Pharm-Olam™
Helping Create A Healthier World

Approaching a Post-Antibiotic Era

Trends in Antibiotic Research

An ebook from
Pharm-Olam International
drawn from its webinar series on
Key Clinical Research Topics.

Superbugs

The Impending Threat

A few decades ago, we thought that the battle against bacterial pathogens was won when research pioneers discovered antibiotics.

But we were wrong. Terribly wrong.

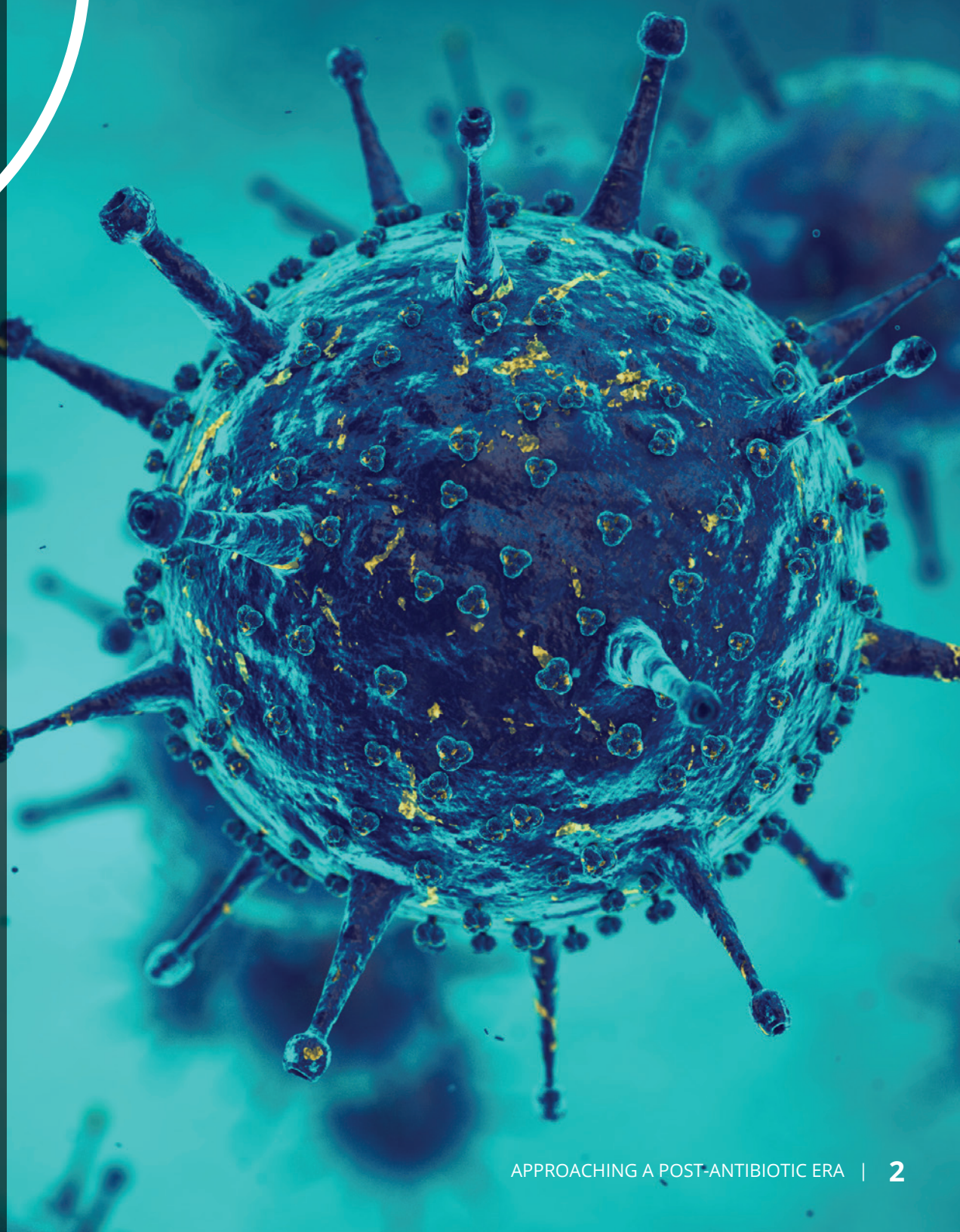
Bacteria, we now know, develop defense mechanisms and become resistant to antibiotics.

Today, antibiotic-resistant microorganisms, or superbugs, have become a major threat to people the world over. The World Health Organization (WHO) reports, "A post-antibiotic era — in which common infections and minor injuries can kill — far from being an apocalyptic fantasy, is instead a very real possibility for the 21st century."*

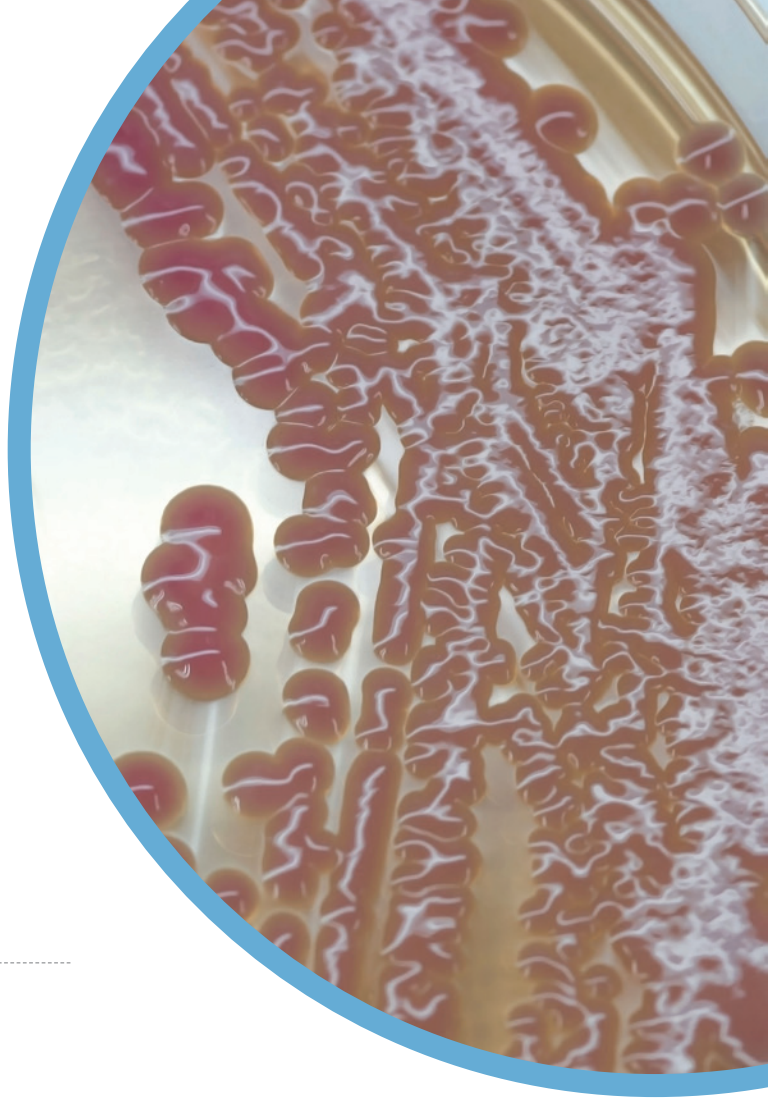
In the US, the Centers for Disease Control (CDC) estimate that, conservatively, more than two million people are infected with drug-resistant strains of bacteria each year, and those infections claim the lives of at least 23,000 annually.**

* Click here to see the WHO Report »

** www.cdc.gov/drugresistance/index.html



The Most Monstrous **Microbes**



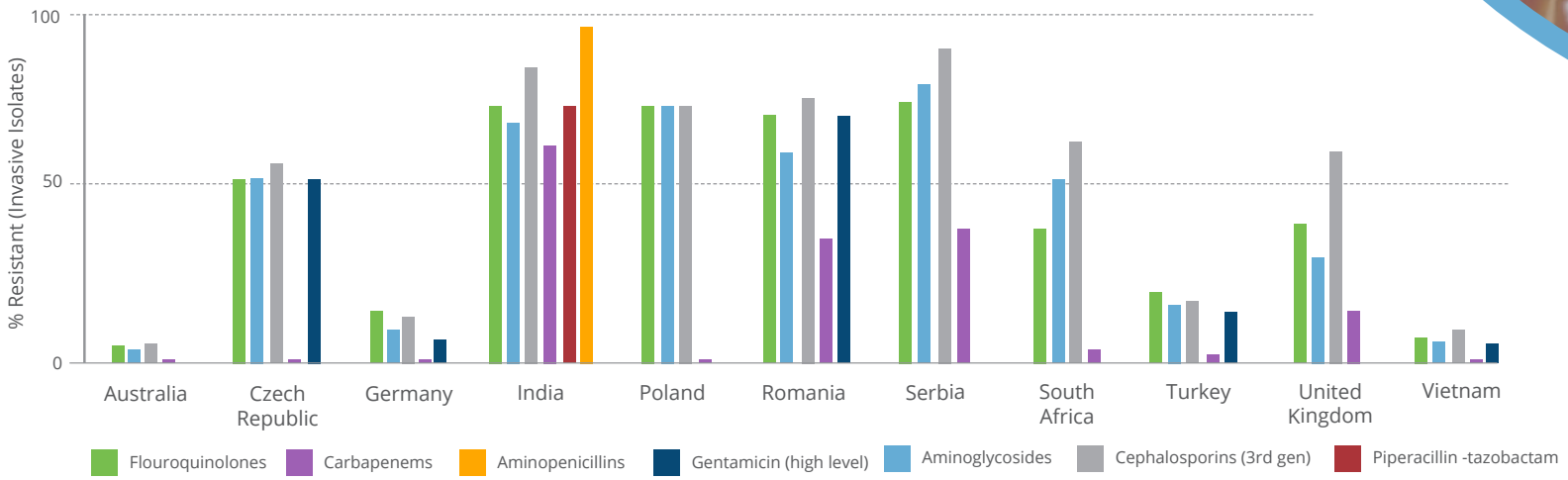
Recently, the biggest bacterial threats we faced were from community acquired Methicillin-resistant Staphylococcus aureus (MRSA). Now, however, our primary treatment challenge is gram-negative "ESKAPE" pathogens.

ESKAPE is an acronym for six pathogens: ***Enterococcus faecium***, ***Staphylococcus aureus***, ***Klebsiella pneumoniae***, ***Acinetobacter***, ***Pseudomonas***, and ***Enterobactor***. ESKAPE pathogens are responsible for the majority of nosocomial infections.*

By most accounts, the three most terrifying of these are the carbapenem-resistant Enterobactor, Pseudomonas, and Acinetobacter. They are capable of deactivating carbapenem antibiotics—our last resort in the struggle against gram-negative bacteria.

In drug-resistant cases, clinicians, desperate for something with which to treat patients, often resort to some old and nearly forgotten treatments such as Colistin, despite the unfavourable toxicity profile.

Antibiotic Resistance of *Klebsiella pneumoniae*



Klebsiella pneumoniae *belongs to the class of Enterobacteriaceae. Clearly, resistance is greater in Eastern countries and occurs at an alarming rate.*

* Center for Disease Dynamics, Economics & Policy (cddep.org)

A Growing Public Awareness

The threat posed by drug-resistant infections is no secret. The news headlines tell the story, and a quick Google search of "Antibiotic Crisis" yields 1.2 million hits. The world has been put on notice.

A Thirty-Year Lull in Innovation

Rip van Winkle would've missed very little on the antibiotic research front, had he fallen asleep thirty years ago and awakened in 2017.

Since the launch of Pfizer's oxazolidinon antibiotic in 1987, there has been no new covered class of antibiotic introduced in the market.

That's an extraordinary dry spell which can be attributed to several factors.

- **Economics.** As antibiotics lose their effectiveness, they also, of course, lose their market, and revenues diminish. Meanwhile, other product classes can remain profitable throughout their lifecycle.
- **Evolving Needs.** Like a dog chasing its tail, manufacturers can find their target perpetually out of reach. They can introduce a new product only to find that the pathogen it was designed to treat is no longer a burning threat.
- **Complexity.** The science of antibiotic R&D is extremely complex and involves complicated protocols. It takes roughly 12 years to usher an antibiotic from the bench to the bedside.

Many large pharmaceutical companies have shifted their focus from Infectious Disease (ID) to oncology.

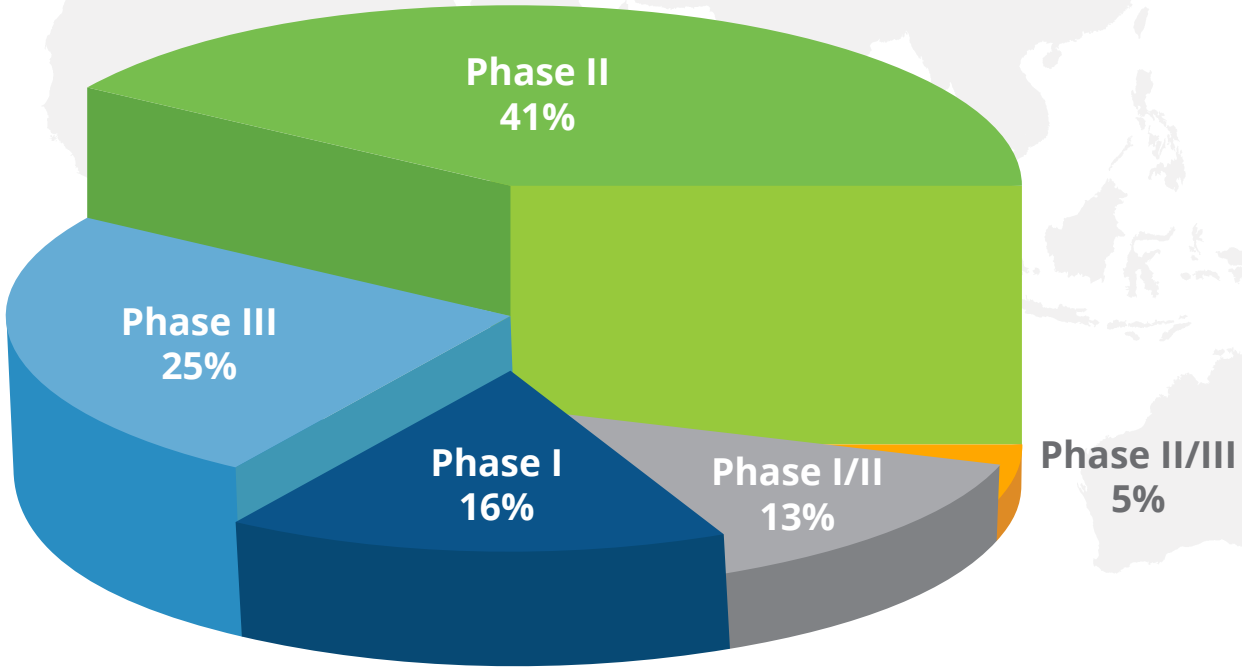
A Full Pipeline, but...

May 2017, there were 1,453 clinical trials being conducted around the world on antibiotics.

Based on this volume of development activity, we might assume that a steady stream of antibiotics would've been entering the market in recent years. Unfortunately, that's not the case.

Since 2014, only six new antibiotic molecules have been approved as novel medications.* Indeed, approvals of new antibiotics have been dropping over the past decade.

And, of the 27 molecules currently in clinical development, none represents a new class.
The Holy Grail of antibiotic development—a new class of antibiotic—is not even close to being approved for use.



Source: ClinicalTrials.gov – Active Phase I-III Antibiotics studies, May 9, 2017.

* The six new molecules are Dalbavancin, Oritavancin, Tedizolid, Ceftobiprole, Ceftazidime-avidbactam, and Ceftolozane-tazobactam.

New Research Incentives

Over the past 10 years, public funding and other incentives have been growing to support antibiotics research. Some of the most notable efforts include:

- The "10 x 20 Initiative" sponsored by the Infectious Disease Society of America, which has set a goal of developing 10 new antibiotics by 2020. http://www.idsociety.org/10x20/
- The "New Drugs for Bad Bugs" program of the Innovative Medicines Initiative, is a public-private partnership to address bottlenecks in the discovery and development process. http://www.imi.europa.eu/content/nd4bb-update-eaad2015
- The Antibacterial Drug Development Task Force formed by the FDA's Center for Drug Evaluation and Research (CDER), which works with academia, industry, professional societies, patient advocacy groups, and other government agencies to jointly promote antibacterial drug development. https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/ucm317207.htm
- Efforts by the US Food and Drug Administration (FDA) to implement the Generating Antibiotics Incentives Now (GAIN) Act by granting Qualified Infectious Disease Product (QIDP) designations to qualified applicants. Under QIDP, drugs can receive priority review, fast-track designation, and an additional five years of marketing

Historically, across all therapeutic areas, drugs in development have had a low-rate of success in terms of actually making it to the market. The picture is slightly more promising in ID than in many other areas; about 17 percent of investigational ID treatments become marketed products as compared to about 7 percent in oncology.*

* Hay, Michael, et al, "Clinical development success rates for investigational drugs," Nature Biotechnology, Vol 32 (1) Jan 2014.

Possibilities Beyond Antibiotics

Future treatments for bacterial infections may not, in fact, be antibiotics. Several companies are currently developing monoclonal antibodies that target certain bacteria such as MRSA and Pseudomonas. Monoclonal Antibodies offer several advantages over antibiotics:

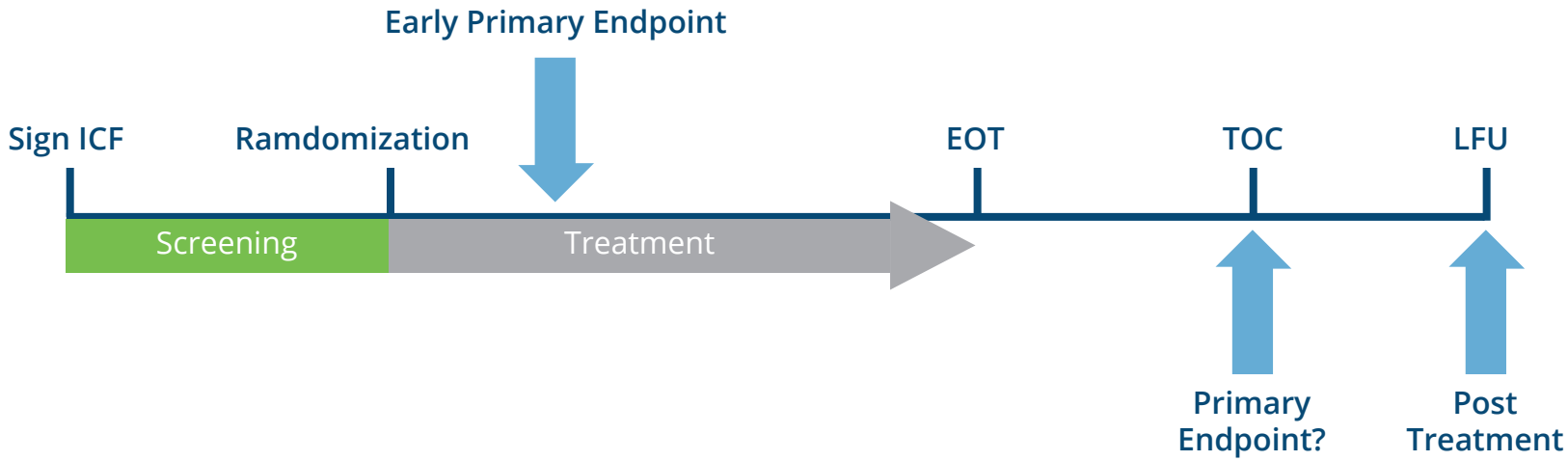
- **Patient Safety.** They're pathogen specific and would not cause drug-to-drug interactions with other small molecules. Nor should they have any effect on the beneficial microbiome. And, we could hope to see a reduction of inflammatory response such as Systemic Inflammatory Response Syndrome.
- **Prophylactic Applications.** Antibodies have a long half-life, which means that they could provide prophylactic coverage to patients.
- **Complementary with Antibiotics.** They could be added to antibiotic treatment

Monoclonal antibodies have significantly transformed existing treatments in a range of diseases with more or less success-predominantly in cancer and immune disorders, in infectious diseaese, they can directly target specific pathogens or their virulence mechanisms.

Unique Study Design Considerations

Typically, late-stage trials for ID treatments are set up as randomized, double-blind studies with an active comparator. In these complex trials, sponsors should give careful consideration to:

- **Screening Logistics.** Usually, the screening period is only 24 hours, followed by immediate treatment. So, everything must proceed in haste, and sites must be equipped to diagnose and treat patients quickly. This is an important factor that is unique to ID trials.
- Designating the visits of outstanding importance to assessing study endpoints. Often, these include an end-of-treatment visit, a test-of-cure visit, and a late-follow-up visit.
- **Vulnerable Populations.** You may need to test an investigational antibiotic in pediatric patients as well as in other vulnerable populations.
- **The Comparator.** The selection of the comparator is an important step in designing antibiotic trial. The selection depends on the route of delivery of investigational product, microbiological spectrum of coverage, availability, and non-inferiority margin. However, you should always reflect current standard of care for the treatment of the disease under investigation. Evaluation of standard of care must consider what is recommended by authoritative scientific bodies and based on clinical evidence and other reliable information that reflects current clinical practice.
- **The Endpoints.** These should be in keeping with regulatory and clinical expectations.



Keep the Protocol Design Flexible

In ID studies, the protocol is apt to change and should be considered a dynamic, rather than static document.

For example, a sponsor may discover that certain inclusion criteria are unnecessary or that the duration of treatment should change. New data may suggest a need to change the list of prohibited or concomitant medications. Or, it may be necessary to change instructions on how to deal with patients for whom certain pathogens have been isolated at baseline.

The inclusion/exclusion (I/E) criteria are, arguably, the most critical part of the protocol. Sponsors should:

- Recognize that KOL-written protocols are not always feasible
- Try to match enrolment criteria to current regulatory and industry guidelines
- Be wary of making the I/E criteria so narrow that patient recruitment suffers
- Review the protocol with an experienced CRO

See our Feasibility in Clinical Research: Tips for Preparing a Successful Trial Infographic »

Focus on **Logistics**

The logistics surrounding an ID trial present some special—but not insurmountable—challenges for sponsors. When selecting countries and sites, sponsors should:

- **Follow the epidemiology.** Target regions with known high prevalence of the pathogen under study. There are instances where the epidemiology changes and the targeted region(s) are notorious for certain bugs (e.g. MRSA) that can emerge with new threats. There's also a matter of resistance (e.g. if targeted region has high percentage of resistance to comparator, you should be very careful with your decision making).
- **Ensure that sites have the necessary resources.** Participating sites will likely need a microbiology lab that is available 24x7 and can provide rapid diagnostics. And, the demands on staff are great, given that screening must be completed within 24 hours and intensive treatment often entails several visits.
- **Understand the local regulations concerning informed consent—especially with unconscious patients.** This is particularly important when studying treatments for conditions such as nosocomial pneumonia or sepsis. In such a case, a sponsor should, of course, not run the trial in a country that makes it difficult to get informed consent from another party.

CASE STUDY
See the Acute Bacterial Skin and Skin Structure InfectionI Case Study »

RULES

STANDARDS

POLICIES

REQUIREMENTS

Seek Regulatory Input on Protocol Development

As often is the case, regulatory agencies around the world are not of the same mind, such that requirements differ—especially with regard to the primary endpoints in an antibiotic study—and may change over time.

Whereas it used to be that antibiotic studies in the US ended with the "test-of-cure" visit and the clinician's opinion of the patient's response to treatment, the FDA has changed that paradigm in favor of more objective endpoints. For example, for ICU studies, the agency now requires 28-day all-cause mortality data. In the EU, however, therapeutic response at the test-of-cure visit is still the primary endpoint.

Before settling on a protocol, sponsors should review the relevant guidelines and, ideally, consult with regulators to ensure that you will be measuring the right endpoints for their consideration.

See the FDA Regulations »

See the EMA Regulations »

REGULATIONS

TRANSPARENCY

LAW

General Tips for Success in ID Trials

The following recommendations, while not applicable exclusively to antibiotic studies, are nonetheless important to their success:

- Conduct a detailed feasibility assessment as part of your trial plan. It is not enough to simply send a synopsis to investigators to assess their interest in participating. You must gather specific information on their resources, experience, and capabilities. This extends to the microbiology lab's availability.
- Heed what the clinicians have to say about the feasibility of the protocol.
- Train the entire site team during the initiation visit. Patient recruitment success, staff motivation, consenting procedures, and overall feasibility all depend upon it.
- Be prepared for potential issues in procuring drug supplies. Comparator products are often in short supply.

"Don't let the perfect be the enemy of the good."

— Voltaire

An Eye to the Future

Clinical research on treatments for bacterial infections is not without its unique challenges. However, with public awareness of the impending health crisis resulting from drug-resistant strains of bacteria and with public-private initiatives to fund and pave the way for research, researchers may venture into developing new classes of treatments. And, with the help of the right partners, sponsors can more easily meet the regulatory requirements and logistical hurdles involved.

See our Be the Big Fish: Get Your Anti-Infectives Treatment to Market Faster video»

See our Webinar: Antibiotics Drug Development »

For more information about Pharm-Olam's experience in infectious disease trials, please contact us at info@pharm-olam.com or visit www.pharm-olam.com.