

The Paradox of Antibiotics Pricing

Despite years of warnings about the threat from antibiotic-resistant bacteria and the infections they cause, the situation globally remains perilous. In the U.S. for example, the Centers for Disease Control and Prevention (CDC) reports that antibiotic-resistant infections are associated with two million illnesses and 23,000 deaths each year. This results in as much as \$20 billion each year in additional direct U.S. healthcare costs and perhaps as much as \$35 billion in annual lost productivity and sick days. In total, resistant bacterial infection is estimated to cost the U.S. \$50 billion to \$70 billion a year.

Moreover, key authorities like the European Centre for Disease Prevention and Control (ECDC) in Europe and CDC in the U.S. indicate the situation is getting worse: some organisms have evolved to the point where they are entirely or nearly untreatable with current drugs. Meanwhile, the need for effective antibiotics continues to grow, as infections proliferate from procedures such as cancer chemotherapy, organ transplantation, and both routine and complex surgery.

Against this bleak backdrop, President Barack Obama issued an executive order in September to address the growing danger to the country from antibiotic-resistant infections. The order, and an accompanying report by the President's Council of Advisors on Science and Technology (PCAST), lays out a reasonably aggressive set of steps including:

- Empaneling a new task force to create a 'National Action Plan' of steps the federal government can take to address the issue
- Improving response to resistant infections by promulgating the use of clinical best practices in hospitals and other health care settings
- Boosting national surveillance to track the emergence of resistant bacteria in both healthcare and agricultural settings
- Promoting the development of new diagnostics and antibiotics to detect and treat resistant pathogens

Despite this encouraging sense of urgency and action, a fundamental market economics problem remains: pricing and reimbursement rates for antibiotics are too low to spur widespread development of new treatments. Simply put, the current Diagnosis-Related Group (DRG)-based hospital reimbursement system in the U.S. and most of Europe presents a significant economic constraint on antibiotic value capture; this system provides a set reimbursement rate for a given patient diagnosis, encompassing labor and non-labor costs including pharmaceuticals. In this context where reimbursement rates per episode of care do not change, hospitals face significant pressure to limit expenditures on antibiotics for a given infection, creating a

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significant practical limitation on pricing and value capture for novel antibiotics.

Until these reimbursement dynamics are meaningfully improved and drug makers are able to successfully shift toward more value-based pricing, the market model will remain broken. Pricing will remain insufficient to drive a meaningful change in the behavior of biopharmaceutical innovators. As the PCAST report summarizes, “The inadequate state of antibiotic development reflects a market failure: while society’s need for new antibiotics is great, the economic return on developing new antibiotics is currently too low to elicit adequate private investment and innovation.”

Novel antibiotics need to be freed from the shackles of the DRG payment system, which has created unique economic disincentives around the use of branded, novel antibiotics.

The Cubicin Experience

More than 10 years ago, I had a rare opportunity to contribute to the development of a novel antibiotic as part of Cubist Pharmaceuticals’ Clinical Development team, which developed the Gram-positive antibiotic Cubicin (daptomycin). Cubist acquired the rights for daptomycin from Ely Lilly and Company in 1997 and received FDA approval for the treatment in September 2003. A key driver of the product’s commercial success has been its effectiveness against resistant, life-threatening pathogens including Methicillin-resistant Staphylococcus Aureus (MRSA), an acronym that has entered the common vernacular and is perhaps the poster child for emerging resistant organisms present in the hospital setting.

Now with the benefit of hindsight, there are three aspects of Cubicin’s development and commercialization that stand out:

- Cubicin ultimately became a blockbuster drug, ramping up faster than any previous antibiotic (although slower than most blockbusters), exceeding \$1 billion in annual sales

- Aside from Cubicin and a handful of other drugs, however, there has been little change in the antibiotics landscape for resistant infections, with relatively few novel drugs launched into the global marketplace and even fewer enjoying commercial success
- Finally despite Cubicin’s commercial success, antibiotics still capture a disproportionately low share of value in the global biopharmaceuticals marketplace – even given their clear life-saving profile and continued increases in multi-drug resistant pathogens

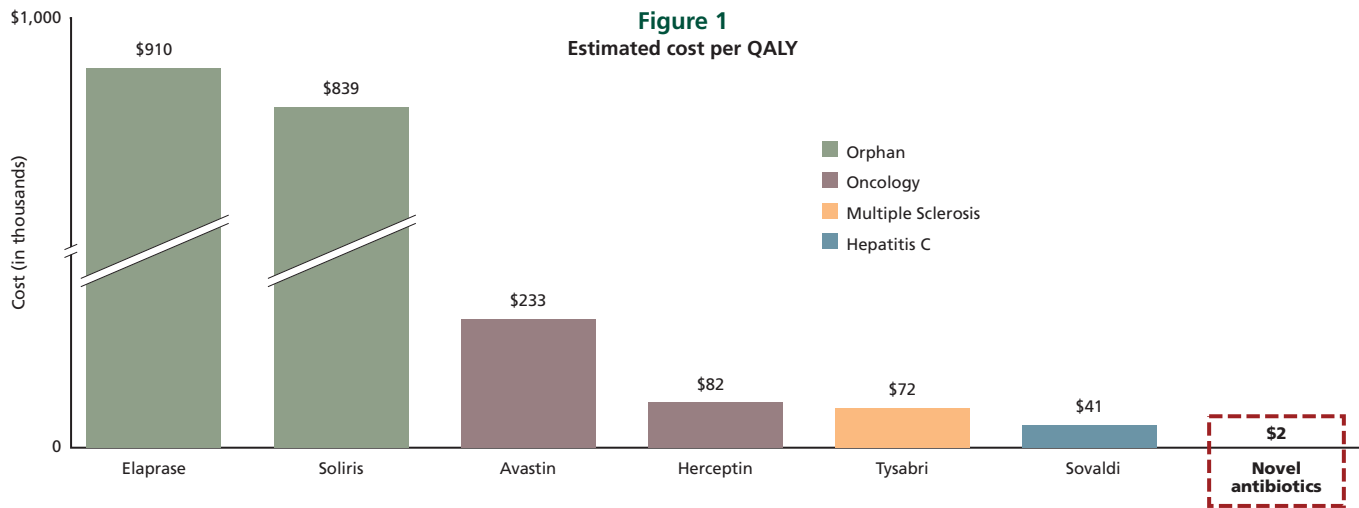
Sadly, Cubicin remains an outlier. Novel, branded antibiotics today are generally priced between \$2,000 and \$5,000

per course of therapy. Though they routinely prevent mortality or significant morbidity within a matter of weeks, antibiotics for resistant infection price at a small fraction of treatments for chronic non-bacterial infectious disease (e.g., Hepatitis C), orphan disease or cancer. In

evaluating data from the U.K.’s National Institute for Health and Care Excellence (NICE) on cost per QALY (quality-adjusted life year; see Figure 1), the results are stark: novel antibiotics are significantly undervalued versus treatments for other disease areas, this despite the growing need and emergence of new multi-drug resistant bacteria with near-term mortality rates of 30 to 50 percent.

Turning the Tide

Unleashing a new wave of antibiotic development will require addressing the reimbursement barrier head-on. Many suggestions (within and beyond the PCAST report) are now being offered as to how to fix the broken reimbursement mechanism in order to spur future investment in antibiotics. However, many focus on “delinking” antibiotic manufacturer revenue from product sales, counter to the market driven model that has historically driven major innovation in pharmaceuticals across the disease landscape. Fundamentally, novel antibiotics need to be freed from the shackles of the DRG payment system, which has created



Note: Estimated costs per QALY are based on estimates from NICE, NHS and the *Journal of Hepatology*.

unique economic disincentives around the use of branded, novel antibiotics. Such drugs are price-referenced against inexpensive generics within hospital formularies, even though generics do not generally provide equivalent efficacy against resistant pathogens. Yet with a hospital's formulary budget and profitability at stake, inexpensive generics often remain the default choice.

One possible solution is the establishment of reimbursement carve-outs from DRG payments for treatment with novel, qualified antibiotics. Under this approach, all aspects of a patient's treatment with a resistant bacterial infection would be covered by the DRG payment, except the actual novel, qualified antibiotic. Hospitals that appropriately use novel antibiotics to treat such cases would be fully reimbursed by public and private payers for the cost of the drug.

While aggregate antibiotics expenditure to payers may increase in this scenario, the overall cost of treating resistant infections will come down, reinforcing the value of these life-saving agents and further spurring development efforts.

As companies advance the development of new treatments – especially for life-threatening Gram-negative infections – they should increasingly look to price treatments to value for appropriate usage. Under an ideal scenario, three elements

will come together to enable future novel antibiotics to achieve a 5-10x multiple on historic pricing models:

1. Biopharmaceutical companies should focus on increasingly targeted treatments for high-need, high-morbidity pathogens and infection types. One example is Carbapenem-Resistant Enterobacteriaceae (CRE) infection, which afflicts about 9,000 patients per year in the U.S., has a mortality rate in excess of 40 percent and has extremely poor existing treatment options.
2. Diagnostics companies, drug makers and other industry stakeholders need to work together to create rapid, point-of-care diagnostics that can be used to quickly triage patients and steer them toward the right targeted treatments (notably, President Obama's executive action to combat resistant bacteria includes the launch of a \$20 million prize for the development of rapid, point-of-care diagnostics).
3. An antibiotic carve-out from the DRG model will enable hospitals and other institutions to prescribe the most clinically appropriate, increasingly targeted treatments without worrying about formulary budget and profitability impact.

Backing Away From the Brink

The specter of the impending crisis from the emergence of resistant microbes is well publicized - but the threat remains real and growing. Resistant bacteria continue to surface while the number of active players developing antibiotics dwindles and the pipeline has virtually dried up.

While President Obama's executive order is a good start, more work needs to be urgently undertaken to address the broken economic incentives and associated dearth of innovation that have left many regions of the globe unprepared. To assess how far behind we have fallen in dealing with resistant infections, consider the recent stunning advances in treating metastatic breast cancer (12 to 18 months additional life expectancy in late-stage trials), or the flurry of groundbreaking treatments for hepatitis C that now offer 95+ percent cure rates. These are examples of the transformational potential that is possible

when the unmatched discovery and development capabilities of the biopharmaceutical industry are aligned with a significant unmet need and clear economic incentives.

As we are all stakeholders in this challenge, we have a responsibility to keep a steady light focused upon the threat of antibiotic resistance to ensure that meaningful investment and progress are achieved in the next decade, and seemingly routine infections don't increasingly end up with catastrophic outcomes.

¹ www.whitehouse.gov/ostp/pcast; originally published in September, 2014.

² Ibid.

³ "Report to the President on Combating Antibiotic Resistance," President's Council of Advisors on Science and Technology, p. 35, available at <http://www.whitehouse.gov/administration/eop/ostp/pcast>, posted in September 2014.

⁴ From the UK's National Institute for Health and Care Excellence (NICE); <http://www.nice.org.uk/glossary?letter=Q>; A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a zero to 1 scale). It is often measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance.

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