Incentivizing the Development of Novel Antibiotics: New Paradigm Needed?

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• Final Paper Proposals: comments back to you today
• Public Comment due October 2nd

• Upcoming guest speakers:
  • September 25th: Leo Beletsky, JD, MPH
  • October 2nd: Shaleen Title, JD
  • October 7th: Faith Khalik, JD

Last-Minute Schedule Change!

• Professor Liu’s talk on Off-Label Promotion will be postponed to late October (date TBA, but during one of the three “Miscellaneous” sessions)
• Debate on off-label promotion postponed as well
• Antibiotics talk today: no pre-reading, but relevant articles will be posted after class

Link to watch webinar (1 hour):

Current Events in Drug Law
#NUSLDrugLaw

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Scope of the AMR Problem:
- WHO: 700,000 people/year die from bacterial infections globally
- CDC: 23,000 people/year die from drug-resistant infections in the US
- The world urgently needs new antibiotics, vaccines, diagnostics and other products to help fight the rise of drug-resistant bacteria
- Many advances of modern medicine depend on fighting infection with antibiotics:
  - Routine surgery
  - Cancer therapy (e.g., neutropenic infections)
  - Treatment of chronic diseases (e.g., diabetes, liver disease)
Scope of the AMR Problem

• Surveillance of drug-resistant bacteria is essential for healthcare providers to deliver effective empiric antibiotic therapy.
• Traditional molecular epidemiology does not typically occur on a timescale that could impact patient treatment and outcomes.
• Blood and other specimen cultures often take days to identify pathogens, during which time broad spectrum antibiotic coverage has usually been administered.
• Broad spectrum antibiotics often disrupt native bacterial flora and result in the development of antimicrobial resistance.

How Do We Currently Incentivize Antibiotic Development?

Push vs. Pull Incentives

• Push mechanisms share research and development costs across several parties to reduce a company’s outlays, which increases the net present value (NPV) of their antibiotic candidates.
• Pull mechanisms increase NPV by guaranteeing or increasing the future revenue of a new antibiotic once it is approved.
Antibiotic Incentives

**Push Incentives**
- Supporting open access to research
- Grants for scientific personnel
- Direct funding (NIAID, CARB-X)
- Conditional grants
- Funding of translational research
- Tax incentives
- Refundable tax credits
- Product development partnerships

**Pull Incentives**
- Lump sum or milestone monetary prizes
- Advance market commitment
- Strategic antibiotic reserve
- Market exclusivity extensions
- Wildcard extensions
- Conservation-based market exclusivity
- Liability limitations
- GAIN Act (regulatory exclusivity)
- Limited Population Pathway (21st CC)
- Priority Review Vouchers (Tropical)

Streamlining the Clinical Trials Process

**Noninferiority Trials**
- Designed to show that the drug is not worse than existing active drugs by an acceptable degree of inferiority (the margin), usually set at 10%.
- Three criteria are required for the noninferiority trials:
  - (1) the control drug must be effective;
  - (2) a small decrease in effectiveness [in the new product] would not be detrimental to patients; and
  - (3) the new product has ancillary benefits such as decreased side effects or improved dosing convenience that would help overcome any small decrease in effectiveness.

- One review of a decade of antibiotic approval found that most pivotal antibiotic trials used a non-inferiority design (78%).
- Another study found that seven of the eight antibiotics approved between 2010 and 2015 were approved using noninferiority hypotheses.
- Only one of the eight—the one tested in a superiority design—had a novel mechanism of action: bedaquiline (Sirturo).

Noninferiority Trials
- Technically, demonstration of noninferiority does not necessarily mean that the new drug is as good as its comparator.
  - This nuance is not usually communicated to physicians and patients.
- When successive drugs are all tested in noninferiority trials against each other, there can be a *downward trajectory in effectiveness* (biocreep).
- Noninferiority testing shows that new products work “at least almost as well as existing products” for treatable conditions.
- Noninferiority studies DO NOT address the need for new treatments for emerging threats from multidrug resistant bacteria.
Limited Population Pathway

• Part of the 21st Century Cures Act (signed into law in the US in 2016)
• Stated purpose of the provision: “expedite the development and availability of treatments for serious or life-threatening bacterial or fungal infections in patients with unmet needs, while maintaining safety and effectiveness standards for such treatments”

Limited Population Pathway

• Antibiotic manufacturers would be able to base applications on:
  • traditional endpoints, alternate endpoints, or a combination of the two datasets of a limited size
  • Types of acceptable data would include:
  • (1) pre-clinical, pharmacologic, or pathophysiologic evidence;
  • (2) nonclinical susceptibility and pharmacokinetic data;
  • (3) data from phase 2 clinical trials; and
  • (4) “such other confirmatory evidence as the Secretary determines appropriate to approve the drug”
• Approved antibiotics would have to carry a disclaimer on their labels
• Data obtained in the post-approval period are intended to replace traditional pre-approval studies

Benefits to LPP?

• Less data means lower threshold for FDA approval
  • More companies may have incentive to develop antibiotics
• Limited Population labeling does not prevent more widespread off-label use
  • Increased market for antibiotic once approved
• Any new antibiotic is a good thing... right?

Downsides to LPP

• Data quality and rigor falls far short of the FDA “gold standard”
• No efficient way to ensure that prescribing is only to limited populations
  • Physician autonomy to prescribe largely unimpeded by Congress
  • Manufacturers will face substantial financial pressure to maximize use for other indications or for off-label uses
• Disclaimers have not been shown to be effective in dietary supplements
• The FDA has limited authority to enforce completion of post-market studies
  • Requesting additional studies at the time of LPP approval will not guarantee completion of those studies
  • Many post-market studies are not completed (or even initiated), several years after their approval
  • See, e.g., Sarepta and Exondys 51

Surrogate Endpoints

• Surrogate endpoints (including biomarkers) are markers of disease, such as laboratory tests or imaging studies, rather than actual clinical endpoints.
  • More convenient and cost-effective
  • Often shorten trial duration and number of patients enrolled
• May not correlate with more meaningful endpoints (like cure or survival)

Surrogate Endpoints

• For bedaquiline (Sirturo), a novel agent for multidrug resistant tuberculosis, the surrogate marker of disease response used was sputum clearance of mycobacteria after 8 and 24 weeks;
  • Bedaquiline demonstrated faster initial sputum clearance, but over time, total clearance was statistically comparable to the placebo control group
  • Most concerning: in phase Ib trials, those taking bedaquiline had a 5-fold increased risk of death compared to placebo!
Priority Review Vouchers

- Priority review vouchers were created by legislation in 2007 and initially applied to drugs treating certain qualifying neglected tropical diseases.
- The goal of the program was to incentivize development of treatments for conditions most prevalent in underdeveloped countries with poor and marginalized populations, where limited possibility for commercial success has not attracted sufficient private investment.
- Priority review vouchers are earned when a qualifying drug is FDA-approved, and the sponsoring company can either use the voucher to obtain priority regulatory review for a different drug (an approval decision within 6 months instead of 10) or sell the voucher to another company.

Medical Countermeasure PRVs

- Expansion of the Priority Review Voucher Program Under the 21st Century Cures Act: Implications for Innovation and Public Health

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Priority Review Vouchers

• Congress loves these indirect incentives – do not involve additional budget appropriation
  • Yet they DO burden the FDA to expedite review of non-priority drugs
• Lucrative to sell, yet value will fall over time as more and more are awarded and not redeemed
• Do not appear to have stimulated additional investment in target areas
  • 4-month time savings (even for potentially lucrative drugs) not worth the other challenges associated with new drug development?

GAIN Act of 2012 (QIDP)

• Generating Antibiotic Incentives Now (GAIN)
• Designates certain new antibiotic candidates as Qualified Infectious Disease Products (QIDPs)
  • Occurs early in development
• FDA lists over 20 “qualifying pathogens” for QIDP applications to be based
  • … and keeps adding to the list
• 5 additional years of regulatory exclusivity (total: 10–12 years)*
  • * If approved (QIDP designation does not guarantee FDA approval)
  • Median patent exclusivity for new drugs between 12-14 years

GAIN Act of 2012 (QIDP)

• From July 9, 2012, through September 30, 2017:
  • 147 QIDP designations (74 designations for novel drugs)
  • 12 drug products with QIDP designation FDA-approved (each received priority review)
• QIDP designation may help provide additional financial guarantees for drugs that reach the market but does not help differentiate important new antibiotics from those with only minor incremental advantages
  • QIDP can be awarded regardless of novelty of drug or severity of infection
    (as long as the condition is on the ever-growing list)

Wildcard Patent Exclusivity

• In 2005, legislators proposed to award a wildcard exclusivity voucher of up to 2 years that could then be applied to extend the patent of any blockbuster drug already on the market.
• Earlier draft of the 21st Century Cures Act had a similar provision
  • Would have amended GAIN to allow one of the five years of added regulatory exclusivity to be applied to one or more other drugs
  • In exchange, the rights-holder of the recipient drug was to donate up to 5% of sales of the blockbuster drug during that year to the NIH

Kesselheim & Outterson
Yale J. Health Pol’y L. & Ethics (2011)

• “Wildcard patent proposals [for antibiotics] may cost many billions of dollars, with doubtful social value. Essentially, wildcard patents tax drugs for heart disease to pay for antibiotic research and development.”

7 years later...

Bipartisan antibiotic pull incentive introduced today in US Congress, REVAMP Act of 2018 (Shinkus-Cardenas)
Most important antibiotic legislation in a generation. Text & summary:

Innovative ways to pay for new antibiotics will help fight superbugs
Funding the development of new antibiotics is tricky. Tradable exclusivity warrants — essentially a vehicle or prize that allows a drug …

Kesselheim & Outterson (2011)

“Wildcard patent proposals [for antibiotics] may cost many billions of dollars, with doubtful social value. Essentially, wildcard patents tax drugs for heart disease to pay for antibiotic research and development.”
Why is the market broken?

- Few buyers for emerging infectious disease medications
- Producer uncertainty over volume
- Cures and preventions require fewer doses than treatments
- Effective products undermine their own markets
  - Eradication causes the market for a product to collapse entirely
  - Positive externalities mean lower volume (e.g., herd immunity)
  - Stewardship limits sales volume
- Poor patients cannot pay high prices (e.g., neglected tropical diseases)
- Concentrated buyer groups (like governments and foundations) exert downward price pressure
- Ethical considerations and public pressure
- Patient characteristics reduce demand (e.g., underestimation of risk)

Few Buyers

- Small markets have long been known to lead to challenges in incentivizing private investment in drug development
  - Orphan Drug Act of 1983 arose from these concerns for rare diseases
- The market for emerging infectious diseases is small because, by definition, emerging diseases initially affect few people
- In 2013, the CDC estimated that drug-resistant tuberculosis, Pseudomonas aeruginosa, and Salmonella typhi affected 1042, 6700, and 3800 people, respectively, in the United States each year
- Vancomycin-resistant Staphylococcus aureus affected only 2 people each year!

Uncertainty Over Volume

- Unpredictability: anticipating need during epidemics is challenging
- Recent outbreaks of influenza, Zika, cholera, and Ebola demonstrate the unusual volatility of many infectious diseases, including their potential to rapidly create large markets or shrink down into small ones
  - Global contagion can occur in a matter of months (1917 influenza pandemic)
- Development efforts may also halt when outbreaks unexpectedly diminish or resolve.
  - Less than two years after WHO declared Zika an international public health emergency, Sanofi announced it was discontinuing development of two Zika virus vaccines due to a decline of new infections and new limits on U.S. government funding

Fewer Doses

- Rapid therapeutic success limits sales potential, since fully recovered patients no longer need medicine
- Drugs in other therapeutic categories that must be taken on an ongoing basis—such as statins or insulin—provide a much more favorable business model
Positive Externalities

• Herd Immunity: Products that prevent or resolve infections benefit not only the patients who are treated, but also those who do not get the medication but whose risk of acquiring the disease is mitigated
• High public health value, but some people may free-ride, knowingly or unknowingly, by relying on or benefiting from others who obtain treatment while declining or not needing to pay for the treatment themselves

Undermining Markets

• To the extent a medicine is effective in preventing further transmission— one of the key benefits that produce high public health value—it prevents growth in market demand
• At the extreme, eradication of an infectious disease (as with smallpox in the 1970s) could cause a market for an antibiotic or other antimicrobial product to collapse
  • Tremendous public health value but entirely eliminated sales potential
• In exceptional cases, a collapsed market might be buoyed if fear of terrorism or other disease resurgence prompts governments to hedge against unlikely risks.
  • In 2011, the U.S. government committed $433 million to obtain 1.7 million doses of a smallpox antiviral medication, which supplements its existing $1 billion stockpile of smallpox vaccine

Stewardship Limits Sales

• The emergence of antibiotic resistance necessitates the sparing and appropriate use of antibiotics to preserve effectiveness, a concept known as “stewardship”
  • Stewardship not commonly seen in non-infectious disease marketplaces
• The need for stewardship is in tension with limited patent and other statutory exclusivity terms, which motivate brand-name drug manufacturers to generate as much revenue as possible before exclusivity expires and generic firms enter the market
• Infectious disease products have a median of 14.4 years of market exclusivity

Poorer Patient Populations

• If a disease is prevalent, but mainly affects those who are poor—as is the case for many diseases that are prevalent in developing countries—drug manufacturers may find more attractive opportunities elsewhere
  • e.g., Neglected Tropical Diseases

Downward Price Pressures

• Governments and foundations are major buyers of vaccines and can help buoy and stabilize volume, but this role may also limit the average price achievable by sellers
  • Unlike drugs, HHS can negotiate vaccine prices and obtains steep discounts on vaccines
• Foundations naturally use their buying power and public purpose to negotiate lower prices, sensibly preferring less expensive generics when available
  • If the product is branded, governments can also issue compulsory licenses or threaten to do so, exerting downward price pressure

Ethical Considerations

• Public pressure to lower drug prices will naturally be greatest for the most highly effective drugs, based on the ethical principle that patients should not be denied access to life-saving or life-sustaining therapy regardless of ability to pay
  • e.g., hepatitis C treatments in the US
Patient/Product Characteristics

• Vaccine skepticism: underestimating disease risks may mean that individuals not suffering from illness may have a very low willingness to accept product risks, costs, or even the inconvenience of a visit to a doctor’s office
  • Underestimating risk also reduces demand!
  • Contributing to cost-benefit miscalculations is optimistic bias (the natural tendency of patients to believe they are less likely than average to experience negative health events)
• Many vaccines are administered by injection
  • Disfavored by many patients, particularly children
  • Requires provider involvement with administration

Alternative Solutions that Sidestep Traditional Markets

Nonprofit organizations

• Less dependent than traditional producers on projected sales revenue
• May collaborate with government, industry, or others to accelerate product development
  • Drugs for Neglected Diseases initiative (DNDi) blends various philanthropic, government, and other funding sources
  • From its founding in 2003 through 2015, DNDi succeeded in making available six new products, although all represented modest clinical advances
• May be able to offer successfully-developed drugs at prices far below those of traditional firms
• Antimicrobials and vaccines could be licensed directly to generic drug manufacturers under contracts that include supply commitments and reasonable price provisions

Government funding of basic research

• National Institute of Allergy and Infectious Diseases (NIAID) spends approximately $4 billion annually on basic and applied research addressing nearly 300 infectious agents, including HIV, Zika, Ebola, and pandemic influenza
• Combating Antibiotic Resistant Bacteria biopharmaceutical accelerator (CARB-X), founded in 2016 to advance global research on bacterial drug-resistance
  • Grew out of a 2014 executive order that directed the Biomedical Advanced Research Development Authority (BARDA), a sub-agency within the Department of Health and Human Services, to develop next-generation countermeasures to address antibiotic-resistant bacteria
  • Focus is on hit-to-lead and pre-clinical studies

Government purchase commitments

• Legally binding commitment to purchase a pre-specified quantity of a new drug or vaccine at a pre-specified price
  • May need to meet buyer specifications such as adequate thermal stability or protection against certain serotypes
  • Once a specified quantity has been purchased by the government or other organization making the commitment, the drug developer could then be obligated by contract to sell further units at a low price, creating an effect similar to patent expiration
  • In contrast to the patent system, however, the initial higher price is set in advance by the purchaser rather than the manufacturer

Enhanced global coordination

• Approach recommended by a WHO Consultative Expert Working Group in 2012
• May occur via a global biomedical research and development treaty
  • “Infectious diseases do not respect national boundaries”
• Advantages:
  • Leverage a global base of potential resources
  • Reduce duplicative effort
  • Ensure equitable contributions by nations that are sensitive to each nation’s ability to pay
  • Help to ensure a stable funding stream over time.