Final Report

Project Title: Assessing the Economic Viability of Bio-based Products for Missouri Value-added Crop Production

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Recipient: The Curators of The University of Missouri 310 Jesse Hall Columbia MO 65211

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Contact: Nicholas Kalaitzandonakes (573-882-0143) KalaitzandonakesN@Missouri.edu

Project Team: Golden Field Office

Summary

An important policy and research issue debated today is the future of the Earth's energy resources. Known global reserves of oil are expected to run dry in approximately 80 years, natural gas in 70 years and coal in 700 years. Waning energy reserves are expected to come under increasing pressure as developing countries require more energy to support their industrialization. Inevitably, alternative fuels will need to be developed to sustain economies around the globe.

Continued depletion of limited global natural resources supports the concept of supplying industrial production and energy needs through the use of renewable, or biobased, resources. For instance, the United States has a highly productive agricultural system, which, in addition to providing basic food, feed, and fiber, can produce feedstocks in the production of industrial products and energy. Corn and soybeans are two examples of crops once used solely for food and feed which are now being used for fuel, chemical and polymer production. Corn is used for the production of alternative fuels, starch based agents, and bio-plastics while soybeans for diesel fuels, inks, industrial proteins and chemicals.

Development of bio-energy and bio-materials is being pursued through large investments both by governments and the private sector. Two of the world's largest petroleum companies - Royal Dutch Shell and British Petroleum/Amoco - have begun investing in renewable energy, including energy from biomass. Similarly, major multinational chemical companies like Dow and DuPont are investing in bioengineered plants for feedstocks and improved bio-manufacturing methods.

The shift away from the petroleum based economy is being facilitated by new advances in science and technology. Plant biotechnology, for example, can increase crop yields on marginal land, and can be used to design plants with specific oil and chemical compositions optimized for energy and industrial uses. New genetically engineered bacteria and enzymes could soon allow ethanol processors to switch from currently used corn to less expensive lignocellulosic

feedstocks, such as corn stover and wood residues. New "biorefinery" technologies can help integrate food with industrial processing. Cereal grains, for example, can be used to produce food and feed while crop residues, fiber by products and other cellulosic materials can be used for industrial power, fuels and biochemicals.

Of course, the successful development of the bio-economy will require both technical and market innovation as new products will need to be effectively positioned in the market and supply chains will need to be redesigned. In this environment, human capital with both technical and economic/management training and skills will be needed to facilitate the transition. Yet training programs that combine a portfolio of technical, economic and management skills have generally been in short supply.

In response, the Economics and Management of Agrobiotechnology Center (EMAC), at the University of Missouri-Columbia, launched a pilot graduate education program aimed at filling this need. This pilot program sought to initially train two M.S. level fellows with the combined economic, management, and science background needed by the emerging bio-product industry.

EMAC provided a fitting environment for this program due to unique research and teaching resources in the areas of bio-innovation, economics, and strategy. In addition, the University of Missouri and other Missouri stakeholders have invested in the development of biobased industries, and offered a deep institutional pool of people and knowledge from which students could draw.

Compare the actual accomplishments with the goals and objectives of the project

Project Objectives

The pilot graduate education program had the following key objectives:

1. To provide fellows with a strong background in innovation economics, management, and strategy.

2. To diversify the fellows' background with coursework in science and technology.

3. To familiarize the student with bio-based policy initiatives through interaction with state and national level organizations and policymakers.

4. To facilitate the fellows' practical training through active collaboration with industry involved in the development and production of bio-based products.

The pilot program was generally successful in meeting these objectives and produced two quality professionals who are expected to contribute to the development of the US bio-based industries for many years to come. Specifically the two graduates:

1. Received strong economics/management/science training (see details below)
2. Developed significant appreciation and understanding for the legal and policy environment (indeed one of them is continuing with a law degree)
3. Interacted effectively with industry partners within the context of their research.

Indeed, the two fellows conducted significant and original research related to the US bio-industry, which is now continued and expanded in EMAC through follow-up projects.

Summarize project activities for the entire period of funding

Curriculum

Significant effort was invested on the development of a program that is specialized, but also flexible to accommodate multi-disciplinary training and the diversity of student interests, while allowing the specialization and focus on specific fields of interest within the bio-based industry. Generally, the program targeted 3 courses in economic theory and methods, 3 elective courses in business management and strategy and 4 elective courses in the life sciences, for a total of 30 credit hours. The MS degree in bio-based economics included additional research credits (leading to thesis and research publications) and could facilitate an internship. For such a program, students and advisors are required to work together to identify needs and interests in order to effectively guide the choice of courses. Students' prior education, interest in specific technologies, industry experience and other factors also influence the structure of the program.

The wealth of existing class offerings at the University of Missouri was leveraged and customized to create an encompassing program for the students interested in bio-based product management. The program's base was economics/management and was designed to provide the students with a strong background in the economics of innovation, management, and strategy. The pilot program was offered as part of the Agricultural Economics and Agribusiness Management degree program.

While the knowledge needed to develop biobased technologies can be broad, one overarching concept key to all technologies is the management of product and process innovation. Innovation Management is a relatively new but fast-expanding body of academic literature that investigates the fundamental dynamics of technical innovation, from discovery to product development, market introduction, adoption and diffusion. A capstone course in the management of biobased technologies, entitled "*Managing Innovation in Biobased Industries,"* was also developed with the general literature of innovation management as a backdrop. The course is currently being revised to reflect the learnings of the pilot training program.

<u>General Course Plan</u>

Following these guidelines the course plan for an MS degree was shaped as follows:

Sequence in Economics (all required)

- Intermediate Price Theory/Microeconomic Theory
- Intermediate Income Analysis/Macroeconomic Theory
- Mathematical Statistics & econometrics

Sequence in Innovation Management (capstone course required)

- Managing Innovation in Biobased Industries
- Economics of Agribusiness Strategy and Organization
- Entrepreneurship management
- Managerial decision making

Sequence in Engineering

- Engineering Analysis of Bioprocesses -Fundamentals and application of biological engineering.
- Physical Principles for Food Processing -Introduction to basic engineering concepts used to process raw materials, including: energy balance, pipe flow, viscosity, heat exchange, and refrigeration.
- Biochemical Engineering Operation-Transport processes in bioreactors, agitation and aeration, scale-up, sterilization, liquid-solid separation and other operations related to product recovery.

Sequence in Plant Science

- Genetics of Agricultural Plants and Animals—Concepts of molecular, transmission and population and quantitative genetics. Special emphasis given to breeding and biotechnological applications in plant and animal agriculture.
- Grain Crops—Production and utilization, as well as growth and development, of a wide range of grain crops. Problem solving tasks include agronomics, economics and environmental questions.
- Crop Physiology—Basic course on crop growth and development. Emphasis on physiological processes and morphology of crop plants, and their application to crop breeding and management decisions.
- Field Crop Breeding—Introduces the application of genetics and the plant sciences to the breeding and improvement of field crops. Classical, current and innovative plant breeding techniques are addressed.
- Plant Breeding Theory—Designed to provide a logical application of genetic concepts to mating and selection theory in general improvement of cross-pollinated crops.

Sequence in Biochemistry

- Contemporary Topics in Biochemistry and Biotechnology -Introduces students to current research methods and problems in Biochemistry. Additionally, the course explores the scientific, social, and ethical issues related to research.
- Plant Biochemistry -Emphasizes biochemistry unique to plants; biochemical events plants share with other organisms are compared. Concepts such as photosynthesis, metabolism, composition, compartmentalization, and regulation of chemical events are addressed.
- Seminar in Biochemistry -Designed to familiarize student with journal papers dealing with current topics of research, techniques, status of field and importance of results.

Other Appropriate Elective Areas

- Statistics, Business (Finance, Accounting, Marketing), Engineering and Biological Sciences,

Student Program

Recruitment

Applications for fellows were solicited with a broad call for applications. To facilitate the process a prospectus of the program was drafted and distributed to key organizations (e.g. American Agricultural Economics Association, Peace Corp) and individuals. For more broad reach, web advertisements were also employed. Emphasis was placed on recruiting minority students. The result of the solicitation was a significant number of qualified respondents, from which the two fellows were eventually selected. The applications were evaluated by a selected group of

University of Missouri faculty and staff. Ultimately, two highly qualified female students from the state of Missouri were selected for the pilot program.

Coursework

The two fellows funded by this project officially began coursework in the summer of 2002. Coursework began with economics courses offering the fellows a theoretical and conceptual framework from which to build as their program became increasingly interdisciplinary.

During the following semesters, the fellows' program focused on management training. Classes included Entrepreneurial Management –focusing on the process of developing a new product/idea in to a successful business, and Advanced Marketing Research –focusing on methods and skills that are necessary for market analysis and positioning of new products.

Finally their program was rounded with classes in plant and molecular biology and statistical analysis. The following list of classes shows the diversity of coursework and the general progression. The fellows finished coursework on 5/14/04 (Winter 2004 semester).

- Economics
    - New Institutional Economics
    - Microeconomic Theory
    - Macroeconomic Theory
    - Economics of Agribusiness Strategy and Organizations

- Management
    - Entrepreneurial Management
    - Managerial Decision Making
    - Advanced Marketing Research

- Statistics
    - Linear Regression and Statistics
    - Spatial Statistics

- Biological Sciences
    - Plant Physiology
    - Plant Genetics

Applied Research

It has been well established in both scientific and business fields that some of the most valuable lessons are learned "by doing". Accordingly science coursework often places a heavy emphasis on lab work, while likewise business schools emphasize case-studies and team projects. In attempts to give students exposure to this type of learning, the fellows were paired with MOVATION –an agribusiness incubator. MOVATION provided the graduate students with case study opportunities to participate in the business development of emerging bio-based technologies in Missouri. As the center's core function is to incubate new agricultural technologies, it offered an opportunity for the fellows to be exposed to a stream of "real world" case studies on technology assessment, process optimization, product marketing, organizational development and regulatory compliance.

The interaction allowed exposure to the following four projects:

- Industrial products derived from methyl Soyate
- Specialized corn-based lactic acid in unique food applications
- Implementation of computerized information systems for the development of an efficient supply chain needed to transact specialty crops (e.g. industrial protein containing crops) for food, feed and industrial applications.
- The feasibility and potential adoption of novel biotechnologies with application to the manufacture of corn ethanol.

Thesis Research
In addition to coursework and applied research the fellows' participated in rigorous and diverse research projects, ultimately leading to the completion of their MS theses.

Initial research projects were identified by members of the industry advisory committee to ensure efforts were consistent with both Missouri's and industries needs. The fist of these projects involved the assessment of the system-wide technical and economic barriers limiting the adoption of biodiesel (whole supply chain analysis). Subsequent research projects gave the fellows the chance to further investigate and address problems associated with specific bio-based technologies (e.g. economic/technical business decisions facing the soyfood and ethanol industries).

Building on their experiences the fellows were encouraged to define their thesis research. Thesis topics were expected to be of interest to the student's future career, but also relevant to the state and the biobased industry, and subject to the approval of their program committee. The selection process resulted in two theses which are abstracted below.

Thesis 1: The Feasibility of Plants in the Manufacture of Protein Therapeutics

Abstract

After years of anticipation biotechnology has begun to deliver an array of promising pharmaceuticals. Already a number of therapeutic proteins, predominantly monoclonal antibodies, have had great success, with many more in the pipeline. Monoclonal antibodies (Mabs) target specific diseases ranging from simple bacterial infections to crippling chronic diseases such as cancer. Mab technology allows the drugs to be manufactured in vitro by fusing cells engineered to produce the specific antibody with an "immortal" cell that can grow continually in cell culture.

Large scale cell cultures require high levels of control only achieved in modern bioreactors. Use of such equipment can lead to manufacturing facilities costing in excess of $250 million, requiring a minimum of 5 years to assemble. These manufacturing costs, have limited the potential of many Mabs. High upfront capital costs have further led to forecasts that Mab manufacturing capacity will continue to be insufficient for the expected FDA approvals. Considering that many of these drugs are for the treatment of chronic diseases that require an ongoing treatment schedule, the need for capacity expansion at reasonable costs is crucial.

Advocates of plant made pharmaceutical (PMP) technology claim that plants offer an opportunity to lower the manufacturing costs and expand the production capacity of Mabs. Instead of amplifying antibodies in expensive bioreactors, they can instead be grown in plants

circumventing much of the fixed production costs. In this system a gene coding for the specific antibody is inserted into the host plant. Following an ongoing breeding program and a careful screening of the progeny the resulting plants produce Mabs in protein tissues. The mature plants are harvested and the antibodies are extracted and purified in a GMP processing facility.

While PMPs may offer great potential to decrease cost and lessen production risks they are not without controversy. A primary concern has been the environmental and health risks associated with outcrossing and commingling of PMPs with food crops. This has lead to a series of strict production protocols called for by industry organizations and regulatory agencies alike. Irrespectively, the possibility of commercial success and the economics of PMPs are still unclear. This is in part because no commercial PMP systems exist yet.

Ex ante evaluating the economics of PMPs requires simulation models that can assess the production system and associated costs under alternative configurations. In order to accomplish this objective we developed two process & economic simulation models –one for a traditional Mab system that utilizes standard bioreactors with mammalian cultures and one with PMPs. Various production levels (facility scales) were simulated with the largest facility capable of producing approximately 1000 kg of purified Mab per year, the equivalent demand of one highly successful drug. Proprietary data for each facility was obtained from companies specializing in the relative manufacturing process.

Empirical results from this study indicated that PMPs can lower the manufacturing costs of Mabs but mainly at large production scale. Cost savings vary by production volume and are significant. The per unit cost for the PMP system may be as much as 2 times less than production in the mammalian facility. The capital investment required for facility construction was also much less for the PMP facility, by up to 3 times less.

The constructed simulation models also allowed for the evaluation of alternative system designs. As regulators expand the strict containment requirements, production costs of PMP will rise.

Even with significant manufacturing cost reductions, their magnitude may not be sufficient to entice wide scale adoption of the PMP technology, at least initially. With an estimated $0.8-$1.7 billion price tag to bring one drug to market and drugs entering clinical trials having only an eight percent chance of making it to market, (FDA, 2004) manufacturing costs are only one of many considerations for pharmaceutical firms. Of paramount importance are the time to market and the risk profile of the technology. The constructed simulation models allowed for such time to market considerations

Thesis 2: Firm Co-location and Clustering in the Life-Sciences

Abstract

Life science and other high technology clusters are increasingly viewed as engines of economic growth and development of innovative industries. However, little is known today about the factors that cause such clusters to emerge and how they might be managed. The study evaluated the propensity of the life sciences industry to cluster and examined the factors behind geographic agglomeration of the life sciences in the US.

In recent years, state and regional development organizations, industry organizations, and academic researchers have taken an interest in the clustering of firms and the resulting economic activity, especially in high tech and “knowledge-based” industries like Biotechnology.

Theory suggests that firms are attracted to other firms as they derive benefits from labor externalities and knowledge spillovers. This attraction has been observed within the context of some spatial unit (e.g. state, county, region or even nation) as empirical studies often measure clustering via a Gini coefficient, location quotient, coefficient of localization, and others. These measures describe the degree of concentration of firms in a predefined geography (region, county, state, etc.) against a benchmark geography.

However, studies of such spatial aggregations leave the relative location of the firms unexamined, often masking important information. Since much of the theory behind clustering suggests that firms would tend to be attracted to specific factors (e.g. research universities) a more micro analysis could prove useful.

In this project we depart from prior practices and use firm level data to evaluate the underlying factors behind the co-location and potential clustering of biotech firms in a particular region. We employ a point process methodology to empirically describe firm co-location and test three general hypotheses: 1) Life Science firms tend to co-locate, 2) firm attraction has spatial boundaries, and 3) intra-regional industry structure and infrastructure impact the propensity of firms to co-locate.

We focused our empirical analysis on the St. Louis metropolitan area which was chosen for its substantial and diverse set of resources including: major research universities, multinational Life Science corporations, and Life Science startups. The data used is a comprehensive inventory of the 541 firms and life science organizations in the 4 counties surrounding St. Louis, delineated by major industrial code, employment, and revenues.

For each of the 541 firms six concentric circles of varying radius were drawn around its geographic point of location. Within each circle a unique data set of co-locators was created for each firm and analyzed using two distinct regression models; a distance and a count model.

For the distance models, the dependent variable was the average distance from the centroid firm to all other firms observed in the constrained area. Decreasing distances indicate co-location. Count data measures the number of firms within the radius distance of the centroid firm, resulting in an estimated intensity of firms. Thus, the resulting dependent variable was the number of firms per area, or density. Increasing values of intensity indicates relative concentration and co-location of firms. In the count models, infrastructure and the existence of anchor organizations were explicitly incorporated. Thus, these variables were hypothesized to have a positive relationship with collocation and clustering.

Empirical results showed that firms co-locate within the metropolitan region and this propensity to co-locate is impacted by regional industry structure and infrastructure. Anchor organizations also play a key role in drawing other firms to locate around them. Vertical and horizontal supply chain relationships were also found to be important suggesting a significant firm ecology that has not been uncovered in prior studies.

The regression models also allowed insights on the spatial scales and the relative spatial impact of various influences on firm co-location. The models examined various scales from the extremely local attraction (half mile) to sub-regional clustering (five mile). Conclusions were

drawn about the spatial dimension of intra-metropolitan clusters. Firm co-location was evident across several distances, but turned out to have spatial boundaries. Thus firm attraction does not necessarily require firms to co-locate directly next to one another, but there are limits to attraction within the region depending on the type and strength of the intra-organizational connection. Other factors we have found to have a very limited spatial influence. This is evidenced by the fact that the influence of anchoring organizations tends to increase over larger geographies.

Comparatively co-location factors such as firm size, industry similarity and research/incubation infrastructure tend to be more evident in the models evaluating smaller geographies (e.g. half and one mile model distances), suggesting that locality is more relevant for such factors.

The importance of delineating the boundaries of clustering is useful for policymakers looking to create incentives for the development of such industrial clusters. The results of the paper suggest that attracting large anchors can have a strong impact on the formation of a cluster, and its influence may also expand well outside of the local area. Investments in infrastructure can have highly targeted impacts on the local economy by helping to target firms to a relatively small geography.

Progress in Performance and Monitoring

Internally, the program was evaluated according to the following three criteria: The effectiveness of the training, the quality and relevance of the research and the facilitation of the student's career path.

The program effectively supplied relevant multidisciplinary knowledge and skills allowing the students to effectively understand technical and market complexities in new bio-based industries. In addition, the program increased the students' appreciation for relevant institutions and policies. The students left the program with a deep appreciation of the key institutional and policy factors that can impact the emerging bio-economy.

The research experience of the program was equally effective. The students produced a number of research papers, as well as two theses that were evaluated by interdisciplinary thesis committees. Ultimately, the research findings of the students are expected to result in quality publications.

Perhaps most importantly the program seems to have advanced the careers of the two fellows. One fellow is in law school expecting to continue to work on emerging legal and economic issues relevant to the emerging bio-based industry. The second fellow has been hired as a financial analyst and is primarily tasked with assessing capital investment opportunities in the agricultural sector. The success and testimonies of the students suggest that the pilot program makes an appropriate and valuable addition to the University curriculum.

Identify Developed Products

The project resulted in both direct and indirect outputs. The most important and direct output being the specialized professionals trained by the program. Specifically the project had the following benefits.

1. Training specialized professionals to participate in the biobased industry
The two professionals graduating from this program will have the knowledge and skills to participate and facilitate the commercial advancement of the biobased industry. Additional professionals are expected to be trained in the future as the pilot program becomes institutionalized.

2. Course and other programmatic developments
The project has lead to the development and teaching course material on the economics and innovation management of biobased technologies. A specialized course "*Managing Innovation in Biobased Industries"* has been developed and is currently being revised.

3. Research
The project resulted in two theses and several working papers that are currently being submitted to journals for publication (see publication list below)

4. Interdisciplinary Collaboration
The research and knowledge generated in this project has resulted in a number of new collaborative research programs such as:

1) Development of simulation models for whole ethanol supply chains (in collaboration with the National Corn to Ethanol Research Center).
2) Valuation of the impact of university life science research on the regional economy
3) Evaluation of the importance of clustering to entrepreneurship in the life sciences

Patents:

None

Publications/Presentations

Theses

Peiter, C. "Firm Co-location and Clustering in Biotech" MS Thesis Dec. 2004, University of Missouri. Columbia.

Walker, M. "The Feasibility of Plants in the Manufacture of Protein Therapeutics" MS Thesis Dec. 2004, University of Missouri. Columbia.

Working Papers/Under review for publication

Peiter, C., Kalaitzandonakes, N., and Kaufman, J. "Firm Co-location and Clustering in the Life Sciences" EMAC working paper 11-334-2004

Kalaitzandonakes, N., Kaufman, J., and Walker, M. "The Feasibility of Plant Made Pharmaceuticals" EMAC working paper 11-335-2004

Peiter, C and Walker, M, "The Bottlenecks of Biodiesel: *A systemic analysis of the factors impacting biodiesel cost and adoption"* EMAC Working Paper *024-2002*

Peiter, C "An Evaluation of the Farm-level Benefits of Biodiesel" EMAC Working Paper 032-2003

Milestone Status Table

Table 1. Milestone Status Table

I.D.	Task/Milestone Description	Planned Completion	Actual Completion	Comments
1.00	**Program Development**			
1.01	Bio-based program plan	8/26/01 (F 01)	1/15/02 (W 02)	
1.02	Develop capstone class	1/15/02 (W 02)	6/09/02 (S 02)	
1.03	Teach capstone class	8/01/03 (F 03)	5/14/04 (S 04)	
2.00	**Fellows**			
2.01	Recruitment & selection	8/26/01 (F 01)	4/15/02 (S 02)	
2.02	Enrollment	8/26/01 (F 01)	6/09/02 (S 02)	
2.03	Class work & research	8/01/03 (F 03)	5/14/04 (W 04)	
2.04	Thesis and publications	8/01/03 (F 03)	11/20/04 (W 04)	
3.00	**Industry Interaction**			
3.01	Select advisory council	1/01/02	12/15/01	
3.02	Begin case study projects	1/15/02 (W 02)	8/26/02 (F 02)	
3.03	Begin internship projects	6/09/02 (S 02)	6/14/04 (S 04)	

Budget Data (as of Aug 31, 2003)

Budget data sent separately