

# A Paradigm Shift in Drug Development for Treatment of Rare Multidrug-Resistant Gram-Negative Pathogens

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Multidrug-resistant (MDR) gram-negative pathogens pose a major threat to patients worldwide. Although the organisms remain relatively uncommon overall, their incidence is steadily increasing with associated increases in mortality and pharmacoeconomic impact. As evidenced by the dearth of new products in the pipeline or in clinical use, the conventional paradigm for the development of drugs against such pathogens is generally ineffectual. We advocate the need for a shift in the current paradigm and propose innovative development programs that involve implementation of a graduated approval process. The initial phase of the proposed regulatory paradigm includes early approval of a new drug based on a robust nonrandomized study, buttressed by data from concurrent controls and a pharmacokinetic-pharmacodynamic package generated from nonclinical studies. The postapproval commitment phase will include a randomized controlled trial, when disease prevalence permits, as well as continued assessment of risks and benefits under “real world” settings.

Gram-negative bacilli account for about two-thirds of pneumonia and urinary tract infection cases as well as substantial numbers of bacteremias and surgical site infections [1]. The emergence of antibiotic resistance in gram-negative bacilli has become a major public health problem in many parts of the world including the United States and the European Union (EU). In fact, >30% of *Escherichia coli* in many countries in the EU are now resistant to fluoroquinolones, and statistical models suggest that resistance rates will rapidly increase over time, severely limiting the utility of this antibiotic class in community infections within a few years [2]. In addition, there is now rapid transcontinental spread of resistance. For example, carbapenemase-producing strains of *Klebsiella pneumoniae* originating

in Israel have appeared in the United States [3] and Colombia [4].

Metallobetalactamases, which require zinc as a cofactor, were relatively uncommon until recently. In 2008 a new enzyme, NDM-1, was described from an isolate recovered from a patient in the United Kingdom who had traveled to India for a medical procedure [5]. Organisms harboring this enzyme characteristically display resistance to all agents other than colistin and tigecycline. NDM-1 has spread rapidly on the Indian subcontinent and several countries in Europe especially the United Kingdom. Even more disturbing is the spread of NDM-1 to multiple gram-negative species [6].

Adequate therapy, where it exists, has been shown to lower mortality [7, 8]. In the case of *K. pneumoniae* carbapenemase (KPC)-producing strains, data are limited, in part because there are few effective options for therapy. Even when it is known that most KPC producers and multidrug-resistant (MDR) *Acinetobacter* isolates are susceptible to such drugs as tigecycline in vitro, there is very limited clinical data to rely on. Alternative therapy may carry increasing risk and

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decreasing benefit; for example, colistin and other polymyxin agents cause nephrotoxicity in up to 30% of patients [9, 10].

One can imagine that some gram-negative pathogens such as NDM-1 could follow the same pattern of spread seen with methicillin-resistant *Staphylococcus aureus* (MRSA) in the early 1980s. MRSA was rare at that time but over a period of 15–20 years comprised 30%–50% of hospital staphylococcal isolates. It is difficult to predict the future prevalence of emerging organisms; but if we are to have therapeutics when increased numbers of certain pathogens do occur, it will take planning and research now in order to respond quickly to changes in the microbial ecology of hospitals.

There is a current unmet medical need for therapies that can improve the clinical outcomes of patients with gram-negative infections particularly for patients who have MDR gram-negative infections. For the purpose of this discussion, MDR is defined as nonsusceptibility to  $\geq 1$  agent in  $\geq 3$  antimicrobial categories. The Infectious Diseases Society of America (IDSA) has publicized this problem with an educational campaign known as “Bad Bugs, No Drugs” [11]. This campaign calls for a renewed commitment to antibiotic discovery and for collaboration between academia, industry and government. Some of the most important variables affecting the lack of enthusiasm for antibiotic discovery in industry include the perception of an unduly burdensome regulatory environment and inadequate return on investment in this therapeutic area.

The current regulatory approach is to conduct large controlled trials with the demonstration of noninferiority to approved agents. Thus, to obtain the requisite number of subjects, the majority of organisms treated are not the target MDR gram-negative rods. This is unfortunate in the current state of antibiotic development, where preclinical in vitro testing, animal pharmacodynamics, and knowledge of human pharmacology and tissue distribution are not fully leveraged as the building blocks for predicting response in developing medicines for human infections. An alternative approach that would allow treatment of a smaller number of patients infected with the target organisms is desperately needed.

In this article we advocate the need for a shift in the current paradigm for the discovery, development and approval of drugs to use against such pathogens, and we propose innovative development programs that involve a graduated approval process, with continued postapproval benefit-risk evaluations in clinical situations of great medical need.

## A NEW PARADIGM OF DRUG DEVELOPMENT AND APPROVAL

Because of the difficulty of conducting standard randomized controlled trials (RCTs) in a timely manner in disease populations with MDR gram-negative rods, there is a need to explore

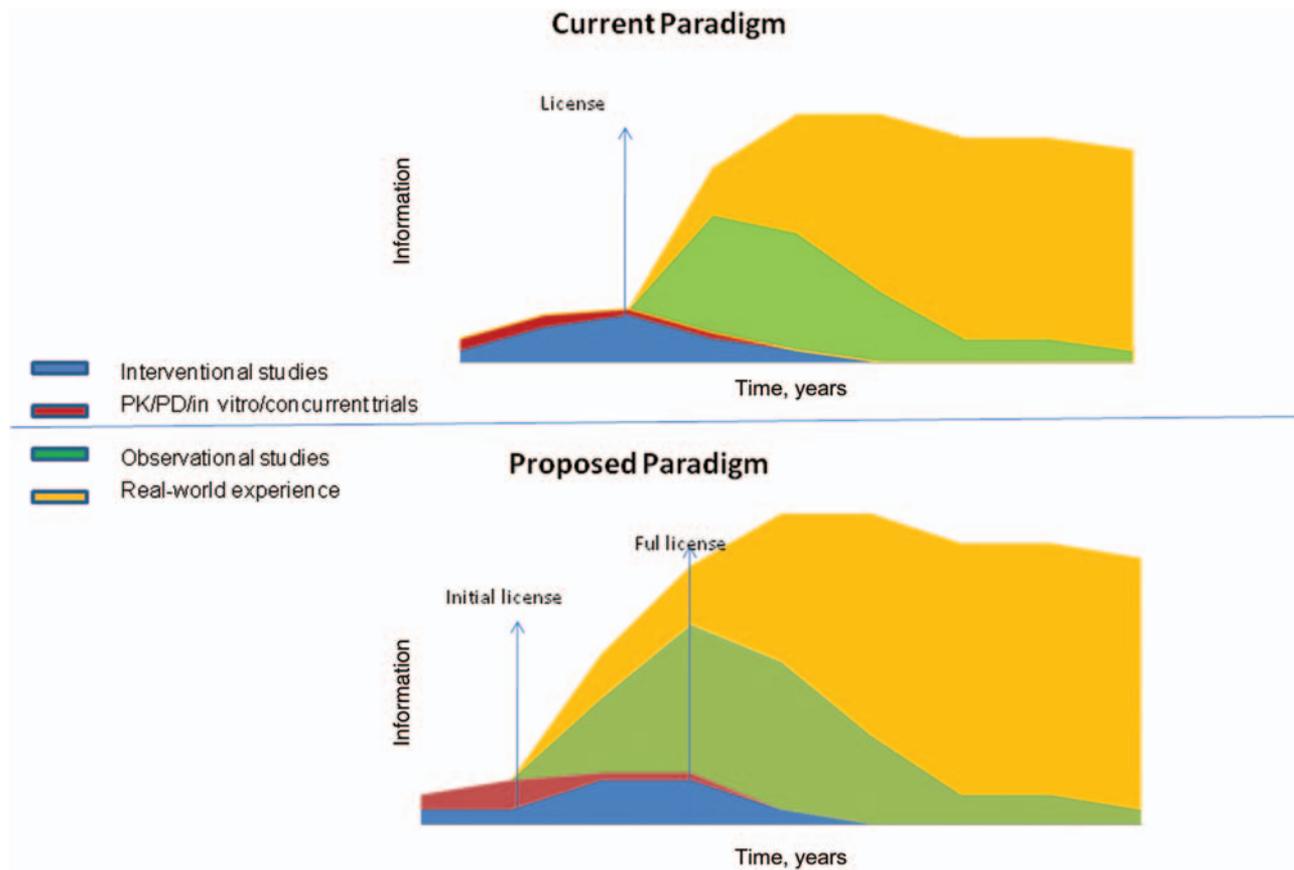
innovative approaches to expedite discovery, research, and approval of new molecular entities. From a safety surveillance perspective, the problem is compounded by the fact that some of the adverse experiences may be even rarer than the outcome measures commonly used to assess efficacy. Consequently, the safety data collected at the time of regulatory review may not be adequate or reliable to make effective risk-benefit assessment.

As depicted in Figure 1, an approach that appears to offer a viable option is a 2-stage approval process, wherein a conditional approval, with limited use and promotion, may be granted with a requirement for additional data in a postapproval commitment. This approach may serve the dual purpose of bringing much-needed medicine to patients in a timely manner, while allowing risk and benefit study after the product is made available to a wider patient population.

In this framework, an effective strategy entails use of robust data from an uncontrolled study, with objective end points to establish efficacy for an initial approval. To strengthen the evidence from such data, it is essential to take appropriate measures to control for overt and covert biases that arise in the absence of randomization and blinding when using historical controls. The measures include use of patient groups with comparable attributes, to the extent possible; ensuring similar experimental conditions; selection of the control group before performing comparative analyses; and prespecification of selection criteria and analytical approaches [12]. The package may further be buttressed by accompanying data from pharmacokinetic-pharmacodynamic (PK/PD) modeling for optimal dose selection.

The initial approval is to be followed by a postapproval commitment, which may include conventional RCTs, depending on resistant pathogen prevalence, and nonconventional trials that reflect real-world scenarios. When RCTs are plausible, conventional clinical trial approaches may need to be modified to reflect the small size of the study populations. Furthermore, if secondary sources of data, such as patient registries and electronic healthcare databases, are included in the risk and benefit assessment, best practices should be adopted to strengthen the value of the data [13].

Effective implementation of the proposed framework requires consensus among various stakeholders, including pharmaceutical companies, regulatory and other governmental agencies, academic institutions and professional associations. In addition, caution is required to balance the accompanying trade-offs between the gains with rapid access to drugs and the risks of failing to accumulate adequate evidence about the drug profile [14]. In the following section, we highlight relevant aspects of the proposed paradigm, including the role of modeling and simulation, use of secondary sources of data, and considerations for the design and conduct of RCTs in rare diseases.



**Figure 1.** A schematic diagram of alternative drug development and approval paradigms adapted with permission from Macmillan Publishers Ltd: Clinical Pharmacology & Therapeutics (Eichler HG, Oye K, Baird LG, et al. *Adaptive licensing: taking the 495 next step in the evolution of drug approval.* Clin Pharmacol Ther 2012; 91:426–37), copyright (2011). Abbreviation: PK/PD, pharmacokinetic/pharmacodynamics.

## MODELING AND SIMULATION TO BUTTRESS INITIAL APPROVAL PACKAGE

The use of PK/PD modeling strategy to understand effects of antibiotics is well established [15, 16]. Correspondingly, there is growing emphasis on the use of modeling and simulation in regulatory decision making, including selection of dosing regimens, approval of regimens that had not been directly studied in clinical trials, and use of such data to support a single pivotal trial [17].

In the proposed paradigm, PK/PD modeling and simulation should play a critical role in providing supportive information for the initial approval of an anti-bacterial agent. There are a number of reasons why the use of preclinical and phase I data are especially informative for antibiotic development. For example, in a recent study DiMasi et al indicated that the current success rate for antibiotics was the highest for any therapeutic class [18]. Whereas most other drugs interact with the

patient's body to elicit their effects, antibiotics act directly on the pathogen [19]. Thus, animal or other models can be used to determine a wide range of exposures that are needed to achieve an effect. Antibiotics virtually never fail in clinical development owing to lack of efficacy when organisms are susceptible; rather, they fail either because of an inability to achieve high enough concentrations or because of problems with safety [20].

The relationship between pharmacokinetics and pharmacodynamics (as measured ex vivo by means of minimum inhibitory concentration [MIC]) to clinical or bacterial outcome is well recognized. For instance, in their literature review Ambrose et al noted that preclinical models were able to consistently identify the PK/PD parameter that best correlated with drug effect [21]. Furthermore, once identified, break points using these parameters were readily established from small clinical trials [21].

It should be noted that there may be instances in which unexpected findings do occur. For example, daptomycin was

unexpectedly shown to be inferior in the treatment of community-acquired pneumonia despite an MIC that indicated sensitivity and good penetration into lung tissues. It was subsequently determined, however, that daptomycin becomes sequestered into the surfactant found in the lung. Interestingly, preclinical tests have been developed that are reasonably predictive of the loss of drug effect [22].

Modeling and simulation have been shown to be useful tools in the determination of effective regimens. Although conventional methods, such as determining time above the MIC, were adequate for this purpose, newer approaches offer a further refinement because they incorporate more mechanistic approaches [23]. Thus with human PK data and *in vitro* characterization of the relationship between concentration and measures of drug activity, simulation can greatly facilitate optimally designed dose- and regimen-finding phase II studies. At the time of full unrestricted licensure, such phase II trials could provide the required strong supportive evidence that some regulatory agencies allow in lieu of multiple clinical trials [24].

It is noted that the development of molecular diagnostic tests that allow more rapid identification of specific bacteria and specific types of resistance may enrich clinical trials of MDR organisms. However, the current technology is very expensive, requires trained personnel to perform and will take 12–24 hours to get results in practice. As these technologies evolve to be immediately available at the bedside, the recruitment of patients with MDR organisms will be significantly enhanced [25].

## POSTAPPROVAL REAL-WORLD STUDIES

Patient registries can play an important role in providing post-approval safety information in the treatment of rare diseases. As noted in recent regulatory guidance documents, patient registries may help sponsors to evaluate safety signals and the factors that affect the risk of adverse outcomes in real-world settings [26]. A major advantage of a patient registry is that uniform data can be collected using observational study methods from a broad range of patients. Although patient recruitment can still be difficult with a rare-disease patient registry, the inclusion criteria of such studies are generally less stringent than those of RCTs. Consequently, these studies have the potential to facilitate the collection of data from a sufficient number of subjects to ensure adequate assessment of the safety of the drug under study. As an alternative source of secondary data, administrative claims and electronic medical records data may also be considered.

Effective use of these data sources, however, requires a careful understanding of their limitations. A major issue with secondary sources of data is the potential effects of

confounding factors, both measured and unmeasured. In addition, there may be significant variation across observational studies in terms of research methods and data quality. Furthermore, registries that collect data over long periods may run into problems of patient retention.

To enhance the value of data from secondary sources, several guidelines and best practices have been developed [27, 28]. These include the need for a valid protocol, standards for data processing and management, and transparency in the reporting of results. The study protocol should clearly specify critical elements, including study design, target population, sample size calculations and, where appropriate, control groups. The analysis plan should be prespecified, with particular reference to the study objectives, the analytical strategy, methods to be used to control for sources of bias, definition of subgroups of interest, and the approach planned to be used to impute any missing values.

As pointed out earlier, bias is a major issue with non-randomized studies, and, as a result, appropriate analytical strategies are required to mitigate the impact of bias on study conclusions. For measured covariates, alternative analytical approaches should be implemented to control for bias, including such techniques as matching, propensity score analysis, and conventional regression models. For hidden or unmeasured covariates, the planned analysis should include instrumental variable analysis or other suitable techniques. Finally, in light of the limitations of all analytical techniques for such data, sensitivity analyses should also be planned and executed to assess the robustness of the findings to departure from underlying assumptions.

Unlike with RCTs, the infrastructure for secondary sources of data is not well developed. Accordingly, it is critical to establish data standards and implement enhanced quality assurance and quality control procedures. This may include ascertainment of completeness, consistency and accuracy of data collection and management; coding practices; and the degree and extent of missing data over time.

Finally, caution should be exercised in the reporting of the results of the study from secondary sources of data. In particular, the results should be interpreted with fair balance, with particular reference to the limitations of the study and analytical strategy, the biological plausibility of the findings, and the consistency of the findings with established knowledge about the drug class.

## RANDOMIZED TRIALS IN RARE DISEASES

When the disease prevalence permits the conduct of RCTs, adaptive and group sequential designs should be an integral part of the pre- or postapproval development program, while recognizing the limitations posed by the small size of the

study populations. Adaptive designs are particularly vital in rare diseases, since they generally permit use of accumulating data to update various aspects of the study using prespecified and statistically sound criteria [29, 30]. In earlier phases, adaptive dose-finding methods may complement modeling and simulation and maximize the probability of technical success. In MDR pathogen trials, careful attention should be paid to the implementation of the usual dose-finding approaches, including the appropriateness of the dose-toxicity model in small samples, the target toxicity-response rate, and the stopping rules [31].

The randomization scheme may also involve either response adaptive randomization [32] (ie, allocation probability based on responses observed in previous patients) or covariate adaptive randomization [33], in which the allocation probability is a function of the covariate balance between groups. When there is uncertainty about effect size for sample size determination, adjustments to the initial sample size may be made based on a review of accumulating data. In adaptive sample size reestimation, appropriate measures should be taken to minimize investigator bias and preserve the overall type I error at the time of the final analysis [34].

From the standpoint of statistical inference, given the small size of studies in resistant pathogens, exact procedures should be used when possible in analyzing the data. With longitudinal data, analytical strategies based on the last-observation-carried-forward approach are generally inefficient. When model assumptions are satisfied, generalized estimating equations and mixed models may be used to increase efficiency [35]. With small samples, inferences are relatively easy to formulate and solve by Bayesian methods. Sequential analyses are readily implemented in a Bayesian paradigm, without a need to adjust for multiplicity. Bayesian hierarchical models also allow combining information from different sources, thereby gaining strength. However, in small samples, different prior opinions may lead to different conclusions, because the influence of the choice of priors on the posterior probability distribution is a function of sample size [36]. Finally, in view of the uncertainties inherent in small clinical trials, the primary analysis results should be corroborated with alternative statistical analyses, to ensure the robustness of the results to departures from model assumptions.

## CONCLUDING REMARKS

As MDR gram-negative pathogens continue to pose a major threat to patients worldwide, there is a critical need for change in the drug development paradigm. The current regulatory requirement concerning stringent end points, narrower noninferiority margins and conventional trial designs should be continually evaluated in light of the growing threat to public

health emanating from the dwindling antibiotic pipeline and research funding. In this paper we propose a framework that involves a graduated approval strategy to ensure delivery of much-needed drugs in a timely manner. Although the approach is widely used in the development of orphan drugs in other therapeutic areas, its implementation in the context of MDR gram-negative pathogens is not fully appreciated.

The commitment of major companies to drug discovery and development of new antibiotics is less now than in decades past. Inherent to the failure of market economics to attract investment in new antibacterial treatment is the notion that antibacterial drugs for resistant pathogens need to be reserved for unique patients and use. Accordingly, there have been several initiatives undertaken to alter the failure of market economics to attract investment in antibacterial research and discovery. A case in point is a recent study by the London School of Economics that highlighted concrete measures involving financial incentives as well as basic regulatory reforms [37]. Similarly, the Transatlantic Taskforce on Antimicrobial Resistance formulated several recommendations in 2011 with a view to enhancing collaboration among EU and US agencies in the area of antimicrobial resistance [38]. As elucidated in a recent study [39] and another by Spellberg et al [40], the graduated approval approach we propose here serves to mitigate the antibiotic market failure, through both development cost minimization and revenue gains accrued from early approval.

Indubitably, antibiotic stewardship and resistance surveillance are forces that often work against incentives to investment, yet they are essential in preserving a common good. Therefore, new paradigms for investment and good antibiotic stewardship are imperative to ensure a steady flow of new antibiotics.

## Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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