RESEARCH BACKGROUND, APPROACH, AND METHODOLOGIES FOR ENSURING SAFETY, INTEGRITY, AND VALUE OPTIMIZATION IN THE GLOBAL BIOPHARMACEUTICAL SUPPLY CHAIN

By

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Submitted to the MIT Sloan School of Management in Partial Fulfillment of the Requirements for the Degree of

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ABSTRACT

As the biomanufacturing (BioMAN) initiative within the MIT Center for Biomedical Innovation enters its third year of active research, the competitive landscape and sources of resources to support biomanufacturing research have rapidly changed. This research is an attempt to provide insight into the following primary questions:

- What research strategies could BioMAN effectively employ moving forward?
- What is a specific example of BioMAN research targeted towards new potential resource sources?
- What are the details of the research approach for a project that would be of interest to both existing and new resource sources?

By leveraging a competitive analysis framework, a recommendation was developed for BioMAN to pursue the market segment of system-based research-centric programs without offering training or custom projects. Specific potential resource sources and collaboration partners were identified towards meeting this target market.

An example interdisciplinary research program proposal was constructed with the intent to submit to the Alfred P. Sloan Foundation. Additionally, the details of planned approach to a project focused on biomanufacture location decisions were developed towards attracting support from both industrial partners and non-profit foundations.

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1 Research Motivation and Intent

1.1 M.I.T. Center for Biomedical Innovation Biomanufacturing Research Initiative

One of the research areas being pursued by the Center for Biomedical Innovation (CBI) is that of biomanufacturing research (with the specific MIT CBI biomanufacturing initiative referred to as "BioMAN"). BioMAN research currently intends to be focused in two areas:(1)

- Evaluation of scenarios of biomanufacturing futures
    - Influence of associated technology, policy, and business dynamics
- New tool and technologies specific to biomanufacturing

Enabling these focus areas is a community of subject matter experts from academia, industry, and government brought together in a safe-haven environment to plan and perform the research deemed to be valuable.(2)

1.2 Research Intent

As BioMAN enters its third year of active research, the competitive landscape and sources of resources to support biomanufacturing research have been rapidly changing. It is the intent of this research to answer the following questions:

- What research strategies could BioMAN effectively employ moving forward?
    - Leveraging a competitive analysis framework, what does a combination of examination of existing consortia and qualitative primary data specific to BioMAN mean in practice?
    - Are there actionable recommendations that can be provided to BioMAN based on the performed analysis?
        - Identification of and rationale for potential resource source(s)
        - Identification of and rationale for potential collaboration partners

- Can a specific example of an actionable recommendation around new potential resource source(s) be formed that would further BioMAN and be of interest to the community of subject matter experts?
- What are the details of the research approach for a project that would be of interest to existing resource source(s), specifically one or more industrial partners, and new potential resource source(s)?

The three main chapters of this thesis aim to address the three primary questions in the list above in an interconnected manner.

In an attempt to create value-adding answers to the final two questions above, the specific example towards a new potential resource source, that has been developed in collaboration with a number of potential principal investigators at MIT and elsewhere, is a proposal to the Alfred P. Sloan Foundation of New York in the area of "Ensuring Safety, Integrity, and Value Optimization in the Global Biopharmaceutical Supply Chain." The details of research approach for a project of interest for industrial partners has been done for a project in the area of "Biomanufacture Location Decisions in the Prospect of Regional Volatility."

2 BioMAN Research Strategy Options

In analyzing the research strategy options for BioMAN, a conceptual framework for determining target market segment(s) is introduced and then detailed with research and examples from three sources:

1. Published academic research on rationale for having and joining consortia
2. Existing consortia and their publicly available information
3. Interviews with Stacy Springs, Ph.D., director of BioMAN

With the determined target market segment(s), specifics of marketing and potential resource source(s) are investigated.

2.1 Conceptual Framework

The determination of a research strategy within the context of an academic consortium has at least two defining dimensions:

- Expected timeframe for return on investment from consortium research
    - For simplicity and application to BioMAN, possible timeframes are described as near-term (e.g. in the next year, shorter than a Ph.D. thesis) and longer-term
- Extent to which existing academic researchers (and their associated strengths and interests) will be utilized compared to building a custom organization

Each of these dimensions is on a continuum and each may change over time for a given academic consortium and/or differ across research projects. However, some governing description of intent along these two dimensions helps determine the relevant potential market(s) and marketplace analysis techniques.

2.1.1 Example of Balancing Timeframes for Consortium Research

In some relevant research consortium situations, the balance of near-term and longer-term value has been explicitly separated. This appears to be particularly well demonstrated by the Dundee Kinase Consortium within the Division of Signal Transduction Therapy in the School of Life Sciences at the University of Dundee, where the University provides both general

consortium research (accounting for approximately two-thirds of the total funds) in the area of dissecting signal transduction pathways to identify novel drug targets and provides custom project services for additional fees (one-third of the total funds). In order to have access to custom project services with the Dundee Kinase experts, the sponsor partner must be fully invested in the consortium. Leveraging this dual opportunity, or bundled research consortium solution, the Dundee Kinase Consortium has been able to retain consortium membership from Pfizer, GlaxoSmithKline, and AstraZeneca amongst others committed for fourteen years and in excess of thirty-four million pounds (approximately fifty million US dollars) and secured fifty research positions.(3; 4)

In its intended two prong research program of analytical tools (near-term) and biomanufacturing futures (longer-term), BioMAN is planning to utilize a similar balancing of timeframes for return on investment from the consortium research. The BioMAN situation is complicated by the possibility of one or more potential consortium member(s) electing to pursue near-term or custom project services directly with one or more of the relevant researchers and not electing to participate in the bundled offering of both near-term and longer-term. While likely to enhance short-term research value for the enterprising consortium member(s) and faculty, such custom projects would detract value to other consortium members and from the longer-term research objectives. In some ways, the strong potential for transformation from a consortium to a custom project was recently demonstrated by a MIT affiliated consortium, Consortium for the Advancement of Manufacturing in Pharmacy (CAMP), which had eight member companies in addition to MIT and Purdue as recently as 2005.(5) Amongst the CAMP research projects were those aimed at designing continuous manufacturing of pharmaceutical products. By September of 2007, Novartis (one of the CAMP members companies) had come to terms with MIT on a ten-year dedicated, custom continuous manufacturing project(6) and CAMP is no longer an active consortium. (5)

2.1.2 Impact of Leveraging Existing Organizational Strengths and Interests

The extent to which existing researchers are to be utilized in the research strategy is dependent upon the relevant expertise of those researchers and the availability of new resources and/or

collaborations to enable a modification of strengths and interests. Of additional consideration regarding the extent of leveraging existing organizational strengths and interests is whether the creation of the research consortium is initiated by the organization expected to conduct the research ("an engineered process") or whether the consortium is created by the resource source(s), which select the relevant consortium partners ("an emergent process").(7) BioMAN is an example of the former origin, where the organizational strengths and interests of principal investigators within the MIT community relevant to biomanufacturing attracted resources to their current and/or potential research. The International Serious Adverse Event Consortium is an example of the latter origin, where a US Food and Drug Administration (FDA) Industrial Advisory Board recommended an "independent industrial biomedical consortium" be formed to bring industry and regulators together to build a better understanding of the biology of drug induced serious events.(7) Representative resulting consortium research strategy roadmaps are presented in Figure 1 for the two extremes of leveraging existing organizational strengths and interests.

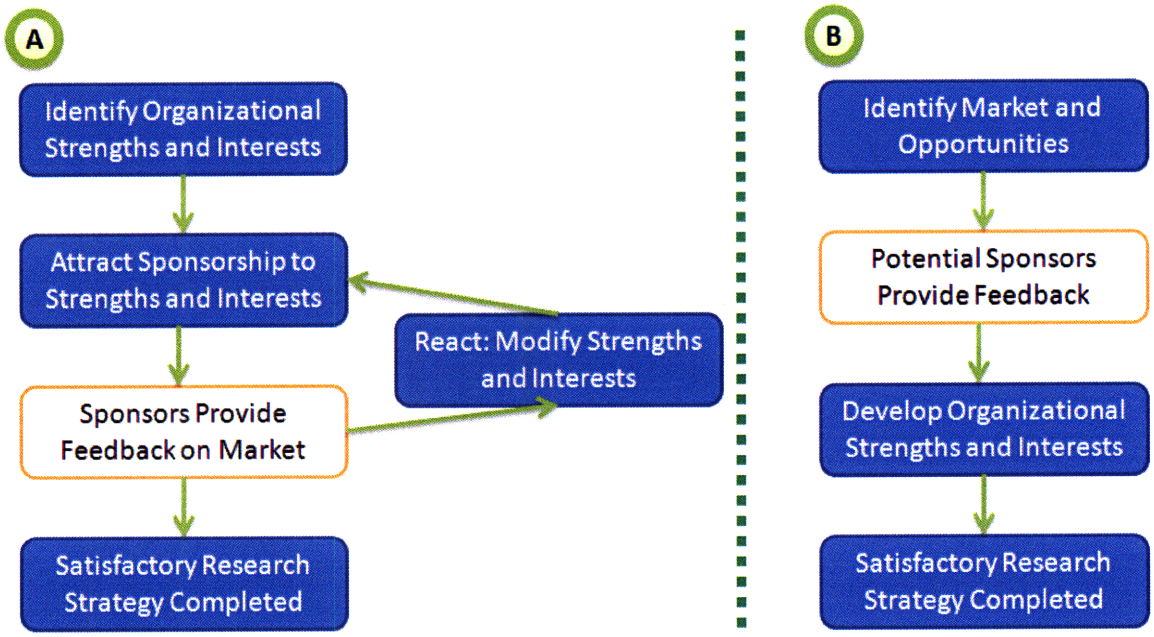

Figure 1. Representative Roadmaps of Consortium Research Strategy for A. Consortium Intending to Primarily Leveraging Existing Organizational Strengths and Interests ("Engineered"); and B. Consortium Originating with Validated Opportunities ("Emergent")

The most notable difference in logic between the two roadmaps depicted in Figure 1 is the inclusion of a reactive feedback loop in the roadmap in Figure 1A as the organization needs to take the extra step of validating its offering in the marketplace, as opposed to the roadmap in Figure 1B where the marketplace (in the form of one or more resource sources) has requested or validated the product in advance of developing the organizational capabilities. Each of the two roadmaps has advantages and challenges associated with it: at a summary level, a consortium leveraging existing potential (Figure 1A) can come up to speed quickly but may not gain significant market traction and the opposites apply to the original validated consortium (Figure 1B).(8) Independent of the origin of the consortium and its associated resources, the underlying marketplace and analytical techniques to investigate that market are consistent.

2.1.3 Analytical Techniques to Investigate the Marketplace of BioMAN

Towards understanding which market segment(s) and/or opportunities BioMAN could effectively target, a marketplace analysis specific to BioMAN under the framework depicted in Figure 2 which is derived from multiple publications on marketing and opportunity

evaluation.(9; 10; 11) This analysis framework attempts to provide insight into the available opportunities and the positioning of BioMAN capabilities relative to those opportunities. Each of the three primary aspects of the framework will be discussed in the subsequent sections.

Figure 2. Contents of the BioMAN Marketplace Analysis

2.2 Market and Attributes

In advance of detailing the competitors and customers for BioMAN, it will be helpful to define the market that encompasses BioMAN. (9; 11) The BioMAN research objective is defined broadly(1) and the potential market will be defined as "interdisciplinary research in technology, policy, and business relevant to biomanufacturing." This broad definition allows for consideration of a number of competitors and customers, which will allow for a rich attribute space and large number of market segments.

One way to simultaneously view the market and the context of participants in the market is with the five forces of market structural attractiveness as first suggested by Michael Porter.(10) This framework groups the market into current rivals within the market, potential entrants, suppliers, buyers, and substitutes. This framework with general groups of each of the five types specific to BioMAN is presented in Figure 3. The current competitors and the customers will be discussed in the subsequent sections along with their defining attributes towards determining targeted market segments.

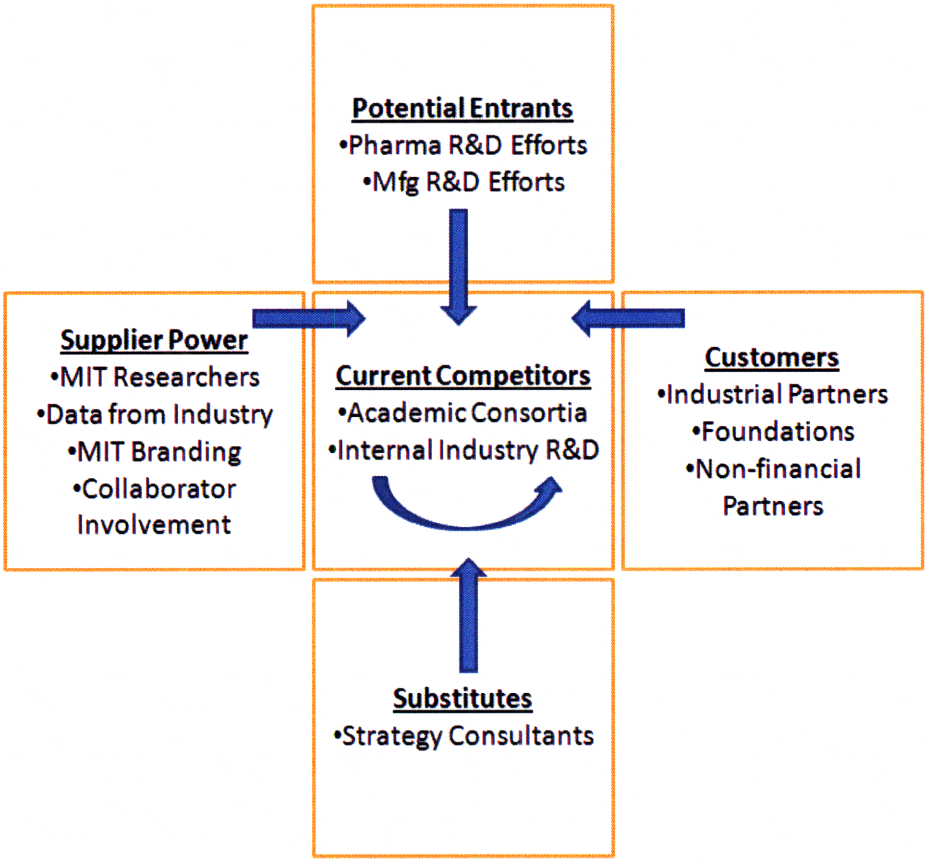

Figure 3. Five Market Forces with General Examples for BioMAN

2.2.1 BioMAN Competitor Attributes

The current competitive environment of BioMAN (within the central box of Figure 3) encompasses identifying competitors, their objectives, capabilities, and other relevant details.(12) By analyzing these competitor attributes, an understanding of the market can be developed and visualized.(10) Additionally, the extent of overlap and/or complements with the BioMAN offering and those of others in the market can be determined.(8)

Specific BioMAN competitors within the context of a market broadly defined as "interdisciplinary research in technology, policy, and business relevant to biomanufacturing" were identified in three ways:

1. The categories presented within the "current competitors" force box of Figure 3
2. Online searches for biomanufacturing research centers
3. Interview with Stacy Springs, Ph.D., BioMAN program director

Within the area of academic consortia, the following competitors and their characteristics in the areas of location, origination date, stated objectives, consortium members, and resources (facilities, personnel, funding) were identified to the extent possible. The consortium are ordered based on geographic proximity to BioMAN (Cambridge, MA):

- Tufts Center for the Study of Drug Development (Tufts CSDD) (13)
    - Location: Tufts University, Medford, MA
    - Origination Date: 1976
    - Objectives:
        - To monitor and report on the development, regulation, and utilization of new drugs and biopharmaceuticals.
        - To explore the economic, legal, scientific, and public policy issues affecting pharmaceutical and biopharmaceutical innovation worldwide.
        - To serve as an information resource on the development and review of new therapeutic agents.
        - To sponsor public forums and conferences which bring together the perspectives of government, industry, academia, and public health advocates.
        - To raise the level of national and international debate on issues related to new drug and biotechnology product development and regulation.
    - Consortium Members:
        - Medium and large pharmaceutical companies (e.g. Wyeth, Eli Lilly, Daiichi Sankyo)
    - Resources:
        - Facility: office space
        - Personnel: medical professionals, pharmaceutical business strategists, attorneys
        - Funding Sources: consortium members (55% of total), foundation support, grants for commissioned projects, registration fees for courses

and conferences, and subscription fees for certain Tufts CSDD publications.

- Massachusetts Biomanufacturing Center (MBMC) (14)
    - Location: UMass-Lowell, Lowell, MA
    - Origination Date: Announced 2007
    - Objectives:
        - Complete applied research problems that improve the quality, cost and productivity of large-scale biomanufacturing production
            - Areas for incremental advances include improved process control of bioreactors, increased expression levels, prolonged cell lifetimes and faster cell growth rates (cell cycle times) and disposable and new purification technologies
            - Areas for breakthrough programs include perfusion reactors to convert batch processes to continuous ones, developing yeast as a replacement for mammalian cell cultures and using E. coli to create antibodies in soluble form.(14)
        - Help biotech companies transition from R&D to validated, cGMP-compliant manufacturing processes
        - Student education and training (Ph.D., certificate programs)
    - Consortium Members:
        - Industrial: Nova Biomedical, Antigenics, Cambrex, Genzyme, Invensys, Millenium, Wyeth(15)
        - Academic: UMass Dartmouth, Worcester Polytechnic Institute, Tufts
    - Resources:
        - Facility: planned $80M, 97,000 sq.ft. emerging technology and innovation center (construction currently delayed by issues with financing)(16)
        - Personnel: faculty leadership with expertise in chemical engineering and cell biology

        - Funding sources: state, federal and university funding(17), Massachusetts Technology Collaborative's John Adams Innovation Institute (15)
- Northeast Biomanufacturing Center and Collaborative (NBC^2)(18)
    - Location: New Hampshire Community Technical College, NH
    - Origination Date:2005
    - Objectives:
        - Sustain an alliance of community colleges to prepare a 21st century technical workforce in biomanufacturing
        - Develop curricula and hands-on SOPs to support biomanufacturing education and training
        - Collect data from the Northeast region on the number of students entering training in biomanufacturing and that go on to work in the field
    - Consortium Members:
        - Industrial: broad range of tens of biotech companies (from Abbott to Wyeth)
    - Resources:
        - Facility: Laboratories and classrooms at participating community colleges
        - Personnel: Faculty at participating community colleges
        - Funding Sources: National Science Foundation - Advanced Technological Education Center (four years, $3M total)
- Biomanufacturing Research Institute and Technology Enterprise (BRITE)(19)
    - Location: North Carolina Central University, Durham, NC
    - Origination Date: 2006
    - Objectives:
        - Research focus in the areas of drug discovery and manufacturing technology
        - Education/training of students (B.S., M.S., Ph.D.)
    - Consortium Members:

        - Industrial: Biogen Idec, Merck, GlaxoSmithKline, Bayer Corporation, Novozymes
        - NC Nonprofits: NC BioImpact , GoldenLEAF, BTEC, BioNetwork ,NC Biotechnology Center, NC Bioscience Organization
    - Resources:
        - Facility: 52,000 sq. ft. dedicated research and office facility
        - Personnel: Twelve research faculty
        - Funding Sources: The Golden LEAF Foundation of North Carolina ($20M)
- Biomanufacturing Training and Education Center (BTEC) (20)
    - Location: North Carolina State University College of Engineering, Raleigh, NC
    - Origination Date: 2008
    - Objectives:
        - Provide educational and training opportunities to develop skilled professionals for the biomanufacturing industry
    - Consortium Members:
        - Undetermined
    - Resources:
        - Facility: 82,500 sq. ft. dedicated laboratory and classroom space
        - Personnel: Faculty in chemical engineering, microbiology, bioprocessing
        - Funding Sources: The Golden LEAF Foundation of North Carolina, training contracts (e.g. FDA contract to train inspectors)
- Center for Process Analytical Chemistry (CPAC) (21)
    - Location: University of Washington, Seattle, WA
    - Origination Date: 1984
    - Objectives:
        - The investigation of new measurement approaches based on the miniaturization
        - The investigation of issues related to the integration of process measurement with process modeling and control

        - The improvement of mechanisms for interaction, collaboration, and communication of Center activities, research programs, government agencies, and the general measurement and control community
    - Consortium Members:
        - Industrial: wide range of processing companies (from ABB to Wyeth)
        - Government: NSF, National Labs
    - Resources:
        - Facility: Undetermined
        - Personnel: Twenty-six associated faculty in chemistry, electrical engineering, etc. at UW and elsewhere (Delaware, UC-Davis, etc.)
        - Funding Sources: Sponsorship from industrial consortium members

By detailing the competitors and many of their defining attributes, contextual positioning of the competitors based on their attributes can be completed.(10) By positioning the competitors by attributes, direct competitors and potential collaborators can be identified. For the specific competitors described above, possible attributes for inclusion in such an analysis include:

- Extent (or fraction) of focus specific to biomanufacturing
- Focus on academic research vs. training workers
- Research focus on management vs. technical research
- Availability of custom projects for industrial consortium members
- Geographic location
- Industrial vs. non-profit financial sponsorship
- Relative size of initiative (as measured by publications, faculty, facilities)

A summary of these identified attributes applied to the six academic consortium competitors is presented in Table 1. This tabulation clarifies that, as BioMAN is primarily interested research (and perhaps both research and training), neither of the two primarily training consortium (NBC^2 and BTEC) are direct competitors to BioMAN. Depending on the BioMAN capabilities and targeted market segment(s), it may be is possible that these two organizations or ones similar to them could be considered for collaboration efforts.

Table 1. Summary of Identified Attributes of Academic Consortium Competitors

Attribute	Tufts CSDD	MBMC	NBC[2]	BRITE	BTEC	CPAC
Extent of BioMfg Focus	Low	All	All	All	All	Low
Research or Training	Research	Both	Training	Research	Training	Research
Management or Technical	Mgmt	Tech	N/A	Tech	N/A	Tech
Custom Projects?	Some	Yes	N/A	Undetermined	N/A	Some
Geographic Location	New England	New England	New England	Southeast	Southeast	Northwest
Financial Source	Both	Non-profit	Non-profit	Non-profit	Non-profit	Industrial
Size	Medium	Large	Small	Large	Large	Large

With the four remaining academic consortia being considered as potential direct competitors to BioMAN, one way to represent their placement in the attribute space is graphically with a perceptual map. (10) All seven of the relevant attributes for those four consortia are plotted in Figure 4, which shows a number of key summary results:

- Tufts CSDD is strongly differentiated from the three others by its placement in the area of management research
- MBMC is differentiated by its placement in the area of technical training and availability of custom projects for industrial partners
- None of the competitors have a primary focus in management training, although Tufts CSDD does offer an Institute for Professional Development which offers three one-day courses of instruction annually(22)

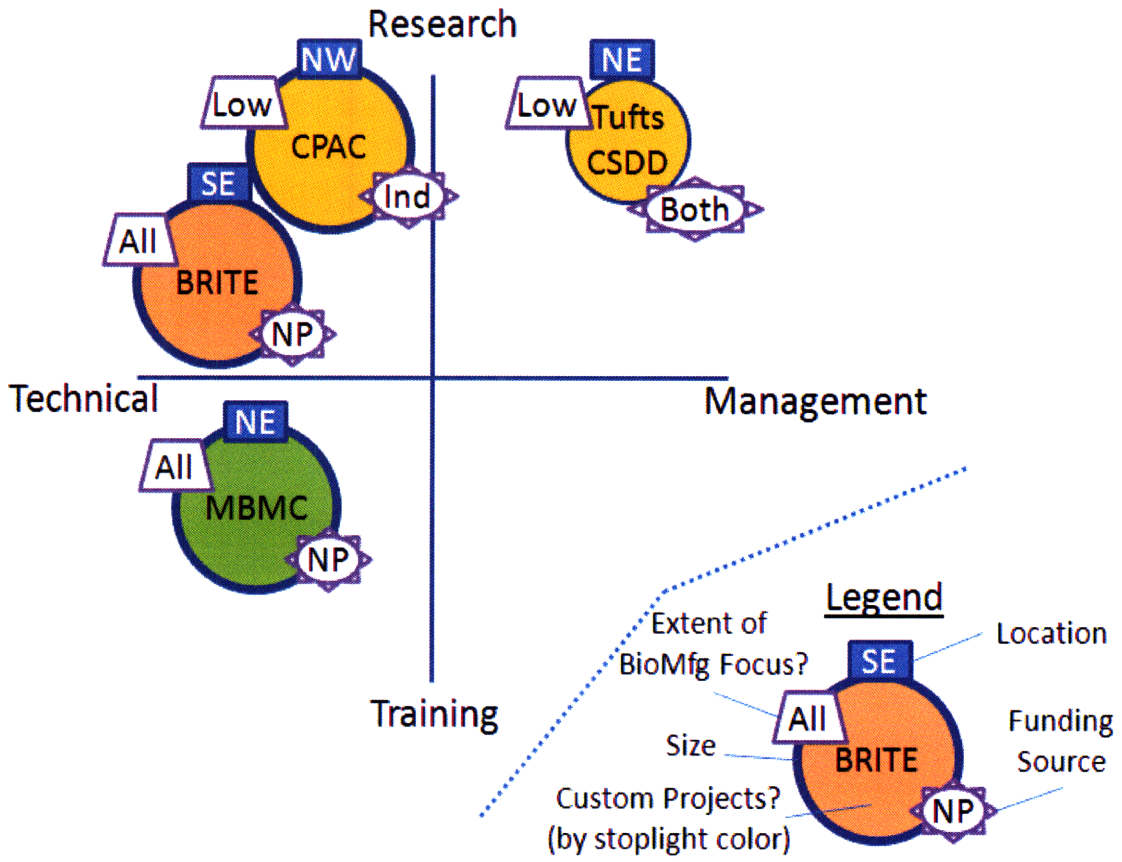

Figure 4. Perceptual Map of Four Identified BioMAN Direct Competitors

Another potential type of competitor to BioMAN is the internal research and development within industry. The details of relevant objectives to internal industrial biomanufacturing research are expected to be specific to each company. Given this variability in the objectives of this set of potential competitors, the context and rationale of customer decisions to enter into or join academic consortia (addressed in the subsequent section) is an important part of determining attractive market segments.

2.2.2 BioMAN Customer Participation Rationale

Academic consortia typically intend to attract industrial and/or non-profit (foundations, government) as customers to fund and provide other resources towards conducting the intended work. The rationale for forming consortia has been previously identified by Doz et al based on data collected on the formation process of 53 R&D consortia.(7) The formation rationale is described as cross-firm environmental interdependence (product standardization,

external threats) of the participants and the formation process facilitated by a triggering entity that can ensure fair share of costs and benefits to participants.

The rationale for an individual firm to participate in consortia has been researched both quantitatively and qualitatively over a variety of industries. For example, Baldi et al(23) examined business-to-business consortia in the automotive industry (to which some large automotive companies elected to join and others did not). In that research, it was found that driving forces for companies to elect to join a consortium centered around the following themes with the advantages and disadvantages (with modifications adapted from Dagnino et al(24)) of a generic consortium cited:

- Cost economics
    - Advantages: lower cost per company to achieve objective; aggregating demand lowers any relevant procurement costs
    - Disadvantages: difficult to build and set-up costs can be high; cost of integration back into the company can be high
- Resource dependence
    - Advantages: pool complementary expertise to create unique knowledge
    - Disadvantages: dependence on a competitor might evolve
- Stakeholder theory:
    - Advantages: consortium members become committed to the initiative (e.g. a standard)
    - Disadvantages: excluded companies might show averse reactions
- Organizational learning
    - Advantages: consortium participants can learn from one another
    - Disadvantages: sharing of confidential and/or valuable information; new intellectual property may reside in the consortium
- Strategic choice
    - Advantages: realize competitive advantages; accomplish complex tasks

- Disadvantages: advantages available to all participants; consortium management and flexibility is complex

Additional insight into the perceived value received by firms for participation in consortia can be found from the marketing material provided by existing consortia. The value identifying in these marketing materials typically are the research projects outcomes, sharing risks, and connecting to others in the industry (including government employees). For example, the Biomarkers Consortium markets the following value to its potential consortium members towards having "a greater voice in the growing world of personalized medicine"(25):

- Shape consortium project concepts into executable projects.
- Share in the risks and rewards of developing these often-times costly, scientifically challenging projects.
- Develop relationships with colleagues from a variety of sectors interested in identifying and developing biomarkers.
- Receive frequent updates on the status of the consortium's efforts, its projects, and new opportunities for involvement.
- As a group, elect four representatives to serve with NIH, FDA, and others on the consortium executive committee.

As another example, the advantages to industrial partners in the Dundee Kinase Consortium are described as: (26)

- Access to Know-how from >70 world class scientists
- Screening facility vs. panel of kinases
- Electronic Information storage / transfer
- Production of proteins & biological reagents
- Custom synthesis of antibodies
- Information on new drug targets

Representatives from GlaxoSmithKline (GSK), a pharmaceutical company that is a Dundee Kinase Consortium member, have also published their perception of value to industry in participation in that consortium:(3)

- Information on new drug targets
- Access to Know-how from >150 world class scientists
- Tangible deliverables for industry:
    - Screen facility vs. panel of kinases
    - Electronic information storage / transfer
    - Production of proteins and biological reagents
    - Custom synthesis of Ab's and transgenics

Given that the dates of origin (2004 and 2008, respectively) of these two perspectives on the value of the Dundee Kinase Consortium are not significantly different than one another and that the size of the consortium did not change significantly over that time, it is noteworthy that the GSK description apparently values the interaction with researchers from others companies as it lists 150 scientists (this number would likely cover the Dundee researchers ***plus*** the participating researchers from other companies) whereas the Dundee number of 70 is comparable to the number of Dundee researchers. Also of note is that GSK has explicitly outlined those deliverables that are perceived to be tangible.

GSK also provided their general rationale for electing to participate in consortia: (3)

- Address large research challenges
- Achieve a critical mass
- Access to:
    - Complementary skills and/or technologies
    - Academic lateral thinking
    - Multi-disciplinary problem solving

Specific quotations from industrial partners in the Tufts CSDD (selected by Tufts for inclusion on the website) also focused on the tangible returns on their participation:(13)

- "I rely heavily on the objective industry benchmarking and performance metrics generated by the Tufts Center for the Study of Drug Development. This information is critical for assessing our own performance and targeting important areas for growth and improvement." – Wyeth
- "The data generated by the Tufts Center are vital to us in our efforts to improve R&D performance and yield. Moreover, the work of the Tufts Center has been enormously influential in political and regulatory debates worldwide on issues related to pharmaceutical innovation." – Eli Lilly

In interviews with Stacy Springs, Ph.D., director of BioMAN, regarding the themes that current and potential industrial BioMAN participants cite as important in their decision to join BioMAN, the following themes surfaced:

- Extent to which BioMAN research is aligned with the strategic research plan of the company
    - The perceived importance of futures planning around a shared vision
- Connection to MIT (e.g. as an alum or past MIT consortium sponsor)
- Geographic proximity to MIT
- Connection to safe haven regulatory discussions
- Networking opportunities with others in industry including FDA personnel
- Economic climate (current recession is impacting industrial partners)

Across the academic research on R&D consortia, marketing materials from current consortia, industrial partners' feedback on consortia value, and interviews with the current BioMAN director, the following two general themes relevant to BioMAN appear:

- Tangible research value to the industrial partner
- Networking opportunities within the industry (particularly with individuals in other companies and in government agencies)

The tangible results that industrial partners are looking for involve either benchmarking data for inter-firm comparisons and goal-setting or technologies for practical use. In the case of

technologies for practical use in biomanufacturing, experience with CAMP and the line of questioning from industrial partners to Professor Alan Hatton's presentation on magnetic separation at the March, 2009 MIT ILP Biomanufacturing Conference suggest that the industrial partners need the following questions answered with reasonable certainty:

- Can the technology be applied to an industrially relevant system?
    - Is it effective for our types of products? Can it be scaled?
- Is the technology safe for the product, the operators, and the equipment?
- Is purchase, deployment, and validation cost effective?

The challenges associated with answering these questions theoretically in a convincing fashion usually drives towards the use of pilot scale testing facilities in advance of industry acceptance of a new technology.

In addition to industrial partners, another set of potential customers are non-profit organizations committed to academic research. These non-profits include private foundations (e.g. Kauffman, Sloan, Gates) and government agencies (e.g. NSF, FDA, NIH). Each individual non-profit has a mission-specific objective (e.g. global health for Gate Foundation) and is interested in systemic, general research questions that can be applied at a broader level than an individual firm. These non-profits typically sponsor research either at the project/program level or at the individual investigator level. Many of the government agencies are currently increasing funding available for science programs through various stimulus packages.

Specific non-profit sponsors that are well aligned with the intended research of BioMAN include:

- Alfred P. Sloan Foundation: original research and education in technical areas(27)
    - Potential focus on biomanufacturing industry and associated economic systems performance (see Chapter 3)
- Gates Foundation: improving global health(28)
    - Potential research program: enabling inexpensive transport of biological products to remote locations (see Appendix A)

- Grand Challenges: working in collaboration with Gates Foundation(29)
    - Requests for proposals in specific research areas are solicited twice annually. Initial grants are in the amount of $100,000 and successful projects have the opportunity to receive a follow-on grant of $1 million or more.
- Broader NIH: Roadmap Transformative R01 Program (30)
    - Focus areas of potential interest (e.g. Novel Protein Capture Reagents)
- NIH New Innovator Award – awarded to individuals(30)
    - Up to $1.5MM over 5 years
- NIH Pioneer Award awarded to individuals (30)
    - Focused on new and emerging research areas

In attempting to serve both types of customers (industrial, non-profit) simultaneously, a challenge arises at the interface of generality vs. specific ("custom") research. However, as mentioned previously, two noteworthy relevant consortia (Dundee Kinase, Tufts CSDD) complete this approach by engaging both types of customers in longer-term transformational research while provided custom near-term projects and educational opportunities for industrial partners.

2.3 BioMAN Capabilities

The current BioMAN organization is an integration of individuals each with their own expertise, or core competences.(8; 31) However, one weakness of the BioMAN consortia being composed of individuals with their own, independent expertise is that BioMAN and these individuals have potentially competing core products in a similar channel ("channel conflict"). An individual marketing their own research may be attempting to directly attract the same resource source(s) as BioMAN.(10) Ways to overcome this potential channel conflict include 1) focusing BioMAN on projects that are sufficiently interdisciplinary and collaborative (e.g. systems based) not to directly conflict with research of individuals; and 2) creating long-term engaging research contracts with BioMAN researchers in the consortium.

Both the BioMAN management and the capabilities of the BioMAN affiliated researchers have the capability to design and enact interdisciplinary and collaborative research programs.

Representatively, the individuals in the MIT BioMAN community that have participated in activities to date and/or expressed interest in doing so represent a wide range of expertise and potential for projects attractive to BioMAN customers. The MIT BioMAN community expands beyond MIT to include collaborators with relevant subject matter expertise and research interests. In completing a review of their capabilities, three areas of core competence (32; 9) emerge:

- Economics, Management, and Policy
- Biochemical Engineering
- Optics and Sensors

With the recent movement of CBI as a research initiative within the MIT engineering systems division (ESD),(33) the emerging collaborations between BioMAN and faculty with expertise in systems engineering have the potential to blossom. Systems engineering projects are interdisciplinary and collaborative as they require both detailed subject matter expertise and broad, mathematical constructs in which to frame the details.

Three significant lacking resources for BioMAN projects are:

- A history of demonstrated projects
- Relevant historical data sets
- A biomanufacturing facility in which to test potential new technologies

The first lacking resource is largely mitigated by the branding of MIT as a research center of excellence. Depending on the type of research project, the other two lacking resources may be able to be added to the BioMAN capabilities through collaboration.

2.4 Marketing Strategy

The marketing strategy is dependent upon the competition, the customers, and the organizational capability and is therefore always dynamic and prone in error.(10) An estimation of market segments that can be logically targeted by BioMAN and product positioning within those segments are described in the following subsections.

2.4.1 Targeted Segments

The potential sources of segmentation of the market are displayed in the table of attributes (Table 1) gleaned from an analysis of the current competitors of significance and the associated perceptual map of Figure 4. Of the seven attributes, four of the attributes are not independently selected for BioMAN, namely:

- Focus on biomanufacturing: this will be the only focus of BioMAN
- Geographic location: BioMAN headquarters and regular meetings will be at MIT
- Financial sources: pursued sources will be interdependent upon the research agenda
- Size: will be dependent upon the financial resources

The remaining three attributes (research/training, management/technical, availability of custom projects) define the possible market segments and set the research strategy for BioMAN. With the current set of BioMAN available or lacking resources (ESD faculty with expertise in systems, MIT technology expertise branding, uncertain funding sources, and no faculty solely dedicated to biomanufacturing research) and the current shrinking of availability of funds from industrial partners, taking on significant commitments in the areas of training and/or custom projects would risk utilizing a small amount of resources towards a few small projects that will not have direct continuity into the future. It is therefore most logical to currently pursue the market segment of systems-based interdisciplinary research in management and/or technical arenas that can be supported financially by non-profit entities and supported conceptually and with data by industrial partners. This is depicted in Figure 5 where the four identified direct competitors have been shaded out and BioMAN has been placed in the market map. To the extent that this pursuit becomes successful and enables the formation of a research team of significant size and expertise to branch out, then taking on training and/or custom project opportunities would be valuable towards strengthening relationships with industrial partners.

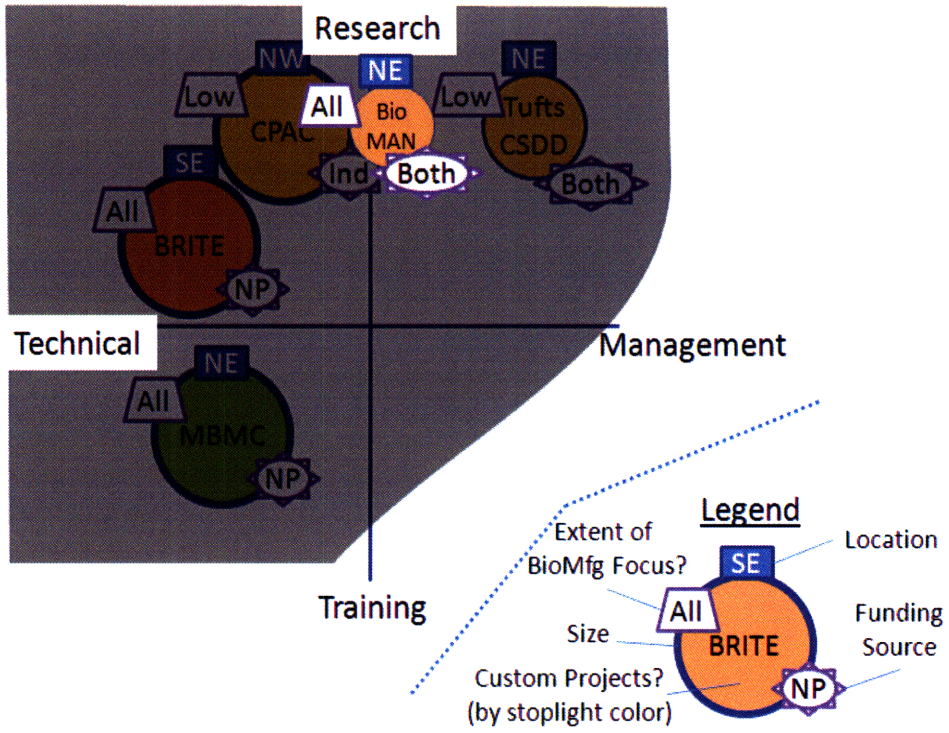

Figure 5. Perceptual Map with the Inclusion of BioMAN in the Market

In order to achieve success in this location of the market, BioMAN will become more dependent upon non-profit funding sources (foundations and government agencies) than BioMAN currently is. This will require BioMAN managerial effort invested in determining the objectives of relevant foundations and government agencies.

One recent example of a successful relevant niche consortium, the C-Path Consortium (which works with the FDA on its Critical Path Initiative) advertises the following specific selection criteria that are well aligned with the objectives of its partners: (34)

- The problem (or the opportunity) must be important to the public health and one that was identified in the Critical Path Opportunity List or one subsequently identified by FDA scientists at multiple levels.
- The project must be acknowledged by the industry as important and therefore one that multiple companies are willing to dedicate the time and efforts of their employees.
- There must be a "neutral source" of funding for C-Path to rise to support the project.

2.4.2 Product Positioning

The positioning of the BioMAN product should be clear both to constituents internal to the MIT biomanufacturing community and to potential resources source(s). Additionally, in the positioning of the product to external constituents, the concept that BioMAN complements existing biomanufacturing efforts in the region (specifically Tufts CSDD and MBMC) should be articulated when helpful. (10) Moving forward, the potential for project-specific collaboration with these two entities would help BioMAN achieve research excellence. The researchers and data available through Tufts CSDD could prove valuable to macroscopic economic performance research conducted through BioMAN. The potential facilities and pilot scale manufacturing expertise at MBMC could enable demonstration of new technology developed through BioMAN in industrially relevant settings.

2.5 Actionable Recommendations

Leveraging the market analysis around competitor attributes, customer rationale for participating in BioMAN, and the BioMAN capabilities, the following recommendations result:

- Internally market the value of interdisciplinary solutions approach to attract potential collaborators within the MIT biomanufacturing community (at MIT and beyond)
- Enable the possibility of taking of ideas from idea/laboratory bench to pilot demonstration
    - Consider partnering with Massachusetts Biomanufacturing Center (MBMC) to leverage complementary activities, geographic proximity, and their early stage of formation (which may give BioMAN some influence in the MBMC design and objectives)
- Pursue research projects that have potential for both tangible results to industrial partners and connection to systematic challenges in biomanufacturing
    - Enables simultaneous pursuit of value creation to industry and non-profit funding sources (e.g. foundations, government agencies)
    - Continue to pursue research project specific collaborations across disciplines

- In the future, consider developing academic content in the area of biomanufacturing management (e.g. student programs, executive education programs) as this appears to be an available market and is well connected to the MIT brand and faculty capabilities
- In the future, consider marketing custom projects to enhance tangible value creation for industrial partners

3 Specific Example of a Proposal to a Potential New Resource Source

The following is a fully developed example of an interdisciplinary, systems-based research program that appears to be well suited to receive support from a non-profit research sponsor with interest in understanding economic systems (e.g. the Alfred P. Sloan Foundation of New York).

3.1 Background: Research Motivation and Intent

Biologics are the fastest growing sector of the pharmaceutical industry with significant growth potential projected for the next 10 years.(35;36;37) Costs associated with the production of biopharmaceuticals have increasingly led companies to explore global supply chains for the manufacture of biologics by outsourcing, owning facilities, and/or establishing joint manufacturing ventures in low cost areas of the world ("off-shore") instead of manufacturing in close geographical proximity to their innovation and discovery centers.(35;36)

Recent studies focused on small molecule pharmaceuticals in areas of off-shoring(36) and global innovation(38) demonstrate the importance of taking both a global and systems perspective of manufacturing. Biopharmaceuticals have special concerns in manufacturing complexity, product fragility, unproven analytical techniques, and cold chain logistics for storage and distribution.(39)

It is the intent of this research program to develop a detailed understanding of the current and future states of biopharmaceutical manufacturing in the context of commercial strategy, global supply chain, and evolving landscape. This program will be accomplished by bringing together subject matter experts in areas of biopharmaceutical manufacturing, economic systems models, the role of regulation, and regional variability.

3.2 The Capabilities of M.I.T. Center for Biomedical Innovation

The Center for Biomedical Innovation (C.B.I.) at the Massachusetts Institute of Technology (M.I.T.) is an established leader in collaborative research at the interface of academia, industry, and government regulator. With this framework already in place, the research program will proceed quickly and effectively under the academic guidance of principal investigators, consultants, and advisors. Research Framework, Approach, and Methodologies

To develop a detailed understanding of the current and future states of biopharmaceutical manufacturing, this research program intends to use the framework depicted in Figure 6. This framework is designed to enable the examination of integrated economic systems models of commercial strategy, supply chain optimization, and anticipated changes in the context of regional effects and regulation. The approach and methodology associated with each of these topics is addressed in the following sections.

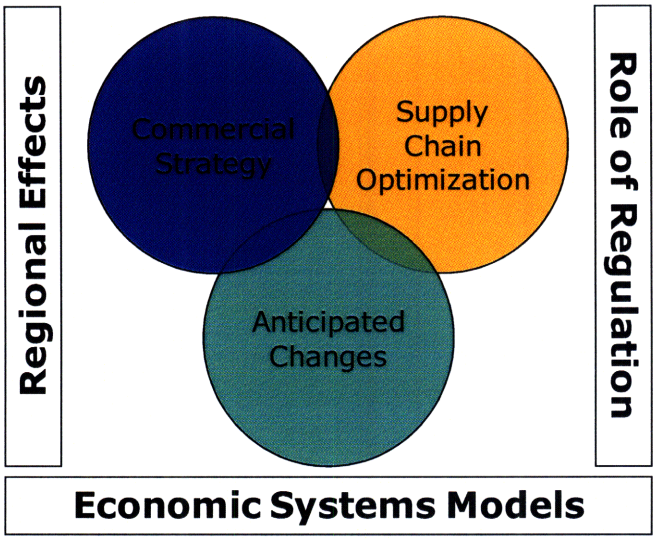

Figure 6: Research Framework for Biopharmaceutical Manufacturing

3.2.1 Commercial Strategy

The commercial strategies of biopharmaceutical manufacturing are strongly dependent upon regional economic incentives (e.g. taxes, labor costs, required capital), core competencies of the companies, appreciation of quality standards, manufacturing capital cost risk mitigation, transportation challenges, communication, and intellectual property protection.(35) As depicted in Figure 7, the influence and the impact of these commercial strategies are reflected

in the economics of the value chain, extent of integration within a company's biopharmaceutical manufacturing, and the physical location of the manufacturing. The intended research in each of these specific areas is described in the following sections.

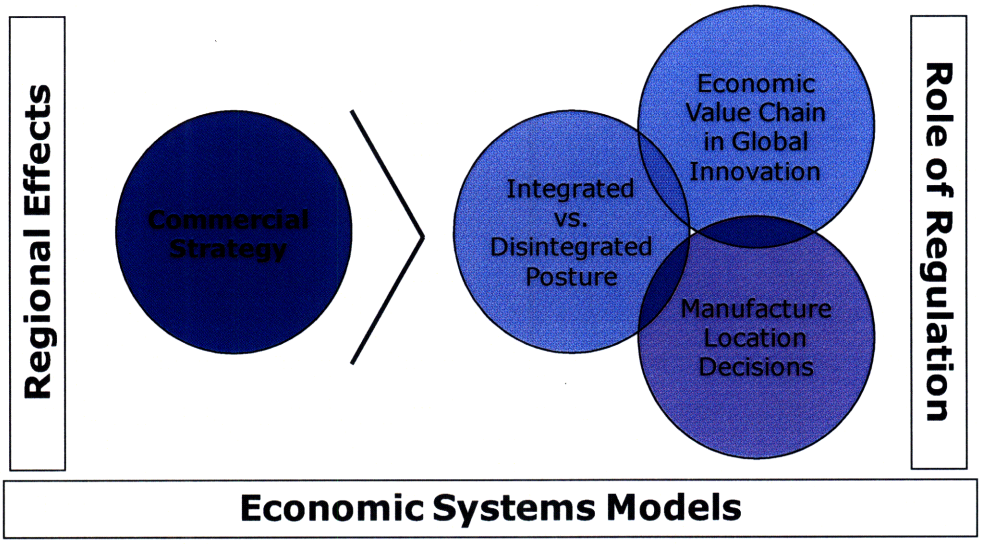

Figure 7: Context of Commercial Strategy Research

3.2.1.1 Economic Value Chain in a Global Innovation System

Innovation is widely held as the key to the sustained competitiveness of the U.S. As biomanufacturing supply chains combine a range of geographies, integrated technologies, and innovative approaches, it is unclear who is capturing the resulting value. As has been done recently for another globally innovated product, the iPod,(6) it is the intent of this research to develop an understanding of the economic value creation across the product lifecycle and thereby determine where innovation within biopharmaceutical manufacturing is sustained (as demonstrated by sustained profit).

This work will involve defining a framework of the biopharmaceutical manufacturing value chain and leveraging specific case studies within that framework to quantitatively determine innovation sustainment. Consistent with recent studies,(6) the approach in this framework will be a value map built from raw materials through to the customers that incorporates geographic locations towards de-convoluting both which innovators and which countries are receiving the value. The data intended for quantifying the value map includes gross profit data available

from annual reports of publicly traded companies, component prices from industry analyst reports, and validation from interviews with participants in the value chain.

The specifics of biopharmaceutical manufacturing will be compared to small molecule pharmaceutical manufacturing and other relevant high-volume, global manufacturing, innovative industries (automotive, electronics).(7) The quantitative value chain framework will also enable a consistent paradigm for describing other aspects of commercial strategy, supply chain optimization, and anticipated changes within this research program.

3.2.1.2Integrated vs. Disintegrated Global Posture

Building on recent data and findings from the semiconductor industry regarding the performance implications of outsourcing decisions,(40) this aspect of the research program will further the value chain framework by determining interconnectivities within the product lifecycle, both from theoretical and data driven perspectives. In the case of semiconductors, recent research suggests that internal knowledge and dependencies in product and process development yields net commercial gains for maintaining internal capabilities.[40] Without this systems perspective, outsourcing appeared more attractive in many cases. Recent research in the pharmaceutical industry suggests possible similarities to the semiconductor industry as contract manufacturing facilities have been documented to generally correspond to inferior performance metrics(41) and the knowledge created from firm experience has been shown to be significant.(42)

This methodology of examining the impact of extent of integration on commercial performance in the context of biomanufacturing will be extended to both biopharmaceutical development companies and biopharmaceutical contract manufacturing organizations. This will be accomplished through extensive data collection with industrial partners and analysis in the context of the full economic systems models.

3.2.1.3Manufacture Location Decisions

It is the intent of this subset of the research to quantify the impact of regional economic and political volatility, particularly in areas of interest for off-shoring and integrate these findings into the comprehensive economic systems model. This is described in detail in Chapter 4 as an

example of an approach to an interdisciplinary project attract to both non-profit sponsors and industrial partners.

3.2.2 Supply Chain Optimization

Supply chain strategies typically focus on the interconnection, competition, and associated risks of key drivers such as:(43)

- Cost pressures (e.g. capital, labor, and tax efficiencies)
- Variability in supply chain quality
- Variability in regional regulation

Recent contamination-related deaths associated with the biologic drug heparin indicate that there is significant potential for improved supply chain optimization by utilizing a comprehensive risk-based economic systems model for biologics.(39;44) Failure to establish and maintain a robust supply chain will reduce consumer confidence in the use of biologics and the competence of the associated regulatory agencies.

As depicted in Figure 8, the focus of the economic systems model for supply chain optimization will encompass security, safety, and resilience in the framework of regional effects and the role of regulation. These three aspects are described in sections below.

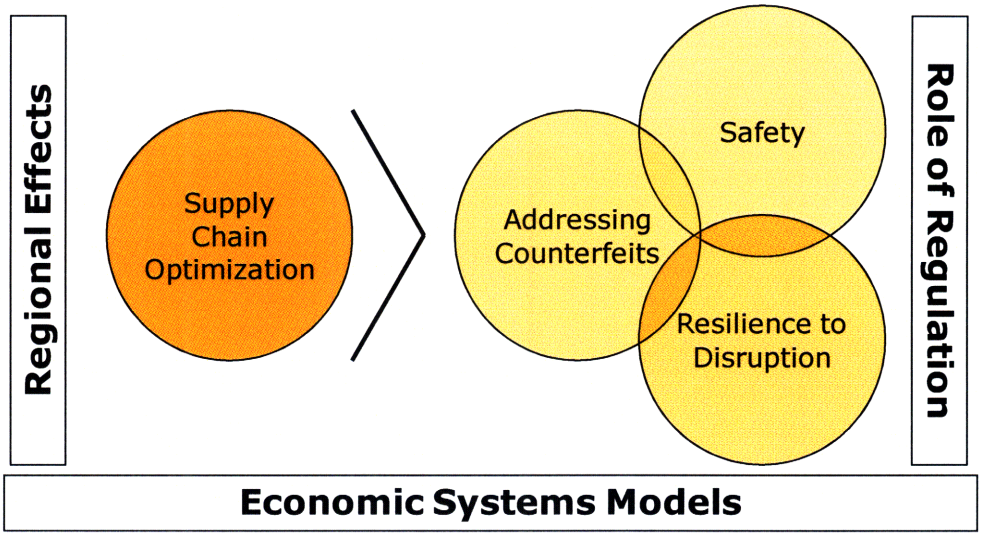

Figure 8: Context of Supply Chain Optimization Research

3.2.2.1Safety of the Biologics Supply Chain

In the face of potential trade-offs between cost and safety, the ability of the supply chain to deliver safe biologic products is critical to patients who could suffer morbidity or mortality from tainted drugs. As described in recent research:

"Cost constraints are forcing enterprises to outsource and off-shore functions once performed within the safe environs of an FDA-regulated manufacturing facility. Movement of…manufacturing to lower-cost locations, in some cases has resulted in reduced quality controls, re-introducing risk factors that haven't existed for decades. The most recent debacle related to the processing of pig intestines—a starting ingredient for the production of heparin, a commodity that is used in a high percentage of medical and diagnostic procedures—highlighted what appears to be the tip of an iceberg." [Reed, 2008](45)

The systems-based models developed in this research will enable ongoing risk-based quality and robustness assurances with considerations including:

- Importance of direct access to monitoring data from suppliers
- Financial health and political risks of suppliers
- Interdependence of suppliers
- Patient data monitoring for unusual events

The approach to accomplish this intent is to integrate existing data on safety standards, safety violations, regulatory policies, and decision making priorities.

3.2.2.2Integrated Approach for Addressing Counterfeits

Globalization of the supply chain has increased the presence of counterfeits as depicted in Figure 9.(46) Counterfeit drugs pose health risks to patients and loss of revenue for pharmaceutical firms.

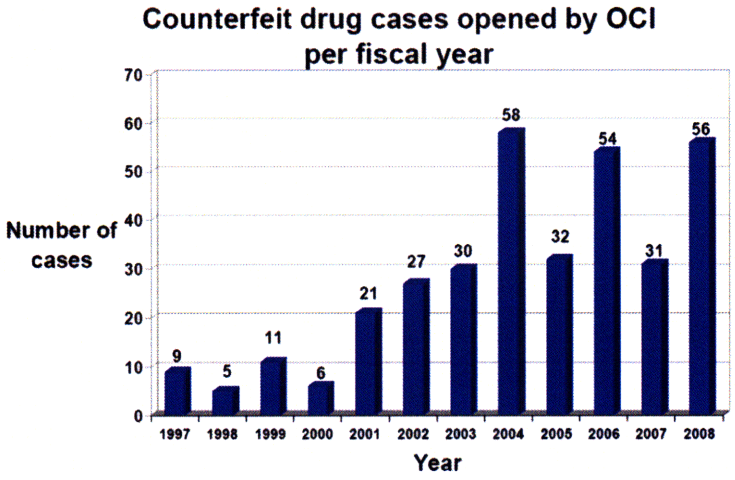

Figure 9: Counterfeit Drug Cases Opened by OCI in the Past Twelve Years(46)

Additionally, the variation in regional regulation around security is significant as exemplified in the following list of emerging state, national, and international requirements:

- States:
  - Individual state pedigree requirements
  - CA required electronic pedigree, manufacturer through pharmacist and requires serialization at saleable unit by 2015
- U.S. National:
  - FDAAA Sec. 913 Calls on FDA to develop a standard numerical identifier (SNI) by March 27, 2010
  - Possible legislation in 111th Congress: Buyer-Matheson

- International:
  - WHO World Health Organization's International Medical Products Anti-counterfeiting (Impact) Task Force
  - EU Proposal: Directive of the European Parliament and the Council
  - Amending Directive 2001/83/EC to prevent entry of falsified medicinal products (e.g. identity, history) into the legal supply chain

The models developed in this research will specify a system solution to combat challenges of counterfeit biologics in global supply chains. Consideration will include techniques such as:

- Serialization to enable traceability
- Secure e-pedigree exchange
- Supply chain event data networks
- "Point of Entry – Point of Exit" validation system

3.2.2.3Resilience to Disruptive Events

The complete biopharmaceutical manufacturing process is typically complex; with many manufacturing stages (spanning time and space) and long production cycles (hundreds of days is common). Given this high level of complexity, the industry consolidates expertise and capability into central facilities and is less invested in secondary components of the supply chain (e.g. suppliers, storage, transport). As a result, the resilience of the supply chain in providing patient-critical product in the case of significantly disruptive events is expected to be fragile:

"In most cases secondary suppliers, storage and transportation are not well addressed. Because these supply chain roles are increasingly played by globally dispersed organizations, there is increasing vulnerability that needs to be addressed." [Reed, 2008](45)

Leveraging existing models of resilience in supply chain optimization and lean manufacturing concepts, strategies that identify optimal trade-off between flexibility and fixed cost required to achieve that level of flexibility will be developed. To the extent that flexibility and redundancy is built into the system, the likelihood of having a robust and resilient supply chain increases and both greater patient care and greater profit can be realized in the case of adverse events.

Specifically, the approach will include working with industrial partners to determine:

- **The extent of flexibility in place today.** Both the current state and the associated rationale with comparisons to other relevant industries (automotive, electronics).
- **Control location of work in progress**. Considering the physical location of work in progress relative to risk-based models of adverse events in the model of resilience.
- **Reduce cycle time**. Reducing cycle time is a key to increasing resilience of the supply chain. It can be directly achieved by lean manufacturing concepts and better utilization of workers, equipment, and workstations.

3.2.3 Anticipated Changes

Three changes that have been identified as having potential to significantly alter the landscape of biopharmaceutical manufacturing are: the role of emerging markets, new technologies and personalized medicine, and the economics of regulatory compliance. These are depicted in Figure 10 and described in the following sections.

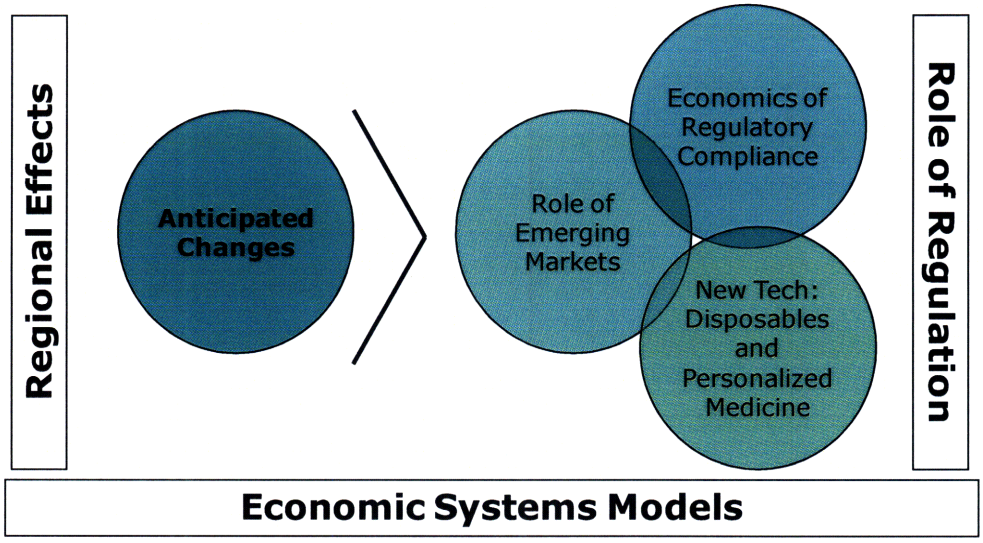

Figure 10: Context of Research on Anticipated Changes

3.2.3.1 Role of Emerging Markets

Beyond the cost advantages of manufacturing biopharmaceuticals in emerging markets, some North American and Western European companies perceive a strategic advantage in ease of

global delivery as the consumption of biological products in emerging markets increases. Additionally, recent research suggests that emerging market companies with manufacturing expertise (e.g. contract manufacturers) are engaging in reverse-off-shoring to "develop in-house R&D capabilities with the intent of becoming major global players."(36) These emerging market companies are leveraging local government initiatives supporting biotechnology and hiring internationally trained scientists and engineers.(36) The significance of these trends on biopharmaceutical manufacturing and associated employment of U.S. scientists and engineers will be the focus of this aspect of the research program.

This aspect of the research will consider scenarios of the role of emerging market and the relevant impact on the commercial strategy and supply chain frameworks developed. Specifically, the research will investigate the following:

- Impact of regional economic and political volatility (described previously as part of the Commercial Strategy component of this research program)
- Details of biopharmaceutical employment trends in emerging market companies and western companies
    - The trend is described in recent research: "Although there may not be an imminent threat to American leadership in technology, the number of young professionals in emerging markets is growing by 5.5% annually, while growth in developed countries is only 1%."(36)
    - With the impact described as requiring "more statistical data on employment and demand for engineering positions broken down by academic majors, degrees, and functions in the industry both in the US and abroad... to produce a clearer picture of how off-shoring will impact the science and engineering workforce in the US pharma industry."(36)
- Details of trends in reverse off-shoring leveraging recent data and conducting interviews with contract manufacturers and government officials
    - Determine the extent to which utilization of off-shore contract manufacturers is expected to change

- The impact of government-sponsored biotechnology and education initiatives in emerging markets

3.2.3.2New Technology: Disposables and Personalized Medicine

The impact of emerging technology on the commercial and supply chain frameworks of biopharmaceutical manufacturing will be investigated in the context of two specific technologies: disposables and personalized medicine. Disposable manufacturing equipment pieces have the potential to enable both distributed manufacturing and reduced capital expenditure. In the context of manufacturing, personalized medicine would reduce batch sizes and increase the value of manufacturing flexibility and product customization.(47)

It is the intent of this aspect of the research program to evaluate future scenarios associated with these two technologies to determine their impact on how and where biopharmaceutical manufacturing will be done. These two technologies would be representative case studies of the role of new technology on the biopharmaceutical manufacturing landscape and provide insight into expectations and hurdles.

3.2.3.3Economics of Regulatory Compliance

As small and medium sized biopharmaceutical firms move towards global supply chains, their ability to meet regulatory expectations is undetermined. Leveraging recent F.D.A. inspection history data for every pharmaceutical manufacturing facility that has shipped product to the U.S.A., this aspect of the research will determine the importance of firm size, experience, and financial status on inspection performance.(41)

Additional investigation into the economics associated with ensuring regulatory compliance of a global supply chain will be undertaken to provide a rationale for small and medium biopharmaceutical companies considering use of a global supply chain. These economic data will be determined in collaboration with the M.I.T. C.B.I. industrial partners and in the frameworks established in the commercial strategy and supply chain optimization aspects of this research program.

3.3 Outcomes of the Research

Intermediate outcomes of the research include continued and extensive interaction between academia, industry, and the U.S. F.D.A. on issues critical to the economics and safety of biopharmaceutical manufacturing. These will include topical roundtable discussions, working papers, recommendations, and collaborative research.

The deliverables of the research program include a series of academic papers describing the economics systems models and their underlying theory and supporting data. These models provide a framework to use in structuring activities to ensure global safety across the biopharmaceutical supply chain. The deliverables further include detailed decision criteria for off-shoring biopharmaceutical manufacturing efforts. Additionally, these criteria will be framed to provide guidance to policymakers in designing incentives for specific activities within biopharmaceutical manufacturing.

Activities under the research provide for training of graduate and post-doctoral students. This training builds a knowledge base in economic systems models, supply-chain logistics, regional variability, and the role of regulation.

4 Approach of a Research Project: Biomanufacture Location Decisions in the Prospect of Regional Volatility

It is the intent of this subset of the research to quantify the impact of regional economic and political volatility, particularly in areas of interest for off-shoring and integrate these findings into the comprehensive economic systems model.

4.1 Background of Regional Volatility

A number of factors influence the likelihood of regional volatility which, in turn, may or may not impact the business operations or costs associated with biomanufacturing. Examples of the influencing factors, institutional structures, and events that may trigger significant volatility are depicted in Figure 11. An underlying influencers analysis model will be employed, as has been done in previous research,(48;49) to identify and quantify impact on different types of foreign investment due to regional volatility. This model will specifically build on:

- Histories and projections of economic and political volatilities and the relevant impact on a variety of types of foreign investment in low cost regions of current interest (e.g. China, India, Malaysia, Latin America)
- A region specific approach to gain insight into the specifics of the regions of current interest
- Histories of impact of regional volatility on small molecule off-shoring and off-shoring in other industries

A simple example of minor economic volatility is recent wage increases in Asia: operating costs for technology off-shoring to India in 2004 was found to be approximately 20% of that in the United States, but wages across the board from accountants to engineers have increased in excess of 10% per annum due to rising demand since that year and are now closer to 30% of that in the United States.(50)

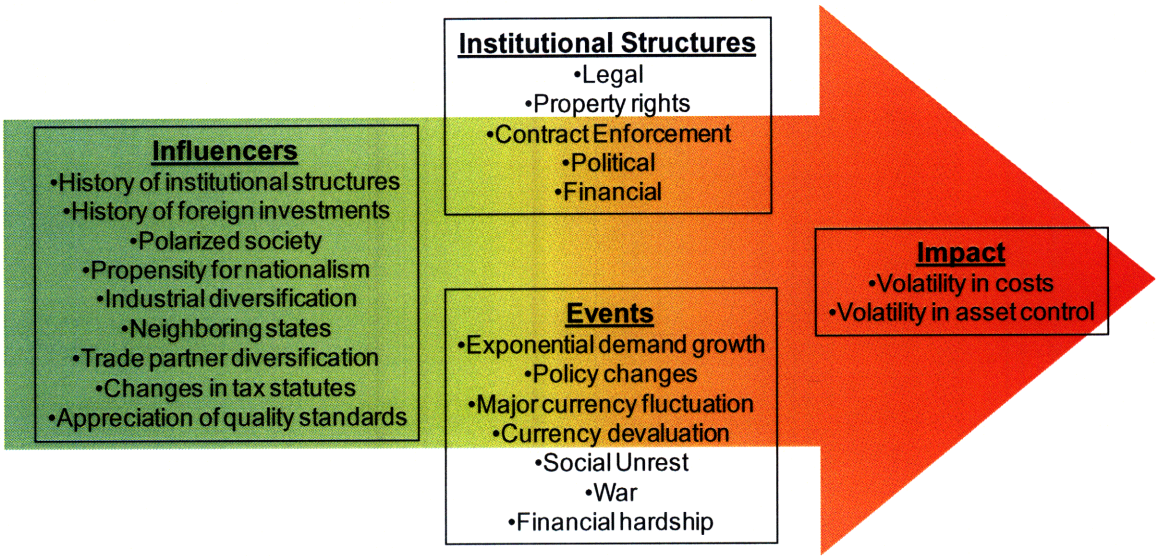

Figure 11. Influencers, Structures, and Events that may Impact Regional Volatility

Based on the research on volatility impact and the cost structure associated with biomanufacturing (provided by M.I.T. C.B.I. industrial partners), a stochastic model of probable scenarios and the resulting economic impact will be developed. An additional aspect of the influencer analysis model will be explicit approaches for risk mitigation of key influencers through detection methodologies.(51) There are parallels in this approach to quality by design (cause and effect, historical precedents, design space estimation, failure mode and effects analysis).

Industrial members of the M.I.T. C.B.I. community have agreed to provide data and interview access to develop case studies of off-shoring decisions. In particular, the industrial members will provide:

- Completed decisions and associated rationale (as available) regarding off-shoring for biologic products
- The manners in which volatility has been incorporated in previous off-shoring or similar decisions
- Cost structures of existing off-shoring activities for both small molecules and biologics
- Intermediate reviews of ongoing research

4.2 Framing the Project

4.2.1 Guiding Information from the Industrial Sponsor

In preliminary discussions with the industrial sponsor, the following general observations were made regarding manufacture location decisions:

- The decision regarding the manufacture location(s) of a product is dependent upon the current and perceived financial climate specific to the company including:
    - Timing of needed facility (e.g. for phase 3) and projected volumes
    - Utilization of internal manufacturing network (current and projected)
    - Cash available for pursuing/enabling other options
    - Risk profile of the project
- Transport costs and local regulatory environment are not typically significant enough to be part of the decision process
- Some companies have a global sourcing group in place to facilitate with the location decision
    - The team of decision makers typically includes representatives of:
        - President, manufacturing
        - VP, API/FG
        - Legal
        - Tax accountants
        - Business development
- The current best thinking is to share risk either with contractors or with governments acting as a financial partner.
- One manufacturing location decision example in the last decade that included the use of a new facility was described:
    - Product that was not expected to fit in the existing manufacturing network
    - Review of potential new sites in Ireland, Puerto Rico, Singapore, and a contract manufacturer near Montreal
    - Rationale for final selection is unclear at this time

Some key information remains to be determined from ongoing interactions with the industrial sponsor around the details of:

- How location decisions are/should be made
- Export/repatriation of funds
- Relative amounts of different types of relevant costs

4.2.2 Expectations of the Modeling Efforts

The industrial partner will work with the MIT researchers to investigate:

- Considerations taken (actual and/or ideal) into the decision making process
- Options considered (e.g. outsourcing, new process technologies)
- Specific individuals involved in the decision making process
- Representative cost structures of biomanufacturing facilities

The MIT researchers will investigate:

- Representative probabilistic models for regional volatility
    - With inputs of volatility influencers
- The impact of volatility on representative cost structures and asset control
    - With outcome of relevance to bottom line as depicted in Figure 12
- Building models with data from the industrial partner
    - Incorporating region-specific inputs
- Analyzing resulting models for impact of selected cost structure and asset ownership

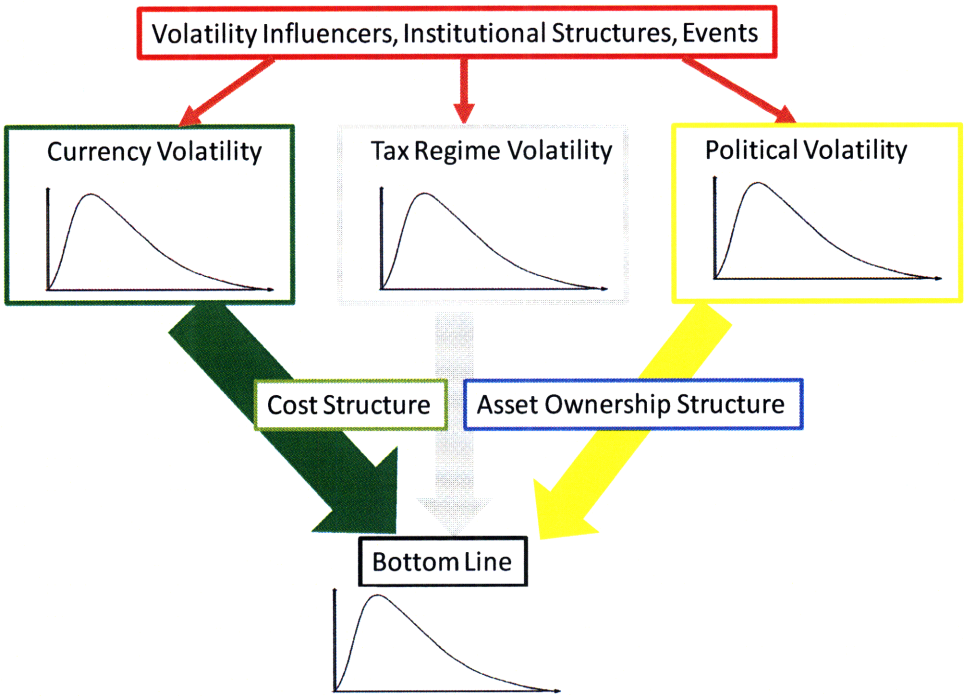

Figure 12. Model framework with inputs creating probabilities of different types of volatility, each of which impact the bottom line depending on the attenuation caused by the cost structure and asset ownership structure in place

4.2.3 Enabling the Model Framework

Determining the full details of the model framework depicted in Figure 12 and the associated analysis of the resulting findings would complete the full intended project. This will require determining the following with representative sources identified:

- Types and magnitudes of influencers, structures, and events relevant to the region of interest
    - Sources:
        - Identified volatility indicators(52; 53)
        - Quantifying political change (54)
        - Interconnection of institutions and policy volatility (55)
        - Empirical relevance of identified volatility indicators(56; 57; 58)
- Resulting probability distributions for the different types of volatility
    - Sources:
        - Realized distribution of volatility(59; 60)

- Representative cost structures and asset ownership structures
    - Sources:
        - Records of publicly traded contract manufacturers
        - Direct data from industrial partner
- The attenuation caused by the cost structure and asset ownership structure
    - Sources:
        - Historical costs from manufacturing as a function of volatility
        - Impact of exchange rate volatility on trade and investment(61)
        - Quantitative link between political instability and asset ownership risk(48)
        - Regional effects of exchange-rate shocks(62)

In this representative approach, one aspect of the model framework will be demonstrated with sample data as representative of the expected approach to the full model. The quantitative attenuation of currency and tax volatility with a sample cost structure is presented in Figure 13 along with associated rationale for the assigned interaction. The sum-product of the relative fraction of cost and impact yields an attenuation total for each of the two types of volatility for the specific cost structure shown. In this example, for a 10% change in currency, the bottom line is altered 8.5% and for a 10% change in tax rate, the bottom line is altered 2.2%. In this situation, the shape of the volatility distribution is not altered by the cost structure, just simply attenuated.

Cost Structure		Impact and Rationale from Volatility Type			
Cost Category	Relative Fraction of Costs	Currency Impact	Currency Rationale	Tax Impact	Tax Rationale
Product Revenue	N/A	N/A	Not within region	N/A	Not within region
Costs of Goods	10%	50%	Goods may be sourced from elsewhere	50%	Raw materials may be taxed
Rented Real Assets	10%	100%	Ongoing payments	10%	Property tax may be relevant
Owned Real Assets	10%	50%	Impact only realized on sale or valuation	10%	Property tax may be relevant
Depreciation	5%	100%	Ongoing expense	0%	Not influenced
Utilities	10%	100%	Ongoing expense	10%	Indirect expense
Insurance	5%	100%	Ongoing expense	10%	Indirect expense
Interest on Loans	5%	100%	Ongoing expense	10%	Indirect expense
Employee Wages	20%	100%	Ongoing expense	0%	Direct wages unchanged
Employee Benefits	10%	100%	Ongoing expense	30%	Payroll taxes
Royalty/License	5%	0%	Likely out of region	0%	Likely out of region
Local Tax	10%	100%	Ongoing expense	100%	Direct expense
Attenuation Total		**85%**		**22%**	**Assumes uniform tax change**

Figure 13. Sample cost structure and quantitative impact of currency and tax changes

Depending upon the firm's appetite for variability in the bottom line, techniques such as hedging for currency fluctuations could alter the shape of the incoming probability distributions to offset some of currency volatility risk.

4.3 Specific Research Outcomes

Specifically, results of the data model, interviews, and case studies will quantify answers to the following questions of importance to manufacturing location decisions:

- What is the relative importance of current determining factors and conditions in decisions to outsource production of biologics to off-shore locations?
- How have these factors changed over time and how are they expected to change in the future?

- How is regional volatility incorporated in these decisions and how should it be?
- How does the relative importance of these factors change over the lifecycle of a product and the maturity of the company?
- What is the impact of these factors on decision models for biopharmaceutical companies, North American biocluster efforts to structure incentives, and economic policy makers related to biologics manufacturing?

5 Comprehensive Bibliography

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6 Appendix A: Executive Summary of Research Program on Reducing Costs of Biologics and Vaccines to Remote Locations

Reducing Costs of Packaging and Delivery of Vaccines and Biologics

Improving the Economic Drivers for Global Access to Disease Prevention and Treatment

Summarized by Reuben Domike, Ph.D.

Based on group discussion at BioMAN Futures Meeting in February, 2009

I. Research Motivation and Intent

Challenges arise in economically delivering vaccines and biologics that have cold chain requirements to remote and/or poor locations. These challenges may include the difficulties in delivering a thermally sensitive product and/or the lack of a profit motive. The largest supply chain logistics challenge and cost for many vaccines and biologics is perceived to be one and the same: maintaining the product within its specified temperature. A recent study concluded that between 14% and 35% of refrigerators or transport shipments expose vaccines to freezing temperatures,[1] which is expected to damage many current and emerging vaccines.[2] Some doses are exposed to elevated temperatures in their transportation, as a recent study of rural Bolivian deliveries demonstrated in finding that seven of the eleven central deliveries exposed the doses to temperature in excess of 8°C.[3] Despite awareness of these issues and detailed policy guidelines from the World Health Organization,[4,5,6] millions of vaccine doses are wasted each year due to a lapse in recommended storage conditions.[7]

To overcome this challenge and cost, it is the intent of this research to make the cost of distribution and packaging small relative to the cost of an inexpensive product (e.g. a common vaccine). Specific avenues of research that will be pursued include thermal stabilization of formulations, multi-dose packaging, improved cold chain logistics, and active cooling transportation options. Aspects of these have been pursued elsewhere. It is the intent of this research to provide a comprehensive solution to this challenge and cost to improve economic drivers of delivering life-saving therapeutics to underserved populations.

II. Coordinated Competencies and Resources

The competencies perceived necessary for providing a comprehensive solution include:

- Stabilization chemistry and engineering
- Product formulation

- Microsensors of temperature and stability
- Material selection
- Regulatory support for the project

The Center for Biomedical Innovation (CBI) at MIT builds on a history of collaborative excellence at the interface of academia, industry (including biopharmaceuticals and vendors), and regulators. CBI believes that MIT and its partners are well positioned with these competencies to coordinate a comprehensive solution.

CBI specifically anticipates this to be a 3-5 year project starting with approximately 6 FTEs (graduate students, post-docs, etc.) in the areas of competency listed above, leveling to 10 FTEs in the second year.

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