

PHARMACEUTICAL MANUFACTURING RESEARCH PROJECT

January 28, 2004

BACKGROUND

Pharmaceutical manufacturing is a substantial and global activity that has several unique facets that make it an interesting context in which to study. Conversations with various manufacturers suggest that these different approaches lead to variation not only in productivity but also in the way in which firms are organized in different countries. There also is some suggestion that human resource (HR) practices and manufacturing productivity also differ in systematic ways.

Surprisingly, pharmaceutical manufacturing, especially with respect to international differences, has been little studied in the management literature. Relatively little is known about the magnitude of these differences or the effects of country-level variation in regulation on pharmaceutical manufacturing.

Our research project will examine two sets of relationships pertaining to the performance of pharmaceutical manufacturing. First, it will investigate the relationship between regulatory oversight through the FDA's current Good Manufacturing Practice (cGMP) on pharmaceutical firm behavior and the resulting production and regulatory performance. Second, it will investigate the effect of pharmaceutical manufacturers' organizational factors on production and regulatory performance.

The key factors of interest that we intend to examine are (1) the organization and management of new process development; (2) the organization and management of deviations and validations; (3) the nature and effect of the production facility's incentive structure(s); (4) the role of corporate headquarters and nature of the corporation's structure; and (5) the nature, sophistication and adoption of manufacturing technology (including information technology and process analytical technology) on the level and rate of improvement in manufacturing performance; and (6) the organization of the manufacturing facility.

The performance dimensions of pharmaceutical manufacturing that we intend to examine include regulatory oversight outcomes (deviations, consent decrees, product recalls, product availability, etc.), manufacturing metrics (yield, cycle time, etc.), and other outcomes appropriate to the industry. Although our unit of analysis will be the product production line (i.e., product manufactured), our study will include information on the specific manufacturing plant and

pharmaceutical firm as well as information on regulatory entities responsible for inspections. Generally speaking, we seek participation from all pharmaceutical manufacturing facilities. The survey asks for data from up to but not exceeding 5 compounds at each facility. We will work with manufacturers to determine which compounds are appropriate to consider.

In addition to receiving the results of our study, each participating manufacturing facility will receive a benchmark scorecard comparing its performance against the performance of anonymous other plants. The scorecard will identify each plant's strengths and weaknesses as well as suggest ways to improve manufacturing productivity and regulatory performance.

RESEARCH PROJECT APPROACH

This research project is proceeding in three stages. The first stage involved a pilot study and fact-finding set of visits and interviews with various pharmaceutical manufacturing plants. These structured interviews allowed us to identify which data was most useful and readily collectable in order to minimize the burden of the participating manufacturing firms. The primary resource requirements for this first stage were access to personnel and manufacturing facilities interested in participating in the pilot study. We have concluded the pilot phase of our study. The output of this first stage was a detailed but focused questionnaire for purpose of wide-scale data collection.

The second stage involves the implementation of the questionnaire. To lower the cost of such a questionnaire and to speed data collection, we implemented the questionnaire over the internet via a secure site. We also plan to use a variety of communications formats with managers—including regular mail, email and voicemail—to insure high participation rates.

Participating pharmaceutical and biotechnology manufacturing plants are asked to identify a liaison to complete and coordinate filling out the questionnaire. Participating firms use individuals from a variety of functional disciplines (quality assurance, quality control, regulatory affairs, manufacturing, etc.) to fill out the questionnaire with the least amount of resources. Arguably the most important criterion for any plant liaison is someone with time available to see the survey to completion. The survey is designed so that the liaison can identify several informants to help enter data. Thus, the liaison can identify the most informed respondent for each section, provide them with the URL, login, and password, and ask them fill in the requisite data section. Or, the liaison alternatively could collect data and coordinate data entry. Many firms have indicated that filling out the survey takes between two and three person weeks of effort; although, in calendar time it may take more than a month. We anticipate concluding the data collection portion by early June, 2004.

The final stage will analyze the data using a variety of econometric techniques. We anticipate that this analysis stage will take between three and six months. Upon completion of our analysis, we will provide a summary of our findings to participating manufacturers as well as the plant scorecard described above.

CONFIDENTIALITY AND INDEPENDENCE

All information obtained in connection with, by reason of, or in preparation of this research project shall be regarded as confidential. All information furnished during the terms of this research program concerning pharmaceutical manufacturers' business activities will be strictly confidential and no firm- or product-specific information will be disclosed. We will hold all

confidential information in trust and confidence. No specific information shall not used by, or on behalf of, any person without prior written consent of the participating firms.

We believe that it is important to maintain independence from the various regulatory entities and the pharmaceutical manufacturers involved in the research project. Thus, the first and second phases of this research project are supported from grants received from the Center for Business and Public Policy in the McDonough School of Business at Georgetown University and the Boeing Center for Technology, Information, and Manufacturing and the Center for Research in Economics and Strategy in the Olin School of Business at Washington University in St. Louis. We have also secured funding for the second phase from the National Bureau of Economic Research (NBER).

We are in the process of securing additional funding from other foundations, which support these types of academic research efforts.

SURVEY PARTICIPATION

We are actively involved in identifying companies and securing their participation. More than a score of pharmaceutical and biotechnology firms with an aggregate number of plants exceeding 200 are participating or have expressed interest in participating in this research project. These facilities include API, product, and biologic manufacturers. To be specific, as of this time we have 37 facilities that are actively participating. Another approximately 100 sites have agreed to participate: we are working on signing confidentiality agreements. We are beginning discussions with firms (e.g., a meeting in Zurich on February 4, 2004, with 11 firms) representing many more manufacturing locations. We continue to work on securing more participating sites.

We have also received moral support from the Center for Drug Evaluation and Research (CDER) and the Office of Regulatory Affairs (ORA) at the U.S. Food and Drug Administration (FDA), which has expressed significant interest in both research projects (described below). Both CDER and ORA believe that our project will help FDA identify potential beneficial changes in the way it regulates pharmaceutical manufacturing.

Firms who participate in our study will benefit in three ways. First, we will provide a scorecard comparing raw score of each facility to comparable but anonymous others. These reports will provide managers a quantitative assessment of where their facility stands versus relevant other plants. Second, we will undertake an econometric analysis to estimate an “efficient frontier” in terms of manufacturing and regulatory performance. This model allows identifying not only a plant’s distance from this frontier but also what changes need to be made for the plant to approach the frontier. These findings will be reported to each plant. Manager’s can then use this information to assess the cost and benefit of moving to the frontier. Finally, we will use our study to advise the FDA on how it regulates manufacturing. At a minimum, we anticipate being able to make suggestions to the FDA on areas (not specific firms or plants) where regulatory relief is warranted.

Please contact us by phone or email with any question, comment or concern regarding this research project. We look forward to meeting with you in person at your earliest convenience.

FDA RESEARCH PROJECT

January 27, 2004

BACKGROUND

This research project is an investigation into pharmaceutical manufacturing strategies and their relationship to FDA oversight and enforcement actions. Specifically, it will investigate the effect of the Food and Drug Administration's (FDA) regulatory oversight through current Good Manufacturing Practice (cGMP) standards on pharmaceutical firm behavior and the resulting production performance.

During the past year, we met with several individuals from FDA. These discussions have been focused on learning about the intricacies of FDA oversight activities for pharmaceutical manufacturing. A turning point of our research project occurred this past April, 2003, when we gave a presentation at the FDA/PQRI (Product Quality Research Institute) meeting held in Washington D.C., at which over 500 people from the pharmaceutical industry attended. The outcome of this meeting attracted a lot of interest to our study.

This research project focuses on the FDA and its management of manufacturing oversight activities. We will collect data from a variety of databases maintained by FDA to investigate the risk-factors that lead the Agency to inspect manufacturing facilities and, conditional on inspection, estimate the likelihood of various regulatory outcomes. In this analysis we will investigate the extent to which technological-, plant-, firm-, and FDA-related risk factors affect regulatory outcomes. This analysis will not only help the FDA determine how best to allocate scarce resources for inspections, but also investigate how its policies for managing its investigators and its choice of inspection assignments influence regulatory outcomes. From a normative perspective, the analysis will help to identify those facilities for which some amount of regulatory relief is appropriate, as well as provide counterfactual analysis for how the FDA manages its inspectorate. Finally, the study will provide deeper insights as to how the FDA should revise its cGMP program.

We have signed a Material Transfer Agreement (MTA) with FDA, and are working toward signing a Cooperative Research and Development Agreement (CRADA) with FDA. We are working under Dr. Janet Woodcock, the director of the Center for Drug Evaluation and Research (CDER), and Jonathan Taylor, the director of Office of Regulatory Affairs (ORA), as well as part of the committee for Pharmaceutical cGMP's for the 21st Century.

RESEARCH PROJECT APPROACH

This research project is proceeding in three stages. The first stage involved a pilot study and fact-finding set of visits and interviews with various FDA personnel. These structured interviews allowed us to identify which data will be most useful and readily collectable within FDA. We have concluding the pilot phase of our FDA study.

The second stage involves the actual extraction of data resident with the databases of FDA into a form suitable for analysis. A committee within FDA has been formed to work with us to collect the data that we require. FDA has committed resources to complete our research project—not something this resource-starved Agency does lightly. Moreover, FDA at its highest levels has

made a commitment to introduce us to the various pharmaceutical industry associations in order to solicit participation in our manufacturer benchmarking study, which we believe will greatly increase the level of participation by manufacturers. We are nearing completion of this stage of the research project.

The final stage will analyze the data using a variety of econometric techniques. We anticipate that this analysis stage will take between three and six months. Upon completion of our analysis, we will provide a summary of our findings to FDA with all manufacturing facility names disguised. Collecting this data from the FDA is a unique and substantial opportunity to evaluate the inner workings of a government agency and how it regulates a substantial portion of our nation's GDP.

CONFIDENTIALITY AND INDEPENDENCE

All information obtained in connection with, by reason of, or in preparation of this research project shall be regarded as confidential. All information furnished during the terms of this research program concerning FDA data will be strictly confidential and no firm- or product-specific information will be disclosed. We will hold all confidential information in trust and confidence. No specific information shall not be used by, or on behalf of, any person without prior written consent of the participating firms.

We believe that it is important to maintain independence from the various regulatory entities and the pharmaceutical manufacturers involved in the research project. Thus, the first and second phases of this research project were supported from grants received from the Center for Business and Public Policy in the McDonough School of Business at Georgetown University and the Boeing Center for Technology, Information, and Manufacturing and the Center for Research in Economics and Strategy in the Olin School of Business at Washington University in St. Louis. We have also secured funding for the second phase from the National Bureau of Economic Research (NBER).

We have refused all funding from FDA so as not to create conflicts of interest and not to appear on the side of the manufacturers with whom we are working on the second project. For the same reason we have refused to accept funding from pharmaceutical manufacturers. We believe remaining neutral and free from any conflict of interest is fundamental to the success of both projects.

ABOUT THE RESEARCH PROJECT INVESTIGATORS

The research project is being led by Professor Jeffrey T. Macher of the McDonough School of Business at Georgetown University and Professor Jackson A. Nickerson of the Olin School of Business at Washington University in St. Louis. Other faculty members and doctoral students working under the guidance of Professor Nickerson will also be involved.

Jeffrey Macher is an Assistant Professor in the Strategy, Economics and Policy Group in the Robert E. McDonough School of Business at Georgetown University. He received his undergraduate degree in computer engineering from the College of Engineering at the University of Michigan; his MBA from the Amos Tuck School of Business Administration at Dartmouth College; and his Ph.D. from the Walter A. Haas School of Business at the University of California, Berkeley. Professor Macher has conducted research on the semiconductor manufacturing and semiconductor equipment and materials industries for a number of years, mainly through the UC Berkeley Competitive Semiconductor Manufacturing (CSM) Research Program. He previously worked for Motorola Incorporated and Braxton Associates, a strategy consulting firm. He can be reached at 202-687-4793 and at jtm4@georgetown.edu.

Jackson Nickerson is Associate Professor of Organization and Strategy in John M. Olin School of Business at Washington University in St. Louis. Professor Nickerson graduated from U.C. Berkeley's Haas School of Business with a Ph.D. in Business and Public Policy. He also received an MBA and a master's degree in mechanical engineering from U.C. Berkeley and a BSME. from Worcester Polytechnic Institute. His research focuses on organizational economics as it applies to business strategy and has published numerous articles on organization, strategy, and manufacturing in industries ranging from pharmaceuticals, chemicals, and semiconductor manufacturing to trucking and garment production. In addition to teaching undergraduate and Ph.D. courses in strategy, he teaches courses in Strategic Management in Health Organizations and Strategic Management in the Life Sciences. Prior to entering his Ph.D. Program, Jackson worked as a control systems engineer for NASA. He can be reached at 314-935-6374 and nickerson@olin.wustl.edu.

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