Firm entry, exit and price competition in the market for multisource specialty drugs, 2006-2012

Rena M. Conti (The University of Chicago), Peter B. Bach (Memorial Sloan Kettering Cancer Center) and Ernst R. Berndt (MIT and NBER)

(I) RESEARCH QUESTION

The increasing use of drugs in the specialty medical care setting is an important determinant of national prescription drug spending trends.[1,2,3] Medicare, the public insurance program providing virtually universal coverage of adults 65 and older in the United States (U.S.), is the most prominent payer of these drugs through the "Part B" program.[4,5,6]

These drugs have been an active target of recent Federal policy making. For example, to stem high and rising spending, the Centers for Medicare and Medicaid Services' (CMS) reimbursement to physicians for the administration of Part B drugs declined January 1, 2005.[7,8] Policies have also expanded the U.S. Food and Drug Administration's (FDA) regulatory assessment of generic versions of patent-protected Part B drugs, (including "biosimilar" products) and accelerated their availability to physicians, hospitals and patients.[9,10,11,12] In addition, the third U.S. Circuit Court of Appeals ruled in July 2012 that so-called pay-for-delay agreements between brand-name and generic drugmakers should be presumed illegal unless the parties prove otherwise; [13], a decision contradicting other lower court rulings and therefore likely to be heard in the near future by the Supreme Court. Finally, policy makers and researchers have questioned whether recent CMS reimbursement changes and generic entry incentives have combined to produce shortages among selected drugs.[14,15,16,17,18]

In order to assess the effects of recent policies on the availability of generic versions of patent-protected Part B drugs and prospectively estimate the cost savings of public policies that would accelerate access to generic "Part B" drugs, reliable empirical estimates are required. U.S. policy makers need to know: What is the extent, nature and impacts of firm entry, exit and price competition among those manufacturing Part B drugs now? Previous economic research has examined entry and price competition among manufacturers of primary care drugs after generic entry.[19,20,21,22,23] We are unaware of any empirical work that has empirically examined trends in entry, exit and price competition among manufacturers of multisource specialty drugs after generic entry. This project aims to provide reliable empirical estimates of the extent, nature and impacts of generic firm entry, exit and price competition in the multisource specialty Part B drug market using state of the art private and public data sources.

This project directly addresses the NBER CRIW conference themes - sitting at the intersection of interests in innovation and the regulatory impacts of FDA, CMS and other policies to foster innovation and improve the efficiency of the U.S. health care system. The research team has extensive experience in the organization, financing and regulation of the specialty drug market. The empirical work uses nationally representative data from IMS Health on specialty molecule firm manufacturing, sales and volume and publicly available Medicare reimbursement schedules and Thompson's Redbook average wholesale prices to measure prices.

(II) RESEARCH DESIGN

The analysis has three parts. First, we will describe trends in the multisource entry, exit and price competition of specialty drugs, 2006-2012, including those reported to be in short supply. Second, we will examine the correlations among branded manufacturing firm's sales/volume, and characteristics of the generic firm's existing portfolio and entry/exit decisions among manufacturers, 2006-2012, including those which reported drugs in short supply. Third, we will assess the extent to which price changes associated with the generic entry and/or exit of firms manufacturing these drugs were incorporated into the Bureau of Labor Statistics' (BLS') producer price indexes (PPIs).

Unit of analysis and variable definition

The unit of analysis is specialty molecules identified by the World Health Organizations' Anatomic Therapeutic Classification system (ATC) marketed in the US between 2006 and 2012.[24] The therapeutic classes

included in the analysis are the following: hematology/oncology, neurology, pain management, blood and plasma replacement products and infectious disease.

The IMS Health *National Sales Perspectives* data (*NSP*) will provide a list of molecules meeting the ATC classification system criteria between January 2006 and December 2012. This list of molecules will be used as the sample universe. Molecules identified in the sample universe will be included in the study sample if they are covered under Medicare Part B. Coverage will be determined by cross-walking the sample universe molecules (from *NSP*) to publicly available CMS coverage and reimbursement policies under Part B.

For each molecule meeting study inclusion criteria, the NSP will provide information on the molecule's chemical and branded names, route of administration, the name of manufacturing firm(s) and nationally representative monthly sales and volume.[25,26] *NSP* will also be used to obtain the name(s) and number of every branded and generic firm selling the multisource molecule in the US market between 2006-2012.

Molecule pricing in this market is complicated, since physicians, clinics and hospitals purchase drugs from wholesalers and other distribution channels and then are reimbursed for their use in patients by insurers. Therefore, we will obtain molecule prices from three sources: wholesale acquisition prices (WAC) will be obtained from the Thompson's *RedBook*[27] and Medicare's reimbursement prices for Part B drugs, called average sales prices (ASP), will be downloaded from CMS's files available online and updated quarterly.[28] As an additional measure, we will estimate monthly prices paid for each molecule using NSP data (Σ_{firms} = monthly sales per molecule/volume of sales per molecule).

Firm entry will be defined using several metrics. We will use *Centerwatch* data to obtain the date of first FDA approval and the date of first generic entry (if any).[29] Then, using *NSP* data we will identify new firms with non-zero monthly sales or volume of a given molecule compared to previous supply at the monthly level. Finally, each firm-molecule pair and entry date identified using the *NSP* data will be verified using Thompson's *RedBook*.[30]

Firm exit will be defined using two metrics. First, using *NSP* data, we will identify firms that had previously had non-zero sales or volume of a given molecule and in a subsequent month have zero sales or volume. Second, each firm-molecule pair and exit date identified using the first strategy will be verified using Thompson's *RedBook* listed as "deactivated".

The definition of firm exit from the manufacturing of a given molecule is complicated because of, among other developments, the potential for consolidation and for outsourcing contract manufacturing between firms. We will identify and quantify consolidation and contract manufacturing between firms through a search of industry sources. The *SBC Platinum* database (available through the University of Chicago's electronic library) will be used to search firm names for mergers and acquisitions between generic firms (horizontal consolidation) and between generic and branded firms (vertical consolidation) executed between 1995-2012 for each molecule.[31] The presence, date and type of consolidation existing between branded and generic firms manufacturing these molecules will be recorded and classified.

Finally, molecules will be classified based on the advent of shortages and their potential resolution by date.[32,33] The University of Utah/American Society for Hospital Pharmacists (ASHP) is the recognized source for data on the molecules, manufacturers and date of reported short supply by molecules/manufacturers in the United States.[34]

As part of this effort, we are very interested in examining trends in physician directed promotion of these molecules during this time period. However, we are uncertain of how good coverage of these molecules is in the IMS Health dataset commonly used to measure physician directed promotion (*IPS*) in the primary care setting. We plan to discuss the availability and coverage of specialty molecule promotion in IMS Health data assets with the data vendor.

<u>Analysis</u>

We will perform a molecule-level analysis in which we will estimate and report summary statistics on the number of molecules experiencing initial and subsequent generic entry, by year, by therapeutic class and by route of administration, as well as the generic penetration rate. We will also estimate and report summary statistics on the number of generic firm entrants, exits and consolidations over all molecules experiencing

generic entry and stratified by current shortage presence, by year and by route of administration, as well as an aggregate generic penetration rate.

We will also perform a firm-level analysis in which we will identify all manufacturers of specialty molecules between 2006 and 2012 using the NSP dataset. We will estimate and report summary statistics on the number of unique molecule entry and exit decisions overall, by shortage report, by year and by route of administration. We will examine whether firms/molecules entering the multisource market after 2006 were the same or different firms/molecules that later exited the market, or were identified as not being able to supply the market. In addition, we will estimate and report the number, date of entry and exit and name of each molecule supplied by each manufacturer using Thompson's *RedBook*. Each drug will be classified by therapeutic class using the ATC and by branded or generic version using Thompson's *RedBook*. The firm-level analysis will therefore consider issues both of economies of scale and of scope.

We will characterize the entry decisions of manufacturing firms in more detail.[35] We will estimate and report summary statistics and the correlation between branded molecule revenue, characteristics of the generic manufacturer's existing portfolio (number of manufactured drugs, routes of administration, sales/volume and therapeutic class), generic entry among the generic manufacturers manufacturing specialty drugs, and the resulting brand and generic average prices. We will estimate and report summary statistics and the correlation between branded molecule revenue, number of generic entrants, characteristics of the generic firm's existing portfolio (routes of administration, sales/volume, therapeutic class) and the reported presence of drug shortages.

We will also examine variations in the BLS's PPIs in the relevant therapeutic classes, and the extent to which market developments were captured by the PPIs. In particular, we will examine reported BLS price growth in those segments in which shortages occurred, and consult with BLS personnel on how drugs in short supply (for which no price can be observed) are treated by the BLS' field representatives.

(III) RESEARCH TEAM

The research team is comprised of three faculty members, Rena M. Conti, PhD (Assistant Professor, The University of Chicago), Ernst R. Berndt, PhD (*Louis E. Seley Professor in Applied Economics,* MIT Sloan School of Management and NBER) and Peter B. Bach, MD, MAPP (Full Member with Tenure, Director, Center for Health Policy and Outcomes, Memorial Sloan-Kettering Cancer Center). All faculty members have extensive experience working with the datasets proposed for completing the project.

(IV) INTENDED COMPLETION DATE AND DISSEMINATION PLANS

Preliminary results will be publicly presented at The University of Chicago Health Economics Workshop (2013), the University of Chicago microeconomics lunch (2013), NBER Summer Institute (pending acceptance, 2013) and the NBER-CRIW conference on health data infrastructure (pending acceptance, 2013). Preliminary results will also be shared with the chairman and ranking member of the Senate Finance Committee's (Senator Hatch and Senator Baucus) health policy staff to help inform pending legislation on the amelioration of drug shortages, and with relevant officials at the FDA. We aim to publish the analyses in a health policy/economics journal in Fall 2013 or Spring 2014.

SELECTED REFERENCES

[1] Aitken M, ER Berndt, DM Cutler. Prescription drug spending trends in the United States; looking beyond the turning point. Health Affairs w.151, 2009.
[2] Mullins CD, et al., "Variability and Growth in Spending for Outpatient Specialty Pharmaceuticals," Health Affairs 24, no. 4 (2005): 1117–1127
[3] Aitken et al, op. cit. and See Schrag D. The price tag on progress – chemotherapy for colorectal cancer. New England Journal of Medicine 351(4); 317-319 2004.
[4] Edwards BK, Brown ML, Wingo PA, Howe HL, Ward E, Ries LA, Schrag D, Jamison PM, Jemal A, Wu XC, Friedman C, Harlan L, Warren J, Anderson RN, Pickle LW. Annual report to the nation on the status of cancer, 1975-2002, featuring population-based trends in cancer treatment. Journal of the National Cancer Institute 97(19):1407-27 2005.
[5] Yabroff KR, Lamont EB, Mariotto A, Warren JL, Topor M, Meekins A, Brown ML. Cost of care for elderly cancer patients in the United States. J Natl Cancer Inst. 100(9):630-41. Epub 2008 Apr 29 2008.
[6] Harlan LC, Greene AL, Clegg LX, Mooney M, Stevens JL, Brown ML. Insurance status and the use of guideline therapy in the treatment of selected cancers. Journal of Clinical Oncology 2005 Dec 20;23(36):9079-88. Epub 2005 Nov 21.
[7] Bach PB. Limits on Medicare's ability to control rising spending on cancer drugs. N Engl J Med. 2009; 360(6): 626-33.
[8] Jacobson M, Earle CC, Price M, Newhouse JP. How Medicare's Payment Cuts For Cancer Chemotherapy Drugs Changed Patterns Of Treatment. Health Aff. 2010; 29(7): 1391-1399.
[9] US Congress, 98th Session. Amended the Federal Food, Drug, and Cosmetic Act. Section 505(j) 21 U.S.C. 355(j) sets forth the process by which would-be marketers of generic drugs can file Abbreviated New Drug Applications (ANDAs) to seek FDA approval of the generic. Section 505(j)(2)(A)(vii)(IV), "Paragraph IV", allows 180 day exclusivity to companies that are the "first-to-file" an ANDA against holders of patents for branded counterparts.
[10] Scherer F.M. Pricing, Profits, and Technological Progress in the Pharmaceutical Industry. The Journal of Economic Perspectives. Vol. 7, No. 3 (Summer, 1993), pp. 97-115
[11] http://aging.senate.gov/publications/s27.pdf
[12] US Congress, 111th Session. Title VII – Improving Access to Innovative Medical Therapies; Subtitle A – Biologics Price Competition and Innovation – Sec. 7002. Approval Pathway for Biosimilar Biological Products.
[13] Gallegos A. Court rules pay-for-delay drug agreements are anti-competitive. Accessed September 2012 at http://www.ama-assn.org/amednews/2012/07/30/gvsc0730.htm.
[14] IMS Institute for Healthcare Informatics. Drug Shortages: A closer look at products, suppliers and volume volatility. November 2011.
[15] Emanuel EJ. Cancer drugs, effective but scarce. The New York Times. August 7, 2011.
[16] Office of the Assistant Secretary for Planning (ASPE) and Evaluation and Office of Science and Data Policy, U.S. Department of Health and Human Services (Haninger K, Jessup A, Koehler K). ASPE Issue Brief: Economic Analysis of the Causes of Drug Shortages. October 2011.
[17] Conti RM, "An economic assessment of the causes and policy implications of current specialty drug shortages", Testimony in front of the Senate Finance Committee, hearing December 7, 2011.
[18] Yurukoglu A. Medicare Reimbursements and Shortages of Sterile Injectable Pharmaceuticals. National Bureau of Economic Research Working Paper No. 17987, April 2012.
[19] Berndt, ER, Kyle MK, Ling DC. The Long Shadow of Patent Expiration: Generic Entry and Rx-to-OTC Switches, Scanner Data and Price Indexes. (Robert C. Feenstra and Matthew D. Shapiro, eds, 2003); Huskamp HG, Donohue JM, Koss C, Berndt ER, Frank RG. Generic Entry, Reformulations and Promotion of SSRIs in the U.S. Pharmacoeconomics. 2008;26:603-616; Lakdawalla D, Philipson T, Wang YR. Intellectual Property and Marketing. NBER Working Paper No. 12577 2006. Scott-Morton FM. Entry decisions in the generic pharmaceutical industry. NBER working paper 6190 1997.
[20] See Huskamp et al, op. cit. and Hurwitz MA, Caves RE. Persuasion or Information? Promotion and the Shares

of Brand Name and Generic Pharmaceuticals. Journal of Law and Economics. 1988;(31)2: 299-320.
[21] Also, challenges to the so-called Paragraph IV section of the Hatch-Waxman Act, providing 180-day marketing exclusivity for generic manufacturers first to file an Abbreviated New Drug Applications (ANDAs) to the Food and Drug Administration (FDA) are active areas of litigation. Court decisions commonly hinge upon whether use of the molecule in question is constant before and after generic entry occurs in the US market. See Panattoni LE, The effect of Paragraph IV decisions and generic entry before patent expiration on brand pharmaceutical firms, Journal of Health Economics. 2011;30(1):12
[22] Cutrona SL, et al. Recipients of Free Prescription Drug Samples: A Nationally Representative Analysis. Am J Public Health. 2008; 98(2): 284-89.
[23] Branstetter LG, Chatterjee C, Higgins M. Regulation and Welfare: Evidence from Paragraph IV Generic Entry in the Pharmaceutical Industry. NBER Working Paper 17188. June 2011.
[24] http://www.who.int/classifications/atcddd/en/
[25] *CenterWatch* is an independent data source that compiles statistics on Food and Drug Administration (FDA) approvals based on the Food and Drug Administration's (*FDA) Orange Book* and national formulary approved compendia. Available at www.CenterWatch.com
[26] Medicare's Part B coverage policy by year is available online at https://www.cms.gov/manuals/downloads/clm104c04.pdf.
[27] The *Red Book* is a Thomson Reuters product that provides accurate and up to date information available from drug manufacturers, price and packaging for branded, generic and over-the-counter drugs. See description available at http://www.REDBOOK.com/REDBOOK /why/.
[28] CMS. Medicare Part B drug pricing files. Accessed September 2012, available at http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/index.html?redirect=/McrPartBDrugAvgSalesPrice/.
[29] *CenterWatch* is an independent data source that compiles statistics on Food and Drug Administration (FDA) approvals based on the Food and Drug Administration's (*FDA) Orange Book* and national formulary approved compendia. Available at www.CenterWatch.com
[30] The *Red Book* is a Thomson Reuters product that provides accurate and up to date information available from drug manufacturers, price and packaging for branded, generic and over-the-counter drugs. See description available at http://www.REDBOOK.com/REDBOOK /why/.
[31] *SDC Platinum*™, a product of Thomson Reuters Financial Securities Data, is a collection of databases on firm financial transactions dating from 1970. See description available at http://thomsonreuters.com/products_services/financial/financial_products/a-z/sdc/
[32] U.S. Department of Health and Human Services and U.S. Food and Drug Administration. A Review of FDA's Approach to Medical Product Shortages. October 31, 2011.
[33] IMS Institute for Healthcare Informatics, op. cit.
[34] American Journal of Health-System Pharmacy. Drug Shortages Resource Center. Last accessed August, 2012, http://www.ashp.org/DrugShortages/.
[35] Scott-Morton FM. Entry decisions in the generic pharmaceutical industry. NBER working paper 6190 1997.