Carrying Antimicrobial Candidates across the Valley of Death: Key Milestones

Deciding whether or when to halt development of seemingly promising antibiotic candidates is an iterative exercise

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What does a company need to do when a promising antimicrobial drug candidate turns up as part of a concerted research and development (R&D) program? First and foremost, said George Drusano of the University of Florida, Gainesville, “You need a hero to push the molecule forward.” However, if the molecule fails to meet critical milestones during that push forward, no matter how good it looked earlier, he added, “At some point, you need to put ‘old yeller’ down.”

Drusano was one of several participants who spoke during the interactive symposium, “I Have a White Powder and Want a Drug: Shepherding New Compounds across the Valley of Death,” convened as part of the 2015 ICAAC, held in San Diego last September. And, no, the white powder in question was not the “suspicious white powders” that Federal Bureau of Investigation (FBI) and other law enforcement officials have had to deal with during the 15 years since the series of real and false anthrax attacks began in 2001 shortly after the September terrorist attacks in the United States.

Instead, the hypothetical “white powder” on stage during the 2015 ICAAC session was a wholly imagined but entirely plausible antibiotic candidate, one said to have promising activity through a novel mode of action against the Enterobacteriaceae and various other bacterial pathogens, to be “poorly water soluble,” to show “high protein binding and a short half-life,” to elicit a “high mutation frequency,” and to be “well tolerated in mice.” It was being developed by a “virtual” company, also imaginary, whose long-term finances were said to be less than robust. The central issue at hand was whether this company should continue to pursue commercial development and, if so, for how long and against what odds. The consultants asked to address these questions were drawn from academic, industrial, and regulatory circles. Here are highlights describing how they weighed in.

At First Blush, Plenty of Flashing Yellow Lights

“Strap in, this is going to be a bumpy ride,” Drusano said, as he began to run through a partial list of pluses and minuses ascribed to this “white powder,” designated NPDR3487, that has promising but circumscribed antibacterial activities. His analytic assignment was to figure out what testing to do during earlier, preclinical phases of drug development—in other words, to identify what tests and which issues would lead to a “rational go-no go decision” for its further development.

One noteworthy fact is that this candidate drug has a narrow spectrum of antibacterial activity, limited mainly to the Enterobacteriaceae, including carbapenem-resistant Enterobacteriaceae (CRE). Presumably, it is not active against some other gram-negative bacterial pathogens, including Pseudomonas aeruginosa, as well as

SUMMARY

➤ Deciding whether to pursue a promising antimicrobial drug candidate or to drop it poses challenges at virtually every stage during development.
➤ Early on, it is important to determine its antimicrobial spectrum, evaluate how it works in several model systems, learn about how resistance develops, map its pharmacodynamics properties, and identify toxicities.
➤ When moving into clinical testing, be sure financial needs can be met and identify a workable and preferably simple indication as early as possible.
➤ Regulatory officials urge drug developers in industry to consult frequently but steer clear of specifying which pathways to navigate.
➤ Even once such products are approved, guaranteeing clinical and commercial success can be elusive.
gram-positive pathogens such as *Staphylococcus aureus*. Little is yet known about its pharmacokinetic (PK) behavior, including what anatomic sites it can reach, and at what speed and concentrations, all of which it would be useful to know, according to Drusano. “The developer needs specific knowledge about its activity against targeted pathogens,” he said.

Interest in answering those questions leads quickly to a barrage of other questions and recommendations for answering them and reacting to answers that they yield. For one, the developer should conduct PK studies in three animal species to learn to which sites the candidate drug penetrates and how much its recognized tendency to bind to proteins will reduce its effectiveness for treating specific types of infections in vivo. “Some people say protein binding doesn’t much matter, that some drugs that are bound still work,” Drusano said. “But . . . if there’s a transporter or a drug target that is readily available . . . protein binding does not matter.”

It also is important to determine the full range of infectious agents that this compound might target, he continued. Knowing that it effectively targets *Enterobacter* suggests it might prove useful in treating some urinary tract infections (UTIs), intraabdominal infections, and also acute skin and foot infections, he points out. However, because it is cleared through the liver, it is not likely to prove effective against UTIs. Moreover, clearance via the liver also “runs the risk of drug–drug interactions,” added John Rex of AstraZeneca in Waltham, Mass.

Drusano recommended using a hollow-fiber model of infections in addition to testing the candidate drug in mice with pneumonia as well as infections at other sites. Part of the goal is to determine the peculiar dynamics of this investigational drug, but also to see how much of its activity is intrinsic versus how much it might depend on its working in concert with the host immune system. The hollow-fiber model, of course, involves no immune system. On the other hand, although studying how well the compound works in mice more closely parallels what might happen in humans, differences in the immune systems and in the body mass of humans and mice can lead to a less-than-perfect correspondence of results. Nevertheless, results in mice (or other rodents) help in “bridging” to humans.

The speed and type of drug resistances that can develop are yet another dataset to develop when deciding how far to go along the R&D path with this antimicrobial candidate, according to Drusano. “I really believe resistance studies are important,” he said. “If there is a very high rate of mutational resistance, my bet is that we’d better load up the gun and put this creature down”—meaning, halt further development.

“We need MIC [minimal inhibitory concentration] data on isolates from around the world,” Rex said, pursuing the importance of knowing more about susceptibility and drug resistances of the new compound under test. “If it works against ‘metallo’s’”—meaning bacterial pathogens that produce metallo β-lactamases and thus are resistant to β-lactam antibiotics—“that’s good and important. And what about the speed with which resistance develops? Those things could matter, too.”

**R&D Costs Rise Sharply in Moving from Preclinical to Clinical Testing**

It is during phase 1 and 2 clinical trials “where it’s very easy to run out of money, investigating things that burn up time,” said Rex, who commented on what to look for during the next stages of R&D for the imagined white powder NPDR3487 with promising antibacterial activities. “And if you run out of money, you may be forced to do a bad deal, and that’s no good.”

One strategy for avoiding this contingency, or at least postponing it, is to “build a syndicate based on knowledgeable investors, who are interested in the science,” Rex continued. While rounding up research-savvy investors, it also makes sense to “consult regulatory agencies early” and to “ask the science guys early, ‘is there anything you can do in the lab to increase potency and get over resistance issues and change protein binding.’

“I want George [Drusano] to tell me if I can dose patients high enough to eliminate resistance,” Rex added. “If not, I want to know if there’s another drug to combine with this new one. If monotherapy were easy, then activity against CREs and metallo β-lactamases would be enough to get you there. However, if it [NPDR3487 or improved derivatives] doesn’t work against *Proteus* spp., you don’t have much of a drug. And you need it to act consistently; is it acting like a nice molecule? All this makes my head hurt, but I really want to know about these things.”

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Even if all those questions were answered, Rex admitted, “We’re a long way from [using it in] man. The hardest question is how would you further develop it. You need a whole path to follow to get there.” Thus, whoever seeks to pursue this promising but imperfect antibiotic candidate into commercial use must shortly choose a specific clinical indication to follow to establish its efficacy—assuming, of course, that no glaring safety issue arises to upset further progress.

Although not active against Pseudomonas, NPDR3487 might be considered as an agent against nosocomial pneumonias, provided a point-of-care diagnostic test were available for choosing this drug in those cases where its specificity would lead it to out-perform other available antibiotics, according to Rex. Alternatively, it might be useful for treating intraabdominal infections or some kinds of complicated UTIs, even though it is not excreted through the kidneys, he said. “Can I be more aggressive, and go straight against bad bugs, for which the best available treatment now is colistin?”

Amid all these optimistic strategies for pushing forward with NPDR3487, “you can still argue that it’s a waste of money,” Rex said. If clinical trial testing yields positive results in only a small portion of the patients in which the drug is tested, sponsors can end up feeling “emotionally confused,” he added. “Think of things that will burn up time. You don’t want to do anything too fancy. I favor simple, not clever. That’s where I would go with this.”

**US and European Options for Reviewing Antimicrobial Agents**

Representatives of the US Food and Drug Administration (FDA) and the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom (UK) both point to special regulatory pathways for evaluating antimicrobial products on an accelerated basis, including, for FDA:

- “Fast track,” a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need
- “Breakthrough Therapy,” designed to expedite the development and review of drugs which may demonstrate substantial improvement over available therapy
- “Accelerated Approval,” to allow drugs for serious conditions that fill an unmet medical need to be approved based on a surrogate endpoints
- “Priority Review,” for FDA to take action on an application within 6 months.

Both officials also urge representatives from companies developing such products to consult early and often with regulatory officials at appropriate agencies. “That’s my key message,” said Sumathi Nambiar, director of the Division of Anti-Infective Products within the FDA Center for Drug Evaluation and Research. “Come, talk to us early, and continue to have frequent interactions.” Added Mair Powell of MHRA, “Let me reinforce the importance of coming to talk with us early and frequently. Advice is available any time to any sponsor.”

This emphasis on the value of frequent consultation dovetails with much of what else Nambiar and Powell said in describing the ins and outs of FDA and MHRA programs for evaluating antimicrobial products. Although the outlines of those programs are straightforward enough, in practice they can prove anything but smooth going for sponsors seeking to shepherd their products into clinical and commercial use. Put another way, judgment and adjustments appear to be involved at each step along a regulatory pathway, and the convolutions of some of those judgments do not lend themselves to ready formulation. “All these programs are unique,” Powell said. “We have guidance, but each program needs to be agreed upon for the product you have.”

FDA recognizes that “patients and physicians are willing to accept greater risks when there are no [treatment] alternatives,” Nambiar said. Thus, the agency may review antimicrobial drug candidates on an expedited basis via one of several distinct pathways, with each having in common the theme that the candidate products in question “are being developed to treat serious or life-threatening conditions and that they can address unmet medical needs,” she said.

Although the overriding criteria may be the same in the US and Europe, in fact, their approaches to evaluating antimicrobial candidate products are “very different,” Powell said. “We are moving toward harmonization.” Absent such harmony, however, product sponsors are faced with divergent regulatory pathways that can add considerably to late-term R&D costs when a sin-
A single product is undergoing parallel review through similar but separate systems. A related complication is that the use of special terminology by FDA (and presumably by agencies in Europe) can prove confusing to the public, raising expectations beyond a realistic attitude, potentially contributing to problems even further down the road, according to Lisa Schwartz and Steven Woloshin of the Dartmouth Institute for Health Policy and Clinical Practice in Lebanon, N.H., and Tamar Krishnamurti and Baruch Fischhoff from Carnegie Mellon University in Pittsburgh, Pa., who were not part of the symposium at ICAAC. “Words like ‘breakthrough’ and ‘promising’ increase people’s beliefs in a drug’s effectiveness—sometimes incorrectly,” Schwartz said. Added Woloshin, “Unless patients fully understand how the FDA is using the term ‘breakthrough,’ they may have unwarranted confidence in the evidence supporting drug claims.” Details of their survey of public perceptions of these terms appeared November 2015 in JAMA Internal Medicine (doi:10.1001/jamainternmed.2015.5355).

Other Challenges Add to Cost—Itself a Challenge

Another regulatory challenge to deal with earlier on is that neither the US nor the European system for evaluating candidate products is well suited to evaluating two or more antimicrobial drugs being used in combination—albeit with several noteworthy exceptions, including for drugs aimed at treating infections caused by Mycobacterium tuberculosis or HIV, and when dealing with well-recognized product combinations such as a β-lactamase inhibitor paired with a β-lactam antibiotic.

“What you’re looking for is robust and simple: two drugs that play together nicely,” Rex said. However, once beyond the range of familiar and widely accepted drug combinations, persuading regulatory officials to accept other product pairs can prove challenging. “Evidence for combining antimicrobial therapeutic products] doesn’t have to be from human studies, but it needs to be very strong,” Powell said.

The proper design of clinical trials for antimicrobial agents is another potential stumbling block. If an antibiotic candidate is intended to address an “unmet” medical need, the anticipated “data package can be smaller, but this means greater uncertainty about risk and benefit,” said FDA’s Nambiar. “In general [FDA is] willing to accept [data from] single, well-controlled trials if [sponsors] have good in vitro and animal models. Also, it is important to evaluate [the candidate drug] in patients with renal and hepatic impairment . . . to enroll patients with comorbidities. If it [candidate drug] has to be used in combination, the clinical trial design] will be very challenging, and will require a lot of back and forth to decide whether it can demonstrate the benefit of the components. It will need a lot of discussion.”

Assuming all those conditions can be met and that candidate drug NPDR3487 or an improved derivative meets FDA expectations and is licensed, there are still challenges to face in producing, administering, and prolonging its commercial lifetime, according to Rex and Drusano. “How as a community can we ensure good stewardship?” Rex asked. Should it be held in reserve for emergencies? If so, how will its corporate sponsors earn a fair and timely return on their R&D investment?

“What you want to do is separate use of drug from profit, and there’s a whole set of discussions about this issue,” Rex continued. “If a sponsor spent $1 billion to get [product approval], that’s real money. We are trying to get [federal officials] interested in buying such agents and to make them available in pharmacies around the world and keep them fresh.” However, doing so costs about $20 million per year, he added.

One idea “is to delineate usage from profit, like happens with insurance, and have governments buy them [the drugs],” Rex said. Government agencies with such mandates would, like fire departments at the local level, stand at the ready to dispense stockpiled antibiotics or other drugs. For instance, this goal could be implemented by extending the responsibilities of the US Biomedical Advanced Research and Development Authority (BARDA), whose duties along those lines now are confined to stockpiling vaccines and therapeutic agents for use as countermeasures to terrorist attacks.

“We create these molecules, but if they are used, resistance will develop,” Drusano said. “To maintain these drugs, it is critical that sponsors know what’s going to happen with resistance and what they are going to do. Otherwise, we’re just going to be hamsters on a wheel. We already know it’s not easy to make new products and get them across the valley of death.”