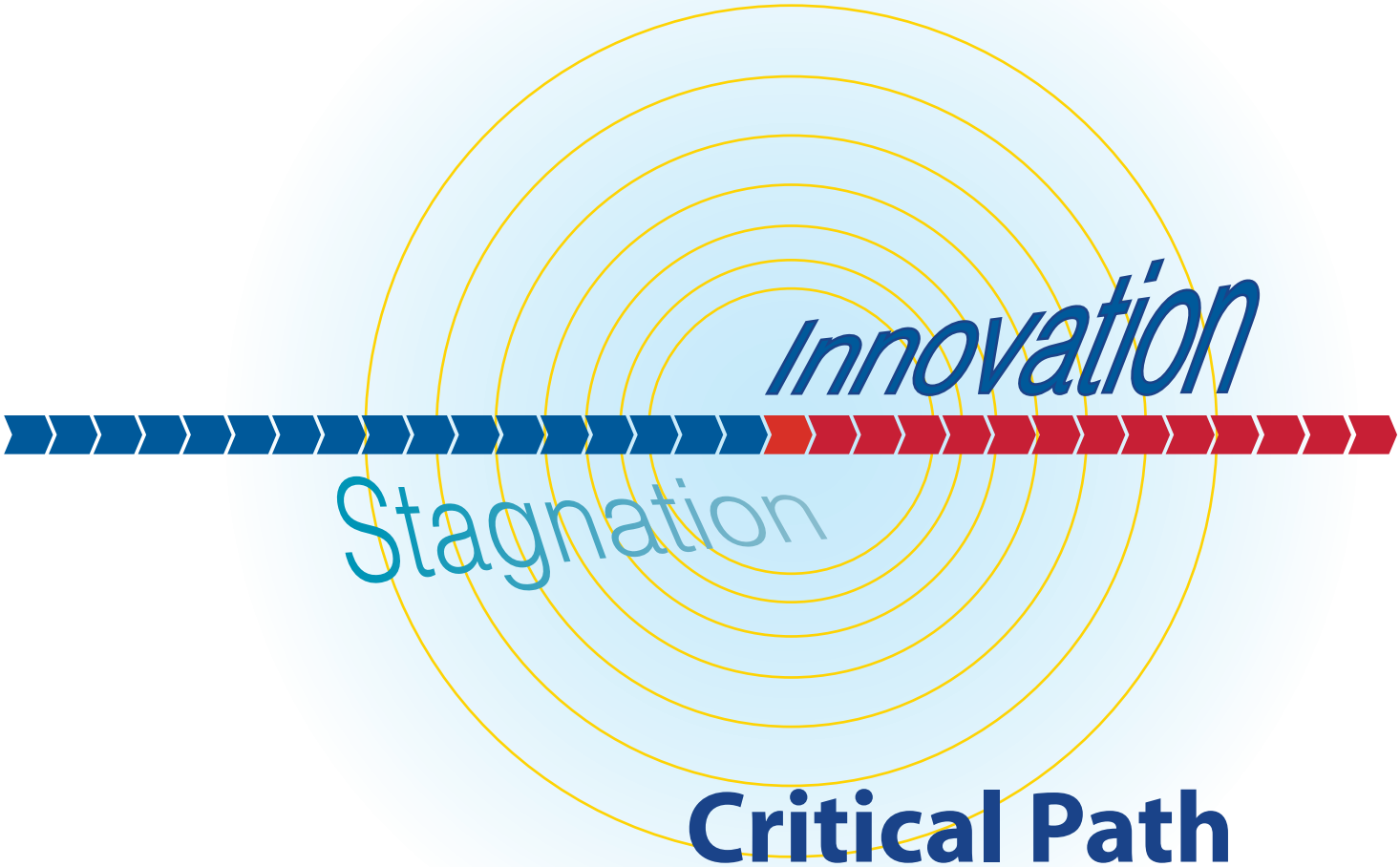

Critical Path Opportunities List

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

This report is divided into two parts. The first part of the report (the Critical Path Report and Opportunities List) discusses what has been learned about the opportunities and challenges along the Critical Path from stakeholders and FDA scientists since the publication in March 2004 of the FDA Critical Path Report. The second part of the report (the Opportunities List) presents specific opportunities that, if implemented, can help speed the development and approval of medical products. Both documents are available individually on the FDA's Web site (http://www.fda.gov/oc/initiatives/criticalpath/).

TOPIC 1: BETTER EVALUATION TOOLS

Developing New Biomarkers and Disease Models to Improve Clinical Trials and Medical Therapy

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Biomarker Qualification and Standards

1. Biomarker Qualification. The process and criteria for qualifying biomarkers for use in product development should be mapped. Clarity on the conceptual framework and evidentiary standards for qualifying a biomarker for various purposes would establish the path for developing predictive biomarkers. Stakeholders, including industry, researchers, and patient groups would have a clear idea of what needs to be done to adopt a new biomarker for regulatory use. Such a framework could stimulate biomarker development and, consequently, shorten the time necessary to develop a successful marketing application.

Identifying the framework and evidence needed to qualify biomarkers for different purposes would put an emphasis on correlative and predictive science to accompany the current emphasis on biomarker discovery. Consensus on the following types of questions is needed to put such a framework in place:

- How can biomarker evidence help demonstrate that a candidate product is not too toxic to test in humans?
- How can biomarkers be used to select dose ranges for initial human testing?
- How can biomarkers be used most effectively to evaluate dose response in later trials?
- What biomarker evidence is appropriate to guide selection of patients for clinical testing?
- What types and levels of evidence are needed to accept a biomarker as a surrogate endpoint for product efficacy?

Similarly, a framework for co-development of a drug and its partner diagnostic could promote biomarker development and facilitate integration of personalized medicine into clinical practice.

2. Standards for Microarray and Proteomics-Based Identification of Biomarkers. Microarray and proteomic technologies hold vast potential to identify biomarkers. However, a gap exists between technologies in use today and the technological level required for their application during product development and regulatory decision making. This gap results from the limited availability of accepted standards for demonstrating comparability of results, for data normalization and analysis, for validation of array results, or for biological interpretation of significant gene expression changes or mutations. Reference RNA samples that could be used to standardize biomarker results would improve the use of microarray technologies during product development, as would standards for RNA and DNA extraction methodologies and for RNA conversion and labeling. Standards for human tissue RNA and external RNA controls (sometimes referred to as *spikes*) are under development, but standards for the other steps associated with the analysis and interpretation of hybridization data still need to be addressed.

Qualifying Disease- and Disorder-Specific Biomarkers

Asthma

3. Role of Beta Adrenergic Receptor Polymorphisms in Asthma Treatments. In clinical trials of beta agonists in asthma patients, polymorphisms of the beta adrenergic receptor seem to predict short-term patient deterioration, but information on long-term consequences has not been developed. Studies to evaluate whether receptor status predicts long-term outcomes could help target treatment in this disorder (possibly to avoid serious side effects) and help sponsors develop and test new therapies.

Pregnancy

4. Measures of Effectiveness of Fertility Treatments. Although number of pregnancies and newborns can serve as rough measures of effectiveness, no reliable markers exist for ovulation induction (e.g., hormone levels, ultrasound determination of follicular development) or other potential predictors of successful pregnancy that could allow early assessment of therapy during product testing and early adjustment of therapy during treatment. Such markers could improve fertility treatment outcomes and reduce toxicity.

5. Markers of Effectiveness of Treatment for Pre-term Labor. Delay of delivery is the standard measure of the effectiveness of treatments for pre-term labor. But what duration of delay time improves fetal and maternal outcomes? Valid biomarkers would decrease the time needed to study potential therapies, reduce unnecessary risk to study subjects, and help physicians determine the best treatment duration for their patients.

Cardiovascular Biomarkers

6. Surrogate Outcomes for Cardiovascular Drug Eluting Stents. A statistical model for qualifying late loss in lumen diameter as a surrogate measure for cardiovascular drug eluting stent trials could facilitate the development of these products and enrich the understanding of their long-term effects.

7. Circulating Biomarkers in Cardiovascular Diseases. A large number of candidate biomarkers for cardiovascular diseases have been identified, but have not been proven useful for product development and regulatory purposes. For example, markers that identify patients at high risk for a cardiovascular event could rapidly improve trial efficiency for interventions intended to prevent such events. Trials could use biomarkers to stratify patient populations by risk status or to limit the study to high-risk patients. New markers that reflect tissue damage or acute inflammation (e.g., troponin sub-types, inflammatory cytokines) could help assess response to novel treatments more efficiently and aid in identifying products most likely to be successful in larger scale clinical trials.

Today, sponsors cannot reliably measure the effects of products intended to reduce inflammation in atherosclerosis without subjecting the patient to invasive procedures. This makes trial enrollment more difficult, increases patient risk and trial costs, and makes study of marketed products very difficult. Developing and qualifying a biomarker for these atherosclerotic inflammatory processes or other aspects of cardiovascular disease would improve innovation in a field affecting millions of Americans. Such markers could also be used in clinical practice to evaluate patient risk and to assist physicians and patients in developing treatment strategies.

Infectious Diseases

8. Proving the Efficacy of Preventive Vaccines. Proving the efficacy of preventive vaccines can be particularly costly, because of the need to study the disease-preventing effects of candidate vaccines in large numbers of subjects for long periods of time. If surrogate markers of protection, such as measurements of the immune response to vaccines, could be correlated with protection from disease, vaccines against influenza, SARS, West Nile Virus,

smallpox, hepatitis C, and parasitic infections could be developed more quickly and more cost effectively.

9. Markers of Disease Progression in Hepatitis C. Is Hepatitis C viral load in blood an accurate predictor of the pathologic changes and progression of liver disease in patients with Hepatitis C disease? How best can immune responses to the virus infection be distinguished from protective immunity due to vaccination for Hepatitis C? Progress toward more effective treatments and preventive vaccines for this disease could be enhanced with the development of a composite endpoint that includes serologic, virologic, and biochemical components.

10. Testing New Therapies for HIV Infection. Numerous therapeutic agents have been identified that may reconstitute immune function in patients with acquired immunodeficiencies; a serious barrier to their clinical development is the absence of well-understood markers of general immune competence that could predict clinical benefit. Preliminary evidence exists that host immune responses to immunization may serve as a valuable marker for evaluating immune-based therapy in HIV disease. A well-designed study testing the ability of a set of recall antigens and neoantigens to generate antibody responses and class I and class II MHC restricted T cell responses could identify markers that predict general immune competence in this population. Responses could be correlated with HIV viral load, a surrogate marker for clinical benefit in patients with HIV infection.

Cancer

11. Markers of Disease Progression in Prostate Cancer. There are no reliable biomarkers for disease progression in aggressive prostate cancer that have demonstrated utility in product development. Although prostate specific antigen (PSA) is used for a variety of purposes (e.g., determining when further diagnostic testing is indicated, assessing response to therapy), there is no consensus on how best to use PSA in cancer therapeutic trials. Uses of PSA that should be further investigated include identifying high-risk populations, providing an early marker of drug activity and dose range, and use of PSA as a marker of disease progression.

Other markers may also prove more predictive of clinical outcomes in some patients (e.g., alpha-methylacyl CoA racemase expression as a predictor of disease progression in local disease). A gap analysis to rigorously identify what is proven and unproven about PSA and other potential indicators would be an important first step to improving prostate cancer biomarkers.

12. Drug Targets as Critical Path Tools: Cancer Therapies. Many molecules are being explored as targets for cancer therapy. For example, sponsors are increasingly focused on activity profiles of groups of such molecules associated with aberrant signaling in the proliferation and survival pathways recognized to be disturbed in many types of cancers, such as the SRC pathway and the P13K/Akt pathway. Similarly, cell surface antigens are being explored as targets. Diagnostic tests evaluating the status of therapeutic targets may prove to be useful markers to predict responsiveness to therapy. Availability of markers assessing the status of therapeutic targets would make development of targeted cancer therapies more effective and efficient.

Neuropsychiatric Diseases

13. Diagnostic Markers for Neuropsychiatric Conditions. Today, diagnosis of psychiatric disorders is based on symptom presentation. For example, there are no diagnostic tests to distinguish an initial presentation of depression from the onset of bipolar disorder or other conditions, or to differentiate various subsets of the autism currently joined under the rubric of pervasive developmental disorders. Identification of such markers would improve clinical trials by making it possible for sponsors to enroll only those patients with the target condition. Similarly, any successful treatments could better target a patient's disease in clinical practice. If specific aspects of mental disorders could be better quantitated, sponsors could test therapies targeted to a particular patient's constellation of symptoms. For example, now that the MATRICS test battery for assessing cognitive impairment in schizophrenia has been developed, we expect to see applications for drugs targeted to improving the cognitive component of this disease. Such targeting would both improve the efficiency of trials and serve to better individualize therapeutic approaches.

Presbyopia

14. Clinically Relevant Measures for Efficacy of Accommodating Intraocular Lenses. Presbyopia correction is currently limited to static devices (e.g., bifocal and reading glasses). The ophthalmic community is currently investigating methods to correct presbyopia by restoring active visual accommodation. However, current measurements of accommodation are subjective and unreliable. Identification of objective measures appropriate for clinical trials would improve sponsors' ability to evaluate the effectiveness of devices for the correction of presbyopia and allow reduced subject testing time.

Autoimmune and Inflammatory Diseases

15. Markers of Disease Activity in Systemic Lupus Erythematosus, Inflammatory Bowel Disease, and Related Diseases. Development of new therapies for these diseases has been hampered in recent years by a lack of reliable markers of disease activity that can be used to predict clinical benefit. Development of predictive biomarkers and accepted clinical outcome measures would help in the evaluation of needed new therapies for these diseases.

Safety Biomarkers

16. Predicting Adverse Reactions to Vaccines. Work to identify biomarkers that predict the development of adverse reactions to vaccines, such as autoimmune disease following therapeutic cancer vaccines, could speed the development of these therapies. Similarly, identification of biomarkers that predict the risk of developing enhanced disease following use of certain vaccines, such as SARS, could make such therapies more attractive to product developers.

17. Early Indicators of Effects of Immune Responses on the Safety of Cell and Tissue Products. The potential for these products to prevent or treat diseases is exciting and vast. With this potential benefit comes the risk of an immune response that reduces product efficacy and/or stimulates autoimmune disease. Years of product development can be wasted if a product triggers a detrimental immune response when finally tested in animals or humans. Better and earlier predictors of this undesirable immunogenicity would help unlock the potential of cellular and tissue products, by helping sponsors invest in product candidates least likely to trigger an unwelcome human immune response.

18. Predicting Cardiac Toxicity. New tools for early identification of cardiac toxicity would improve product development for a wide array of conditions. Research investments that could produce tangible benefits quickly include creation of an ECG library from clinical trials that could be used for identifying potential early predictors of cardiac risk.

19. Gene Therapy. Several gene therapy products have been successfully used in early human testing to treat severe diseases, including life-threatening inherited immune deficiencies. However, the future of these products is at risk due to the demonstrated potential for carcinogenesis. Biomarkers to predict the general risk or patient-specific risk for cancer and work to reduce these risks could improve product performance in long-term safety studies of these therapies.

20. Modernizing Predictive Toxicology. Identifying preclinical biomarkers that predict human liver or kidney toxicity would speed innovation for many different types of therapeutics.
Activities to develop genomic biomarkers for the mechanistic interpretation of toxicological observations—complementary to but independent of these classic toxicological observations—could begin to create the data foundation for qualification of new safety biomarkers. Collaborations among sponsors to share what is known about existing safety assays could be a first step toward the goal of safer medical products.

Advancing the Use of New Imaging Techniques

21. Performance Standards for Imaging Displays. The ability to use imaging results as biomarkers would be enhanced by development of standards and performance assessment methods for displays used by newer imaging devices. Compared with older imaging technologies, the displays used by today's digital imaging technologies are complex; in some cases, they are miniaturized to facilitate remote and portable viewing. Common criteria that can assess the performance of multi-dimensional display devices for the presentation of dynamic volumetric image sets with color coding would enhance the understanding of and confidence in imaging results.

22. Using Medical Imaging as a Product Development Tool. A key hurdle to using imaging as a biomarker in clinical trials is lack of standard protocols for using imaging technologies, ranging from patient positioning to instrument calibration to the settings used for particular images. As a result, sponsors and others cannot compare imaging results across trials, sometimes not even within a trial. This also means it is difficult or impossible to compile data needed to demonstrate that a particular technique correlates with clinical course sufficiently for use as a biomarker. Standard, publicly available, protocols for use of imaging in clinical trials would enable the development of biomarkers for a wide array of conditions.

23. Imaging Biomarkers in Cardiovascular Disease. To advance efficient development of new therapies, new imaging techniques are needed to measure progression and treatment of cardiovascular disease. Examples include the potential use of intravascular ultrasound (IVUS), MRI, or multi-slice CT in the assessment of atherosclerosis progression and volumetric measures of cardiac function in trials of congestive heart failure. Development of these techniques for measuring progression will require a complete analysis of the current state of knowledge of the imaging modality, standardization of the technical aspects of the measurement, and performing the trials necessary to evaluate the degree of correlation with clinical responses.

24. Imaging Biomarkers in Arthritis. Targeted research could identify how to apply MRI technologies to measure the effects of potential therapies on cartilage and joint soft tissue for rheumatoid arthritis and osteoarthritis. In this regard, MRI has demonstrated promise for detecting soft tissue inflammation and cartilage erosion in rheumatoid arthritis. If established as a reproducible biomarker, use of MRI could help determine the potential of a new therapeutic product, identify dose ranges, and stratify patients by risk while serving as an early response measure.

25. Imaging Biomarkers in Neurocognitive Diseases. Currently, therapeutic trials in chronic neurologic disorders, such as Parkinson's disease and Alzheimer's disease, rely on symptomatic endpoints that may require observation over many years to evaluate progression. Functional imaging, such as FDG-PET as a measure of glucose metabolism, may provide a biomarker to assess earlier, more subtle, changes in the progression of these diseases. Studies would be needed to determine how these markers correlate with symptomatic progression. Focused efforts to apply new imaging techniques as diagnostic and response measures in neurocognitive disorders and depression could also produce new ways to monitor treatment of these conditions. For example, quantitative MRI measurements as well as amyloid content assessments by PET scan may be useful imaging techniques to demonstrate the effect of potential Alzheimer's therapies. Imaging markers that provide information on early disease states could make prevention trials more feasible. These approaches have not yet been proven clinically meaningful, however, and, in many cases, there is no consensus on the most promising approach.

26. Imaging in Cancer. Cutting edge imaging techniques hold vast potential for tumor staging and assessing response to therapy. The list of promising biomarkers in need of qualification is long. For example, it is possible that one additional, well-designed study could qualify FDG-PET as an additional response measure in non-Hodgkins lymphoma, thus creating a new tool that improves both product testing and treatment decisions. Similar opportunities exist for other tumor types.

27. Imaging in Chronic Obstructive Pulmonary Disease. High-resolution chest computed tomography may be a useful assessment of disease progression in chronic obstructive pulmonary disease where emphysema is a prominent component, especially the disease associated with alpha 1 anti-trypsin deficiency. Although data to date suggest that high-resolution CT (HRCT) can offer reliable assessment of underlying lung structure in fewer patients and for shorter periods of time than would be needed to show a difference in lung function testing or in mortality, it remains unclear if changes in HRCT meaningfully predict change for the patient. It also is unclear what level of change in the HRCT parameters could be considered significant in terms of disease modification. The ability to use HRCT demonstration of disease modification as an endpoint in clinical trials could pave the way for new product indications that are now infeasible due to the rarity of alpha 1 anti-trypsin deficiency and the trial size and duration needed to show an effect using traditional endpoints. New trials, perhaps with innovative designs, are needed to evaluate the use of imaging techniques in rare conditions.

28. Noninvasive Therapeutic Monitoring. Today, the distribution of a drug in the human body is typically evaluated by measuring its concentration in the blood, which may not accurately reflect distribution to the target tissue (e.g., an infected bone, a tumor, or a malfunctioning organ). Noninvasive means of monitoring drug concentration, for example, using molecular tags that can be located through imaging techniques, could dramatically improve product development by enabling sponsors to correlate response with drug availability at the target site and to evaluate the relationship between organ toxicity and drug distribution to that organ.

29. Imaging Implanted Devices. *Practice guidelines* should be developed that outline the nature and frequency of imaging needed to follow the on-going safety and efficacy of an implanted device, when to suspect a problem, and what confirmatory tests are recommended. Such guidelines could not only improve patient safety but could also produce pooled data to inform premarketing development and testing of the next generation of implanted devices. (*Practice guidelines* are developed by professional associations on specific topics to help healthcare professionals make treatment decisions.)

Improving Predictions of Human Response from Disease Models

30. Improving Extrapolation from Animal Data to Human Experience. We urgently need new methods to bridge from animal data to predicted human experience, for both product efficacy and for product safety. The need is particularly acute for situations in which it is unethical to conduct human tests (e.g., therapies against bioterror agents). Establishing reliable correlations between animal pharmacokinetic/pharmacodynamic data and human outcomes would dramatically improve the safety of human testing and treatment and the ability of sponsors to invest in only those candidate products most likely to be effective in humans. Conversely, re-examination of existing data could identify features of preclinical studies that were not predictive of human response. We especially need more predictive preclinical models for therapies that use innovative delivery mechanisms (e.g., image guided interventional therapies, or local delivery of therapy via percutaneous catheter) and for combination therapies.

31. Better Model of Wound Repair. The lack of a reliable animal model for human wound healing is a significant hurdle to developing new wound repair products.

32. Better Animal Disease and Tissue Injury Models. Better animal disease or tissue injury models could provide more accurate predictions of the toxicity of drugs, devices, and biological products that are used in ill or injured patients. Use of such models could also enhance our understanding of the potential toxic effects of compounds associated with many types of medical devices (some devices may expose patients to sterilants, disinfectants, plasticizers, and metals).

33. Better Disease Models for Predicting Biological Product Toxicity. Better predictive disease models to support the development of more quantitative cellular, or molecular, toxicity testing paradigms for product safety evaluation would improve development of many biological products. For example, development of an in vitro cell-based system to evaluate and predict the toxicity of hemoglobin-based oxygen carriers would help identify some of the serious safety issues surrounding these products.

TOPIC 2: STREAMLINING CLINICAL TRIALS

Creating Innovative and Efficient Clinical Trials and Improved Clinical Endpoints

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Advancing Innovative Trial Designs

34. Design of Active Controlled Trials. Many clinical trials compare two or more active therapies, rather than comparing an active therapy with placebo. This design is being increasingly used as more therapeutic choices become available. When treatment options exist, it may be unethical or infeasible to ask patients to take a placebo. Today, there is confusion regarding key statistical issues underlying design and analysis of active-controlled trials. In placebo controlled trials, the question is whether the active treatment is highly likely to be superior to placebo.

In active controlled trials, the question is often whether the new treatment is highly unlikely to be inferior to the comparator. Such trials are called non-inferiority trials. Statistical methods for demonstrating non-inferiority can be challenging. We need to reach agreement and clarify appropriate statistical methods and standards for such trials to facilitate product development in a wide array of conditions for which non-inferiority trials are used. Issues that need clarifying include:

- How should the confidence interval for demonstrating non-inferiority be determined?
- What data should be used to estimate the effect of the control agent (e.g., all prior studies?) How should they be weighted?
- What drugs should be included as the active control? How should inconsistent results (i.e., size of treatment effect) from prior studies of the active control be approached?
- What are appropriate sample size requirements in non-inferiority and active-controlled studies?

Non-inferiority trials rely in part on prior studies to estimate the assumed treatment effect of the comparator. In some conditions, however, only a single trial is required for drug approval. This is often the case for new cancer therapies. New methods for conducting non-inferiority trials are needed for cases when prior data are insufficient to estimate the effect of a therapy. For example, it might be possible to use biomarker data to circumvent some of these difficulties.

35. Enrichment Designs. If biomarkers can reliably identify individuals with a high probability of response to a therapy, trials could focus on such patients. Conducting a trial in a potential high-response subgroup is called *enrichment*. Enriched trials have greater power and could result in therapies targeted at those most likely to benefit. Enrichment raises some difficult issues:

- How will data on the marker status of potential trial enrollees be used in trial design?
- How much data are needed on the un-selected population?
- What types of retrospective subset analyses are valid (e.g., what can be reliably learned from subgroup analyses that were not prespecified in the original trial design)?

36. Use of Prior Experience or Accumulated Information in Trial Design.

<u>Adaptive Trial Design</u>

Stakeholders are looking for clear rules on when it is valid to make changes to a clinical trial protocol, based on early or interim study results, when unblinded treatment results may be known.

Consensus and clarification is needed on questions such as:

- When can extra trial arms be dropped?
- When can an early marker be used to choose which treatment to carry forward or to choose a subset for analysis?
- When is it valid to modify randomization based on results, for example, in a combined phase 2/3 cancer trial?
- When is it valid and under what situations can one stage or phase of a study be combined with the second stage or phase?

Non-Frequentist Methods

Statistical techniques that allow for increased reliance on historical data, under assumptions and models that can be justified, might be used to develop predictive inferences. The use of these techniques in product development holds promise, but work remains to adapt and qualify such methods for use to answer specific product development questions for both clinical and preclinical applications. For example, we urgently need to improve use of animal data to predict human experience (see Opportunity 30). Many believe that Bayesian and similar non-frequentist statistical methods that use empirically derived prior information and models to develop predictive probabilities could provide a basis for supplementing the traditional methods for human equivalent dose calculations and for maximizing the usefulness of data derived from animal safety and efficacy studies.

37. Development of Best Practices for Handling Missing Data. All clinical research studies experience some level of subject attrition, ranging from a few patients to more than half of the study subjects. When patients are lost to follow-up, an intent-to-treat analysis requires imputation of missing data. Depending on the extent of the imputation, the validity of the trial results can come into question, causing delays and possibly unnecessary failures. There is increasing dissatisfaction with one common approach, Last Observation Carried Forward (LOCF), and broad agreement that alternatives are needed. Evaluation of different analytical approaches (e.g., testing potential alternative to LOCF against existing data sets) and development of consensus on how to impute missing data in a variety of different situations would enhance efficiency of product development in nearly every therapeutic area.

38. Development of Trial Protocols for Specific Therapeutic Areas. Consensus on trial designs that are tailored to specific diseases or conditions (e.g., how to select participants, structure of the trial, outcome and endpoint measures, duration) would facilitate development. For example, new clinical trial designs and end-points for age-related macular degeneration therapy trials could unleash innovation in this area of unmet medical need. Some suggest that it will be possible to develop a library of standard disease-specific trial protocols. For example, the assessment of drugs for their abuse liability is an important societal and development concern and requires the conduct of specific clinical trials. The available data need to be reviewed and discussed to develop guidance on the best ways to conduct those trials.

39. Analysis of Multiple Endpoints. In many diseases, more than a single efficacy endpoint may be of importance. Stakeholders are looking for clarification on appropriate statistical methods for handling multiple trial endpoints. Key issues include the statistical implications of requiring success on more than one endpoint, appropriate statistical adjustment when endpoints are correlated, and handling of secondary endpoints. Stakeholders are also looking for clarification of appropriate methods for sequential analyses of endpoints.

Improving Measurement of Patient Responses

40. Measuring Disease-Related Symptoms. For many diseases, it is possible to measure a variety of important indicators, but there are no rigorous or standard measures of disease symptoms. As a result, important information about patient response may be poorly captured and described. For example, standardized outcomes and endpoints are needed for symptomatic gastrointestinal disorders, psoriasis, and atopic dermatitis. Pain scores are needed for abdominal disease, irritable bowel syndrome, and endometriosis.

41. Measuring Patient-Centered Endpoints. Identifying endpoints of value to patients and integrating them into clinical trials would make trials more effective by improving the connection between trial results and clinical improvement. Today, however, it is often unclear which signs and symptoms matter most to patients and, in many cases, there are no standard agreed-upon scales to measure patients' preferred endpoints. This issue has been raised for diseases ranging from Parkinson's disease to COPD to lung cancer. More rigorous methods for determining and measuring patient priorities in clinical testing would provide more pertinent information than the broad measures of quality of life typically used today.

42. New Trial Design in Oncology. Most cancer trials identify and test the maximum tolerated dose, to maximize efficacy. Such trials cannot answer key questions about dose/response relationships: Do blood levels of drug relate to outcomes? At what dose does the response plateau? Because survival is often their primary endpoint, cancer trials are not designed to identify potential response measures that change early in treatment. New trial designs that allow a better understanding of concentration response, as well as early indicators of response, could improve the safety of both cancer trials and cancer therapy.

43. Improving Efficacy Endpoints for Infectious Diseases. Typically, to determine whether an antibiotic or vaccine is effective against a particular pathogen, the presence or levels of the infectious agent in the patient are followed. However, the presence of a pathogen does not always correlate with illness, and the purpose of some vaccines is to arrest the disease process, rather than prevent infection or clear the infectious agent. For many infections, there is no consensus on what patterns of symptoms define the disease. Therefore, it is difficult to measure how an experimental product affects the disease. Consensus on what changes in symptoms could constitute a benefit in the treatment of infectious disease and how to measure them would significantly improve efficacy endpoints in clinical trials of agents that target certain infectious diseases. Similarly, studies of the natural history of specific infections could provide reliable data on the likely length of the infections to help sponsors design trials in which efficiency endpoints can be measured sooner.

Streamlining the Clinical Trial Process

44. Development of Data Standards. Currently, clinical investigators, clinical study personnel, data managers, and FDA reviewers must cope with a plethora of data formats and conventions. Some clinical investigators report the presence of many different computer systems for data entry at their sites (for various trials), each of which uses different data conventions. Lack of standardization is not only inefficient, it multiplies the potential for error. Important standards work is underway, but much remains before the promise of shared data standards for clinical trials is realized. CDISC is paving the way by developing its Study Data Tabulation Model for describing observations in drug trials.[1] That model could someday encompass observations needed for other types of trials. Health Level 7 and CDISC are working to create standards that can be

[1] For more on CDISC (the Clinical Data Interchange Standards Consortium), see http://www.cdisc.org/.

used for the exchange, management, and integration of electronic healthcare information to increase the effectiveness and efficiency of healthcare delivery.[2] In addition to improving and expanding the Model, sponsors and the FDA must undertake the hard work of retooling hardware and software to apply the new standards. This retooling includes training researchers to collect and FDA reviewers to expect data in these formats. Standardizing data archiving conventions would also enable the creation of shared data repositories, facilitating meta-analyses, data mining, and modeling to improve clinical trial design and analysis.

45. Consensus on Standards for Case Report Forms. Clinical trial data collection, analysis, and submission can be inefficient and unnecessarily expensive. A wide array of different forms and formats are used to collect clinical trial information, and most data are submitted to the FDA on paper. Differences in case report forms across sponsors and trials creates opportunities for confusion and error. Standardization of the look and feel of case report forms could reduce these inefficiencies and also help accelerate progress toward electronic data capture and submission.

[2] See also http://www.hl7.org/.

TOPIC 3: HARNESSING BIOINFORMATICS

Data Pooling and Simulation Models

46. Identification and Qualification of Safety Biomarkers. Collaborative efforts to pool and mine existing safety and toxicology data would create new sources for identification and qualification of safety biomarkers. For example, a robust database of preclinical and clinical data on cardiac arrhythmic risk could help us understand the clinical significance of QT interval prolongation, reduce the need for clinical studies, and, possibly, help identify individuals who are at risk for this side effect. Similarly, evidence-based simulation models of drug metabolism that correlate preclinical and clinical toxicity, and new criteria for use of such models, would enable sponsors to make smarter dose selection decisions for clinical trials and promote development of more predictive safety biomarkers.

47. Virtual Control Groups in Clinical Trials. Databases, models, and/or imaging collections could be used by multiple sponsors across different product types as historical controls to reduce the necessary size of control groups in clinical trials. This approach would be of particular benefit to product development for rare disorders when sponsors cannot find a large number of patients to study. These techniques would also be of special benefit in instances when use of placebos is infeasible or unethical. Trusted third parties could be used to hold data or images and create an open source library. For example, today it is impossible to test a new drug as monotherapy in epilepsy. Patients need to maintain existing therapies, so new therapies can only be studied in combination with existing drugs. Use of historical controls might enable sponsors to demonstrate effectiveness of a new drug as monotherapy if the data could be assembled and rigorously analyzed.

48. Adverse Event Data Mining. Combining adverse event data related to a product, a class of products, or a disease could enable identification of previously undetected patterns of safety events and/or comorbidities and could elucidate drug-drug interactions. This knowledge could then be applied to investigational products to better avoid known safety pitfalls.

49. Multiple Complex Therapies. Pooled data on the effects of combined use of complex technologies—for example, multiple implanted devices, microwave therapy to coronary vessels followed by a stent, or radiation therapy in a person with an implanted device—would create information that would improve both patient safety and new product development.

50. Modeling Device Performance. A rigorous model of specific aspects of human physiology could allow more predictive in-silico (computer-based) testing of implanted devices, prior to human testing. Such models could also yield information about the likely long-term performance of implanted devices to identify problems that may occur beyond the time periods studied in clinical studies and could answer current questions about device failures. Simulation technologies that model the physiological environment and dynamic forces acting on an implanted device could also provide information to bridge gaps in knowledge when clinical testing is difficult, such as with pediatric populations. For example, computer modeling of pediatric cardiac physiology could streamline development of devices for this population.

51. Clinical Trial Simulation. Clinical trial simulation—using in silico modeling—can predict efficient designs for development programs that reduce the number of trials and patients, improve decisions on dosing, and increase informativeness. Clinical trial simulation requires the development of a disease model, with subsequent integration of information on the investigational product. Such models could also help refine some of the innovative trial designs described in Topic #2, above.

Stakeholders are looking for first steps, such as identification of tools and best practices.

52. Failure Analysis. Development of a public database of information from trials of unsuccessful products could allow identification of patterns associated with failure and help sponsors avoid repeating past mistakes. Failure analysis is a routine and rigorous aspect of engineering and other applied sciences. Combining efforts to learn more about the causes of problems—using anonymized, safe harbor methods—would provide the best opportunity to create useful generalized knowledge.

53. Natural History Databases for Rare Diseases. Many rare diseases are hard to study due to both the difficulty in enrolling subjects and the long duration of clinical trials. Databases recording the natural history of patients with rare diseases, incorporating observations on clinical progression and biomarkers, could assist in creating disease models and better designing clinical programs and, possibly, contribute virtual historical control groups

TOPIC 4: MOVING MANUFACTURING INTO THE 21ST CENTURY

Manufacturing, Scale-up, and Quality Management

Manufacturing Biologics

54. Improving Manufacture of Influenza and Other Vaccines. The use of poultry eggs to produce influenza vaccine has been associated with a variety of public health problems, ranging from limitation on vaccine supply (due to the process needed to grow vaccine stock in eggs) to product contamination. A well-characterized and publicly available library or banks of cell lines certified to be free from adventitious agents, known to remain genetically stable, with documented low risk for tumorogenicity, and known to grow easily for scaled-up manufacture would resolve this key hurdle to innovation in development of cell-based influenza vaccines. Such a cell bank would also promote more efficient development of other biological products, including therapeutic protein products, gene therapy products, and other types of vaccines.

55. Characterizing Cell Therapies. Cell therapies hold tremendous promise for treating an array of conditions, ranging from heart muscle disorders to brain disease. To date, there are no cell therapy biomarkers that accurately establish the essential characteristics of cord blood stem cells used to treat cancer and radiation injury, pancreatic islet cells used to treat diabetes, and cardiac cells derived from stem cells for treatment of heart disease. Additionally, cell therapies present special safety concerns. For example, there is risk that the administered cells will migrate to the wrong tissue, or settle into the right tissue but over time develop into cancer cells. Scientific tools are needed to better characterize the cells to ensure that cell therapies will reliably travel to and stay in the appropriate tissue and will develop into normal healthy cells.

56. Novel Approaches to Characterizing and Standardizing Biological Products. New methods of measuring the physical characteristics of biological products, such as nuclear magnetic resonance, x-ray crystallography, and/or mass spectroscopy could be used to provide a link between the physical characteristics measured by these tests and the clinical outcomes. Today, these techniques remain underused, pending scientific and consensus development work to understand how physical characteristics predict the purity and performance of biological products.

57. Detecting Contamination in Biological Products. A significant scientific hurdle in developing biological products is contamination with undesirable infectious agents, because the product is developed from living organism sources that may harbor these pathogens. To demonstrate that the product is safe for human use, sponsors must be able to detect contamination from viruses, bacteria, and other organisms that are found in living organisms (e.g., the prion agent of *mad cow* disease). New microarray technologies hold promise for detecting contamination—deliberate or accidental—of biological products. But more work needs to be done in this important field.

58. Enabling Manufacturing Changes for Well-characterized Proteins. Currently, production scale-up can be a rate-limiting step in the development of investigational proteins. New tools are needed to predict and assess the effect of manufacturing changes on product performance and to assess comparability to product made using previous processes. Availability of such tools could improve

development efficiency and early patient access to investigational proteins.

59. Tissue Engineering. A key hurdle holding back innovation in tissue engineering is the difficulty in sufficiently characterizing a finished product to enable development of meaningful quality controls and release specifications. Often, conventional techniques, such as simple cell morphology, used to evaluate cell characteristics cannot be applied to these products because, for example, the engineered product may also include nonbiological materials (e.g. a support matrix). Consensus on how to assess these products and ensure manufacturing consistency would give product sponsors the predictability they need to unlock innovation in tissue engineering.

60. Vaccine Potency. Improved, more quantitative and reliable non-animal based tests of vaccine potency would assist in development of vaccines for conditions such as rabies and smallpox.

Manufacturing Devices

61. Device Interaction with Blood Flow. Better predictive modeling of the shearing forces and rate of thrombosis caused by implanted devices would enable innovation in physical design and materials.

62. Development of a Biocompatibility Database. A publicly accessible database of the biocompatibility profile of materials used in the design and manufacture of implanted medical devices would facilitate continuous improvement in design of these products.

Manufacturing Drugs

63. Identifying Safety Effects of Excipients. Inactive ingredients in drugs have been identified as the cause of safety problems and, in some cases, have stalled progress or caused product development to fail. Earlier studies of the safety effects of excipients would allow sponsors to identify problems before making significant investments in testing a particular formulation.

64. Manufacturing Novel Dosage Forms. Examples of novel dosage forms include patches, liposomes, topicals, and nasal and pulmonary inhalers. Such products are developed to target delivery of drugs, improve compliance and ease use for patients, and deliver drugs that are difficult to formulate. It can be difficult to assess the quality of a manufactured product. For example, extracting a drug from patch products for quality assurance analysis can cause changes in the product. Aerosol quality is affected by difficult-to-measure characteristics such as spray density. New methods and testing instruments for consistent manufacture of such products are needed. Similarly, existing analytical techniques are often not designed to assess the quantities or forms of drugs found in some drug-device combination products.

65. Developing Standards for Spectroscopic Instruments. A number of rapid, noncontact, nondestructive, data-rich analytical methods that are new to drug manufacture could be more widely used if accepted scientific standards to ensure proper operation of instrumentation were developed. For example, studies to identify appropriate instrument qualification and calibration standards for new techniques such as Raman and Terahertz spectroscopy—to specify both a suitable set of material samples along with a corresponding set of specifications determined by a common statistical procedure—could dramatically improve manufacturing quality and predictability.

Nanotechnology

66. Characterizing and Qualifying Nanotechnologies. Nanotechnology holds huge promise for the design and manufacture of many types of novel medical products—from devices to therapeutics to combination products. There remain, however, a number of questions about the behavior of nanoparticles and the potential effects of products containing nanoparticles once they are introduced into complex human physiology. We need to better understand the physical and chemical characteristics of different nanomaterials, and we need new test methods, characterization protocols, and standards so sponsors can efficiently move nanoproducts from preclinical through clinical development, to commercialization.

TOPIC 5: DEVELOPING PRODUCTS TO ADDRESS URGENT PUBLIC HEALTH NEEDS

Rapid Pathogen Identification

67. Improving Anti-Microbial Product Testing. New scientific technologies hold the potential for developing rapid, point-of-care tests for pathogen identification. These technologies could also improve the speed and accuracy of resistance testing. Use of rapid diagnostic tests (either a single test or a panel of tests) could greatly improve the efficiency of clinical trials for infectious diseases.

68. Screening Donated Blood and Tissue. Research to adapt these new technologies for rapid pathogen identification would also facilitate the development of novel screening tests for biological products. Of particular interest in screening donated blood and tissue are technologies that can perform rapid analysis for multiple organisms, on smaller quantities of blood and tissues. In a public health emergency involving infectious agents, such screening tools would be a key bulwark against the risk of inadvertent or deliberate transmission of infection to recipients of donated blood and tissues.

Better Predictive Disease Models

69. Animal Models to Test Bioterrorism Countermeasures. Today, limited animal models exist for determining biological activity of anthrax lethal toxin, and those that are available have questionable relevance to the mechanism of action of this virulence factor in humans. A nonhuman primate model for testing the efficacy and safety of antibiotic treatments and vaccines against inhaled anthrax—the most likely route of exposure to this agent in the case of a bioterror attack—would facilitate development of such products. New animal models more appropriate to the human condition also are needed for smallpox infection, radiation injury, and SARS.

70. New Small Animal Models for Vaccine Testing. Developing new small animal models to replace current primate models would greatly facilitate the development of vaccines for potential bioterror agents and emerging or re-emerging infectious disease (because many primate models are expensive and have not been qualified). Of particular interest are new small animal models that predict the neurotoxicity of vaccines.

71. New Tissue Models. Before a product is tested in animals, it is tested in living cells in the laboratory. A major hurdle facing the development and evaluation of vaccines for emerging viral diseases, such as West Nile virus, SARS CoV virus, and smallpox virus, is the lack of a tissue culture assay that quantitatively measures and reliably predicts the protective immune response to candidate vaccines. Similarly, better cell culture systems to study the hepatitis C virus are needed to improve progress toward a hepatitis C vaccine.

TOPIC 6: SPECIFIC AT-RISK POPULATIONS — PEDIATRICS

Unlocking Innovation in Pediatric Products

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72. Better Extrapolation Methods and Best Practices in Pediatric Trial Design. Pediatric product testing often begins with extrapolating safety and efficacy data from adult experience to determine the dose and administration schedule to be tested. During the past several years, a substantial number of pediatric trials have been conducted using this approach. If the data from those trials could be compiled into a database for quantitative analysis, sponsors could exploit past experience to assess the accuracy of different methods of extrapolation and reveal the most effective methods. Analysis of such a database could reveal best practices for other aspects of pediatric trial designs as well, enabling sponsors to avoid repeating less useful or inefficient trial designs. As a result, fewer children would be exposed to unnecessary or suboptimal clinical studies.

73. Drug Metabolism and Therapeutic Response. It is likely that differences in drug metabolism among adolescents affect their responses to antidepressant drugs. With improved knowledge, sponsors could tailor drug doses being tested to the study participants according to their drug metabolic genotype. The hard work of identifying specific genetic polymorphisms and signals in children and teens that predict a heightened risk for adverse events or nonresponse to treatment is in the early stages. Improving dosing could reduce side effects and increase successful outcomes.

74. Diagnosing Depression Subtypes. Many scientists and clinicians believe that depression (including adolescent depression) is not a single disease, but a collection of several related but biologically distinguishable conditions. However, there has been little success in furthering our understanding of the genetic/physiologic basis of depression. Better clinical definitions of depressive subtypes, along with better tools for classifying individuals, should help in achieving the goal of developing treatments targeted to the adolescent's particular syndrome. For example, advanced imaging techniques targeting neurotransmitter activity may be able to identify depressive subtypes. Unfortunately, the best first steps toward this mechanistic understanding of depression have yet to be identified.

75. Animal Models for Maternal Vaccines. In the first few weeks of life, infants may be exposed to respiratory syncytial virus, group beta hemolytic streptococcus, and E. coli bacteria. Even if a vaccine existed, several weeks are required post-vaccination to develop a protective response, leaving infants at risk during that time. One approach to this public heath issue would be safe and effective maternal vaccination, in which the pregnant woman develops a protective antibody response that is transferred to the fetus through the placenta or to the infant through breast-feeding. Obvious fear of the risks of exposing a fetus to vaccines and the associated immune stimulation have limited development of such approaches. Development of animal models to evaluate the safety outcomes of maternal vaccination on infants could unlock innovation and eventually lead to products that reduce illness and death due to infant infections.

76. New Therapies for Juvenile Diabetes. Development of an artificial pancreas for children (and adults) with diabetes could be accelerated by creating new clinical protocols (based in part on reassessing clinical outcomes from prior research) and improved outcome measures for evaluating the performance of continuous glucose sensors and a closed loop artificial pancreas. This work could also revolutionize diabetes care and management.