IDSA
Infectious Diseases Society of America

October 31, 2018

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Food and Drug Administration
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SUBJECT: NOT-FD-18-16: Development of New Antibacterial Drugs Active Against Multi-Drug Resistant Bacteria

Dear Ms. Malhotra:

The Infectious Diseases Society of America greatly appreciates the opportunity to provide comments to help the Food and Drug Administration develop a list of regulatory science initiatives for antimicrobial products. New tools to support antibiotic research and development will further our shared goals of strengthening the antibiotic pipeline and bringing urgently needed new antibiotics to market.

IDSA represents over 11,000 infectious diseases physicians and scientists who care for patients with serious or life-threatening infections, including those caused by multidrug-resistant pathogens. In addition, IDSA members lead antimicrobial stewardship programs at their institutions; inform public health interventions aimed at reducing the threat of antimicrobial resistance (AMR); and conduct basic, translational, and clinical research aimed at furthering our understanding of resistance and developing urgently needed new therapeutics, diagnostics and vaccines. IDSA first sounded the alarm on antibiotic resistance in our landmark 2004 Bad Bugs, No Drugs report, and since then has remained at the forefront of national and international responses to AMR.

IDSA is pleased to offer the following comments on specific priority areas identified by FDA:

Evaluate potential innovations in clinical trial design for new antibacterial drugs such as enrollment strategies, data collection streamlining, drug development tools, clinical endpoints, and new statistical analytic approaches.

IDSA agrees that we must advance the field of clinical trial design. Areas for consideration include improved enrollment strategies and streamlining data collection. Efforts to increase patient participation in clinical trials through early enrollment could be extremely beneficial, especially for hospital-associated

bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP) or ICU-based studies. Currently, HABP/VABP trials experience a 100:1 screen: enrollment ratio, at the cost of approximately $89,000 per patient enrolled. Current requirements that patients have no more than 24 hours of prior empiric antibiotics in order to enroll in Phase 3 HABP/VABP trials pose a significant barrier to enrollment. Specific strategies to improve enrollment, including by enrolling patients before they reach the 24 hours of prior antibiotic use limit, could help advance Phase 3 HABP/VABP trial feasibility. Strategies could include enrolling patients at risk prior to onset of illness and enrolling patients after 24 hours of antibiotic use (perhaps up to 48 hours depending on clinical status. Trials for new antifungal agents face similar enrollment challenges and these should also be included in efforts to improve clinical trial enrollment. FDA should also consider more options for improving the use of rapid diagnostics to assist with rapid identification of potential subjects for studies.

IDSA also recognizes that enrollment of patients with severe infections such as HABP/VABP, sepsis and septic shock is further complicated by difficulties obtaining informed consent. We encourage FDA to consider approaches for obtaining prior consent from patients at risk for developing such severe infections.

IDSA also recommends that FDA standardize required data collection and case report form elements for common Phase 3 registrational pathways (e.g., acute bacterial skin and skin structure infections, intra-abdominal infections, complicated urinary tract infections, and HABP/VABP). We encourage FDA to utilize previously submitted datasets, map the key variables to common definitions and terms, and make them publically available to sponsors on the FDA website. This approach would streamline analysis by companies, interpretation by FDA, and the ability to analyze data post-approval. Additional case report form pages could be added to capture drug or study specific details as needed.

IDSA encourages FDA to continue evaluating non-inferiority trial designs for antimicrobials. Non-inferiority trials against usual drug-resistant pathogens, combined with robust preclinical and PK/PD data, can be used to predict responses to multidrug-resistant and extremely drug-resistant pathogens. Further consideration could be given to developing or exploiting these types of approaches.

IDSA would also appreciate feedback from FDA on how new “right to try” legislation, signed into law in May 2018, could impact antibiotic clinical trials. It would be helpful to understand the FDA perspective on the potential drawbacks and benefits of providing access to experimental antibiotics outside of clinical trials, what data should be collected in such instances, and how data from such cases may be utilized and analyzed.

IDSA acknowledges that adaptive trial design is being actively considered in other disease areas, including sepsis and oncology. While adaptive designs may, unfortunately, be unlikely to speed antibiotic trials, it may be worth following the progress of this approach in other areas to determine if anything from such an approach might be worth pursuing for antimicrobial studies.

Advance the science of in-vitro, animal model, and/or pharmacokinetic studies to facilitate antibacterial drug development, including studies focused on drug development for special

populations such as patients with unmet need, children and patients with renal or hepatic dysfunction.

Because large phase 3 clinical trials for new antibiotics that address unmet needs are incredibly challenging and often infeasible, IDSA encourages FDA to advance the science of alternative approaches that together can enhance certainty and supplement smaller phase 3 clinical trials. Specifically, we support initiatives to advance the science of PK/PD-based dosing regimen selection; studies that can confirm that targeted drug exposures are attainable in relevant patient populations, including children; a range of animal models to confirm regimen efficacy, and use of validated external controls. IDSA also encourages more formal empirical testing of the utility of spare modeling PK data as compared to conventional assays to potentially allow for a reduction in the complexity of PK data collection.
IDSA urges FDA to develop improved preclinical and early clinical trial methods to establish the safety of a compound that might follow the LPAD pathway. The requirement for 300 patients at the intended dose and duration may be infeasible. FDA should consider whether new biomarkers or other methods of safety evaluation could be developed to allow for a smaller safety database for a limited population approval. Similar approaches have been successfully utilized in oncology. This type of approach would be very helpful for pathogen-focused development, particularly for areas of significant unmet need such as in treating infections caused by *Acinetobacter baumannii*.

As IDSA mentioned in our response to the FDA draft guidance on the Limited Population Antibacterial Drug (LPAD) approval pathway, some of the small studies conducted under this new pathway may not be amenable to non-inferiority designs. IDSA encourages FDA to provide guidance on feasible approaches to superiority designs, particularly within the LPAD pathway. In such instances, FDA could use $p < 0.1$ or another less stringent value for type 1 error control if the risk-benefit ratio is favorable when considering the totality of the data available. Even in instances in which approval may be granted based upon a non-inferiority trial, FDA should consider opportunities for sponsor companies to perform post-market superiority studies to inform optimal use of new antibiotics.

Many patients with some of the most serious bacterial and fungal infections and significant unmet need with regard to treatment options have underlying diseases or immunosuppression that are exclusion factors for most trials. Expanding enrollment opportunities by including some populations historically excluded from trials may be worth exploring, particularly since new agents under study are often employed disproportionately among such patients after they are brought to market. IDSA encourages FDA to consider patients with impaired renal function (including those on hemodialysis and those treated with renal replacement therapy) in efforts geared toward special populations. Clinicians have very limited data for these populations with the newly approved beta-lactamase inhibitor agents, and any additional data to inform therapy for these patients would be very useful. In addition, we encourage FDA to include obese patients in these efforts as well. While these patients likely do not require different antibiotics from other populations, clinicians need appropriate dosing guidance for these patients. Lastly, site-specific PK/PD data are badly needed, particularly for a disease like HABP/VABP for which drug responses are often poor, resistance is high and collection of human samples may be feasible. Here, there is potential for combining human data with high quality animal model data.

Evaluate the use of rapid diagnostic tests in clinical trials for new antibacterial drugs to enrich enrollment of patients with the condition of interest

IDSA encourages FDA to focus on the mechanics of incorporating rapid diagnostic tests into clinical trials of multidrug-resistant pathogens. One approach could be a study that compares enrollment into a non-registrational trial with a screening strategy that included rapid diagnostics against one that did not include rapid diagnostics. This approach could enable development of pathogen-specific agents that are currently unlikely to be developed due to complexity with empiric treatment. In addition, new diagnostics would likely also have utility in defining antibiotic discontinuation or de-escalation strategies and shorter-course treatment regimens.

Advance the science of antibacterial drug susceptibility evaluation

IDSA greatly appreciates FDA efforts, facilitated by the 21st Century Cures Act, to more rapidly update susceptibility test interpretive criteria. Making updated breakpoints available online is an important improvement that allows the latest information to be more rapidly communicated to clinicians. We also appreciate that the 21st Century Cures Act allows FDA to utilize work performed by standard-setting bodies, such as the Clinical Laboratory Standards Institute (CLSI), EUCAST and USCAST. IDSA emphasizes the importance of harmonizing breakpoints among these bodies and the FDA. Discrepancies in susceptibility test interpretative criteria make it extremely difficult for clinicians to optimally utilize antibiotics.

IDSA also appreciates FDA efforts to narrow the gap between the availability of a new antibiotic and the availability of a susceptibility test. Without susceptibility testing, it can be very challenging to appropriately manage use of a new antibiotic. This scenario can lead to overuse of the new antibiotic or underutilization, in cases when a hospital is unwilling to permit any use until susceptibility testing is available. Both instances cause significant concerns for patient care, public health and antibiotic R&D. We encourage FDA to pursue additional opportunities to work toward immediate availability of antimicrobial susceptibility testing upon launch of a new antibiotic.

Evaluate potential endpoints in clinical trials in the area of unmet medical need

IDSA believes this topic should be a very high priority. IDSA urges FDA to focus on development of endpoints for combination antibacterial studies and weighted composite endpoints in antibacterial trials, both of which will advance LPAD drug development. Combining multiple endpoints into one composite effect measure would overcome the need to have co-primary endpoints and could reduce the required sample size. Multiple theories exist on how to develop composite endpoints, each with advantages and challenges. The promise of this approach, in our view, definitely warrants further attention from FDA. Such endpoints would need to be validated before use, and this effort would be worthy of FDA investment.

Initiatives focused on 30 day all-cause mortality endpoints are needed. While demonstrating a new antibiotic's impact on mortality is highly desirable, current approaches to mortality endpoints require large sample sizes, and mortality may only be partially related to infection.

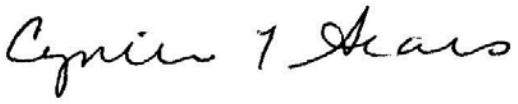
Standardization of desirability of outcome ranking (DOOR) endpoints and other composite endpoints, for exploratory analyses, would be useful to allow comparison across clinical trials. Surrogate endpoints have been very helpful in other disease areas in speeding new therapies to market and these should be considered in greater depth for antibiotics.

FDA should consider how additional tools can support efforts to develop new endpoints. For example, molecular diagnostics may have an important role. Clearance of DNA may be a useful surrogate marker. Better understanding of molecular markers versus culture kinetics might offer insight into better definitions for treatment duration and prognosis. In addition, innovative statistical methods, such as Bayesian analyses, could make attainment of clinical trial endpoints more feasible. We also encourage FDA to explore opportunities to gather more long-term outcome data. For example, it may be valuable to consider the possibility of a multiplier effect of good antibiotic treatment that is more evident after 6 months or a year.

Lastly, we encourage FDA to explore further opportunities to advance studies of non-traditional alternative therapies, including antibodies and phages. Efforts to further inform how such potential products could be studied and evaluated would be useful in advancing this promising field.

Once again, IDSA thanks FDA for its commitment to antibiotic R&D and specifically for its interest in developing a regulatory science agenda in this area. IDSA shares your goals and looks forward to working with you to advance these important efforts.

Sincerely,



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