Antibiotic Renaissance: Technology and Market Advances in the War against Drug-resistant Bacteria.

Ken Rubenstein, Ph.D.

New to Insight Pharma Reports is Antibiotic Renaissance: Technology and Market Advances in the War against Drug-resistant Bacteria. This report covers evolutionary growth of antibiotic resistant bacteria with a focus in research aspects, commercial aspects, market aspects, and trends in antibiotic resistance. Antibiotic resistance has a historical presence in the big pharma industry (documentation of its understanding leads back to 1940); however it has only recently been on the incline of popular adoption. Because of the rapid development of antibiotics and the growing pharma industry, most professionals felt secure in the belief that for every antibiotic fallen by the wayside, new ones would emerge to replace them, much to the chagrin of the smaller population of physicians and medical scientists. Due to technical difficulty, regulatory complexity, and relatively poor returns on investment, commercial drug developers became progressively less enamored with nurturing the antibiotic industry. One by one, big pharmas dropped out of the bacterial infectious disease space in favor of therapeutic areas offering greater blockbuster potential.

Although researchers have reached a point to develop antibiotics to drug-resistant bacteria, the morbidity and mortality from drug-resistant infections have resultantly scourged a variety of regions and industries, including our most useful medical facilities. In an effort to raise awareness and take action, governments, professional societies, and a growing body of medical researchers have published papers and reports that highlight the problems, call for remedial action, and propose action plans. Accordingly, academic, governmental, and commercial players have begun to ramp up activities in response to these calls to arms.

Specific Highlights Include:

- History, status, and progress of drug resistant bacteria
- Evolution of today's antibiotic resistant bacteria
- Diagnostic and therapeutic research programs directed at alleviating medical problems caused by antibiotic resistant bacteria
- Survey results exploiting commercial diagnostic and therapeutic programs and market-related aspects of antibiotic resistance
- Trends developing in the field
- Exclusive interviews with six individuals who are highly knowledgeable in the subject area
Executive Summary

The phenomenon of antibiotic resistance has been understood and documented since the 1940s. Despite alarms sounded by a small coterie of physicians and medical scientists, most professionals have felt secure in the belief that for every antibiotic fallen by the wayside new ones would emerge to replace them. As time progressed, however, commercial drug developers became progressively less enamored with antibiotics on grounds of technical difficulty, regulatory complexity, and relatively poor returns on investment. One by one, big phamas dropped out of the bacterial infectious disease space in favor of therapeutic areas offering greater blockbuster potential.

We’ve now reached a point in history when the ability of bacteria to develop resistance to existing drugs has begun to outpace industry’s willingness to supply replacements. Morbidity and mortality from drug-resistant infections have now grown to the extent that governments, professional societies, and a growing body of medical researchers have published papers and reports that highlight the problems, call for remedial action, and propose action plans. Accordingly, academic, governmental, and commercial players have begun to ramp up activities in response to these calls to arms.

This report, *Antibiotic Renaissance: Technology and Market Advances in the War against Drug-resistant Bacteria*, covers the area’s history, status, progress, and trends in response to the growing crisis. Following a brief introduction, Chapter 2 covers the evolution and status of today’s antibiotic resistance crisis. Chapter 3 deals with diagnostic and therapeutic research programs directed at alleviating medical problems caused by antibiotic resistant bacteria. Chapter 4 turns to a survey of commercial diagnostic and therapeutic programs, including description and discussion of recently introduced products.

Chapter 5 covers market-related aspects of antibiotic resistance, including coverage of recent relevant deals and an opinion survey of individuals active in the field. Chapter 6 examines trends developing in the field, and a final chapter contains full transcripts of interviews with six individuals who are highly knowledgeable in the subject area. Extracts from these interviews are also to be found at relevant places elsewhere in the report.

Research Aspects of Antibiotic Resistance

Academic and industry players currently conduct diverse programs aimed both at diagnostic and therapeutic solutions for the problems posed by antibiotic resistance. In the diagnostic realm, we need improved methods to rapidly identify the responsible pathogen in cases of serious infection, and then determine which antibiotic to employ as therapy. Much of the research in progress today employs gene-based molecular diagnostic technology for
rapid ID and susceptibility testing, with emphasis on point-of-care utility and sample-in-answer-out simplicity. The obvious advantage of these approaches in speed over growth-based culture methods are tempered by the possibility of identifying nonviable organisms or free nucleic acids. A further disadvantage lies in potentially inadequate coverage of resistance mechanisms when counting on already characterized resistance markers. Still, multiplex molecular diagnostic assays should be quite effective based on their coverage of the most prevalent resistance sequences found in particular classes of serious infections. Growth-based methods for ID and susceptibility require more time, but have the advantages of assuring encounter with live, functioning pathogens, and of allowing one to directly test susceptibility to diverse candidate antibiotics. One advanced commercial program features reasonably rapid growth-based ID and susceptibility, and several less advanced programs appear headed in the same direction.

A number of research programs directed at therapeutic approaches to combating antibiotic resistance employ diverse and novel approaches. Several early-stage programs center on compounds that target previously ignored or under-exploited targets and mechanisms to kill or inhibit growth of bacterial pathogens. One company has developed a method to culture many bacteria that have so far resisted growth in the laboratory, and using them to discover new natural products as antibiotic candidates. Another group is attempting to improve on whole-bacteriophage therapies employing a phage protein component to kill bacteria. Another program features drug repurposing, and has identified an antipsychotic that shows antibacterial activity. Yet, another has repurposed an abandoned antibiotic to attack persistor bacteria that manifest drug tolerance.

**Commercial Aspects of Antibiotic Resistance**

From the diagnostic perspective, most of the recently marketed products and advanced product development programs are based on molecular diagnostic detection of nucleic acid sequences. Among these, more than half of those noted in the report address MRSA (methicillin-resistant *Staphylococcus aureus*), the highly problematic cause of the first antibiotic-resistant infection class to draw massive public attention. Vancomycin-resistant bacteria also draw considerable attention. Several development programs address a broad array of sequences, both for identification and antibiotic resistance detection. Two programs noted in the report address growth-based methodologies, the most advanced of which uses microfluidics, automated imaging, and image analysis in an attempt to cover identification and susceptibility within six hours from the time the sample is collected.

In the therapeutic category, projects surveyed for this report range in status from preclinical development on up to recently marketed. Of the more than 30 projects considered, nine specifically address Gram-positive indications, while seven address the more refractory Gram-negatives. Another seven projects feature antibiotics designated broad spectrum, although most aim at least initially at Gram-positive infections. Two programs
utilize bacteriophages or parts of them. Three programs involve development of vaccines or anti-toxins against staph, and two of these are conducted in big phamas. Three programs aim to develop β-lactamase inhibitors to block resistance and allow accompanying antibiotics to function effectively. Notably, more than one-third of all the projects or products considered here involve new, previously unexploited targets. Seven programs are in preclinical development, four in Phase 1, eleven in Phase 2, five in Phase 3, and seven have reached the NDA filing stage or gone to market in one or more regions of the world.

**Market Aspects**

The current market for antibiotics, worth around $40 billion, is stagnant and may even be declining slowly as existing drugs fall victim to resistance. In light of big phama’s essential withdrawal from discovery and development in this area, replacements for fallen drugs have been few and far between. However, a number of promising signs have started to emerge. Favorable shifts in regulatory policies, together with indications that healthcare systems and insurers are likely to accept significant price increases for antibiotics targeted against specific serious infections involving resistant bacteria, have influenced several big phamas to reenter the antimicrobial field and also accelerated relevant entrepreneurial activity. Public-private collaboration, as illustrated in the U.S. by BARDA grants, also helps drive this resurgence.

Deal activity, although still relatively light, especially in the diagnostic realm, shows signs of resurgence as well. Among 18 recent therapeutic deals tabulated herein, three involve Roche (including one for their Genentech unit), two involve Sanofi, and three involve Cubist Pharmaceuticals (two acquisitions and one development deal). A notable entry involves GSK, which received a BARDA grant worth up to $200 million that addresses their antibacterial portfolio rather than specifying compounds.

**Trends in Antibiotic Resistance**

In addition to aforementioned regulatory and pricing factors, the emerging renaissance in discovery and development of antibiotics and associated diagnostic assays is driven by efforts emanating from various associations and initiatives. IDSA (Infectious Disease Society of America) for example, has started a decade long drive to incentivize new antibiotic development under the banner, 10 x ’20 (i.e. ten new drugs by 2020). Although early results in terms of new products have yet to demonstrate much progress toward this goal, resurgent activity suggests it may yet be attainable. However, IDSA states that progress against Gram-negative bacteria “remains alarmingly elusive.”

IDSA and (informally) FDA also support a bill currently before the U.S. Congress called ADAPT (Antibiotic Development to Advance Patient Treatment), which calls for further regulatory reform under the title LPAD
(Limited Population Antibacterial Drug). In parallel with IDSA’s efforts, the European Innovative Medicines Initiative (IMI) supports several relevant programs including COMBACTE (Combating Bacterial Resistance in Europe), which aims to boost antibiotic drug development through pioneering new ways to design and implement efficient clinical trials for novel antibiotics. IMI also funds ND4BB (New Drugs for Bad Bugs), one aspect of which addresses difficulties in getting drugs to penetrate Gram-negative bacterial cell walls.

Big pharma companies wishing to re-enter the antibiotics space face difficulties stemming from prior disbanding of relevant R&D groups, notably in medicinal chemistry where the passing down of key heuristics has now been interrupted. Another key issue, as just mentioned, involves finding compounds able not only to act once inside the cell, but also able to penetrate the Gram-negative cell wall. One interviewee for this report supports prodrugs as a solution, while others stress the inadequacy of general compound libraries and the need for collections focused on structures with potential antibacterial activity. Yet another key issue centers on the role of bacterial tolerance via persister cells, which are phenotypically, but not genotypically, resistant to antibiotics. Interviewee Kim Lewis and his associates recently published results that appear to constitute a major breakthrough in this area.
Q-linea AB
Roche Molecular Systems
STAT-Diagnostica
Culture-based Approaches
Accelerate Diagnostics
Axela Inc. and Hutman Diagnostics
Mass Spectrometry-based Diagnostics
Therapeutic Products and Projects
Achaogen
Achillion Pharmaceuticals
Affinum Pharmaceuticals
Allecra Therapeutics
AstraZeneca
Basilica Pharmaceutical
Biota Pharmaceuticals
Cellceutix
Cempra Pharmaceuticals
ContraFect
Cubist Pharmaceuticals
Durata Therapeutics
Enanta Pharmaceuticals
Forest Laboratories
GlaxoSmithKline
Helperby Therapeutics
Johnson & Johnson
Melinta Therapeutics
Merck
Nabriva Therapeutics
Novolytics
Paratek Pharmaceuticals
Pfizer
Phico Therapeutics
Polyphor Ltd.
Shionogi and Co., Ltd.
TaiGen Biotechnology
Tetraphase Pharmaceuticals
The Medicines Company

CHAPTER 5
Market Aspects of Antibiotic Resistance
Deals
Survey Results

CHAPTER 6
Trends in Antibiotic Resistance
Consortia, Regulatory Initiatives, and Collaborative Programs
Difficulties for Infectious Disease Drug Discoverers and Developers
New Approaches to Discovering Drugs to Avoid Antibiotic Resistance

CHAPTER 7
Interview Transcripts
Glenn Tillotson, PhD, Senior Partner, Transcrip Partners, USA
David Shlaes, MD, PhD
Kim Lewis, Ph.D.
Lawrence Mehren
Stuart B. Levy, M.D.
Shana Kelley, Ph.D.
Bacteria have developed means to resist attack by every antibiotic we’ve developed to date. We’ve known about the existence of the resistance phenomenon since the 1940s. Since then, the problem has grown in scope until now when individual scientists, professional groups, and government agencies are sounding alarms with increasing frequency and stridency. A few stalwarts, including Dr. Stuart Levy who we’ve interviewed for this report (see Chapter 7), tried to sound the alarm decades ago, and met with limited success in their attempts to stimulate large-scale efforts to address the problem.

Large pharmaceutical companies innovated their way through a golden age of antibiotic development, which covered roughly the period of 1940 through 1960. They followed this massive and highly successful commercialization effort with another five decades of productive medicinal chemistry in which structures/scaffolds of earlier antibiotics were modified and elaborated for improved function and, sometimes, the ability to overcome specific bacterial resistance mechanisms.¹

Changes in size and research strategies of large pharmaceutical companies, which became increasingly apparent during the 1980s, culminated in drastic reductions in antibiotic drug discovery and development activity. Until recently, new or previously ignored antibiotics stood ready to take over as older ones fell victim to bacterial resistance. A gap between new antibiotic demand and old antibiotic obsolescence developed and grew, until the recent era which might be characterized as one of antibiotic resistance crisis.

In response, hospitals and physicians have initiated antibiotic stewardship programs in an attempt to extend the useful lifetime of existing drugs; a growing number of countries have sharply curtailed or even eliminated the use of antibiotics for growth promotion in food animals; a few large pharmaceutical companies have begun to ramp up their antibiotic efforts; funding for research in the field is on the rise; and investment in relevant therapeutic and diagnostic start-up ventures is trending upward as well.

This report, Antibiotic Renaissance: Technology and Market Advances in the War Against Drug-resistant Bacteria, covers history, status, progress, and trends in response to the growing crisis just described.

Scope and Contents

The report, which provides a survey and analysis of this newly revitalized field of scientific and commercial endeavor, comprises seven chapters. Following this brief introduction, Chapter 2 covers the evolution and status of today’s antibiotic resistance crisis. Chapter 3 deals with diagnostic and therapeutic research programs directed at alleviating
medical problems caused by antibiotic resistant bacteria. Chapter 4
turns to a survey of commercial diagnostic and therapeutic programs,
including description and discussion of recently introduced products.
Chapter 5 covers market-related aspects of antibiotic resistance, including
a survey of recent relevant deals and an opinion survey of individuals active
in the field. Chapter 6 examines trends developing in the field, and a final
chapter contains full transcripts of interviews with six individuals who are
highly knowledgeable in the subject area. Extracts from these interviews are
also to be found at relevant places elsewhere in the report.

Before we examine the origins and status of the problem, it would be well to consider the meaning of the term: antibiotic resistance. A 2009 report from the American Academy of Microbiology offers the following definition:

The specific meaning of “antibiotic resistance” depends entirely on context. The clinical definition used in this document refers to the ability of a microorganism—a bacterium, virus, fungus, or parasite—to survive concentrations of antibiotics that kill sensitive cells of the same strain. It is important to note that for every antibiotic, there are sensitive strains, which are killed or inhibited by the drug, and naturally resistant strains. When a sensitive strain gains the ability to withstand an antibiotic, it is “antibiotic resistant.”

In bioclinical terms, antibiotic resistance simply means that a pathogen is less susceptible than its counterparts and may not respond to the antibiotic administered. In genomics, organisms that possess a resistance gene are resistant. Like all other living things, the evolution of microorganisms is Darwinian: in the face of change, the fittest survive. Antibiotics represent an evolutionary challenge that microorganisms must surmount or perish.

The entire world finds itself in the midst of a full-blown antibiotic resistance crisis. This is not an impending crisis, but one that is already generating worrisome levels of morbidity and mortality, not only in hospital and other institutional settings, but increasingly within communities at large. The CDC (US Centers for Disease Control and Prevention) recently issued an extensive report on the subject in which they state:

> CDC estimates that in the United States, more than two million people are sickened every year with antibiotic resistant infections, with at least 23,000 dying as a result. The estimates are based assumptions and are likely minimum estimates.

The report goes on to describe particular threats with estimates of their current impact. Three infectious agents were given a threat level assessment of urgent: *Clostridium difficile*, carbapenem-resistant *Enterobacteriaceae* (CREs), and drug-resistant *Neisseria gonnorrhoeae*. *C. difficile* is considered an urgent threat because of its ubiquitous presence in the human gut together with its natural resistance to antibiotics used to treat other infections. Another 12 infectious agents were designated serious threats. These include the notorious MRSA (methicillin-resistant *Staphylococcus aureus*), ESBLs (extended spectrum β-lactamase producing *Enterobacteriaceae*), VREs (vancomycin-resistant *Enterococcus*), and drug-resistant tuberculosis.

Numerous other reports and documents containing similar assessments appeared during 2013, including a particularly comprehensive one from
the UK. Warnings about impending antibiotic obsolescence are not just a recent phenomenon. Perhaps the most dramatic support for this observation came from Alexander Fleming, who in 1928 discovered penicillin, which didn’t enter mass production until 1944, in time to save many wounded soldiers from death by infection. In 1945, Fleming was co-awarded a Nobel Prize and said in his Nobel lecture:

*But I would like to sound one note of warning. Penicillin is to all intents and purposes non-poisonous so there is no need to worry about giving an overdose and poisoning the patient. There may be a danger, though, in underdosage. It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body.*

*The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug making them resistant… Moral, if you use penicillin, use enough.*

As is now abundantly clear based on numerous reports, accounts, and presentations, bacteria are becoming resistant to existing antibiotics much faster than replacements enter the market. As has been amply documented, antibiotic discovery and development in big pharma have gone quiescent in recent times, a trend from which the industry may now be slowly emerging. As it’s been, new antibiotics were seen to lack sufficient revenue-generating potential and return on investment to compete with certain other classes of drugs, notably those indicated for chronic diseases as opposed to acute infectious conditions.

Perusing a table published online in February 2014 by a UK journal, *The Telegraph* provides an eye-opening experience. Their data on years in which individual or classes of antibiotics were discovered versus the times when resistance was first identified are shown in Exhibit 2.1. For drugs or classes with relatively long periods between discovery and emergence of resistance, penicillin for example, the explanation lies more in the frequency of use than in any drug’s power to avoid becoming resistant.

<table>
<thead>
<tr>
<th>Drug or class</th>
<th>Year discovered</th>
<th>Year resistance identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>1928</td>
<td>1941</td>
</tr>
<tr>
<td>Sulphonamides</td>
<td>1932</td>
<td>1942</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>1943</td>
<td>1947</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>1943</td>
<td>1949</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>1945</td>
<td>1953</td>
</tr>
<tr>
<td>Nitrofurans</td>
<td>1946</td>
<td>1952</td>
</tr>
<tr>
<td>Phenicols</td>
<td>1947</td>
<td>1956</td>
</tr>
<tr>
<td>Polymyxins</td>
<td>1947</td>
<td>1978</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>1948</td>
<td>1966</td>
</tr>
<tr>
<td>Pleuromutilins</td>
<td>1950</td>
<td>1982</td>
</tr>
<tr>
<td>Macrolides</td>
<td>1952</td>
<td>1953</td>
</tr>
<tr>
<td>Streptogramins</td>
<td>1963</td>
<td>1956</td>
</tr>
<tr>
<td>Nitroimidazoles</td>
<td>1953</td>
<td>1978</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>1953</td>
<td>1986</td>
</tr>
<tr>
<td>Novobiocin</td>
<td>1955</td>
<td>1961</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>1955</td>
<td>1965</td>
</tr>
</tbody>
</table>
Chapter Two: History and Background

Antibiotic Renaissance

Exhibit 2.1 Time between antibiotic discovery and appearance of resistance

<table>
<thead>
<tr>
<th>Drug or class</th>
<th>Year discovered</th>
<th>Year resistance identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoprim</td>
<td>1961</td>
<td>1972</td>
</tr>
<tr>
<td>Fusidic Acid</td>
<td>1962</td>
<td>1966</td>
</tr>
<tr>
<td>Quinolines</td>
<td>1962</td>
<td>1966</td>
</tr>
<tr>
<td>Lincosamides</td>
<td>1962</td>
<td>1979</td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>1969</td>
<td>1973</td>
</tr>
<tr>
<td>Mupirocin</td>
<td>1971</td>
<td>1987</td>
</tr>
<tr>
<td>Carbepenems</td>
<td>1976</td>
<td>1985</td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>1978</td>
<td>1999</td>
</tr>
<tr>
<td>Monobactams</td>
<td>1979</td>
<td>1981</td>
</tr>
<tr>
<td>Lipopeptides</td>
<td>1987</td>
<td>2005</td>
</tr>
</tbody>
</table>

Source: Adapted from http://s.telegraph.co.uk/graphics/projects/antibiotic-resistance/index.html, accessed February 6, 2014

Dr. Stuart Levy, a Tufts University researcher, has long served as a pioneer and advocate in the fight against antibiotic resistant bacteria. In his interview for this report, he produced the following exchange:

**IPR**: I know you’ve been a long-time advocate of dealing with antibiotic-resistant bacteria. Sometimes it must have felt as if you were a lone voice in the wilderness. Did you get some cooperation from others along the way?

**SL**: I got just enough cooperation mainly from those in my age group who were working in the areas of drugs and antibiotic resistance. We even had some meetings to complain about how little support for research on antibiotic resistance there was in the US, especially when compared to Europe. In the mid-1980s, three of us, David Schlaes, Gordon Archer and I went to the NIAID council [National Institute of Allergy and Infectious Diseases] to argue for more funding for research on drug resistance. We did not succeed.

We were left with two options. One, the NIH Council believed that it was industry’s job to solve antibiotic resistance, not theirs; and two, there wasn’t enough money to go around. I felt frustrated, but there were just enough other people with whom to go to and share concerns. We joined together to complain about the situation, and get excited about the small advances we were able to make. A meeting held in the Dominican Republic (Santo Domingo) in 1981 was a good example of what we could do to get non-Americans as well as Americans involved in new drug discovery and the issue of antibiotic resistance. The meeting covered what had been happening, why we were in this situation, and it gave us a boost. An antibiotic resistance statement emerged. The **Alliance for Prudent Use of Antibiotics** arose out of the Santo Domingo meeting.

There were events like that which were gratifying. On the other hand they were not very definitive in terms of providing sufficient amounts of money for research into the problem. There’s NIH, where it is still hard to get money. You feel that it’s going to improve, and I’ve felt that way for 10 or 20 years. I think it’s better now than it has been, and I think it’s going to get still better.
Antibiotics and the Pharmaceutical Industry

By any measure, the number of new antibacterial drugs coming on the market or in late-stage development has decreased drastically in recent years as many big phamas have grown still larger via mergers and acquisitions as managements came to recognize that pursuit of drugs in other disease areas promises better returns on investment. One recent analysis dramatically illustrates the shift away from antimicrobials in time segment ranging from 1983 to 2012 (Exhibit 2.2).

<table>
<thead>
<tr>
<th>Period</th>
<th>Approvals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983-1987</td>
<td>16</td>
</tr>
<tr>
<td>1988-1992</td>
<td>14</td>
</tr>
<tr>
<td>1993-1997</td>
<td>10</td>
</tr>
<tr>
<td>1998-2002</td>
<td>7</td>
</tr>
<tr>
<td>2003-2007</td>
<td>5</td>
</tr>
<tr>
<td>2008-2012</td>
<td>2</td>
</tr>
</tbody>
</table>

Source: C. Cain, Rediscovering antibiotics. Antibiotic Resistance. SCIBX Collections, Published Online, November 29, 2012 DOI:10.1038/SCIBX.2012.1198

A 2013 report on current global risks offers another view on the subject: "Although several new compounds for fighting bacteria are in development, experts caution that we are decades behind in comparison with the historical rate at which we have discovered and developed new antibiotics. More worryingly, none of the drugs currently in the development pipeline would be effective against certain killer bacteria, which have newly emerging resistance to our strongest antibiotics (carbapenems) and fatality rates of up to 50%...A post antibiotic era means, in effect, an end to modern medicine as we know it. Things as common as strep throat or a child's scratched knee could once again kill."

From yet another perspective, of 14 antibiotics approved for sale between 1998 and 2010, only four featured novel mechanisms of action. The rest were derivatives or modifications of existing chemical scaffolds. We note here that in the mid-1980s, Beecham (now absorbed into GSK) introduced a drug combination consisting of amoxicillin and clavulanic acid, which is a β-lactamase inhibitor. The inhibitor knocks down the resistance mechanism so that the drugs can once again function. As we shall see, a number of ongoing commercial programs feature such inhibitors to be used in combination with existing antibiotics.

Research programs directed at new antibiotics and alternative therapeutic approaches are presented and discussed in Chapter 3, whereas commercial development projects and recently introduced products appear in Chapter 4.

Infections caused by Gram-negative organisms are proving particularly difficult to combat with existing antibiotics for reasons due, at least in part, to their inability to penetrate the cell wall that covers the microbes' inner membrane. A particular group of pathogenic bacteria are flagged as especially problematic with regard to antibiotic resistance, and have been granted their own acronym, ESKAPE, members of which are Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species. These microbes are responsible for more than their share of morbidity and mortality, not only in hospital settings, but increasingly in the community as well.

Resistance has a cousin, as it were, that thwarts the action of antibiotics in ways that do not require genotypic alterations in bacterial genomes. These phenotypic shifts generate a phenomenon called tolerance, in which the bacterial participants become the so-called persisters, which
exist in a transient, non-dividing dormant state.

In his interview for this report, longtime research and drug discoverer Kim Lewis commented on this issue:

50% to 65% of all infections in the developed world are chronic infections, biofilm-associated primarily. So it looks like the majority of infections that people seek help with are chronic infections, and these infections are due primarily to tolerance rather than drug resistance. They are caused by pathogens that we would normally call drug-susceptible rather than drug-resistant, meaning that they do not necessarily express any particular resistance mechanisms. So that addresses the question of clinical significance.

The relationship between tolerance and resistance seems to be pretty straightforward. The probability of acquiring resistance, of course, is proportional to the size of the population of pathogens. The more pathogen cells, the higher the probability that there will be resistance acquisition either through a mutation or acquisition through mobile genetic elements like plasmids. So if an antibiotic rapidly eliminates the pathogen, which often happens in acute infections, the drug plus the immune system will resolve the infection so that the effective size of the pathogen population is small. Chronic infections are very different; because of tolerance you get a relapsing infection. Persister cells, which are tolerant to antibiotics, will survive the antibiotic hit. They will resuscitate and restore the original population. So the result is that you have a lingering infection that can drag on for weeks, months, and, in some cases, for years. Of course the effective size of that population is proportionately larger compared to an acute infection, and that is fertile ground for resistance development. It is conceivable that the majority of resistance actually results from this vast reservoir of pathogens.

Diagnostics Background

Infectious disease physicians in treating patients with serious infections are especially need two pieces of information: (1) which microbe is responsible for the infection, and (2) which drugs will kill this microbe. Rapid gene-based identification within a matter of hours is feasible for many common pathogenic microbes and sites of infection, but more comprehensive identification requires overnight or longer culture procedures. The entire process not infrequently stretches to three or more days. There are methods, mass spectrometry for example, which can rapidly identify a great many bacterial species and strains starting from such culture isolates. This report does not offer extensive coverage of rapid bacterial identification, opting instead to focus on rapid drug susceptibility testing, whether growth-based or molecular diagnostic.

In the realm of susceptibility testing, classical disk-based methods, which rely on culture, are sufficiently time-consuming that physicians must usually prescribe antibiotics an empirical basis (i.e. best educated guess). A number of R&D programs and a few current commercial offerings attempt to address the need for rapid antibiotic susceptibility testing. These are covered in Chapter 3 for research-level approaches, and in Chapter 4 for commercial development and recent products.

Clearly, new and improved rapid diagnostic methods, especially sample-in-answer-out kinds, are vitally important alongside the need for new antimicrobials and alternative therapeutic approaches.
Chapter Five: Market Aspects of Antibiotic Resistance

### Exhibit 5.3 Type of organization where respondents work

<table>
<thead>
<tr>
<th>Organization Type</th>
<th>Response Count</th>
<th>Response Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial drug discovery/development</td>
<td>49</td>
<td>47.1</td>
</tr>
<tr>
<td>Commercial diagnostic products/services</td>
<td>6</td>
<td>5.8</td>
</tr>
<tr>
<td>Academic, government, or service organization.</td>
<td>28</td>
<td>26.9</td>
</tr>
<tr>
<td>Consultancy</td>
<td>12</td>
<td>11.5</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>8.7</td>
</tr>
<tr>
<td>Totals</td>
<td>104</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Source: Insight Pharma Reports

The next question also addresses organization types, but from another perspective. Exhibit 5.4 shows that a plurality (29.8%) of respondents work in big pharma or biotech, and 23.1% work in an academic institution. A total of 21.1% come from smaller phamas or biotechs, with the largest proportion (10.6%) in companies with revenues below $10 million per year.

### Exhibit 5.4 Answers to query further specifying employer type

<table>
<thead>
<tr>
<th>Organization Type</th>
<th>Response Count</th>
<th>Response Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academic institution</td>
<td>24</td>
<td>23.1</td>
</tr>
<tr>
<td>Pharma/biotech, sales &gt;$1B</td>
<td>31</td>
<td>29.8</td>
</tr>
<tr>
<td>Pharma/biotech, sales $100M to $1B</td>
<td>7</td>
<td>6.7</td>
</tr>
<tr>
<td>Pharma/biotech, sales &lt;$100M</td>
<td>4</td>
<td>3.8</td>
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<tr>
<td>Pharma/biotech, sales &gt;$10M</td>
<td>11</td>
<td>10.6</td>
</tr>
<tr>
<td>Diagnostic product company or lab</td>
<td>4</td>
<td>3.9</td>
</tr>
<tr>
<td>Consultancy</td>
<td>10</td>
<td>9.6</td>
</tr>
<tr>
<td>Other</td>
<td>13</td>
<td>12.5</td>
</tr>
<tr>
<td>Totals</td>
<td>104</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Source: Insight Pharma Reports

In additional demographic categorization, Exhibit 5.5 tabulates respondents’ position within their organization. The largest segment (27.9%) work in either middle management or in some supervisory capacity. Segments ranging from 14.4% to 16.3% serve as R&D directors, principal investigators, or bench scientists. Top managers and marketing/business development managers represent single-digit percentages.

### Exhibit 5.5 Respondents’ position in their organization

<table>
<thead>
<tr>
<th>Position</th>
<th>Response Count</th>
<th>Response Percent</th>
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</thead>
<tbody>
<tr>
<td>CEO/President/General Manager/etc.</td>
<td>8</td>
<td>7.7</td>
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<tr>
<td>Research and/or development director</td>
<td>15</td>
<td>14.4</td>
</tr>
<tr>
<td>Principal investigator</td>
<td>14</td>
<td>13.5</td>
</tr>
<tr>
<td>Research and/or development manager/group leader/supervisor</td>
<td>29</td>
<td>27.9</td>
</tr>
<tr>
<td>Bench scientist</td>
<td>17</td>
<td>16.3</td>
</tr>
<tr>
<td>Marketing or business development manager</td>
<td>4</td>
<td>3.8</td>
</tr>
<tr>
<td>Other</td>
<td>17</td>
<td>16.4</td>
</tr>
<tr>
<td>Totals</td>
<td>104</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Source: Insight Pharma Reports

Exhibits 5.6, 5.7, and 5.8 represent all respondents and the two breakout segments in regard to work activities. Exhibit 5.6, which represents the full set of respondents, shows antimicrobial drug development in the lead (38.5%), followed closely by antimicrobial drug discovery and antibiotic resistance research. All other categories fell in a second tier around the 20% range.
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