Antibacterial drug discovery was a major therapeutic focus of pharmaceutical research activities for at least 50 years. Almost every large pharmaceutical company had a group that focused on the identification of novel antimicrobial agents, usually through a combination of natural product research and semi-synthetic medicinal chemistry. The results were profound, as new β-lactams, glycopeptides, aminoglycosides, macrolides, streptogramins and tetracyclines emerged to treat bacterial infectious diseases that had accounted for high morbidity and mortality in the pre-antibiotic era. Synthetic chemistry became the source for other antibacterial classes such as the fluoroquinolones and oxazolidinones that have proved to be valuable additions to the antibacterial armamentarium. In 1980, at least 50 major pharmaceutical companies were contributing to the antibacterial pipeline. With the introduction of new drugs, bacterial resistance continued to develop, leading to a persistent medical need. Regulatory approvals were almost automatic when antibacterial agents were shown to perform in a similar manner to their closely-related predecessors. As a result, companies made huge profits and infused large amounts of resources into these activities.

As companies began to merge, and the pharmacy shelves began to be filled with effective anti-infective agents, the glamour of antibacterial research began to fade. Those companies that were still conducting discovery research moved from the examination of natural products in whole cell screens to high throughput enzymatic screens with random chemical libraries. Novel targets were identified, based on genomic and proteomic approaches to select essential enzyme targets that could be assayed on a large scale. However, these approaches did not provide sufficient numbers of new compounds that could meet increased developmental and regulatory hurdles. Excellent enzyme inhibitors were identified and optimized using sophisticated crystallographic and structure-based drug design approaches. However, compound libraries were not designed to mimic the properties of effective antibacterial drugs; few compounds were able to cross bacterial membranes, and even fewer were able to pass the test for “druggability”. In addition, regulatory requirements became more stringent for those compounds that completed clinical trials at the same time that companies set higher hurdles for financial gains. Greater consolidation of large companies resulted in fewer companies that invested in antibacterial research, such that less than a half dozen large companies are still engaged in antibiotic drug discovery.

However, antibiotic resistance continues to rise, especially in Gram-negative pathogens that now include organisms with no safe and efficacious therapeutic options. The medical need for new agents is critical. Fortunately, a number of smaller biotech companies are responding to this need with some innovative early compounds in the areas of protein synthesis inhibitors, fluoroquinolones, β-lactams, and metabolism inhibitors. Novel antibacterial compounds that have recently entered Phase 2 or Phase 3 clinical development include the aminoglycoside ACHN-490, the fluorocyclolide TP-434, the oxazolidinones radezolid and torezolid, the fluoroquinolones delafloxacin (ABT-492) and finafloxacin, β-lactamase inhibitor combinations with NXL104, the cephalosporin CXA-101, and the fatty acid biosynthesis inhibitor AFN-1252. At least another dozen new agents are in early clinical development. Most of these compounds have originated from small companies that are willing to take a higher risk. However, for most of these new agents, development costs for later clinical trials and commercialization will still need to be assumed by a larger company.

Antibacterial drug discovery is thriving in small companies. An unknown factor in all these activities is the role the regulatory process will play in the design of appropriate clinical trials and the final marketing approvals for these new agents. There will need to be a concerted effort among the discovery companies, the development companies and the regulatory agencies to be sure that new agents continue to move forward into the pipeline for the treatment of multidrug resistant Gram-negative infections.

Background references
Discovery of Novel Antibacterial Agents: Looking Backward, Moving Ahead

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Antibacterial drug discovery was a major therapeutic focus of pharmaceutical research activities for at least 50 years. Almost every large pharmaceutical company had a group that focused on the identification of novel antimicrobial agents, usually through a combination of natural product research and semi-synthetic medicinal chemistry. The results were profound, as new β-lactams, glycopeptides, aminoglycosides, macrolides, streptogramins and tetracyclines emerged to treat bacterial infectious diseases that had accounted for high morbidity and mortality in the pre-antibiotic era. Synthetic chemistry became the source for other antibacterial classes such as the fluoroquinolones and oxazolidinones that have proved to be valuable additions to the antibacterial armamentarium. In 1980, at least 50 major pharmaceutical companies were contributing to the antibacterial pipeline. With the introduction of new drugs, bacterial resistance continued to develop, leading to a persistent medical need. Regulatory approvals were almost automatic when antibacterial agents were shown to perform in a similar manner to their closely-related predecessors. As a result, companies made huge profits and infused large amounts of resources into these activities.

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