

Challenge and Opportunity on the Critical Path to New Medical Products

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Summary

1. The current medical product development path is becoming increasingly challenging, inefficient, and costly.
2. A new product development toolkit is urgently needed to improve predictability and efficiency along the critical path.
3. In FDA's view, the applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic sciences.
4. For medical technology, performance is measured in terms of product safety and effectiveness.
5. Not enough applied scientific work has been done to create new tools to get fundamentally better answers about how the safety and effectiveness of new products can be demonstrated, in faster time frames, with more certainty, and at lower costs.
6. In many cases, developers have no choice but to use the tools and concepts of the last century to assess this century's candidates. As a result, the vast majority of investigational products that enter clinical trials fail.
7. A new product development toolkit — containing powerful new scientific and technical methods such as animal or computer-based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques — is urgently needed to improve predictability and efficiency along the critical path from laboratory concept to commercial product.

The medical product development process is no longer able to keep pace with basic scientific innovation. Only a concerted effort to apply the new biomedical science to medical product development will succeed in modernizing the critical path.

Highlight: Tools for Assessing Safety

Opportunity: Proteomic and toxicogenomic approaches may ultimately provide sensitive and predictive safety assessment techniques; however, their application to safety assessment is in early stages and needs to be expanded. Targeted research aimed at specific toxicity problems should be undertaken.

Opportunity: As biomedical knowledge increases and bioinformatics capability likewise grows, there is hope that greater predictive power may be obtained from in silico (computer modeling) analyses such as predictive toxicology. Some believe that

extensive use of in silico technologies could reduce the overall cost of drug development by as much as 50 percent.

Opportunity: There is an urgent need to develop tools to accurately assess the risk of new drugs causing heart rhythm abnormalities. For instance, there are ongoing international efforts to develop, test, and validate nonclinical models that may be useful in predicting human risk. In addition, the clinical risks associated with a small degree of QTc interval prolongation need to be fully defined.

Opportunity: "The appearance of new quantitative measuring technologies absolutely galvanizes new drug research." Additional bio-markers (quantitative measures of biological effects that provide informative links between mechanism of action and clinical effectiveness) and additional surrogate markers (quantitative measures that can predict effectiveness) are needed to guide product development. In some cases, datamining and analysis, with possibly a single additional clinical trial, may be all that is necessary to confirm the surrogacy of a particular marker. In other cases (e.g., the NIH's Osteoarthritis Initiative²⁷), epidemiologic studies on disease natural history must be undertaken to provide data on markers of disease processes. For biomarkers that currently appear promising, specific projects need to be undertaken to:

- Assemble existing data on the association of the marker with clinical outcomes
- Assemble existing data on the performance of the marker during intervention trials compared to the performance of current outcome measures
- Identify any data gaps or remaining uncertainties
- Identify clinical trials under development in which the remaining questions could be addressed in a straightforward manner

Opportunity: Imaging technologies, such as molecular imaging tools in neuropsychiatric diseases or as measures of drug absorption and distribution, may provide powerful insights into the distribution, binding, and other biological effects of pharmaceuticals, but their predictive value needs further study and evaluation. New imaging technologies will ultimately contribute important biomarkers and surrogate endpoints, but how soon these new tools will be available for use will depend on the effort invested in developing them specifically for this purpose.

Opportunity: For many therapeutics, effectiveness criteria are best defined by the practitioners and patients who use the products. Much work needs to be done on clinical trial design and patient-driven outcome measures to ensure that endpoints in new therapeutic areas accurately reflect patient needs and values. Community (health professional and patient) consensus on appropriate outcome measures and therapeutic claims can lay a clear development path for new therapeutics, especially when there is international regulatory harmonization.

Opportunity: The concept of model-based drug development, in which pharmaco-

statistical models of drug efficacy and safety are developed from preclinical and available clinical data, offers an important approach to improving drug development knowledge management and development decision making. Model-based drug development involves building mathematical and statistical characterizations of the time course of the disease and drug using available clinical data to design and validate the model. The relationship between drug dose, plasma concentration, biophase concentration (pharmacokinetics), and drug effect or side-effects (pharmacodynamics) is characterized, and relevant patient covariates are included in the model. Systematic application of this concept to drug development has the potential to significantly improve it. FDA scientists use, and are collaborating with others in the refinement of, quantitative clinical trial modeling using simulation software to improve trial design and to predict outcomes. It is likely that more powerful approaches can be built by completing, and then building on, specific predictive modules.

- There are many important additional opportunities in the area of clinical trial design and analysis. More clinically relevant endpoints need to be developed for many diseases. Enrichment designs have the potential for providing much earlier assurance of drug activity. Bayesian approaches to analysis need to be further explored.

Opportunity: The emerging techniques of pharmacogenomics and proteomics show great promise for contributing biomarkers to target responders, monitor clinical response, and serve as biomarkers of drug effectiveness. However, much development work and standardization of the biological, statistical, and bioinformatics methods must occur before these techniques can be easily and widely used. Specific, targeted efforts could yield early results.

Towards a Better Manufacturing Toolkit

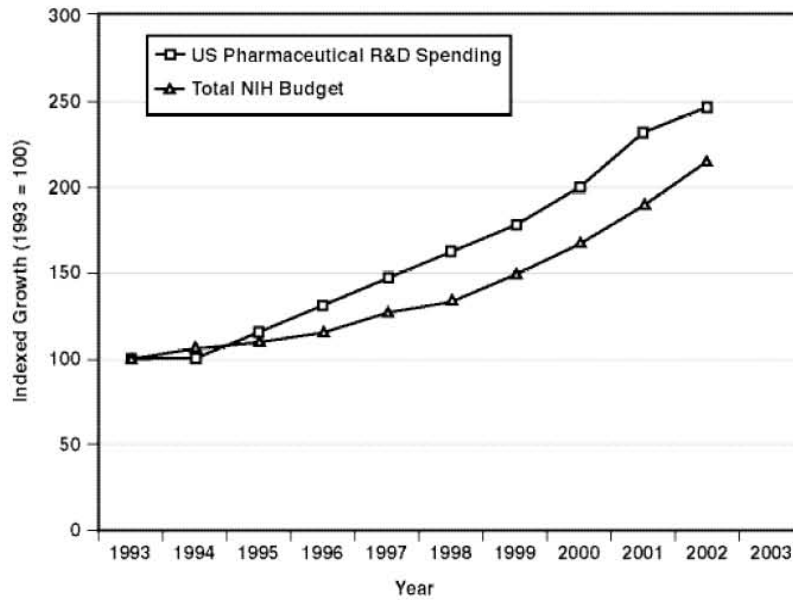
Opportunity: Additional characterization procedures and standards for expanded stem cell and other cellular products, bioengineered tissues, and implanted drug-device combinations (e.g., drug-eluting stents) are urgently needed. For example, developing test standards for coronary stent compressibility will decrease the likelihood of failed designs and allow smaller clinical trial programs.

Opportunity: The pharmaceutical industry generally has been hesitant to introduce state-of-the-art science and technology into its manufacturing processes, in part due to concern about regulatory impact. This led to high in-process inventories, low factory utilization rates, significant product wastage, and compliance problems, driving up costs and decreasing productivity. FDA has led an initiative to stimulate the use of process analytical technologies — automated sensors that monitor and control processes — and other modern manufacturing technologies that can improve efficiency and increase flexibility while maintaining high-quality standards. Further research and data sharing

are necessary to make these efficiencies a reality.

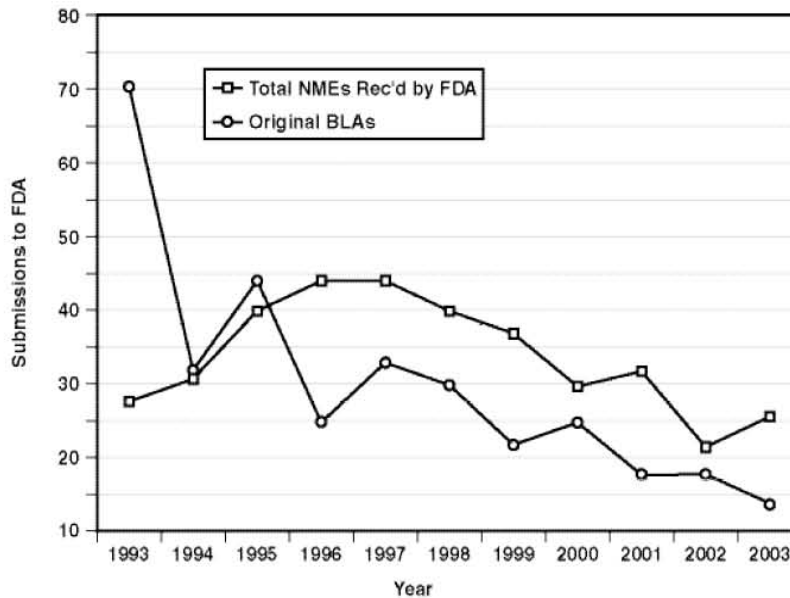
Opportunity: Scientists involved in reviewing medical devices at FDA report an urgent need for predictive software to model the human effects of design changes for rapidly evolving devices. We believe that such software may be attainable with a concentrated effort, by assembling currently available data and identifying existing data gaps.

Figure 1: 10-Year Trends in Biomedical Research Spending



The figure shows 10-year trends in biomedical research spending as reflected by the NIH budget (Budget of the United States Government, appendix, FY 1993-2003) and by pharmaceutical companies' research and development (R&D) investment (PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2002/2003).

Figure 2: 10-Year Trends in Major Drug and Biological Product Submissions to FDA



The figure shows the number of submissions of new molecular entities (NMEs) — drugs with a novel chemical structure — and the number of biologics license application (BLA) submissions to FDA over a 10-year period. Similar trends have been observed at regulatory agencies worldwide.