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Problems of Innovation-Deficient Pharmaceutical Manufacturing

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PROBLEMS OF INNOVATION-DEFICIENT PHARMACEUTICAL MANUFACTURING

Physicians are usually focused on which drug to prescribe, but recent developments suggest that they should be looking at something they have long taken for granted: that their chosen drug is available, high quality, and free from contamination. Unfortunately, the pharmaceutical industry has for decades lagged behind other industries, such as consumer goods, electronics, and food, in developing modern manufacturing processes, and today their processes are expensive, inefficient, and riddled with problems. (http://www.amazon.com/Pathway-Operational-Excellence-Pharmaceutical-Industry/dp/3871934003) This innovation deficiency has major negative impacts for patients, providers, the pharmaceutical industry, and the health care system as a whole. It also creates significant opportunities for firms willing to address technical and regulatory hurdles, although large-scale change will most likely demand legal and regulatory solutions.

Manufacturing is a far larger cost driver for the pharmaceutical industry—and, consequently, for the health care system—than is commonly appreciated. Even large, research-oriented drug makers spend about 26% of their revenues on manufacturing—approximately twice what they spend on research and development—and generic firms spend an average of 52%. (http://link.springer.com/article/10.1007%2Fs12247-008-9024-4) The widespread perception that manufacturing is inexpensive is probably driven by the low marginal costs of high-volume blockbuster drugs, but the industry also has high fixed costs, high compliance and quality costs, and higher marginal costs for other drug types. The industry spends approximately $200 billion annually on manufacturing, and process inefficiencies account for a large fraction of that total.

Despite the expense of making drugs, manufacturers frequently churn out their products for decades using the same processes, without modernizing techniques to improve efficiency or product quality. (http://www.nature.com/clpt/journal/v93/n2/full/clpt2012220a.html) Continuous process improvement, which has proved central to high-quality manufacturing in other industries, is restrained in the drug industry by regulatory barriers to change—most straightforwardly, by the procedural barriers of manufacturing supplement filings and preapproval requirements for major changes—and by an industry mindset that resists altering regulator-approved and validated procedures. At least partly as a result of outdated manufacturing techniques, an estimated 7 to 16% of drugs must be discarded before sale because they fail predistribution testing. (http://www.amazon.com/Pathway-Operational-Excellence-Pharmaceutical-Industry/dp/3871934003) Keeping plants unmodified for decades also promotes neglect; Food and Drug Administration (FDA) Warning Letters describe plants with rusty tools in sterile areas, ceiling leaks, the presence of mold, and numerous other violations. (http://www.nytimes.com/2012/10/18/business/drug-makers

-stalled-in-a-cycle-of-quality-lapses-and-shortages.html?pagewanted=all&_r=2&)

The innovation deficiency manifested in old plants and outdated manufacturing processes, and the attendant problems with drug quality, contribute to major problems in the health care system, including recalls, related contamination events, and drug shortages affecting both brand-name and generic products.

Manufacturing problems have spawned an increasing number of dramatic quality failures. 2011 saw over 2000 drug recalls, the vast majority from contamination during manufacturing or packaging or from other manufacturing problems, including cracked glass syringes, penicillin cross-contamination, stainless steel particulates in injectables, and packages with tablets from multiple drugs. (http://www.pharmamanufacturing.com/articles/2012/159/) Recent high-profile instances have included the shipment and subsequent recall of overfilled vials of morphine made by Hospira and bacterially contaminated propofol made by Teva. Some quality problems are expected and unavoidable, but many result from insufficiently controlled manufacturing facilities and the failure to develop and implement innovative techniques for continuous monitoring and recalibration. When processes are held static for decades rather than updated, the expected entropic drift of process precision and parameters is likely to lead to decreases in quality rather than steady-state quality maintenance.

Drug manufacturing problems have also been linked to increasing shortages of drugs, including several front-line chemotherapeutics. (http://www.nature.com/clpt/journal/v93/n2/full/clpt2012220a.html) For sterile parenteral drugs, which made up 73% of shortages in 2011, 56% of shortages were directly caused by manufacturing quality problems and an additional 20% were caused by capacity issues or manufacturing delay. The direct cause of another 16% was shortages of related drugs or voluntary discontinuance, but each of those causes frequently results from manufacturing problems. Particularly for drugs with tight supply chains, plant shutdowns to remedy quality problems, whether voluntary or FDA-mandated, can easily lead to overall shortages or to supply-chain disruptions that generate regional or institution-specific shortages.

These problems directly impact patients, providers, drug companies, and the health care system. Any patient who takes contaminated drugs or whose treatment is altered, postponed, or suspended owing to drug shortages is clearly negatively affected by manufacturing quality concerns. In addition, patient confidence in the drug-production system may be broadly damaged by high-profile quality failures. Providers, especially oncologists, already cope with the problems of drug shortages and may need to weigh manufacturer quality when prescribing drugs, particularly if recalls and other quality problems continue to increase. Pharmaceutical companies risk the potential loss of consumer confidence in drug quality, adding to other reputational threats that already face the industry. Finally, the health care system as a whole faces substantial costs from both shortages and recalls, as well as far greater costs from drug prices that are increased by inefficient and overly expensive manufacturing methods.

Direct regulatory oversight is only part of the solution for quality issues- and even less for the underlying innovation problems. The FDA and other regulators—including the European Medicines Agency, Health Canada, international inspectors from other Organization for Economic Cooperation and Development countries, and overseas manufacturers' domestic regulators—have a limited number of inspectors with which to oversee a complicated and highly globalized supply chain. For shortages in particular, regulatory oversight, quality lapses, and lack of available drugs interact: regulatory actions to ensure compliance with manufacturing-quality regulations and prevent quality problems and loss of drug availability can themselves close plants and lead to shortages. To address this interaction, the FDA Safety and Innovation Act of 2012 requires that the FDA take the potential for shortages into account before initiating regulatory action in response to manufacturing problems. Thus, the FDA's greatest regulatory threat—shutting down a plant—is difficult to deploy prospectively or to use as a credible threat. More broadly, FDA oversight

can identify problems but cannot itself readily drive innovation. While manufacturers may spend hundreds of millions of dollars to fix specific problems at the plants that the FDA does shut down, those fixes fail to resolve the structural problems that limit industry innovation and cause quality problems in the first place.

The causes of innovation deficits in pharmaceutical manufacturing are complex. They include an industry culture in which manufacturing, unlike investments in research and development or sales and marketing, has not been seen as a source of competitive advantage, regulatory barriers to introducing new technology or changing manufacturing techniques, and an absence of effective incentives for manufacturing innovation in the patent system or from other sources. Eventual solutions will be accordingly complex as well. In addition to changes in corporate focus, they will most likely require regulatory reform and perhaps greater incentives that reward innovation in manufacturing. FDA officials have already proposed steps to target drug-manufacturing quality, including FDA's Quality by Design initiative, an increased regulatory focus on quality, and the possibility of leveraging market incentives by providing manufacturer quality grades to consumers. (http://www.nature.com/clpt/journal/v93/n2/full/clpt2012220a.html) In addition to these quality-directed reforms, the FDA could potentially change intellectual-property incentives for innovation through regulatory channels as currently helps shape patent incentives for drug discovery and development. The FDA's current approaches will probably help to improve drug quality, but other creative methods are needed to increase manufacturing innovation. To find and implement such wide-reaching solutions, the medical and pharmaceutical communities must first recognize that drug manufacturing, rather than an afterthought, is in fact a locus of major health care problems and needs serious and sustained attention.