THE ROLE OF THE CENTRAL MICROBIOLOGY LAB IN STREAMLINING ANTIBIOTIC DEVELOPMENT

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In the early 2000s, alarms were raised by several groups—most notably the Infectious Disease Society of America (IDSA)—that the antibiotic development pipeline was inadequate to address the increasing prevalence of antimicrobial resistance. In their 2004 report, “Bad Bugs, No Drugs,” the IDSA reported on the increasing prevalence and spread of multi-drug resistant organisms. They also noted a dramatic decline in new antibiotic approvals, as well as a troubling exodus of companies engaged in the research and development of new antibiotics.

BARRIERS TO ANTIBIOTIC DEVELOPMENT

Many antibiotics discovered in the 1970s and 1980s are still used today for many infections. The availability of antibiotics and their overwhelming effectiveness for several common infections have provided a false sense of security that we have conquered many infectious diseases. Unfortunately, the rising rate of antibiotic resistance in several groups of organisms portrays a different story. The CDC estimates that over 2 million infections are caused each year due to multi-drug resistant organisms resulting in 23,000 deaths.

Antibiotic development has been negatively impacted by a few key factors. First, it is difficult to identify novel compounds that have favorable pharmacodynamic / pharmacokinetic (PK/PD) properties for bacterial killing, while also being safe for administration. In general, larger doses of antibiotics are required in the serum to achieve bactericidal or bacteriostatic effects. Moreover, antibiotics have different chemical properties compared to other drugs and many proprietary compound libraries do not include potential antibiotics.

Secondly, for antibiotic clinical trials, because there are often effective treatments available, it is unethical to include untreated placebo groups. Therefore, most antibiotic trials are conducted using non-inferiority designs. Non-inferiority trials often require longer timelines to meet enrollment objectives and as such, may incur greater costs compared to superiority trials, and in some models, completing the entire cycle projects a net overall loss for a pharmaceutical company.
POSSIBLE SOLUTIONS TO ENCOURAGE ANTIBIOTIC DEVELOPMENT

The assertion that antibiotic development is not economically feasible for pharmaceutical companies is beginning to be addressed by legislative initiatives. One example is the Generate Antibiotic Incentives Now (GAIN) act that was signed into law in 2012, as part of the Affordable Care Act in the United States. The GAIN act provides several competitive advantages to companies that bring an antibiotic to market.

The GAIN act calls for a priority review process and fast-track approval for new drug applications for qualified antibiotics. Shortening the length of time spent in the approval process may increase the time the antibiotic spends on the market generating revenue. The GAIN act also calls for increasing the exclusivity window by five years once an antibiotic hits the market—the exclusivity window can further be increased by coupling the antibiotic with a companion diagnostic. Moreover, the GAIN calls for further study on incentivizing antibiotic development and encourages the generation of new streamlined approval process guidance.

The GAIN act may be an appropriate and positive first step to stimulate more companies to invest in the development of antibiotics. However, the complete impact of this legislation will not be realized for several years, as the antibiotic development lifecycle can span 10-20 years.

In response to the GAIN act, the IDSA, and the concerns expressed from pharmaceutical representatives and stakeholders, the FDA has recognized the emerging issue of antibiotic resistance and the current state of antibiotic development is inadequate to meet this challenge. In 2013, the FDA published a draft guidance document for industry engaged in the development of antibacterial therapies. When fully implemented, the draft guidance for smaller trials to address “unmet medical need” may be most appropriate to identify effective therapies for individual pathogens, including those organisms that currently harbor rare, but emerging forms of resistance.

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The exodus of pharmaceutical companies from antibiotic development has also had impacts on Central Laboratories and their respective Central Microbiology services. The willingness of the FDA to accept less clinical efficacy data to support NDAs for antibiotic submissions requires that the microbiology data used to support efficacy outcomes is especially robust. A central lab offering comprehensive microbiology services may be in a strong position to generate and integrate the strongest possible safety and microbiology data set to support antibiotic trials.

Because there is very little overlap in the techniques performed in microbiology as compared to other lab disciplines, staff employed by central microbiology labs are specifically trained to perform the analyses required to support antibiotic development. Testing requirements in antibiotic trials may be vastly complex, requiring antigen detection or molecular diagnostic approaches, which are often beyond the capabilities of a local diagnostic microbiology lab. Additionally, the microbiology data generated for antibiotic new drug applications are generally more complicated than safety data.
The testing requirements in an antibiotic trial may be vastly different from one trial to another, based on the identified efficacy endpoints. Given that many of these approaches are not standard or available “off the shelf,” central microbiology labs must have the capability of performing de novo method validations and provide ongoing quality assurance measures. While the concepts may appear intuitive, the infrastructure required for performing this type of testing is often beyond the capabilities of a local diagnostic microbiology lab.

Moreover, increasing the complexity of microbiology testing creates significant challenges in data management. The microbiology data generated for antibiotic new drug applications are generally more complicated than safety data, as the data generated may be numerical, comment-based or a combination thereof. While a significant amount of data in a trial may be standardized and predictable, the organisms studied may reveal novel phenotypes or resistance patterns. Thus, the flexibility to develop data management solutions for accommodating the wide array of possible organisms detected, as well as interpretation of antimicrobial susceptibility profiles is critical.

The continued emergence of antibiotic resistance, coupled with industry and governmental initiatives for improving the process to identify and develop novel antibiotics, has challenged central microbiology labs with developing robust capabilities to support new clinical trials. As pharmaceutical companies begin to design smaller scale, pathogen-specific trials, the importance of identifying valid microbiology endpoints and partnering with a flexible, responsive central microbiology lab to meet those objectives will be crucial.
REFERENCES


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