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COMMENTARY

Biomedical Innovation In The Era Of Health Care Spending Constraints

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ABSTRACT Insurers, hospitals, physicians, and consumers are increasingly weighing price against performance in their decisions to purchase and use new drugs, devices, and other medical technologies. This approach will tend to affect biomedical innovation adversely by reducing the revenues available for research and development. However, a more constrained funding environment may also have positive impacts. The passing era of largely cost-unconscious demand fostered the development of incremental innovations priced at premium levels. The new constrained-funding era will require medical technology firms to design their products with the features most valued by payers and patients, price them at levels justified by clinical performance, and manage distribution through organizations rather than to individual physicians. The emerging era has the potential to increase the social value of innovation by focusing industry on design, pricing, and distribution principles that are more closely aligned with the preferences—and pocketbooks—of its customers.

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Innovation in biomedical technology has contributed to improvements in the quality of care as well as to the escalation of expenditures in the nation's health care system. New drugs, devices, diagnostics, and other medical technologies permit interventions into previously untreatable conditions; more precise assessment and reduction of risks; and an expansion of medicine's purview over a broader range of individual and social activities.^{1,2}

But if biomedical innovation has been a cause of spending growth, it is also a consequence. Costs for payers constitute revenues for technology manufacturers and stimulate continued investments in research and development. Historically, this strong flow of funding has nourished the innovation ecosystem, rewarding and motivating the scientists, entrepreneurs, venture capitalists, patent lawyers, and others who have transformed ideas into products and products

into firms.

Now, under pressure from rising costs, the structure of purchasing and the flow of funds for medical technology have been changing.³ Insurers are tightening coverage criteria and managing utilization more aggressively. Hospitals are pushing back on the prices charged for supplies and equipment. Physicians increasingly are being paid through methods that discourage prescription of costly treatments. Consumers are being asked to pay more for their care, both through higher premiums and through higher cost sharing at the time of service.

Insurers, hospitals, physicians, and consumers together constitute the purchasers of medical technology. Their evolution toward cost-conscious choice will adversely affect innovation by reducing the revenues available for research and development. This more constrained funding environment may also, however, have positive impacts on biomedical innovation. The new

era will challenge the technology industry to improve the value of its innovations, defined as emphasizing performance improvements that justify the prices charged. This will have significant impacts on product design, pricing, and distribution.

Design To Value

Innovation in medical technology enjoys strong public support, but this popularity is not accompanied by commensurate sympathy for the high prices needed to finance it. The life sciences industry is under pressure to shift the focus of innovation from improvements in product performance, regardless of cost, toward improvements for which increasingly cost-conscious purchasers are willing to pay.

For certain improvements in performance, society appears willing to pay premium prices. Insurers cannot lightly deny coverage for—and hospitals cannot long refuse to adopt—new technologies that significantly improve patients' health and for which there are no therapeutically equivalent alternatives. Without the credible threat to deny coverage or forgo payment, purchasers have little power to negotiate price discounts with suppliers.

Most biomedical innovations, however, do not enjoy the luxury of uncontested pricing. Most seek to enter a therapeutic niche already occupied by products that perform reasonably well, offering incremental rather than breakthrough performance improvements. Purchasers can refuse to cover, prescribe, or adopt a new product unless its price is lower than that of the incumbent offerings. This downward pressure on prices has direct implications for the design of new technologies.

If they are not to be pushed into a narrow luxury market niche or out of the market altogether, medical technology firms will need to structure their product development strategies according to the principles of design to value.⁴ Design to value begins with the recognition that firms often add new functions, materials, and packaging that may improve performance but also increase development and manufacturing costs and, therefore, sales prices. These price increases can, over time, outstrip the value of any increased performance in the eyes of customers. The products then are at risk from new entrants that offer reduced functionality but at lower cost—particularly if new competitors enter markets where the ability to pay is very restricted—and thus design their products from the beginning to emphasize low cost and price.

In the face of recalcitrant purchasers and upstart competitors, firms may need to redesign

their products to retain or enhance the dimensions of performance most valued by customers while stripping away dimensions where costs exceed their benefits. This requires collaboration among research engineers, procurement managers, marketing specialists, financial analysts, and carefully selected and representative groups of customers. In these collaborative processes, products are broken down into features and functions, which then are analyzed in terms of their incremental contribution to the overall performance and cost. Features and functions that add more cost than benefit are removed. This process of analysis and redesign sometimes can identify previously overlooked opportunities for new methods of manufacturing and distribution.

Within health care, the imperative of design to value is most prominently observable where dominant products have featured both high performance and high price. In one example provided by Ananth Narayanan and colleagues, a major US medical equipment firm found itself losing market share to a new entrant from Asia that offered an apparently inferior product manufactured at what appeared to be higher cost but marketed to customers at a discount.⁵ After a systematic breakdown and analysis of its and the competitor's products, the incumbent firm found that its product was indeed perceived to be superior in several areas, including quality, but lagged behind the competitor's in other key dimensions, many of which were more important to customers. Upon further analysis, the firm discovered that its manufacturing costs were higher, not lower, than the competitor's, and the competitor's lower prices were indeed sustainable. These insights led the firm to redesign its product to make it more competitive.

Design to value is accelerating in response to fears that firms from emerging economies are willing to enter the low ends of markets in developed nations and compete for cost-conscious customers.⁶ Firms in low-income nations have proven themselves adept at developing "good enough" products that can be sold for substantially less than comparable products developed in high-income nations.

Some technology firms seek to replicate this capability by establishing subsidiaries in emerging nations, moving beyond low-cost manufacturing to low-cost design. Products designed in emerging nations tend to be marketed eventually in developed nations. For example, GE has established a major research center in India to develop diagnostic and therapeutic radiology equipment that is cheap, can easily be transported to rural areas, and does not require the services of highly skilled staff. India, in particu-

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lar, is being targeted as a source of innovation because its health care industry shares commonalities with the US industry.⁷

Competition from lower-price products is well established in the market for traditional drugs, where generic versions dominate many therapeutic categories by being priced at discounts of up to 85 percent.⁸ Generic drugs lack the brand recognition enjoyed by the original pharmaceuticals, but they are generally perceived by patients as similar and as offering a higher value, given their lower price. In some cases, however, generics are viewed as being inferior to branded products, thereby opening a market niche for mid-price “branded generics” that have lost patent protection but are still marketed by the original manufacturer. Branded generics, priced between on-patent products and unbranded generic rivals, appeal to middle-income consumers especially in emerging nations that are wary of poorly manufactured or fraudulent generics.⁹

Competition is also beginning to emerge for specialty biological drugs that target cancer, immunological failures, and other complex conditions.¹⁰ So-called biosimilars, which mimic the effects of branded biopharmaceuticals even though they are not precise copies (generics), are gaining acceptance in the European market. They enjoy much lower design and development costs because drug manufacturers are able to take advantage of the scientific insights and clinical data of the products they imitate. Biosimilars typically cost 25 percent less than comparable branded products in Europe and may enter the US market through the Food and Drug Administration’s new regulatory approval pathway.¹¹

New firms are entering the global market for pharmaceuticals. Manufacturers in India, China, South Korea, and Israel are already proficient in manufacturing small-molecule generic drugs and are expanding their product development expertise to biosimilars. In 2012, for example, the South Korean company Celltrion developed a biosimilar that completed Phase III comparison trials to a Johnson and Johnson–Merck product

for rheumatoid arthritis.¹² Some firms from emerging nations are now moving upstream into the development of branded pharmaceuticals. In its transition to an innovator role, for instance, the Israeli firm Teva Pharmaceuticals has recently made a series of acquisitions and created new alliances to bolster its technological platform and manufacturing capabilities.¹³

Pricing Based On Performance

Breakthrough innovations will continue to support premium prices, but these will need to be supported by strong clinical evidence of performance. In contrast, incremental innovations often need to be priced at a discount in order to gain market share from incumbents.

PREMIUM PRICING REQUIRES PREMIUM PERFORMANCE Breakthrough innovations targeted at conditions lacking effective treatments will continue to command premium prices because insurers will not wield a credible threat to deny coverage. However, premium prices will require evidence of premium performance. The life sciences industry has won every battle but appears to be losing the war against the use of comparative clinical and cost-effectiveness research. The industry successfully lobbied Congress for provisions limiting use of comparative clinical evidence and banning the use of cost-effectiveness analysis for Medicare coverage policy.^{14,15} The Centers for Medicare and Medicaid Services (CMS) is also prevented from using these data in its reimbursement policies.¹⁶ But drug and device firms must submit comparative data when seeking coverage and reimbursement from payers in Europe and other nations. It may be difficult for these firms to avoid providing analogous dossiers to payers in the United States.

In some cases, they already do. The pharmacy and therapeutics committees of major insurers often require drug companies to supply studies and observational data on the clinical performance of their new products; committees increasingly use these data when deciding which products to include or exclude from formularies. Firms must also supply data on the cost implications of their new products, extending beyond unit price to include cost per course of care; cost for the covered enrollee population; and, in some cases, indirect costs through impacts on workforce productivity. If the firm cannot prove that its product is meaningfully superior in safety and effectiveness, insurers may assume that it is equivalent and not superior to products already on the market. They then make coverage decisions on the basis of price.^{17,18}

Data on clinical and cost performance are increasingly demanded by hospitals and integrated

delivery systems as they accept capitation and other forms of prospective payment. Leading hospitals maintain technology assessment committees that draw on staff physicians and surgeons to help inform purchasing decisions with respect to implantable devices and other technologies.¹⁹ These committees not only assess the potential clinical and cost implications of a new technology relative to the existing inventory but also serve the cultural function of encouraging physician-leaders to consider trade-offs between price and performance.²⁰ Comparative performance data may also be used in purchasing decisions by accountable care organizations (ACOs) serving the Medicare fee-for-service population, even if CMS is unable to use them directly for national coverage policy.²¹

DISCOUNTED PRICING FOR INCREMENTAL INNOVATION Premium pricing for incremental innovation is not sustainable. Plans and providers are ever less willing to pay more for this year's artificial hip or drug-eluting stent if they offer little improvement over last year's model. Incremental innovations will need to compete for market share by charging prices no higher than those of incumbent products or, increasingly, by offering price discounts.

As multiple firms target the same unmet needs, therapeutic niches that once commanded high prices will become increasingly competitive. This is illustrated in the pricing pressure on once-breakthrough specialty drugs for autoimmune disease. The past twenty years have seen the launch of a remarkable series of infused, injectable, and oral drugs that halt the progression of rheumatoid arthritis, psoriasis, Crohn's disease, and other debilitating immunological conditions. Pharmaceutical costs to insurers have increased commensurately. The three drugs commanding the highest current global revenues all target autoimmune conditions: Humira (AbbVie), Enbrel (Amgen/Pfizer), and Remicade (Janssen/Johnson and Johnson).²²

Continued innovation also permits insurers to limit coverage to one or two therapeutically equivalent drugs, with others restricted to patients who do not respond to the insurer's preferred first-line product.²³ Insurers negotiate with manufacturers for discounted prices as a condition for preferred placement in the formulary. The insurers' step-therapy requirements, which deny payment for nonpreferred drugs unless the patient has already failed to respond to a preferred product, severely limit sales of nonpreferred agents.

The tendency for innovation to erode prices is evident in the market for implantable devices, where innovation is largely limited to incremental changes in product size, materials, or method

Premium pricing for incremental innovation is not sustainable.

of administration. Hospitals are aligning with their physicians to limit the number of device vendors with which they contract as a first step toward demanding price concessions.³ Prices for implantable devices tend to fall during the first years after market launch, and industry revenues have been sustained only by the introduction of new models.²⁴ Now hospital and physician purchasers increasingly demand price discounts even at the time of initial market launch.

Some hospitals are beginning to insist that prices for implantable devices not exceed a defined percentage of the procedure revenues they obtain from insurers and that supply prices follow procedure prices downward as insurers drive harder bargains.¹⁹ For example, after creating a joint venture with shared financial equity with its practicing surgeons, Hoag Hospital in California was able to fully restructure its supply-chain strategy for orthopedic implants. The hospital established a target reimbursement rate defined as a percentage of procedure revenues and accepted price bids from manufacturers only at or below that target. Although firms initially resisted this pricing principle, one vendor eventually put in an acceptable bid that was pegged to sales volume. This induced competitors to revisit their negotiating positions. Hoag eventually obtained 25 percent savings in its orthopedic supply costs, while the two winning vendors obtained significant increases in market share and sales volume.^{3,25}

Product Distribution And Service

The biomedical industry's traditional customer has been the individual physician. Sales tactics have centered on convincing the doctor that the new product is good for the patient and, incidentally, profitable. The primary customer now is shifting to the provider organization, including multispecialty medical groups, hospitals with employed physicians, and ACOs. Product distribution is shifting from the traditional "detailing" of individual physicians to "account management" for provider organizations. The technology industry also is moving from an exclusive

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focus on new products to a broader focus that includes services to improve care processes.

Changes in distribution strategy are most evident in the market for implantable medical devices, which constitute the core of the hospital's financially important service lines in orthopedic surgery and interventional cardiology. Historically, company representatives provided technical assistance to surgeons in the operating room and to interventional cardiologists in the cardiac catheterization laboratory, helping hospital staff members stay current with the changing medical armamentarium. Industry representatives brought a full set of devices with them into the clinical setting, thereby ensuring that the right implant was available for the patient at the right time, even if the case turned out to be more complicated or to require a different mode of administration than originally anticipated. This outsourcing of inventory management reduced the hospital's risk of tying up capital in expensive supplies that might soon become obsolete.

Unfortunately, from the viewpoint of the hospital, medical device representatives often used their relationships with physicians to promote the most expensive products. Representatives who are paid on commission have faced financial incentives to "upsell" new product variants, which command higher prices than older models. Professional relationships between industry distributors and practicing physicians have extended beyond the operating room, and brand loyalty has been supported by consulting contracts, speaking honoraria, and other financial inducements for the physicians. Personal ties between physicians and device representatives have impeded hospitals' ability to threaten contract termination to vendors that would not discount their prices.²⁶

The ability of medical technology firms to dominate the hospital supply chain is eroding

as facilities increasingly employ physicians, offer joint ventures to physician groups, and develop gain-sharing programs with their medical staffs.²⁷ Leading hospital systems are insisting on disclosure of financial relationships between their physicians and technology suppliers—a once-difficult demand now facilitated by "sunshine" legislation requiring public disclosure.²⁸

Many organizational relationships currently are characterized by considerable friction, as purchasers seek to recover ground lost during the era of physician detailing. This difficult phase likely will pass, however, as purchasers continue to need technology training and support. Over time, buyers and sellers of medical technology may develop more collegial relationships based on interdependence and long-term contracts.

One example of this trend has been provided by the orthopedic service line at Kaiser Permanente in Southern California.²⁵ The health plan had regionalized orthopedic surgery to one major facility but was facing capacity constraints as a result of growing enrollment. It needed to increase patient throughput in the operating room and in postoperative recovery, as well as in the process of identifying appropriate candidates prior to surgery and managing rehabilitation after hospital discharge. The plan contracted with the consulting subsidiary of one of its principal medical device vendors, using its expertise to analytically break down the orthosurgery production process into each component and each hour of the typical patient's stay.

This analysis led to significant reductions in variance and in average time for surgical preparation, operating room procedures, and postoperative treatment. The collaboration on service-line redesign further strengthened the underlying organizational relationship between the provider and its technology supplier, and similar process redesigns subsequently were extended to other surgical service lines and other hospitals in the Kaiser Permanente system. Richard Bohmer and colleagues present an analogous example of orthopedic redesign at an academic medical center in Philadelphia.²⁹

Policy Implications

Changes in the purchasing of medical technology may have positive implications for innovation but will require supportive changes in the policy environment.

DESIGN If the life sciences industry is to embrace the principles of design to value instead of retreating to high-price, high-performance niches, policy makers will need to accept technologies whose value lies in their affordability as

well as quality. The concept of patient protection will need to evolve away from a standard that requires the highest level of performance to a standard that matches product functionality with patient need, lest the perfect become the enemy of the good. Regulators will need to permit and foster market access for generic drugs, biosimilars, patient-administered diagnostic tests, plain-vanilla implantable devices, and other “good enough” technologies.

PRICING If policy makers want breakthrough innovation, they will need to accept premium pricing. In this respect, the political outcry over the steep prices charged for Sovaldi, a drug that offers a cure to millions of patients worldwide suffering from hepatitis C, sends an inappropriate message to the industry.³⁰ Sovaldi prices are creating severe strains on public and private budgets, but the clinical benefits are so large that the drug is cost-effective, according to standard metrics of cost per quality-adjusted life-year.³¹ The cost of a cure for hepatitis C will fall as competing manufacturers offer follow-on products priced at a discount.^{32,33} Regulators can stimulate price discounting by permitting insurers and hospitals to use comparative performance evidence in their formularies and supply chains. Medicare could be allowed to consider comparative clinical and cost-effectiveness in its coverage and reimbursement policies.¹⁶ Private insurers could be exempted from regulatory mandates to cover all of the drugs within a class so long

as there exist multiple alternatives.^{34,35}

DISTRIBUTION Regulators often interpret collaboration between technology firms and physicians as a form of inappropriate inducement. Yet collaboration is essential to innovation. The geographic clustering of life sciences firms around research universities illustrates the importance of two-way flows of ideas and people between the worlds of science and business. Collaboration also is important for incremental innovation, as evidenced in innumerable physician-initiated improvements in designs, materials, and methods of use for surgical instruments and supplies.³⁶

Conclusion

The passing era of unsophisticated and cost-unconscious purchasing provided a steady flow of revenues to finance biomedical research and development. But it also permitted—and, indeed, fostered—the development of products that were priced at premium levels despite offering only minor improvements. The emerging era of more sophisticated and cost-conscious purchasing will likely reduce the flow of funds to the medical technology industry. But it has the potential to increase the social value of innovation by focusing the industry on principles of design, pricing, and distribution that are aligned with the preferences and pocketbooks of its customers. ■

NOTES

- 1 Congressional Budget Office. Technological change and the growth of health care spending. Washington (DC): CBO; 2008.
- 2 Chandra A, Skinner J. Technology growth and expenditure growth in health care. *J Econ Lit.* 2012;50(3):645–80.
- 3 Robinson JC. Purchasing medical innovation: the right technology, for the right patient, at the right price. Oakland (CA): University of California Press; forthcoming 2015.
- 4 Chilukuri S, Gordon M, Musso C, Ramaswamy S. Design to value in medical devices [Internet]. Washington (DC): McKinsey and Company; 2010 [cited 2014 Dec 19]. Available from: http://www.mckinsey.com/~media/mckinsey/dotcom/client_service/pharma%20and%20medical%20products/pmp%20new/pdfs/774172_design_to_value_in_medical_devices1.ashx
- 5 Narayanan A, Padhi A, Williams J. Designing products for value [Internet]. Washington (DC): McKinsey and Company; 2012 [cited 2014 Dec 5]. Available from: http://www.mckinsey.com/insights/innovation/designing_products_for_value
- 6 Christensen CM. The innovator's dilemma: when new technologies cause great firms to fail. Boston (MA): Harvard Business School Press; 1997.
- 7 Timmons H. GE chief sees India helping cut costs of US health care. *New York Times.* 2009 Oct 3; Sect. B:3.
- 8 Food and Drug Administration. Facts about generic drugs [Internet]. Washington (DC): FDA; 2012 Sep 19 [cited 2014 Dec 9]. Available from: <http://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/understandinggenericdrugs/ucm167991.htm>
- 9 Singer N. Drug firms apply brand to generics. *New York Times.* 2010 Feb 16;Sect. B:1.
- 10 Spatz I, McGee N. Health policy briefs: specialty pharmaceuticals [serial on the Internet]. 2013 Nov 25 [cited 2014 Dec 9]. Available from: http://www.healthaffairs.org/healthpolicybriefs/brief.php?brief_id=103
- 11 Megerlin F, Lopert R, Taymor K, Trouvin JH. Biosimilars and the European experience: implications for the United States. *Health Aff (Millwood).* 2013;32(10):1803–10.
- 12 Bourgoin AF, Nuskey B. An outlook on US biosimilar competition. Philadelphia (PA): Thomson Reuters; 2013 Apr.
- 13 Barei F, Le Pen C, Simoens S. The generic pharmaceutical industry: moving beyond incremental innovation towards re-innovation. *GaBI J.* 2013;2(1):13–9.
- 14 Neumann PJ. Why don't Americans use cost-effectiveness analysis? *Am J Manag Care.* 2004;10(5):308–12.
- 15 Mohr P. Looking at CER from Medicare's perspective. *J Manag Care Pharm.* 2012;18(4 Suppl A):S5–8.
- 16 Pearson SD, Bach PB. How Medicare could use comparative effectiveness research in deciding on new coverage and reimbursement. *Health Aff (Millwood).* 2010;29(10):1796–804.
- 17 Sullivan SD, Lyles A, Luce B, Grigar J. AMCP guidance for submission of clinical and economic evaluation data to support formulary listing in US health plans and pharmacy ben-

- efits management organizations. *J Manag Care Pharm.* 2001;7(4): 272–82.
- 18 Spooner JJ, Gandhi PK, Connelly SB. AMCP format dossier requests: manufacturer response and formulary implications for one large health plan. *J Manag Care Pharm.* 2007; 13(1):37–43.
- 19 Health Care Industry Committee. Navigating the new era of technology assessment: strategies and tools for working with value analysis, capital budgeting, and technology assessment companies. Washington (DC): Advisory Board Company; 2010 Apr.
- 20 Gutowski C, Maa J, Hoo KS, Bozic KJ. Health technology assessment at the University of California–San Francisco. *J Healthc Manag.* 2011; 56(1):15–29.
- 21 Pearson SD, Bach PB. How Medicare could use comparative effectiveness research in deciding on new coverage and reimbursement. *Health Aff (Millwood).* 2010;29(10):1796–804.
- 22 Palmer E. The 10 best-selling drugs of 2013 [Internet]. Thousand Oaks (CA): Fierce Pharma; 2014 Mar 25 [cited 2014 Dec 10]. Available from: <http://www.fiercepharma.com/special-reports/10-best-selling-drugs-2013>
- 23 Dautel N, Haren M, Bluestein K, Sadiwnyk K. Prior authorization tracking tool for rheumatoid arthritis: trends in the marketplace, second quarter 2011. San Francisco (CA): Zitter Group; 2011. (Report in author's possession; not publicly available.)
- 24 Long G, Mortimer R, Sanzenbacher G. Recent average price trends for implantable medical devices, 2007–2011 [Internet]. Washington (DC): Analysis Group; 2013 Sep [cited 2014 Dec 10]. Available from: <http://advamed.org/res.download/365>
- 25 Robinson JC. Case studies of orthopedic surgery in California: the virtues of care coordination versus specialization. *Health Aff (Millwood).* 2013;32(5):921–8.
- 26 Montgomery K, Schneller ES. Hospitals' strategies for orchestrating selection of physician preference items. *Milbank Q.* 2007;85(2): 307–35.
- 27 Ketcham JD, Furukawa MF. Hospital-physician gainsharing in cardiology. *Health Aff (Millwood).* 2008;27(3):803–12.
- 28 Arnold and Porter LLP. Final rule issued for physician payment sunshine provisions of the Affordable Care Act [Internet]. Washington (DC): Arnold and Porter LLP; 2013 Feb [cited 2014 Dec 10]. Available from: http://www.arnoldporter.com/resources/documents/Advisory%20Final_Rule_Issued_for_Physician_Payment_Sunshine_Provisions_Affordable_Care_Act.pdf
- 29 An interesting case study of orthopedic process improvements at a major Philadelphia hospital is provided in Bohmer RMJ, Huckman RS, Weber J, Bozic KJ. Managing orthopaedics at Rittenhouse Medical Center. Cambridge (MA): Harvard Business School Case 607-152; 2007 (revised 2010).
- 30 Loftus P. Senate committee is investigating pricing of hepatitis C drug. *Wall Street Journal.* 2014 Jul 11.
- 31 Liu S, Watcha D, Holodniy M, Goldhaber-Fiebert JD. Sofosbuvir-based treatment regimens for chronic, genotype 1 hepatitis C virus infection in US incarcerated populations: a cost-effectiveness analysis. *Ann Intern Med.* 2014;161(8): 546–53.
- 32 Rockoff JD. Once-a-day hepatitis pill approved. *Wall Street Journal.* 2014 Oct 11.
- 33 Loftus P. Lucrative drug niche sparks legal scramble. *Wall Street Journal.* 2014 Jul 20.
- 34 Hanson K, Bondurant E. Cancer insurance mandates and exceptions. Denver (CO): National Conference of State Legislatures; 2009.
- 35 Centers for Medicare and Medicaid Services. Medicare prescription drug benefit manual [Internet]. Baltimore (MD): CMS; 2010. Chapter 6, Part D drugs and formulary requirements; [cited 2014 Dec 10]. Available from: <https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/downloads/Chapter6.pdf>
- 36 Zenios S, Makower J, Yock P, Brinton TJ, Kumar UN, Denend L, et al. Biodesign: the process of innovating medical technologies. Cambridge: Cambridge University Press; 2009.