Combinatorial Discovery of Catalysts:
An ATP Position Paper Developed from Industry Input

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A. EXECUTIVE SUMMARY

Global market pressures are driving the chemicals and advanced materials industries to significantly reduce R&D cycle times yet provide higher quality (e.g., at six sigma) and performance. A solution to these industries is the recent development of high throughput research, including "combinatorial chemistry" methodologies, where a parallel approach to discovery and process development can deliver thousands of target materials and produce "libraries" of new solid-state and soluble materials in a matter of hours and days rather than months and years. Discoveries have already occurred for materials with superconductive, magnetoresistive, luminescent, ferroelectric, and dielectric properties. Catalysis research is receiving attention in homogeneous organometallic complexes, in heterogeneous inorganic oxides, and in biocatalysis.

There are substantial technical challenges in leveraging this technique from the drug discovery methodologies to advanced materials. There is a role for the ATP to play in bringing this capability to U.S. industry. ATP can facilitate the emergence of new technologies through the development of unique partnerships; it can spur the fusion of these new technologies for subsequent diffusion to other areas; it can facilitate the integration of complex systems; it can facilitate the integration of otherwise diverse technologies; and it can reduce the cost of combinatorial chemistry as a tool so that more R&D cost-sensitive sectors will invest in this new capability.

This position paper encourages the development of a portfolio of projects in the Advanced Technology Program for FY1999 in the area of combinatorial discovery for new catalyst materials. This report is a collection point for information gleaned from industry input, for example as obtained at an Industry Probe Working Group Discussion held in March, 1998. Additional input will be obtained from a public Workshop to be held November 18, 1998 in Atlanta, GA.

ATP is responding to external input to consolidate information on:

- market drivers
  - market sizes, market factors, penetration potential
  - return on R&D investment
- economic advantage
  - market failure, broad-based benefits, and cost/benefits
- technology challenges
  - discontinuous innovation in different application areas
  - fusion of emerging technologies as future technology enablers
  - systems integration.

Technology fusion will occur in the domains of the hardware and software industries, and will be directed toward solving specific problems in various industries, such as polymers, catalysts, smart materials, electronic materials, specialty & fine chemicals, biomaterials, optical materials, glass formulations, structural materials. Many technological problems are being solved in some application areas (for example, electronic materials and catalysts) while other applications await enabling technologies.

B. THE ATP PROCESS

The goal of the ATP is economic growth and the good jobs and quality of life that come with economic growth. ATP awards are made strictly on the basis of rigorous peer-reviewed competitionsdesigned to select the proposals that are best qualified in terms of the technological ideas, the potential economic benefits to the nation (not just the applicant), and the strength of the plan for eventual commercialization of the results; ATP protects the confidentiality of documents submitted by industry. The ATP does not fund basic research or product development.

The ATP is industry-driven. In the form of “white papers”, position papers submitted by industry, academia, and government facilities might outline a specific technology area and describe the potential for U.S. economic benefit, the technical ideas available to be exploited, the strength of industry commitment to the work, and the reasons why ATP funding is necessary to achieve well-defined research and business goals. These position papers must contain no proprietary information and should state as succinctly as possible the goals of a proposed technology area. The FY 1999 Competition introduces a new mechanism for developing Focused Programs: program areas will be developed in response to confidential proposals submitted to the Competition, i.e., a market-driven response to technology challenges seen by industry.

ATP project proposals submitted to a Competition are evaluated two criteria, 1). the scientific and technical merit of the proposal; and 2). the potential for broad-based economic benefits to the United States. A fifty percent weighting of the proposal applies to the scientific and technological merits: innovations in the technology; high technical risk and feasibility; and quality of the research plan. A 50% weighting will be applied to the economic merits of the proposals: economic benefits; need for ATP funding; and the pathway to economic benefit.

Competitions are announced in late Autumn with proposal due dates generally in early Spring. Proposal reviews are conducted through the Summer, and awards are announced in the September-October time frame. Applicants are strongly urged to initiate proposal preparations early and to follow instructions carefully; Proposal Preparation Kits for each new competition are distributed via the ATP Mailing List and on the ATP internet world wide web site http://www.atp.nist.gov/atp/apply.htm, following the announcement of a new competition.

C. PROBLEM STATEMENT: COMBINATORIAL CHEMISTRY AND CATALYSTS

Major forces—globalization of markets and the pace of technology change—continue to drive private sector R&D to narrower, shorter-term investments to maximize returns to the company. Increased pressure on manufacturers to produce “faster/lower cost/better” has increased the demand for new products made from new materials and/or utilizing new processes.

During the 1990’s, the pharmaceutical industry responded to these market pressures and significantly reduced the cycle time for the discovery of new chemical targets by generating and analyzing large numbers of possible chemical targets all at once by using massively parallel (also known as “combinatorial” or “high-throughput") research methods. This semi-empirical method could therefore determine the relevance of 96 possible candidates (a “library”) in a matter of hours or days as compared to weeks or months using traditional synthesis techniques. Recently the number of samples in a library has multiplied 100-fold with increased purity and significantly expanded analytical output, and the ability to screen upwards of 1 million distinct compounds per year has been realized in the larger firms. The capability to conduct research on this scale was the direct result of the fusion of several distinct technologies in the areas of software (informatics, molecular modeling, and statistics), more powerful computers, robotics, micro-technologies (micro-fluidics, micro-machining), and sensors applied to a well-defined market opportunity.

Industrial sectors beyond the pharmaceutical industry have described the need for high throughput screening for new chemicals and advanced materials. On March 24, 1998, the ATP held an Industry Probe Working Group Discussion that brought together fourteen representatives as a cross-section of the specialty chemicals and materials industries, as well as leading suppliers of enabling hardware and software tools and NIST Laboratories. The information gained from this Discussion has been expanded by additional industry input in the form of position papers submitted to the ATP. In addition to identifying key areas of technology development and application market areas, these data described the technical and commercial barriers to success of this methodology in U.S. industry. Continued industry input will be collected, and a public Workshop will be held on November 18, 1998 in Atlanta, Georgia.

Many, but not all, of the market factors that influenced drug discovery are now driving a need for reducing the cycle time for the discovery of new advanced materials and lower-cost chemical products compared to high-value pharmaceuticals. The technology spill-over from drug discovery has resulted in the embryonic development of combinatorial methodologies and technologies for inorganic materials and non-pharmaceutical organic compounds and materials. Combinatorial techniques are especially suited to complex mixtures containing many different elements. This methodology, therefore, lends itself to new advanced materials that are gaining performance through the use of 3, 4-, or 5-component mixtures or small quantities of additives, for example as dopants. In addition, rapid screening permits research into compositions containing elements that would not otherwise be attempted.

While the methodologies developed for drug discovery can be leveraged for other applications, the complexities of chemicals and materials discovery far out-weigh the current capabilities developed for drug discovery. New drug candidates (“leads”) are tested by chemical means such as gas chromatography, nuclear magnetic resonance spectrometry, mass spectroscopy, and incremental biological activity; biological activity to a single component of a lead mixture is adequate in many cases. Advanced materials, on the other hand, need to characterized according to their ***performance***, and these analytical techniques are often peculiar to the targeted application area. For example, selectivity and conversion analysis for a new heterogeneous catalyst formulation will require the development of novel microscopic sensors for sampling the complex product/reactant mixtures, possibly in the gas phase, for a large number of (microscopic) metal oxide “samples”. While organic chemical leads are being successfully analyzed at purity levels of 80% or less, typically advanced materials require very high purities to differentiate their performance. Industrial chemistry typically utilizes more energetic reaction environments than pharmaceuticals, with processes with temperature and pressure requirements of several hundred degrees and thousands of p.s.i. pressure, respectively. Finally, while drug discovery can utilize traditional chemical scale-up processes, advanced materials have been dealt significant challenges in “scalability” from microscopic to lab- or pilot-scale preparation while retaining the discovered properties.

In order to understand the technological hurdles, industry representatives have described the key steps of a combinatorial methodology:

1. Target Definition utilizing expert opinion and hypothesis;
2. Library Design using computational inputs such as molecular modeling and statistics;
3. Library Validation, which determines the quality of the library design using robotics, hardware manipulation of materials, and statistics;
4. Library Construction and Processing involves the automated deposition or synthesis of an n-dimensional matrix of physical samples;
5. High Throughput Screening (HTS) involves the use of robotics and sensors to rapidly and automatically analyze the library of chemical targets for desired properties;
6. Data Collection/Searching and Decision Making using the data-basing tools developed originally for genomics—informatics—expanded into the more complex realm of materials properties.

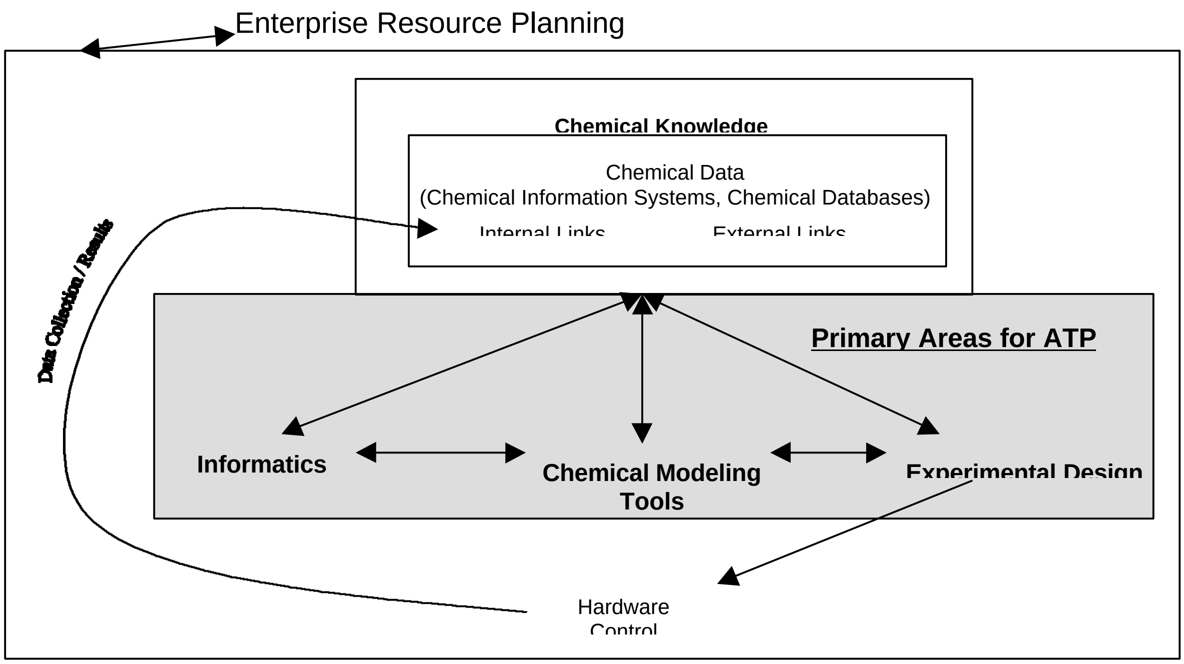
The widespread implementation of combinatorial methodologies for the discovery of new materials and chemicals represents a significant technical challenge for U.S. industry. The development of new technologies to meet the demand for combinatorial methods will amalgamate otherwise diverse industries, and diverse market opportunities will present themselves to otherwise focused enterprises. Tangible revenues will develop from the application of combinatorial discovery in a variety of industries and intangible returns, for example licensing and service revenues, will develop in industries that traditionally avoid them.

D. TECHNOLOGY CHALLENGE

The application of combinatorial discovery and innovation for new materials will drive the integration of a hardware- and software-based infrastructure toward specific product applications. The long-term vision is to have high-throughput research become part of expanded enterprise-wide systems that include tools for hardware interfaces, technology assessment/decision, and logistics. Because combinatorial discovery currently is capital intensive, with start-up costs in the $1-5 million range, discontinuous innovation in ***generic*** hardware and software technologies will be necessary to drive down costs and facilitate its implementation in the industrial sectors that have lower returns on R&D investment and highly capitalized, amortized manufacturing assets (*vide infra*).

- *Software.* The basic underlying software technology is the ability to chemically represent the material in a manner suitable for data-basing. Due to the sheer number of potential candidates available on a statistical basis to combinatorial techniques, library design will also require chemical synthesis expertise integrated with experimental design tools and statistics to reduce the number of samples and experiments. New tools will have to be developed to enable the input of this information into modeling engines; the increased number of data that can be input into computational engines will increase their power in iterative cycles. The overall view of software integration is shown in Figure 1.

Figure 1. The Integration of Software Systems



- *Hardware:* The basic underlying hardware technologies are in improving computer throughput, and in micro-scale sensors and micro-machines (MEMS) for the synthesis, processing, and analysis of libraries. Automated library construction requires that n-dimensional libraries are made by machines, for example using ink jet deposition, laser ablation, or chemical vapor deposition (CVD). Homogeneous reaction systems will require fluid handling capabilities. Library screening ("high throughput screening" or HTS) will drive the development of advanced sensors and sensor arrays; robotics, next-generation "titer plates", "lab-on-a-chip" designs, and rapid scanning devices will require development along specific application areas with physical properties that can be analyzed at microscopic levels. Automated library processing is especially challenging for new materials development since samples within a library may require different or non-equilibrium processing parameters across the matrix.

Broad technical needs have been identified by industry (Table 1 below).

TABLE 1: TECHNOLOGY CHALLENGES

Base Technologies	Database/Informatics
Robotics	Patent and prior art reviews
Micro-fluidics	Search engines/Inferential Engines
Micro-machining	Indexing
Decision Tools	Entity Inventory
QSAR/QSPR	Electronic Laboratory Notebook (ELN)
Prioritization	Screening
Promotion analysis & tools	Thermal properties (e.g., conductivity)

Polymer architecture/morphology
Optical characterization
Molecular Speciation (mass spec.)
Molecular Weight
Mechanical Properties
Interfacial Properties
Luminescent properties (e.g., XRD)
Electrical properties
Electrochemical properties
Catalyst Turn-over
Catalytic Selectivity, Conversion

Processing

Control of physical environment
Sample size--control of interfacial diffusion, mass transport properties, etc.

Library Validation

Molecular Modeling, QSAR. QSPR

Deposition

Thermally-driven (e-beam, laser, etc.)
Laser ablation
Ink jet
Chemical Vapor Deposition

Library Design

Statistics, modeling
Literature/Patent Databases
Diversity analysis/clustering/analysis
Computational (Molecular Modeling, Atomistic Simulations, QSAR, QSPR)

Degradati

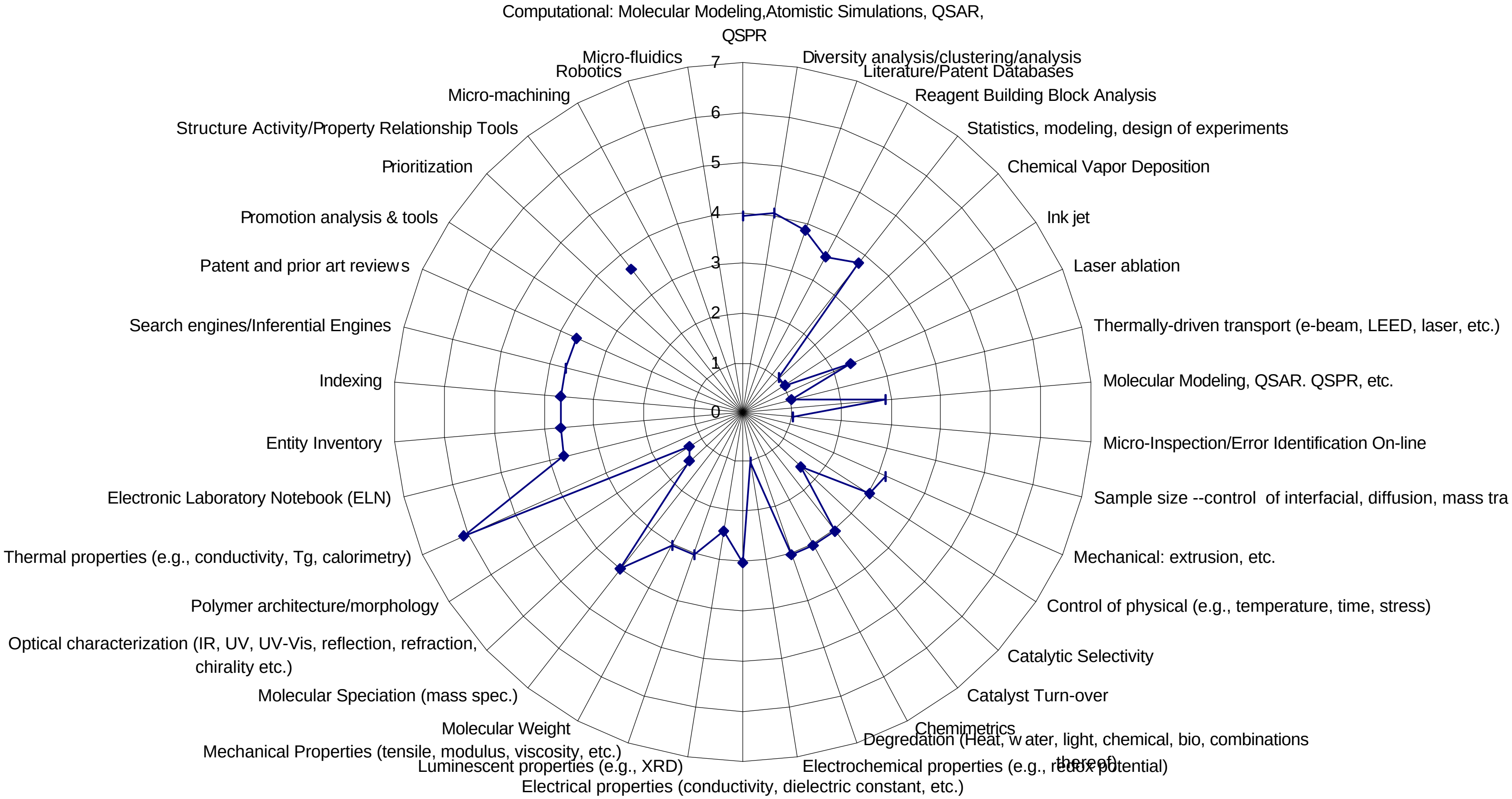
Mechanica

Assessment of the commercialization time frame, and hence technical risk, for these technologies was based on industry input. Participants in the March Working Group Discussion developed a list of market-specific technology needs and their approximate commercial usage. The responses are summarized into a radar map (Figure 2) where the radial axes represent time to commercial use (1 = 0 –1 years; 3 = 2-4 years; 9 = 5 or more years) plotted against individual technology needs. These data indicate that most of the technology challenges are at least three years from commercial use. The highest technology risk is in deposition, determination of catalyst selectivity and yield, and in the analysis for thermal and mechanical properties. More recently, scanning mass spectrometers have been employed for the analysis of solid inorganic oxides and metal alloys.

The most significant technical challenge is the determination of bulk properties based on microscopic sample sizes. It is well known in the heterogeneous catalyst arena that the support system, whether surface interactions or three-dimensional crystallite morphology, plays an important role in catalyst activity. Therefore, screening for ultimate catalyst activity using microscopic samples deposited on an essentially non-porous inorganic oxide wafer shall require the prediction of bulk properties from microscopic thin films or pixels. The solution to this problem lies principally in the software arena; interestingly, the combinatorial approach will accelerate this research due to the large number of sample that can be used to validate the software model.

FIGURE 2: TIME TO USE--TECHNOLOGY CHALLENGES

(1 = 0-1 years out; 3 = 2-4 years out; 9= 5 or more years out)



E. MARKET NEEDS AND SCOPE OF APPLICATIONS

A broad spectrum of applications, as identified by industry representatives, would benefit from the implementation of combinatorial discovery and process optimization methodologies, particularly any application that derives results from formulations and empirical mixture designs.

Various market factors (installed asset sensitivity, operating margin, % return on R&D investment, etc.) control the implementation of combinatorial discovery in the different markets. Industry developed a preliminary list of applications in various industries having substantial market sizes (Table 2, below) The preliminary list included all potential industry sectors except the pharmaceutical/drug discovery arena. The application areas that, in the view of industry representatives, have the longest time-to-use of combinatorial methodologies (Figure 3) are in bio-compatible materials, polymers (blends/alloys, fibers, optoelectronic), catalysts, and specialty formulations such as polymer additives. In general, these are applications that are awaiting an enabling technology, such as electro-mechanical or catalytic sensors, as indicated above.

TABLE 2: MARKET NEEDS—APPLICATION AREAS

<u>Polymers</u>
- Commodity
- Engineering and Specialty Resins
- Adhesives

<u>Catalysts</u>
- Heterogeneous
- Homogeneous
- Supports

<u>Smart Materials</u>
- Solids
- Fluids

<u>Electronic materials</u>
- Polymers-optical
- Polymers-conducting
- Display Materials
- Magnetic materials
- Ceramics
- Semi-conductors
- Encapsulants/packaging

<u>Specialty & fine chemicals</u>
- Coatings
- Anti-oxidants
- Impact modifiers
- Pigments/dispersants
- Refrigerants
- Surfactants

<u>Biomaterials</u>
- Bio-sourced polymers
- Bio-compatible materials
- Bio-degradable polymers

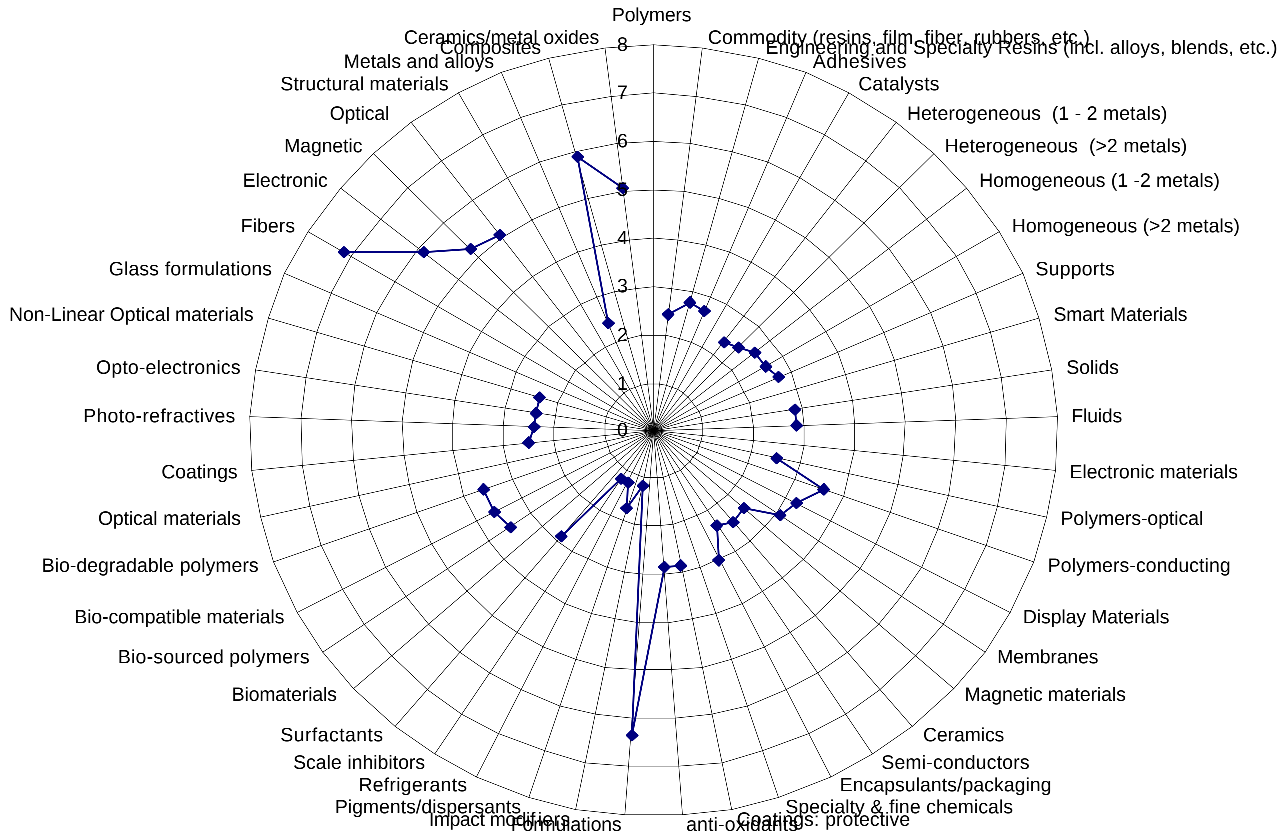
<u>Optical materials</u>
- Photo-refractives
- Opto-electronics
- Non-Linear Optical materials

<u>Glass formulations</u>
- Electronic/Magnetic/Optical

<u>Structural materials</u>
- Metals and alloys
- Ceramics/metal-oxides

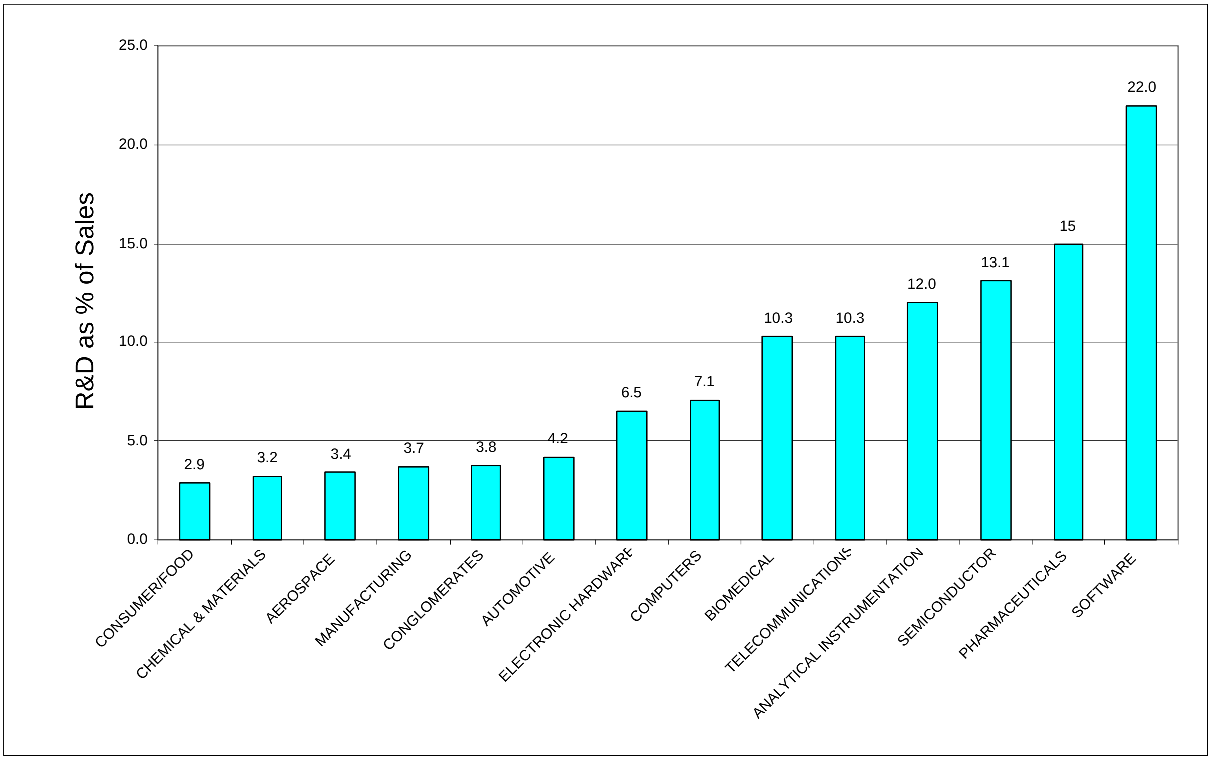
This broad spectrum of applications was reduced based on the level of support the technology implementation would receive without Federal support in view of the criteria for the Advanced Technology Program. The Program Development Team determined that industrial risk sensitivity might best be ranked according to industry's ability to implement combinatorial methodologies into their research efforts. Such sensitivity would include the return on R&D investment, funding levels for R&D, return on installed manufacturing assets, and profit margins reflecting new product sales. The role of ATP, therefore, is to develop lower-cost methodologies and tools based on new, generic technology to permit entry of combinatorial methodologies into industries that would a). not otherwise be able to implement them, and b). require an the development of one or more enabling technologies prior to implementing the integration of the systems mandated by successful implementation of a combinatorial approach.

FIGURE 3: TIME TO COMMERCIALIZATION--APPLICATION AREAS
(1 = 0-1 years out; 3 = 2-4 years out; 9= 5 or more years out)



R&D spending against sales revenues was utilized to rank industries (source *R&D Magazine*, October, 1998) according to their spending habits for innovation as an indirect measure of their sensitivity to implement a significant program in combinatorial methodologies.

Figure 4. Technology Industry Spending on Research



These data (Figure 4) indicate that chemical and materials companies (excluding petrochemical, which average less than 1%) spent approximately 3.2% of revenues on R&D activities in 1997, ranking near the bottom of technology-oriented industries. Pharmaceutical companies, which average 15% of revenues spent on R&D and have actively pursued combinatorial methodologies to remain competitive, and are assumed to be less sensitive to large expenditures in view of the significant revenues gained from the sale of new drugs.

R&D spending in for large chemical and pharmaceutical industries were evaluated on a company-wide basis (Table 4). Similar data on small companies is being compiled.

Table 4. R&D Spending in the Chemical and Pharmaceutical Industries

CHEMICAL COMPANIES	1990	1991	1992	1993	1994	1994 R&D spending as % of sales
Dow Chemical	$1,136	$1,159	$1,289	$1,256	$1,261	6.3%
DuPont	1,428	1,298	1,277	1,132	1,047	2.7
Monsanto	612	627	651	626	609	7.4
Rohm and Haas	178	183	199	205	201	5.7
Union Carbide	191	190	155	139	136	2.8
W.R. Grace	148	150	151	135	132	2.6
Air Products(a)	72	80	85	92	97	2.8

Lubrizol	74	80	90	89	91	5.7
International Flavors	57	62	71	75	81	6.2
Morton International(b)	48	59	61	69	66	2.3
Hercules	92	86	70	76	65	2.3
Praxair(c)	-	-	62	58	58	2.1
Ethyl	65	69	73	76	50	4.9
Nalco Chemical	45	47	48	50	46	3.4
Olin	66	41	39	41	35	1.3
Albemarle(d)	-	-	-	-	28	2.6
Petrolite(e)	12	11	12	14	13	3.5
TOTAL	$4,224	$4,142	$4,333	$4,133	$4,016	3.9%

PHARMACEUTICAL COMPANIES	**1990**	**1991**	**1992**	**1993**	**1994**	**1994 R&D spending as % of sales**
Merck & Co.	$854	$998	$1,112	$1,173	$1,231	8.2%
Pfizer	640	757	863	974	1,139	13.8
Bristol-Myers Squibb	881	993	1,083	1,128	1,108	9.2
Eli Lilly(f)	703	767	925	955	839	14.7
Schering-Plough	380	426	522	578	620	13.3
Upjohn	432	497	553	613	607	18.5
TOTAL	$3,890	$4,438	$5,058	$5,421	$5,544	11.3%

Note: Prior years are not restated to reflect company revisions. a For fiscal year ending Sept. 30. b For fiscal year ending June 30; data for Morton Thiokol prior to 1985. c Spun off from Union Carbide in 1992. d Spun off from Ethyl in early 1994. e For fiscal year ending Oct. 31. f Spun off and sold off medical devices businesses in 1994. Source: Chemical & Engineering News, August 28, 1995 (http://pubs.acs.org/hotartcl/cenear/950828/art04a.html)

Based on these data, it is apparent that both large and small chemical and materials industries would benefit from ATP funding in the area of combinatorial methodologies. Until data reflecting return on R&D investment (R&D ROI) and return on assets (ROA) can be accumulated, these data on R&D spending will be used to estimate need levels on an industry basis.

There is a significant role for both small and large companies to participate in this activity. In general, small companies, provide a focused, fast-response invention/innovation process, and large companies provide capital assets, innovation needs, and access to large markets.

F. PROGRAM OBJECTIVES, SCOPE, AND TARGETS

The opportunity will develop the fusion of technological advances in software (database administration, machine control, artificial intelligence, structure-activity and structure-function relationships, modeling, etc.) and hardware (robotics, reactor design, semi-conductor development, sensors, process control, MEMS etc.). It will *leverage*, not duplicate, the knowledge- and technology bases that have been developed for discovery in the pharmaceutical and agricultural chemical industries. Development of generic tools will be encouraged in order to facilitate the diffusion of technologies.

The goal of establishing a project portfolio on combinatorial methodologies is to facilitate the widespread utilization in the U.S. chemicals and materials industry of high throughput research specifically in the area of catalysis and biocatalysis discovery and process development. This project portfolio encourages the development of a technology infrastructure via integration of software and hardware tools focused toward specific application areas and recognizes that systems integration entails high risk. This "fused" technology base therefore would be applied to a specific market opportunity via a manufacturer in the chemical or materials industries. Therefore, the portfolio strategy is to utilize the power of the value chain to bring end-user needs to the infrastructure development companies and focus the technology base to a specific market need. There is a significant role for small businesses to contribute to this strategy: in general, it was observed that smaller companies will contribute to the infrastructure by inventing and presenting products of discontinuous innovation to the (possibly larger) manufacturing sectors. The Advanced Technology Program encourages small companies to participate in building the technological infrastructure to support combinatorial methodologies. For example, a NIST Small Business Innovation and Research Program (SBIR) was announced in October to address software issues.

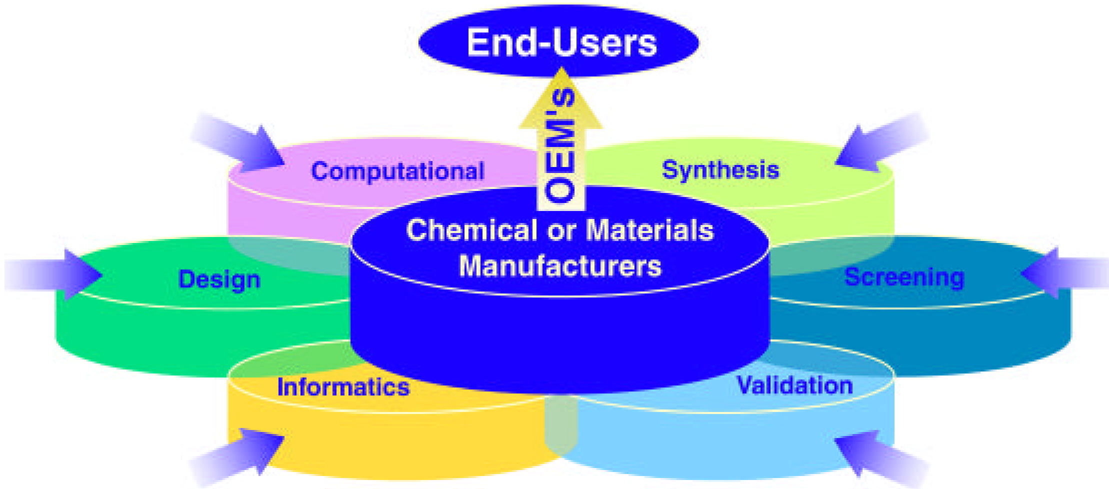


Figure 5. ATP Strategy Focuses Infrastructure Onto Markets

Three project scenarios have been developed to indicate the spectrum of risk and technology diffusion that would result from proposers. The three scenarios indicate three degrees of risk and, consequently, differing amounts of technology diffusion and economic benefits that might develop from a given project structure.

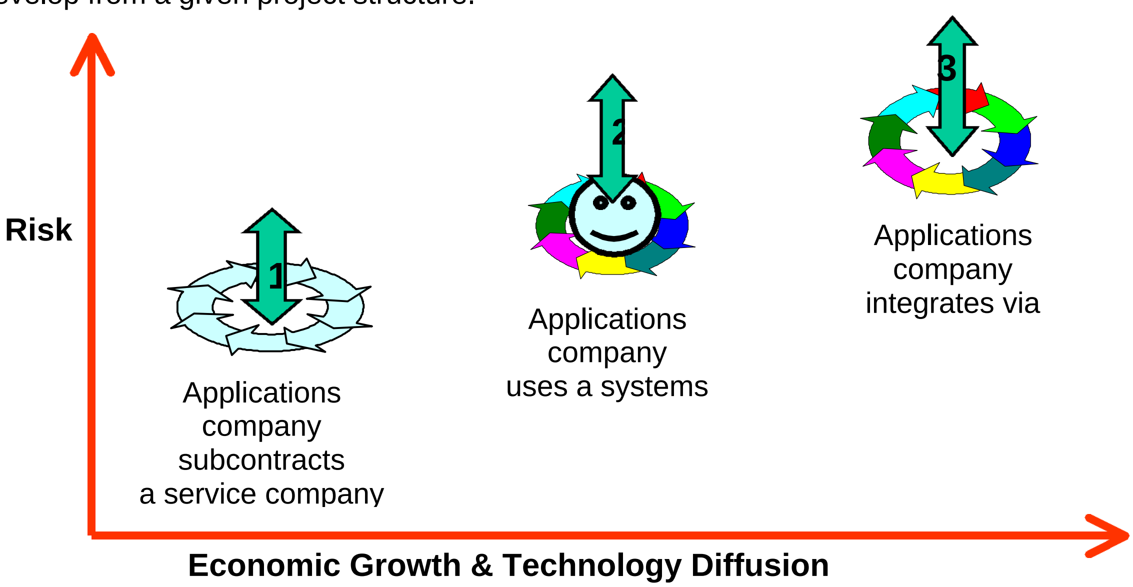


Figure 6. Project Strategy Technology Diffusion and Broad-Based Economic Benefits

ATP funding is required for five key reasons:

1. To develop new generic technologies in the high-risk areas of robotics, sensors, informatics, computers, and software control. In addition, the fusion of advanced technologies would be facilitated by bringing together multi-disciplinary teams from industry, academia, and government laboratories. The integration of these different systems will be a major challenge.

2. To improve U.S. competitive position relative to foreign entities. Foreign competitors are assembling the capability to conduct high-throughput materials discovery and development. A first-to-market position could advance many global industrial sectors for many years.

3. To significantly increase the development of alliances. Development of a competitive infrastructure will require the assembly of strategic alliances with partners having diverse competencies. ATP support is uniquely positioned to reduce the risk of collaboration, which can be expensive without appropriate returns, particularly for small, focused vendors of software and hardware tools, and will facilitate investment to gain non-core competencies.

4. To facilitate application of the infrastructure technology challenges toward industries in need of competitive advancement. Technology development using combinatorial approaches is considered too risky for many industries to tackle alone. Small applications companies will be impacted by the costs of entry and larger companies do not want to invest in capabilities away from their core business areas. The development of advanced integrated technologies will require a high degree of cooperation between companies, especially small, "inventive" companies working with larger applications companies in partnerships. The chemical industry can effectively leverage advances in catalysts into huge increases in benefits to society when downstream benefits are accounted for.

5. To facilitate recognition of revenue streams from intangible products. This is especially important for companies that would not otherwise recognize their ability to develop service capabilities that can generate revenue from similar, but non-competitive, companies.

A competitive project funded by the ATP would develop a horizontal partnership among the “infrastructural” industries (hardware and software) directed to the emergence of one or more technically challenging application areas in catalysis or biocatalysis discovery or process development. This horizontal-vertical partnership structure would enable the technology base to focus on the needs of a specific application and its downstream customer(s).

Competitive project proposals would indicate why a combinatorial approach needs to be applied to a specific application area and what high-risk aspects could be targeted to significantly advance tools and/or methodology. The underlying criteria for ATP involvement—broad-based economic benefits and technology diffusion—will have to be addressed in view of an application’s inability to fund these developments privately.

G. Significance of ATP Funds

In sharing the relatively high development risks of technologies that potentially enable a broad range of new commercial opportunities, possibly across several industries, the ATP fosters projects with a high payoff for the nation as a whole—in addition to strong corporate rates of return. ATP projects are expected to make significant contributions to scientific and technical knowledge between the proof-of-concept stage and product development stage. The goal of the ATP is economic growth. The ATP benefits companies of all sizes.

Therefore, the opportunity for ATP in the area of combinatorial chemical and materials discovery is in enabling the implementation of high-throughput experimentation into industries that would otherwise find the investment too risky technically and in capturing large benefits for the tool investment. Through investment in combinatorial methods, ATP has the opportunity to drive many of the chemical/materials markets (currently perceived as mature or commodity-based) into a second generation stage, well ahead of foreign competition. The opportunity to achieve "first-to-market" status will be exceptionally large for many industries implementing combinatorial methodologies. The spill-over benefits will cascade back into basic research as new phenomena are discovered and explanations are sought.

H. POTENTIAL FOR U.S. ECONOMIC BENEFIT

ATP can significantly reduce the risk of entry into combinatorial research in industries where the return on investment would not otherwise be favorable. *This impact will have significant broad-based benefits* by facilitating broader use of technologically advanced methods; by enabling the growth of hardware and software to applications that would not otherwise be considered; by spreading the resulting intellectual property over more applications and materials; and by producing more research to explain newly-observed phenomena. Benefits beyond the proposers would include technology advancements and methodologies that would cross application areas.

The ATP has estimated, with industry input, the market sizes of several application areas that will be directly impacted by combinatorial discovery methodologies. In an effort to estimate the economic impact of implementing combinatorial discovery in catalysis, shown below is a comparison of the 1997 North American sales of catalysts for polyolefin production and for polyolefins produced. The 100-fold difference in sales indicates that a relatively small improvement in the productivity of polyolefin manufacture via improved catalysts can result in relatively large changes in the economy. This leveraging of the value chain can be extended to other catalysis or biocatalysis applications. Incorporation of these materials into systems and components will create benefits removed from the actual discovery of new materials, however the size of these terminal markets is large.

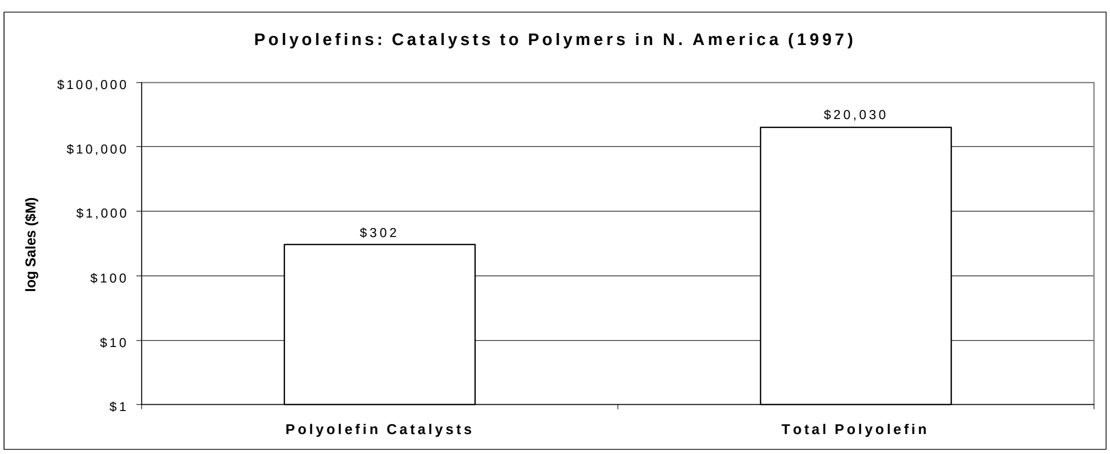


FIGURE 7. CATALYST TO POLYMERS SALES RATIO (LOG SCALE)

This analysis focuses on sales revenues, however it does not account for the benefits obtained from increasing the national R&D budget with ATP funds. These estimates have not assumed significantly reduced innovation cycle times available using combinatorial research methodologies because this data is not directly available to the ATP. Actual penetration of high throughput screening into industrial research may reach 2-5% by the year 2003, with estimated impact in the end-use markets not readily described, however estimates by the industry indicates that the value chain following catalysts through commodity polymers into end-user markets may approach hundreds of billions of dollars.

The ATP Economics Assessment Office is currently studying the influence of an increase in the total industrial research budget through federal funding and the downstream benefits to society can be estimated. Preliminary estimates of the downstream benefits to society range from $3-$10B. These estimates assume that the Advanced Technology Program's monetary contribution to the focused program in combinatorial chemistry is valued at $30 million over the life of the program and addresses the polymer and catalyst markets.

I. PROGRAM IMPACT

Industry Commitment

Strong interest by industry was shown in the Working Group Discussion attendance and industry position papaers. There was a strong signal from industry that federal assistance would accelerate their own efforts, provide tools to industries that would otherwise be available only in the distant future, and, finally, improve global competitiveness. The ATP has received industry position papers (“white papers”) describing the need for federal assistance in this area. These views are reflected in this Working White Paper. Verbal support for an ATP project portfolio has been expressed in national catalysis meetings.

Another (perhaps stronger) indicator of industry commitment to work in this area is existing or proposed efforts in this area. Over a half-dozen ATP awards made through previous competitions have been identified as having strong overlap with the agenda of the proposed project portfolio. Additional projects have proposed using combinatorial methods.

Market Impact: Synergies

The fusion of technologies to meet new market needs has been identified as a major component in the emergence of combinatorial research methodologies. The biotechnology arena has seen substantial growth in new industries that have sprung up to fill market needs. For example, the bridging of database software and genetics research has yielded the fast-growing field of informatics. Now, significant developments in sensors, micro-machines (MEMS), smart materials, and massively parallel computers bring new capabilities to industries selling into the chemicals and advanced materials marketplaces. By bringing together the high-tech infrastructural industries with the more conservative manufacturing sectors, ATP can accelerate co-development of new technologies. ATP has a vital role to play in stimulating the development of new technologies that will place competitive capabilities into the hands of those industries that would not otherwise be able to invest in these areas.

Technology Impact: Technology Diffusion

Efforts outside of the NIST ATP arena are just now yielding a wide range of results that are being widely publicized and published through various channels. The strongly pro-collaborative climates in Asia and Europe will pick these developments up first if the U.S. does not, giving early access to offshore manufacturers and granting a foothold to offshore vendors. ATP funding can make it happen here first, leveraging existing U.S. strengths to ensure continued leadership in the targeted markets.

There is a strong need in industry for work in the area of high-throughput research and development. As mentioned above, it is known in the drug discovery applications of combinatorial chemistry that significant reductions in time and cost can be achieved. Due to the high profit margins anticipated for the introduction and sale of pharmaceuticals, the expected return on investment is favorable. ATP can help to make the economics as favorable for high-valued specialty chemicals or engineered materials.

Impact on Employment

Implementation of high-throughput research is expected to increase the number of jobs in the target industries. Combinatorial methods have supplemented research facilities, not replaced them, as observed in the pharmaceutical and agricultural chemical industries. Additional employment is expected in the infrastructure industries due to increased need for software and hardware development. U.S. competitiveness was indicated by a number of industries as being a primary reason to implement combinatorial techniques in their discovery and innovation efforts.