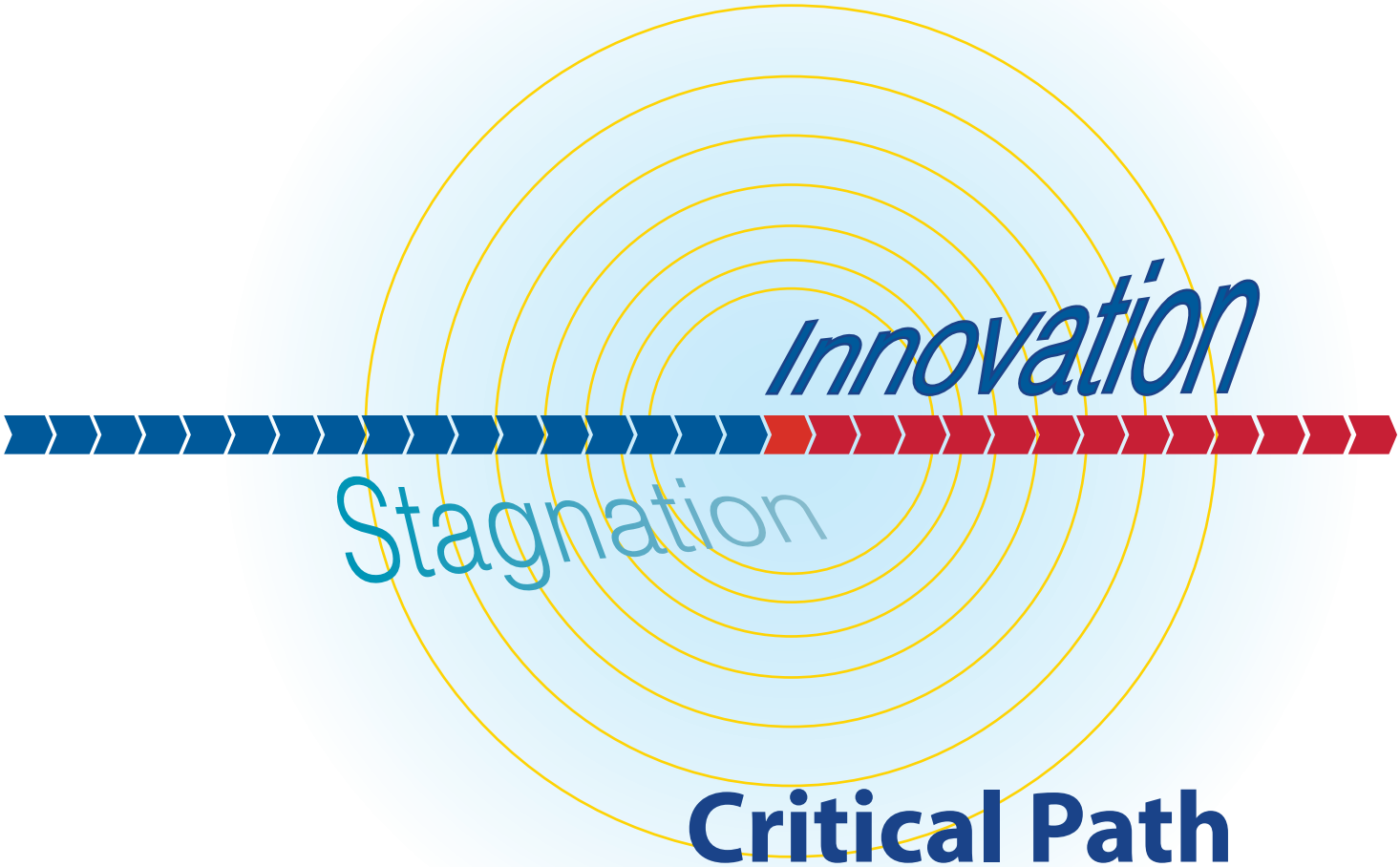

Critical Path Opportunities Report

U.S. Department of Health and Human Services
Food and Drug Administration
March 2006

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Critical Path List

The Report and the Opportunities List are also available on the Internet as stand alone documents
at http://www.fda.gov/oc/initiatives/criticalpath/.

MESSAGE FROM THE ACTING COMMISSIONER

How can science make it possible for us to know so much about disease, and yet we remain frustrated that so many people are suffering from, or are affected by, disease. The basic sciences responsible for those discoveries are thriving as we gain greater insight into the molecular basis of disease, but their progress has significantly outpaced progress in the product development sciences, which are used to transform those discoveries into new medical products. The scientific tests used to develop products (to understand whether candidate products are safe and effective and to enable their reliable mass manufacture) are decades old. They have not been modernized to incorporate new knowledge and approaches. For example, most development programs must rely on *trial and error* empirical testing, rather than on more mechanistic approaches built on new molecular and genomic knowledge. As a result, novel therapies are not moving through development and to patients as quickly as they could be. A recent study showed that in 2004, we hit an all time low for the past 20 years worldwide in the number of new medical therapies reaching the market.[1]

With sufficient funding and effort, the Critical Path sciences could be modernized. Targeted investments, for example, in biomarker development, could help companies identify sooner those product candidates that are likely to fail, while directing more resources to develop promising candidates. Investments in the science of medical product development could also help us better understand new products so they can be used more widely, safely, and effectively, once approved.

The FDA is committed to rapidly enhancing the Critical Path sciences; however, modernizing the Critical Path of medical product development is a national challenge. It will take the combined efforts of government, industry, academia, and patients to create the robust science needed to fulfill the promise of new biomedical science. We, at FDA, envision progress in medical product development as having new predictive tools to identify early those product candidates of greatest efficacy against molecular and biological processes and new evaluative tools to improve the performance of clinical trials and treatment choices. Animal models of human disease, statistical methods for analyzing test results, sophisticated scientific instruments and tests that measure product quality, new biomarkers and diagnostic devices that reliably measure human response to treatment—all of these will be necessary if we are to reap therapeutic rewards from biomedical discoveries.

Often, Critical Path work is not glamorous. Innovations in clinical trial design and new animal models that more accurately mimic human disease rarely make headlines. But without them, we would not have the medical products we use today. And without more modern, more predictive tools, we will not have the products of tomorrow.

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[1] Centre for Medicines Research (CMR) International, *2005/2006 Pharmaceutical R&D Factbook*, Chapter 6, September 2005.

Although we are only one organization among many with a role to play in moving innovative medical products to the marketplace, FDA is uniquely positioned to provide national leadership in this effort. Because FDA oversees testing of all medical products in the United States and because our scientists have special expertise in the sciences of product testing and manufacture, we can identify the scientific hurdles that commonly cause setbacks for companies. Because of FDA's regulatory role, we often have the opportunity to promote innovation industry-wide, for example, by setting standards and providing guidance. Because we are not a market competitor, FDA can serve as the catalyst for the consensus development that is needed to identify new scientific standards.

FDA has begun exploiting these opportunities and is encouraging a national effort to advance medical product development sciences that can turn discoveries into medical miracles. We are doing this on a foundation of solid science, and we are working with other agencies, academia, and industry. The Critical Path Initiative is anchored in our mission, and it is now part of our long-term vision.

Many of the Critical Path opportunities described in this report cannot be accomplished by one entity alone. No single company, university, or governmental agency will have sufficient resources, expertise, or information base to undertake the work. We will need to develop new ways to collaborate and share data to accomplish our common goal of a robust Critical Path infrastructure. I encourage all who read this report to consider ways they can make a contribution to this critical nationwide effort.

EXECUTIVE SUMMARY — SIX PRIORITY PUBLIC HEALTH CHALLENGES

In its 2004 Critical Path Report,[1] the FDA presented its diagnosis of the scientific challenges underlying the medical product *pipeline problem*.[2] The report then laid out a path forward, beginning with extensive outreach and consultation with public and private stakeholders. Our diagnosis of stagnation in the product development sciences struck a chord. Stakeholders confirmed our diagnosis and provided examples of scientific investments that could revolutionize medical product development.

Our goal was to develop a Critical Path Opportunities List intended to bring concrete focus to specific tasks needed to modernize the product development sciences. In this report, we describe what we have learned and present a list of specific opportunities.

The Critical Path Opportunities List identifies targeted research that we believe, if pursued, will increase efficiency, predictability, and productivity in the development of new medical products.

[1] The March 2004 Critical Path report is available at http://www.fda.gov/oc/initiatives/criticalpath.

[2] The recent slowdown in innovative medical therapies reaching patients.

Each opportunity on the list represents a highly targeted research project intended to improve product development in the short- and mid-terms. Topics were chosen based on issues identified by stakeholders through our outreach efforts and on FDA scientists' views of industry-wide product development hurdles. Our choice of priority topics was also informed by the public health mission of the Food and Drug Administration and by external advisory committees charged with advising the FDA on scientific issues of regulatory importance. The opportunities are organized into six broad topic areas.

Note that our numbering of opportunities is for convenience and does not suggest a particular order of importance.

Our outreach efforts uncovered a remarkable consensus that the two most important areas for improving medical product development are ***biomarker development (Topic 1)*** and ***streamlining clinical trials (Topic 2)***. Stakeholders from most sectors agreed that a new generation of predictive biomarkers would dramatically improve the efficiency of product development, help identify safety problems before a product is on the market (and even before it is tested in humans), and facilitate the development of new types of clinical trials that will produce better data faster. Similarly, stakeholders from all sectors stressed that reforming the clinical trial process—both trial design and trial conduct—would dramatically improve the efficiency of product development.

The application of mathematics, statistics, and computational analysis to biological information—***bioinformatics*** (***Topic 3***)—is our third challenge area. It holds the promise of reducing the size and scope of human and animal trials while improving development efficiency and predictability of results. For example, the concept of *model-based drug development* holds vast potential to support more efficient and effective development of drugs and medical devices. Development of data pooling consortia and methods for protecting personal and proprietary information will be needed to support this work. There is widespread agreement that such an investment would pay off handsomely.

The ability to reliably manufacture a high-quality product on a commercial scale is a frequent stumbling block on the Critical Path. Tools that help identify and analyze critical product attributes hold the promise of improving both efficiency and quality in ***manufacturing (Topic 4)***.

We also urgently need new ***antibiotics and countermeasures to combat emerging infections and bioterrorism (Topic 5)***. Rapid methods for identifying infectious agents will improve our ability to develop new treatments and to respond to emergencies. We need qualified models in which to test new treatments when testing in humans is unethical.

Developing therapies for children and adolescents (Topic 6) poses unique challenges. One way to find better methods for predicting if treatments will work in children and adolescents is to combine and analyze data from existing pediatric studies. Additionally, new genomic technologies hold promise for improved diagnosis and treatment of adolescent depression. Finally, infections in newborns are a significant public health problem and pose difficult development issues that could be overcome with better animal models.

Finally, we believe it is critical to build a ***national infrastructure*** to support and continually improve the Critical Path sciences. To make our efforts to modernize the Critical Path lasting, we must reach beyond the specific opportunities outlined in this report. For example, we need academic programs in experimental medicine as well as clinician researchers who can work effectively in the laboratory as well as with animal and human studies. We need to develop clear career paths for researchers who want to work in this multidisciplinary environment.[3] We need new collaborations to develop coordinated plans to attack scientific hurdles in product development, or to attack specific illnesses, and new models of data sharing and protection to facilitate those collaborations. Government, academia, and industry, as well as patient and professional groups, must work together to encourage continued support in the development of the Critical Path sciences.

Our stakeholders have pointed out that modernizing development science alone is not enough; we must also modernize FDA policies and standards to keep up with the evolving science. We agree with this analysis and will work to ensure that regulatory modernization keeps pace with scientific advances.

[3] The National Institutes of Health (NIH) is expanding its support of such programs as part of the NIH Roadmap (http://nihroadmap.nih.gov).

The opportunities, discussed broadly in the following sections, then listed specifically in the Opportunities List, describe targeted research that could be undertaken by industry or academia and could be sponsored by patient groups, foundations, or government agencies.

During the next few months, we will assess our ability, based on available resources, to support some Critical Path priorities listed in this report. We also plan to announce the Critical Path projects that FDA will undertake during the coming year. We hope stakeholders will use this report to begin planning their activities in the national effort to modernize the Critical Path sciences.

This report is divided into two parts. The first part of the report discusses what we have learned about the opportunities and challenges from stakeholders and FDA scientists since the publication in March 2004 of the Critical Path Report and, in particular, discusses in more detail the six major topics identified in the List. The second part of the report, also available as a stand alone document, presents specific opportunities.

INTRODUCTION

In its 2004 Critical Path Report,[1] the FDA presented its diagnosis of one of the scientific challenges underlying the medical product *pipeline problem*.[2] The report laid out a path forward, calling for extensive consultation with public and private stakeholders. Soon after publication of the report, we opened a public docket to facilitate the submission to FDA of examples of areas where research was needed. We began outreach to collect stakeholders' views on the most urgent scientific hurdles in medical product development.

Our diagnosis of stagnation in the product development sciences struck a chord. From well-established companies to small biotech pioneers, from patient advocacy groups to venture capitalists, stakeholders confirmed our diagnosis and provided examples of scientific investments that could revolutionize medical product development. Both in the comments submitted to the open docket and in meetings, stakeholders overwhelmingly agreed with both our diagnosis of a serious problem with the sciences necessary for efficient product development and our prescription for targeted, collaborative research, new science-based standards, and collaborations.

Stakeholders have already begun calling on FDA to undertake research, develop guidances, initiate collaborations, and convene consensus-developing activities on a wide range of scientific issues. The Critical Path Initiative is FDA's response to that call.

We promised to compile the results of our outreach efforts along with the observations of FDA scientific staff, who can see the success and failures across all types of medical products. Our goal was to develop a Critical Path Opportunities List intended to bring

[1] The March 2004 Critical Path report is available at http://www.fda.gov/oc/initiatives/criticalpath.

[2] The recent slowdown in innovative medical therapies reaching patients.

concrete focus to the most urgent and promising opportunities to help modernize the product development sciences. In this report, we summarize what we have learned from extensive discussions with stakeholders and FDA scientific staff and present the Opportunities List.

Some stakeholders are already working on some of the opportunities discussed in this report. We support those efforts, and do not mean to imply that the efforts are inadequate, or to suggest that duplicative efforts are needed. Indeed, a number of important efforts are underway worldwide, and we have listed some in an attachment to this report.

We view the List of Opportunities as an ***initial summary*** of key scientific opportunities to improve product development, not as the final word. As biomedical discoveries evolve, the Critical Path sciences will need to evolve with them. Over time, new opportunities will arise. We hope that many of the problems on this list will be solved in the near term. In short, we view this list as the beginning of an evolutionary focus on improving the Critical Path sciences.

We have been overwhelmed by the positive reactions to our 2004 Critical Path Report—the demand for FDA action exceeds our capacity to respond. During the next few months, however, we will be reviewing internal resource issues and matching available resources to Critical Path priorities. We will then announce the Critical Path projects that FDA will undertake during the coming year.

Finally, a note on the organization of this report. The first part of the report details what we have learned about the opportunities and challenges from stakeholders and FDA scientists since the publication of the March 2004 Critical Path Report and discusses in detail the six major topics identified in the List. Readers who are interested in specific opportunities may want to proceed directly to the Opportunities List, also available as a stand alone document.

CRITICAL PATH — A CALL TO ACTION

Turning Discoveries Into Products

New scientific discoveries are not easily transformed into medical products, ready to treat patients. Painstaking scientific work is needed to take a new laboratory discovery and turn it into a high-quality product that is beneficial and safe. Along this *Critical Path* are an array of difficult scientific and technological hurdles for medical product developers that are very different from the scientific challenges encountered in discovery. For example, from thousands of candidate drugs, developers must use *predictive tools* to screen out those candidates most likely to have serious undesired effects and identify those most likely to become safe and effective treatments. Even if a potential medical product reaches the stage of development when it can be tested in people, its journey to commercialization is far from guaranteed. Developers need good *evaluative tools*, such as biomarkers and informative clinical trial designs, to efficiently assess human safety and efficacy. Developers must also design the best way to reliably mass produce a high-quality product.

Often, however, good predictive and evaluative tools are not available, causing delays and failures in product development—failures that may occur even after marketing. This is because, in many cases, the only testing methods and concepts available to product developers to predict the performance of promising candidates are decades old. If predictions are inaccurate, enormous resources can easily be wasted testing products that eventually will fail—resources that could have been directed to developing and testing products more likely to succeed. This inefficiency is contributing to the *pipeline problem*, the recent slowdown in innovative medical therapies reaching patients.

During the past two decades, there has been enormous public and private investment in biomedical research. Between 1994 and

2003, U.S. biomedical research funding increased from $37 billion to $94 billion, doubling when adjusted for inflation. The largest funder was industry (57 percent).[1] Despite this investment, new product applications to the FDA have not increased. A new compound entering human trials in 2000 was no more likely to reach the market than one entering human testing in 1985. A recent study by the Centre for Medicines Research International Ltd. showed that 2004 represented a 20-year low in the number of new medical therapies (new molecular entities) launched on the market worldwide.[2] We are spending more on biomedical discovery and product development, but getting fewer new products to market.

Without a new generation of product development tools, the biomedical revolution may not deliver on its promise of better health. There is an urgent need for tools that will give product developers the information they need to make good decisions about which products to move forward in testing, which doses to test, and how to design clinical trials that will provide clear information about product benefit and safety. Only by investing in the medical product development sciences will we develop the tools needed for the future.

Improving Development Sciences Will Help Modernize Product Regulation

FDA is charged with ensuring that marketed medical products are both effective and safe. To this end, FDA sets product performance standards and also requires that product developers test product performance prior to marketing. FDA uses available scientific knowledge to specify testing procedures (e.g., toxicology and carcinogenicity protocols, clinical safety testing) and to establish standards based on test results. FDA's process for reviewing product applications consists of evaluating a product's test results within the context of established FDA standards.

Ambiguous results emanating from currently available test procedures are the greatest obstacles encountered by FDA scientists during product review. Most current tests are empirical

[1] Moses, H., E. R. Dorsey, D. H. M. Matheson, and S. O. Thier, "Financial Anatomy of Biomedical Research," *JAMA*, Vol. 294(11), September 21, 2005.

[2] Centre for Medicines Research (CMR) International, *2005/2006 Pharmaceutical R&D Factbook*, Chapter 6, September 2005.

(i.e., trial-and-error, not designed to explore the underlying mechanistic explanation) and are, therefore, difficult to interpret when results are unclear. A reasonable, conservative approach to an ambiguous result is to require additional, more extensive, empirical testing. Additional empirical testing, however, often does not provide enough certainty, and questions about product performance (i.e., quality, safety, or effectiveness) remain.

These frustrating questions occur daily within the FDA review process. With new evaluative tools and techniques, we can improve medical product assessment. Specific examples of such tools—new biomarkers, improved animal models, better clinical trial designs and endpoints, *in silico testing* (computer simulation, rather than laboratory or animal testing)—are included in the Opportunities List. Critical Path research can help develop tools that can provide more confident predictions of how medical products will perform when used, resulting in a more informative product development process and a more efficient assessment process.

The research called for in this report can ultimately form the basis for improved FDA standards and new guidances, helping to modernize FDA product regulation. Stakeholders have identified areas in which new FDA policy guidance and standards would facilitate smarter, faster, more informative product development, and many of the opportunities in the list are based on those requests. FDA is in a unique position to drive the modernization of medical product development as new scientific methods become available.

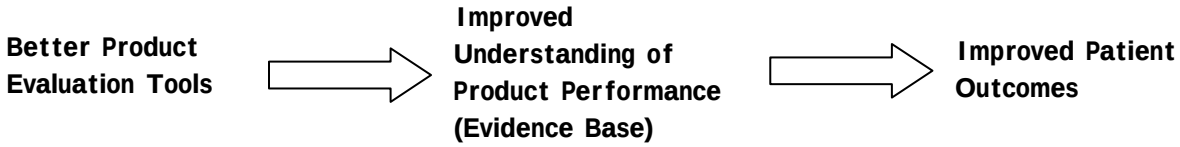
Improving Development Sciences Will Improve Treatment

Many of the new tools resulting from this effort will also provide healthcare professionals with critical information to use in treating their patients. For example, better methods for selecting patients and assessing their responses during a clinical trial can translate directly into better methods of diagnosing and monitoring patients in the clinic. Biomarkers (incorporated into relevant diagnostics) used to select high-risk populations for clinical trials will also, once the product is on the market, help physicians target treatment to the patients who are likely to benefit most. Such tools will help bring individualized medicine into the physician’s office to help shape the medical practice of the future. Right now, the work necessary to prove that a given biomarker is sufficiently correlated with clinical response is rarely undertaken.

Improving Development Sciences Will Improve Safety

Modernizing the medical product development sciences will also create new opportunities to improve product safety. It is important that we strengthen our postmarketing surveillance of adverse events, but our ultimate goal should be to prevent adverse events from occurring in the first place. We need to build safety into products from the ground up. New areas of science, particularly genomics, proteomics, and related disciplines, as well as bioinformatics, hold great promise for better scientific understanding and prevention of safety problems. The premarket safety evaluation needs to change from a passive, empirical (i.e. trial and error), patient-exposure-based assessment of adverse events to a predictive evaluation based on a robust body of prior knowledge about the molecular and/or physical mechanisms of a product. Like markers that predict which patients are likely to respond positively to a product, the use of new safety biomarkers can translate rapidly from the experimental setting to the clinic. Patients with a high probability of an adverse effect can be identified and their exposure avoided. In addition, safety biomarkers could be used to monitor patients for emergence of toxicity during treatment, so that therapy can be stopped before harm has occurred. These outcomes are achievable, given a concerted effort to apply currently available scientific knowledge principles to safety evaluation.

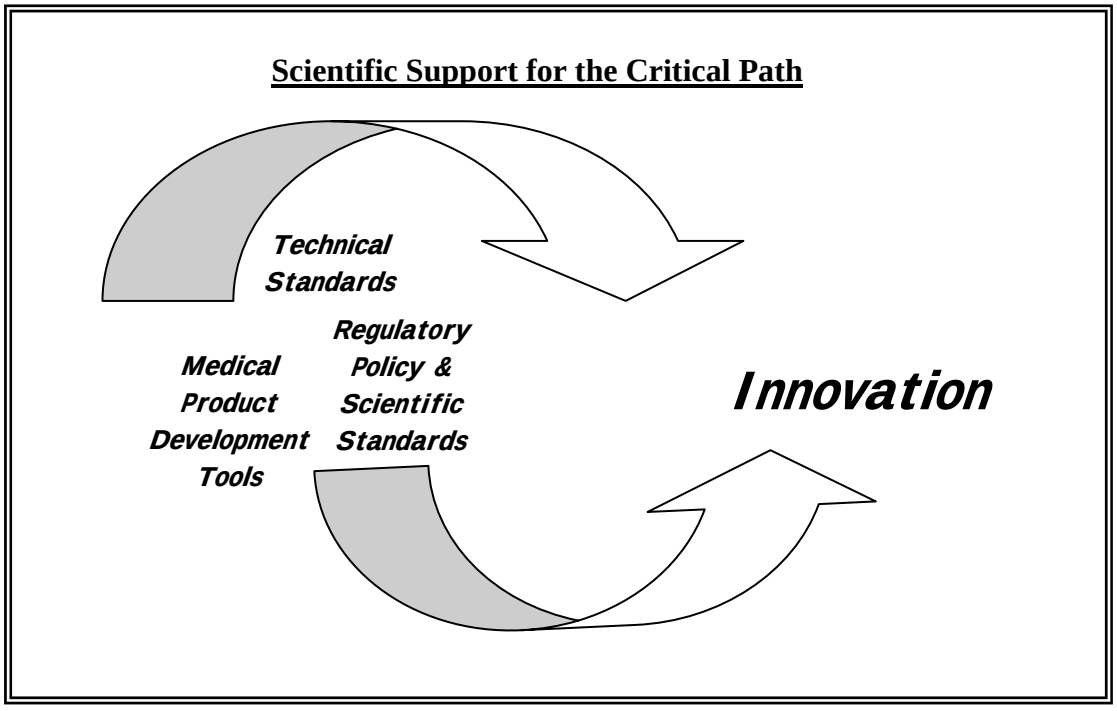
Modernizing Critical Path Science Will Improve Patient Outcomes



What Scientific Areas Support the Critical Path?

In its 2004 Critical Path Report, the FDA analyzed the development process that takes a medical product from discovery to the market. The report identified the Critical Path of medical product development and described in detail the scientific and technical hurdles that developers must overcome before they can market a new medical product. The report also described the types of scientific research that must be carried out to address these barriers.

However, our stakeholders pointed out that there is additional scientific infrastructure, beyond these research activities, that must also be put in place to improve development. Technical standards, either private or public, must be established. This has been shown in other sectors (e.g., the Internet or the semiconductor industry). In addition, regulatory modernization must keep pace with scientific changes. Thus, improving medical product development will require continuous modernization of three interrelated and mutually informing scientific areas: (1) medical product development tools, (2) technical standards, and (3) regulatory policies and scientific standards.



WHAT WE HAVE LEARNED

The Critical Path Opportunities List identifies specific opportunities that, if implemented, will increase efficiency, predictability, and productivity in the development of new medical products. The opportunities are organized into six broad topic areas. The topics were chosen based on priorities identified by stakeholders through our outreach efforts and on the experience of FDA scientists, who are very familiar with product development hurdles through their work reviewing product applications. We also consulted FDA's Science Board and other FDA external advisory committees. Finally, our choice of priority topics also was informed by our public health mission and vision.

The six topic areas are discussed in the following report. Specific opportunities are presented in the Opportunities List, which is also available as a stand alone document.

TOPIC 1: BETTER EVALUATION TOOLS — DEVELOPING NEW BIOMARKERS AND DISEASE MODELS

Medical product development involves a sequence of tests intended to progressively reduce uncertainty about a candidate product's performance. At the start of the Critical Path, developers form hypotheses about performance characteristics such as safety, biological or mechanical action, and biocompatibility. They then seek to evaluate and confirm these hypotheses using in vitro, animal, and human testing. Once uncertainty about benefits and risks of a product has been reduced to an acceptable level, the product may be approved for marketing—if the benefits outweigh the risks. The great challenge in development lies in predicting a potential product's performance as early as possible with the greatest degree of certainty.

Some of the most important signposts along the development pathway are quantitative measures known as biomarkers. *Biomarkers* are measurable characteristics that reflect physiological, pharmacological, or disease processes in animals or humans. Changes in biomarkers following treatment reflect the clinical response to the product. Techniques as disparate as imaging, serum or genetic assays, or psychological tests can yield biomarkers that are useful in product development. Biomarkers can reduce uncertainty by providing quantitative predictions about performance. The existence of predictive efficacy biomarkers in particular can revolutionize product development in a disease area.

There is clear consensus that new biomarkers and animal models—qualified for a wide range of product testing purposes—are urgently needed to unlock innovation in product development and treatment and could be developed with concerted scientific effort.

With a robust set of qualified biomarkers, the safety of new medical products could be increased, the cost of clinical trials could be reduced, products could get to patients sooner, and treatment decisions could be more informed. The specific opportunities in the list contain concrete projects that can move us toward the next generation of biomarkers and diagnostics.

Qualifying New Biomarkers

Many of the biomarkers used in medical product development today have been in use for many years, even decades. These longstanding biomarkers were empirically derived; they often lack predictive and explanatory power. New biomarker development has stalled. A large number of potential new biomarkers have been proposed, but the essential work needed to evaluate their utility—known as biomarker qualification—has not been carried out. In the Critical Path List, we enumerate some opportunities to qualify new biomarkers that are particularly promising.

Genomic, Proteomic, and Metabolomic Technologies

The new *-omic* technologies (genomics, proteomics, and metabolomics) hold great promise as a source of powerful biomarkers. Some in vitro diagnostic tests that detect specific genetic variations that affect an individual's response to treatment are ready for use. For example, recently FDA approved several genomic tests for drug metabolizing enzymes. These assays can identify patients who are at high risk for serious toxicity from

cancer therapies because the recommended doses are too high for them. Pharmacogenetic tests for drug metabolism status are only the first in a new generation of diagnostics that could transform product development.

Safety Biomarkers

Development of more predictive safety biomarkers for use in animal toxicology studies would improve the effectiveness of safety screening prior to introducing products into humans, enable better selection of initial human doses, and help target toxicity monitoring in early trials. Clinical trial safety could be improved, as could overall development efficiency.

New safety biomarkers are also crucial to improving the safety of products used in clinical practice. Biomarkers are urgently needed to monitor for early signs of toxicity and to signal the potential for severe toxicity. Such biomarkers could significantly improve the development and use of products that patients will take over time periods far longer than the length of clinical trials, such as implanted devices and drugs that treat chronic conditions. In addition, development of markers and diagnostics to identify individuals at high risk for serious drug side effects—such as cardiac arrhythmias—could dramatically improve medical product safety while simplifying product development.

Personalized Medicine

Biomarkers are crucial for individualizing, or personalizing, medical treatment. For example, markers can be used to create more precise classifications of disease to target or stratify therapy. Similarly, for a therapy directed at a molecular target (e.g., many cancer treatments under development), markers of that target may provide reliable predictions of who will respond—and thus who should receive that therapy. Markers of drug metabolism can be used to individualize drug dosage, preventing, for example, predictable underdosing (and resultant lack of efficacy) in more rapid metabolizers and serious side effects from overdosing in slow metabolizers. For example, we now know that genetic variants in metabolizing enzymes play a significant role in the large variability among patients in warfarin dosing. Harnessing this knowledge to develop rigorous dosing protocols based on a patient's unique genetic profile should reduce safety problems associated with initiation of warfarin therapy. Biomarkers are also useful for predicting dose-response characteristics and for

monitoring response during treatment.

Surrogate Endpoints

There is great interest in qualifying additional surrogate endpoints. A *surrogate endpoint* is a biomarker that is used to predict clinical benefit (a direct measurement of how a patient feels, functions, or survives). Often, changes in such biomarkers can be detected earlier, or more readily, than the corresponding clinical endpoint (an outcome being used to measure drug effect). In disorders where the clinical endpoint is hard to assess (e.g., joint deterioration in rheumatoid arthritis) or takes a long time to occur (e.g., certain preventive therapies), use of a qualified surrogate endpoint can markedly accelerate the development process for treatment breakthroughs. Before a biomarker can be accepted as a surrogate endpoint, however, there needs to be a great deal of confidence that changes in the marker reliably predict the desired clinical endpoints. There must also be a comprehensive and thoughtful discussion of possible risks (e.g., trials using a surrogate endpoint for effectiveness can be shorter and thus will not evaluate longer term risks). One opportunity in the list involves more clearly laying out a path for qualifying a biomarker as a surrogate endpoint.

New Imaging Techniques

New imaging techniques hold vast potential for use as biomarkers for an array of purposes in product development—measuring treatment efficacy, patient stratification, and improved diagnosis. Although preliminary data are promising, the predictive capacity of most new imaging techniques has not been rigorously evaluated. A lack of standardization of imaging methods and evaluation techniques further complicates their use in product development. Research to qualify imaging techniques for particular uses in product development would enable developers to measure the effects of candidate products earlier and more accurately. In addition, data gained from the standardization and qualification processes could provide the evidence base for clinical use.

Improving Predictions of Human Responses from Disease Models

Animal models of disease are additional important tools in the selection and refinement of candidate medical products. Frequently, candidate products need to succeed in animal models prior to moving into testing in humans. For some diseases, current

animal models have not been predictive of success in humans, leading to a succession of failed clinical development programs in that indication (e.g., neuroprotection). Opportunities to develop more predictive animal models are outlined in the Opportunities List.

TOPIC 2: STREAMLINING CLINICAL TRIALS

Within the context of medical product development, clinical trials are tools for evaluating the performance of investigational medical products in people. Clinical testing is the most expensive aspect of medical product development, often requiring the enrollment of large numbers of people and the collection of massive amounts of data. Stakeholders point to the costs of clinical trials as a barrier to innovation.

Advancing Innovative Trial Designs

The majority of clinical trials currently conducted during product development, particularly for pharmaceuticals, are empirical (i.e., designed to assess whether patients improve or have adverse reactions, not designed to explore the underlying physiologic mechanisms of product performance). This is due to a dearth of knowledge and evaluative tools for exploring pharmacologic mechanisms (either of benefit or risk). Another major drawback of empirical trials is their limited ability to address more than a few questions within a single trial. Consequently, after a long and expensive development program, numerous questions about product performance frequently remain unanswered.

The situation is better for some medical devices, where there are reliable metrics to evaluate specific aspects of device performance (e.g., physical, electrical, mechanical, imaging). However, for other devices (e.g., certain drug-device combination products), problems similar to those of pharmaceuticals also occur.

As tools to elucidate the causal mechanisms underlying product safety and efficacy become available, new trial designs and clinical development programs will need to evolve to make use of the knowledge gained. Such new designs are often referred to as *learning trials.* Learning trials have a different underlying conceptual framework and require a statistical approach different

from empirical trials. One type of learning trial in use today is the dose- or concentration-controlled trial, which uses biomarkers or other intermediate measures as endpoints to explore dose- or concentration-response relationships. In the future, we hope that such trials can employ multiple biomarker assays, such as advanced imaging techniques and genomic- and proteomic-based tests, to quickly reduce uncertainties around product performance. Knowledge gained from learning trials can be incorporated into quantitative computer models of disease and product performance to refine their precision and lead to more efficient *confirmatory* trials. More conceptual work needs to be done in advancing the design and analysis of these trials.

In the Opportunities List, several projects are delineated—appropriate use of enrichment designs within a development program and methods for use of prior knowledge—intended to stimulate innovation in trial design in the areas discussed above. Additionally, the list identifies several serious challenges in existing trial design and analysis that require resolution to improve innovation in clinical development. Challenges include developing reliable methods for use of noninferiority designs, treatment of missing data, and use of multiple endpoints.

Improving Measurement of Patient Responses

Today, most clinical trials investigating product effectiveness compare the overall response of the treated population to the untreated population (i.e., the control population). These trials do not seek to understand which individuals respond to an intervention or why they respond. Again, this is primarily due to a lack of tools to perform such evaluations. However, as a new generation of biomarkers emerges—capable of distinguishing among individuals with different variations of a disease or rapidly signaling status changes in organ systems or disease processes—trial designs will need to evolve to make effective use of this information. Trials that define and measure variations in individual response and seek correlation with biomarker status are the necessary first steps toward personalized medicine.

Disease- or Indication-Specific Trial Designs

As new designs and analytical principles of innovative trials are implemented, effort must also be invested in developing trials and outcome measures tailored to specific diseases. Because each disease has a particular time course, constellation of symptoms,

need for monitoring, and set of therapeutic alternatives, disease-specific trial designs that incorporate appropriate safety monitoring and standardized disease-specific efficacy measures are highly desirable. Standardized designs and metrics will (1) reduce the need to *reinvent the wheel* for each new trial, (2) assist clinical investigators and study personnel (who often conduct multiple trials in a given disease), (3) help reduce variation and error, and (4) facilitate cross-study analyses. The opportunities in the list only scratch the surface of the work that is needed to advance disease specific trial designs.

Measuring Patient Preferences

During development of disease-specific outcome measures, substantial attention must be given to patient values and preferences (e.g., assigning weight to the value of relief of various symptoms in composite endpoints). Much more effort needs to be expended in eliciting patient points of view about the burden of disease and the relief of symptoms. Improved linkage of outcome measures to established patient benefit will help identify the overall benefit of therapies with more precision and enhance product development.

Streamlining and Automating Clinical Trials

Finally, standardizing and automating clinical trial procedures, conduct, and data processing to the greatest extent possible could dramatically improve the efficiency of clinical development. Efforts are underway in many areas, including standardizing terminology and developing data standards.[3] Yet many opportunities remain in this area.

[3] A number of collaborations are underway to develop standards with, for example, the Clinical Data Interchange Standards Consortium (CDISC), Health Level 7, the National Cancer Institute.

TOPIC 3: HARNESSING BIOINFORMATICS

The goal of the Critical Path Initiative is to take advantage of new scientific tools to meet existing challenges to medical product development. In no field is the opportunity greater than *bioinformatics*—the application of mathematics, statistics, and computational, quantitative analysis to biological data. With recent advances in the bioinformation sciences, it should be possible to analyze and mine large sets of biological data about patients, with the goals of creating robust, quantitative computer models of normal human physiology, of the natural history of certain diseases, and of the course of a disease as affected by standard treatments.

The concept of model-based product development can also be applied to drug, device, and biological product safety. It should be possible to exploit a variety of existing toxicology and adverse events data to facilitate more accurate predictions of product safety and more rapid postmarket identification of safety issues that could not be identified during product development. By making better use of data to improve knowledge about key aspects of product development, such as exposure-response relationships and long-term performance of devices, and by supporting innovative trial designs, a model-based development program could reduce uncertainty about dose selection, device design, and other key safety and efficacy issues.

Such *data libraries* and drug and disease modeling approaches have the potential of unlocking knowledge about patterns that cannot be seen today—patterns in product efficacy and failures, in product-related safety signals, and in relationships between animal and human test results. The findings from *in silico testing* (computer simulation, rather than laboratory or animal testing) could reduce the risk and cost of human testing by helping product sponsors make more informed decisions on how to proceed with product testing and when to remove a product from further development.

Predictions of the safety and efficacy performance of medical product candidates would be more accurate, thus increasing the chances of product success. Model-based product development is particularly

attractive to spur innovation in areas where human testing raises special concerns, such as with pediatric products or products to treat pregnant women.

TOPIC 4: MOVING MANUFACTURING INTO THE 21ST CENTURY

The characterization, manufacture, testing, and quality management of medical products are components of the third dimension of the Critical Path—industrialization. *Industrialization* means developing the capacity to reliably manufacture a high-quality product at commercial scale. Problems in industrialization are frequent hurdles along the Critical Path, delaying trials, limiting access to products, and sometimes completely blocking development.

In addition, manufacturing problems are a hidden public health challenge. Manufacturing problems sometimes occur when scale-up to mass production is attempted after product approval. In the postmarket setting, poor product design, inadequate characterization and testing, or poor manufacturing process design can result in problems with product performance or malfunctions. These problems can cause patient injury, regulatory action, recalls, or lack of product availability. In many cases, manufacturers lack the scientific tools to adequately identify and characterize critical product attributes; design well-controlled manufacturing processes, using modern process control technologies; or tightly manage product quality during production.

Combination products can present significant new challenges in characterization, manufacturing, and quality assessment. For example, existing analytic techniques are often not designed to assess the *micro* quantities of drug found in some combination products, such as drug-eluting stents. New techniques and standards are needed so individual companies do not have to *reinvent* new paradigms and testing tools for each new product.

A number of opportunities in the list offer the potential to improve the industrialization process across a wide spectrum of medical products. In the pharmaceutical area, FDA's *Pharmaceutical Quality for the 21st Century* initiative has taken significant steps in this direction.[4]

[4] See http://www.fda.gov/cder/gmp/2ndProgressRept_Plan.htm.

TOPIC 5: DEVELOPING PRODUCTS TO ADDRESS URGENT PUBLIC HEALTH NEEDS

There is urgent need for successive generations of antibiotics and evolving medical countermeasures (including new vaccines and improved tests for screening donor blood and tissues) against emerging infections and bioterror attacks. Although multiple hurdles to innovation exist, modernizing the Critical Path sciences could play a significant role in solving public health needs.

Rapid Pathogen Identification

Today, culture methods are often used to identify which pathogen is causing an infection. Because test results may not be available for several days and delaying treatment is often not an option, patients are usually treated empirically, often with a drug that turns out not to be optimal for that infection.

These types of delays also cause inefficiencies in clinical trials of new antimicrobials. Because the cause of infection may not be known at the time the patient seeks treatment, many patients are enrolled in trials, treated, evaluated, and then later found not to have the infection being studied in the trial. Similarly, although tools to screen donor blood and tissues for infectious agents have become increasingly sophisticated during the past decade, we remain limited in our ability to test for several agents of concern with sufficient speed and certainty.

New discoveries in genetics, immunology, and other fields are ripe for development into efficient pathogen identification tools. Promising technologies for study include PCR-based technologies[5] and immune-based methods (including some new approaches that pair the immune-based techniques with more sophisticated instrumentation). Other novel technologies may also be useful in rapid diagnostic testing, such as the use of nanotechnology to detect DNA, RNA, proteins, or other molecules. Harnessing these technologies for rapid point-of-care identification of pathogens could create significant efficiencies in clinical testing of antibiotics and enable innovation in the development of blood screening products.

[5] Polymerase chain reaction (PCR).

Better Predictive Disease Models

A key hurdle on the Critical Path to developing therapies against potential bioterror agents is the poor predictive capacity of current animal and tissue models for some infections. Although animal models for many infectious diseases are excellent, current animal models of several key infections caused by threat agents do not adequately reflect the human form of the disease.

In the case of many serious bioterror threat agents, estimates of clinical efficacy of counter-measures will likely be based on animal models, since human studies would be unethical (deliberate exposure of humans to life threatening illnesses) or infeasible (field testing of smallpox vaccine is not possible because smallpox has been eliminated as a natural disease). The absence of reliable predictive nonhuman models for these conditions is, thus, a particularly important hurdle to overcome.

TOPIC 6: AT-RISK POPULATIONS — PEDIATRICS

At-risk populations present unique challenges for product development. The Critical Path Opportunities List focuses on eliminating hurdles to efficient development of products for infants, children, and adolescents.

Children's bodies are not just small versions of adult bodies. Modifying the adult dose of a medicine might not result in the safe and effective treatment of a child. Some devices cannot be shrunk without significant design changes, and a device that fits appropriately when implanted may soon be too small for a child's growing body. Ethical issues surrounding testing products in children often mean that children are faced with using devices, drugs, and biological products that have been rigorously tested only in adults. Finding appropriate and safe medical products for children presents many challenges.

Stakeholders tell us that mining existing product review data sets could produce new and better methods for extrapolating from adult data to pediatric populations for better predictions of whether a product will work in children, whether a product will be toxic to children, and what dose is likely to have an acceptable benefit/risk profile.

Another public health problem that would benefit from Critical Path attention is adolescent depression. Application of genomic technologies have the potential to improve both diagnosis and treatment selection.

Similarly, infectious diseases in young infants pose unique and difficult product development issues—even if a vaccine existed, the weeks after vaccination required to develop a protective response could leave an infant at significant risk. Maternal vaccination is a potential solution, but there are no effective animal models in which to test such vaccines.

Critical Path research in these areas could help alleviate the twin problems of developing medical products for children and adolescents that address their unique physiologies and the uncertain ethics of testing products in these populations.

STAKEHOLDER INPUT — ROLE OF THE REGULATORY PROCESS

In comments to the docket, many stakeholders emphasized that FDA efforts to stimulate innovation through new Critical Path tools should not detract from improvements in the regulatory process, nor divert resources from marketing application review. Stakeholders also emphasized that new Critical Path standards should replace old standards, not constitute additional requirements. We agree. The goal of the Critical Path Initiative is to modernize standards, not create roadblocks. Stakeholders also suggested that clarification of the regulatory pathways for certain types of products (e.g., combination products, tissue engineered products) would make product development more efficient. Other regulatory actions identified as contributing to more efficient product development included:

- Create the opportunity for more meetings with FDA staff earlier in the development process
- Improve the consistency of FDA policies and procedures both within and across divisions and over time
- Create more venues for collaboration with FDA
- Improve staffing levels and staffing continuity
- Accelerate guidance document development

Many efforts are underway within the FDA to accomplish the above, within existing resource constraints. We believe that success in the Critical Path Initiative will synergize with this work.

CONCLUDING THOUGHTS — A NATIONAL CRITICAL PATH INFRASTRUCTURE

To make the effort called for in this report a lasting one, we must reach beyond the specific opportunities in the Opportunities List.

Government, academia, and industry must work together to encourage support and development of the medical product development sciences. We need new ways of doing business—new training programs and career models for professionals who want to develop expertise in the sciences we use to demonstrate safety, effectiveness, and manufacturing quality—and new ways of working together to share information and remove scientific hurdles to effective product development. In short, we need to build a robust national Critical Path infrastructure.

The National Institutes of Health, through its Roadmap initiative, has identified certain large gaps in translational research, including investigation, training, and the need for specific funding of projects through which such research can be performed.[6] Implementation of the Roadmap Initiative will provide opportunities for advancing product development science. In addition, private foundations are also concerned with better funding of translational research (see Attachment for examples).

Academic Programs

Stakeholders consistently tell us that, today, few academic programs have the expertise needed to train product development professionals. There is a need for better trained physician-investigators, pharmaceutical scientists, pharmacokineticists, and for more training in statistics. Some call for an integration of quantitative skills into the medical school curriculum.

Some stakeholders point to the need for a new area of expertise in *experimental medicine*—new types of clinician-scientists, trained in the translational medicine and diagnostics that bridge the discovery and clinical R&D phases, and in clinical trial management.

Another key area of need is *animal physiology*. Stakeholders tell us that we need experts who understand how animal physiology data predict human responses, and we need clinician-researchers who can work effectively with both animals and humans.

[6] Zerhouni, E. A., "Translational and Clinical Science — Time for a New Vision," *The New England Journal of Medicine,* 353;15, October 13, 2005.

Career Models for Multidisciplinary Clinical Researchers

Many stakeholders note that, today, no clear models exist for people who want to develop a career bridging the basic sciences and clinical research. Those who manage to develop the unique combination of skills for this work often have difficulty finding an organizational home in research or R&D organizations. Better career options for people who want to work in this multidisciplinary environment are urgently needed. This work also calls for new kinds of multidisciplinary teams that may cross the lines of traditional academic departments or corporate divisions. The challenge is to define how such a team can come together and to create models for such collaborations.

New Collaborations

Many of the Critical Path Opportunities on the list cannot be accomplished by one entity alone. No single company, university, or governmental agency will have sufficient resources, expertise, or information base to undertake the work. We will need to develop new ways to collaborate and share data to accomplish our common goal of a robust Critical Path Infrastructure.

Biomarker Consortia

Qualifying a new generation of biomarkers (Topic 1) will require collaborative efforts to enable the pooling of resources, data, and expertise. Evaluation of a potential new biomarker often requires cross-disciplinary and cross-sector collaboration. Although pharmaceutical and device firms have generated extensive information on the performance of particular biomarkers in specific development programs, these data have not been pooled to allow an assessment of what is known about their overall performance.

Consortia organized around common areas of interest—disease-specific consortia, marker-specific consortia, and technology-specific consortia (e.g., to validate use of a new imaging technique as a biomarker)—could make significant contributions.

Similarly, consortia to pool data to identify rare side effects and safety signals or markers for organ toxicity are badly needed. For example, use of biomarkers to study organ toxicity during animal toxicology testing is a very promising area. New pharmaceutical

compounds are uniformly subjected to animal toxicology studies prior to human testing. This animal-to-human test sequence provides an ideal setting in which to evaluate the predictive value of new markers of organ toxicity. However, doing this will require setting up extensive collaborations among the private sector, academia, and government, as well as among scientists with expertise in the particular biomarker technique, animal toxicologists, and those performing clinical evaluations. Such consortia do not currently exist, and there is no ongoing mechanism for systematically evaluating novel toxicity markers in pharmaceutical development.

Activities ripe for collaboration also include compiling inventories of qualified biomarkers and their proven uses.

Building an Electronic Clinical Trial Infrastructure

Stakeholders recognize the logistical and resource issues involved in moving from current practices and computer systems to an electronic clinical trial environment that includes more standard data elements, forms, and formats (Topic 2). Many also recognize that the efficiencies to be gained far exceed the up-front costs and have been working with the Clinical Data Interchange Standards Consortium, Health Level 7, the FDA, and others to ensure that such standards meet the needs of all parties. Collaborative approaches will reduce the risk of re-tooling for a future of more efficiently administered clinical trials.

Creating a Bioinformatics Infrastructure

No one company, university, or governmental agency has the necessary information bases to create computer models sufficiently robust to accurately predict product safety and efficacy (Topic 3). Collaborative efforts will be needed to reap the benefits of model-based product development. Useful, but untapped, sources of data include publicly available data, and pooled and anonymized data from companies, FDA, and/or other parts of the Department of Health and Human Services.

New strategies for information sharing and safe information housing will be needed. New models for collaboration and data protection among industry, academia, and others could stimulate the creation of new consortia for turning information into knowledge.

The logistical, technical, and resource issues involved in intelligent mining of large data sets are real. To support such collaborations, stakeholders will need to address an array of technical issues, including determining how to access, organize, and ensure data quality, and the need for new IT systems and data exchange standards. Development of and consensus on database structure and content, algorithms, and data quality standards are necessary, but remain unexploited Critical Path opportunities.

Collaboration on Specific Diseases

Many stakeholders identify the absence of coordinated, collaborative plans to attack specific illnesses as a hurdle to product development. These stakeholders believe that if companies, patients groups, and providers engaged in long-term planning for developing therapies for specific conditions and worked together to implement those plans, product development would be both more efficient and effective.

For example, a very successful collaboration in the development of therapies to treat multiple sclerosis is underway at the Sylvia Lawry Centre for Multiple Sclerosis Research in Munich, Germany. See the Attachment for specifics on this program.

ATTACHMENT: EXAMPLES OF OTHER CRITICAL PATH-RELATED EFFORTS UNDERWAY

A number of efforts are underway worldwide to modernize the medical product development process and help move products from discovery to patient. The following brief summaries capture some of these efforts.

U.S. National Institutes of Health — Roadmap

The NIH Roadmap for Medical Research is a series of far-reaching initiatives designed to transform the Nation's medical research capabilities and speed the movement of scientific discoveries from the bench to the bedside. It provides a framework for the priorities the NIH must address to optimize its entire research portfolio and lays out a vision for a more efficient and productive system of medical research. Additional information about the NIH Roadmap can be found at *http://nihroadmap.nih.gov*.

On October 12, 2005, National Institutes of Health (NIH) Director Dr. Elias A. Zerhouni announced the most recent Roadmap initiative, a new program designed to spur the transformation of clinical and translational research in the United States so that new treatments can be developed more efficiently and delivered more quickly to patients. The Institutional Clinical and Translational Science Awards (CTSAs) program, unveiled in the October 12 issue of *The New England Journal of Medicine (NEJM)*, is designed to energize the discipline of clinical and translational science at academic health centers around the country. The grants will encourage institutions to propose new approaches to clinical and translational research, including new organizational models and training programs at graduate and post-graduate levels. In addition, they will foster original research in developing clinical research methodologies, such as clinical research informatics, laboratory methods, other technology resources and community-based research capabilities. Plans are to award four to seven CTSAs in FY 2006 for a total of $30 million, with an additional $11.5 million allocated to support 50 planning grants for those institutions that are not ready to make a full application.

NIH expects to increase the number of awards annually so that by 2012, 60 CTSAs will receive a total of approximately $500 million per year. Funding for the new initiative will come in part from the Roadmap budget and existing clinical and translational programs. This will be accomplished entirely through redirecting existing resources, including Roadmap funds. Possible benefits to be reaped from this effort include new home use medical monitoring devices; improved methods for predicting the toxicity of new drugs in specific individuals; and safer, more efficient clinical trials. A complete list of the NIH Roadmap initiatives is available at http://nihroadmap.nih.gov/initiatives.asp.

The European Union

The European Union supports research and development through multiannual Framework Programmes designed to enhance Europe's economic competitiveness. In the Sixth Framework Programme, running from 2002 to 2006, the EU included 2.4 billion euros to fund research in the life sciences, genomics, and biotechnology.

The European Commission's proposal for the Seventh Framework Programme, which will run from 2007 to 2013, includes a specific initiative to promote more effective drug development. This *Innovative Medicines Initiative* would create a new public-private partnership to undertake research to accelerate the development of safe and effective medicines. The new entity would be jointly supported by the EU and the European pharmaceutical industry. Its objective will be to remove bottlenecks hampering the efficiency of the development of new medicines and to promote European leadership in the pharma/biotech industries. Stakeholders have developed a strategic research agenda, focused in four areas:

- Prediction of safety
- Early indication of efficacy
- Knowledge management
- Education and training

Current plans foresee a total public-private investment of 440 million euros per year for 7 years. For more information on the Seventh Framework Programme, see the Web site at http://europa.eu.int/comm/research/future/index_en.cfm.

Sylvia Lawry Centre for Multiple Sclerosis Research, Munich Germany

The Sylvia Lawry Centre for Multiple Sclerosis Research has compiled the world's largest database of clinical information about multiple sclerosis. Pharmaceutical companies, clinics, and universities have provided data to the Centre free of charge from the placebo arms of clinical trials. Information from registries has also been included. Today, more than 20,000 patients (81,000 patient years) are represented in the database. This powerful Critical Path tool is now enabling innovative mathematical modeling of the course of the disease. The Centre is also partnering with Ludwig-Maximilian University in Munich to take advantage of the University's expertise in information science, mathematics, and medicine. Center projects include:

- Determining whether such models can provide the evidence base for potentially replacing some or all of the placebo arms of clinical trials with "virtual placebo groups" in future trials

- Using models to help identify the factors associated with the "point of change" in MS, at which an individual's disease changes from an intermittent to a chronic condition (today, this is considered unpredictable)

- Developing new study designs for all phases of clinical research

- Evaluating the use of MRI imaging to assess disease status

As with many Critical Path tools, this database may also provide the evidence base for significant improvements in treatment decisions, in particular, by helping providers select treatments and tailor regimens to the characteristics of each individual—personalized medicine. The Centre has a project underway to use the database to create evidence-based decision-making aids for selection of therapies for individuals.

C-Path Institute

The C-Path Institute (C-Path) is a non-profit 501(c)3 organization co-founded by the University of Arizona and Stanford Research Inst., (SRI) Intl., with input from the FDA. Goals are to accelerate the development of safe medical products and foster education and training in applied research and regulatory sciences. A memorandum of understanding (MOU) between the FDA and C-Path was executed on October 14, 2005, to serve as the framework for future collaboration. C-Path will bring together academic faculty, local clinicians and researchers, and scientific staff from SRI Intl., industry, patient advocacy groups, and others to accomplish projects of public health importance. C-Path can also serve as a *neutral ground* to bring together resources towards multiple goals in support of FDA's Critical Path Initiative.