NATIONAL PHYSICIANS ALLIANCE

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21st Century Cures: Examining Ways to Combat Antibiotic Resistance and Foster New Drug Development

Thank you for inviting me to testify. I am a practicing infectious disease and internal medicine physician and a medical researcher who actively cares for patients. I was a scientist at FDA for almost a decade and while at FDA I was one of the co-chairs of the Inter-agency Task Force on Antimicrobial Resistance and the Lead Medical Officer for Antimicrobial Development and Resistance Issues. I would like to share with you today my perspectives as a clinician, researcher and patient myself on appropriately developing antibiotics where there is the greatest need in order to provide benefit to patients. I am speaking on behalf of the National Physicians Alliance.

The National Physicians Alliance (NPA) serves as a professional home to physicians across more than 40 medical specialties who share a commitment to patient-centered health care, evidence-based health policy, and professional integrity. The NPA strictly refuses funding from pharmaceutical or medical device companies. We believe in the scientific advancement of knowledge through empirical research that is conducted free of financial conflict of interest; subjected to professional peer-review; and transparent in process.

The NPA's FDA Taskforce was established to support the organization's work in defense of a strong, scientifically rigorous FDA that does not stray from its mission "to protect public health by ensuring the safety and effectiveness of drugs and medical devices." The FDA is under increasing pressure, much of it from industry, to speed innovation. We are here today because we are concerned about a growing threat to the scientific rigor with which the agency reviews drugs and medical devices. We all believe in the goal of providing patients with therapies that result in improved outcomes but this can only be accomplished through a comprehensive approach and adequate and well-controlled studies in patients who benefit.

When innovation maximizes meaningful clinical outcomes for our patients, it is a tremendous good for society; but innovation does not always do this. New is not always better. Sometimes new is dangerous. Sometimes new is deadly. As prescribers who pass both risk and cost on to our patients

when we recommend a particular drug or device, our aim is to help ensure thorough, independent review of the medical products under the FDA's purview. We too want powerful, effective treatment options for our patients: we want treatments to work, and we want them to work safely. This means that integrity of the label "FDA-approved" is critically important to physicians.

Learning from History

The study of infectious diseases has gone hand in hand with the development of better methodologies to evaluate whether medical interventions result in more benefits than harms for patients. Studies of infectious diseases were the first to use the modern methods of adequate and well-controlled trials that are part of law today.[1] The reason for the development of these methods was the realization of investigators and members of Congress that only through adequate study of new medical interventions can we separate the harmful from the helpful for patients.

The problems of antibiotic resistance and the discussion of appropriate scientific and regulatory responses to that problem are not new. Dr. Scott Podolsky of Harvard Medical School in his recent book The Antibiotic Era[2], recounts that during the rise of resistance to common staphylococcal infections in the 1950s, drug companies marketed ineffective antibiotics with claims of improved effectiveness based on test tube testing and animal models, with resultant increased costs to the medical system and unclear benefits for patients. Dr. Maxwell Finland, the first President of the Infectious Diseases Society of America, with 19 other prominent infectious diseases investigators as co-signatories pointed out the need for adequate and well-controlled studies in patients as the basis for determining whether these new interventions were beneficial to patients:

> "To be sure, properly conducted clinical studies may, in the future, support the claims and justify the enthusiasm for these or other …antimicrobial agents, but it is incumbent upon those of us who are intimately concerned with the welfare of our patients to wait until such data are presented before we accept and acclaim any new agents or special formulations and recommend them for general use, particularly in view of their great potential for harm when they are used extensively and indiscriminately"[3]

In 1962, Dr. Finland made these same points as he testified at the Senate hearings that resulted in adding the requirement for demonstration of effectiveness of new drugs based upon "substantial evidence" from "adequate and well-controlled studies". Dr. Finland's remarks point out that like with other drugs, antibiotic effectiveness cannot be assumed based on test tube tests and animal studies or mathematical modeling but can only be verified by studies that ask the right questions, with the right outcomes, in the patients who might benefit from the test drugs.

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[1] The James Lind Library. Principles of Fair Testing of Medical Treatments. http://www.jameslindlibrary.org/context/principles-of-testing.html

[2] Podolsky S. The Antibiotic Era. Johns Hopkins Press. In press for release December 2014

[3] Maxwell Finland, "The New Antibiotic Era: For Better or For Worse?" *Antibiotic Medicine and Clinical Therapy* 4 (1957): 18

Defining the Problem: Unmet Medical Need in the Setting of Antibiotic Resistance

The problem of antibiotic resistance today is the same as it was in years past. Patients with disease caused by antibiotic resistant organisms for which there are no effective therapies are more likely to die or suffer serious disability from their disease. Therefore **the unmet medical need exists in those patients that have no effective treatments**. The need is for treatments with *improved effectiveness* than those that have become less effective over time. The outcome that is most relevant to patients is decreasing death or irreversible disability. Defining unmet medical need in the setting of antibiotic resistance clearly leads to how and in whom studies should be performed and the outcomes that should be measured. There is also an unmet medical need based on lack of effectiveness in setting outside of antibiotic resistance, such as the need for improved effectiveness in disease due to *Clostridium difficile*.

It is ethically questionable to expose our patients who have current effective and safe treatments to less effective treatments in order to have a "robust pipeline" of new drugs or to provide an economic stimulus to drug companies. Therefore studies of new interventions to treat infectious diseases should be done in the patients who are expected to live longer or live better lives with the new interventions.

Furthermore legal precedent points out that patients with life threatening diseases should be not receive less protection under the law from less effective or unsafe drugs. In 1979, Justice Thurgood Marshall wrote in a landmark Supreme Court decision:

> "The [Food Drug and Cosmetic] Act makes no express exception for drugs used by the terminally ill and no implied exemption is necessary to attain congressional objectives or to avert an unreasonable reading of the terms 'safe' and 'effective'. Nothing in the legislative history suggests that Congress intended protection only for persons suffering from curable diseases" [4]

Comprehensive Approach to Addressing Improved Therapies for Infectious Diseases

In order to ensure improved patients outcomes a comprehensive approach is needed to address the worse outcomes in patients caused by antibiotics resistance. New antibiotic drugs alone, especially if not studied properly, will not only fail to address the problem but may make it worse since ineffective drugs can still cause side effects in patients and spread antibiotic resistance further. We propose a comprehensive set of suggestions to help patients and develop better therapies:

1. **Requirement for expanded access programs for all drugs and biologics under any expedited review programs including qualified infectious diseases products (QIDP):** Patients who wish to gain access to experimental therapies and who wish the take an informed risk for themselves should have access to these drugs. Drug sponsors should be required to have such programs under existing FDA expanded access programs for all patients who do not qualify for ongoing clinical research studies. These programs were developed during the early years of the HIV epidemic so that patients could obtain access while the new therapies continued to be evaluated in adequate and well-controlled studies prior to widespread marketing. Such programs should be streamlined, including rapid distribution and efficient Institutional Review Board

[4] US v Rutherford 1979.

(IRB) review to that patients can obtain access to experimental therapies.[5] The current program allows companies to recoup costs.

2. **Studies should be performed in patients who have *no* effective therapies to show *improved* effectiveness:** Programs based on less data should focus on only on therapies that have added benefits for patients. The ethical conduct of clinical research requires that studies be done in types of patients who might benefit from the test therapies. The current paradigm of approving antibiotics based on studies designed to rule how much *less effective* a new therapy might be in studied patients compared to an older standard of care therapy already known to be safe and effective puts current patients in harms way without benefit. FDA's own guidance on the mis-named "non-inferiority" studies states:

> "Because the intent of the trial is… to show that the new drug is not materially worse than the control, they are now called non-inferiority (NI) trials. But that… is a misnomer, as guaranteeing that the test drug is not any (even a little) less effective than the control can only be demonstrated by showing that the test drug is superior. What non-inferiority trials seek to show is that any difference between the two treatments is small enough to allow a conclusion that the new drug has at least some effect or, in many cases, an effect that is not too much smaller than the active control." [6]

These studies do not address the need for therapies with improved effectiveness in patients who do not have effective therapies. Patients who have current effective therapies should not be asked to accept more risk, as the risk-benefit decision in patients who do not have effective therapies is different than in patients who have effective and safe therapies. Therapies with substantial toxicity may be acceptable if they are life saving in patients who have no effective therapies. Drugs with increased toxicity are not acceptable in patients who already have effective and safe options. So-called "non-inferiority" studies ask the wrong question in the wrong types of patients.

In cancer there is also a substantial problem of drug resistance. New cancer drugs to address resistance are performed in patients who have cancer drug resistance to show improved outcomes in those patients, rather than doing studies to show somewhat lesser effectiveness in patients with drug-susceptible disease. The substantial toxicity of cancer drugs is acceptable because the goal is to decrease death, and because the patients studied do not have other effective therapies.

In HIV-AIDS, patients who have resistant viruses and who have received prior HIV therapies are studied in clinical trials to show improved effectiveness of new therapies as well.

Clinical studies should be performed in patients with well-defined disease syndromes and not based on pooling diseases with widely differing types of patients or diseases merely because the

[5] US Food and Drug Administration. Access to Investigational Drugs Outside of a Clinical Trial (Expanded Access)
http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/accesstoinvestigationaldrugs/ucm176098.htm

[6] US Food and Drug Administration. Guidance for Industry Non-Inferiority Clinical Trials.
http://www.fda.gov/downloads/Drugs/Guidances/UCM202140.pdf

same "bugs" cause the diseases. Clinicians treat patients, not "bugs", and patients present for care with recognized disease syndromes. Clinicians prescribe treatments based on those recognized disease syndromes. Current antibiotic studies show that antibiotics have differing effects in different diseases; such as current FDA warnings on increased mortality in pneumonia with various antibiotics while the drugs claim effectiveness for other diseases.[7]

3. **Outcomes in clinical studies in patients should show decreased deaths and/or decreased disability in patients:** Since patients die or experience irreversible disability with resistant infections the outcomes in studies should be decreased deaths or decreased irreversible disability for patients. Many types of bacterial infections are acute diseases where the direct outcomes of death and disability in patients occur in a matter of weeks to months. In this setting there is no need to use outcomes based on laboratory outcomes or clinician judgments since the direct outcomes as easily measureable. Drugs that are marketed as "life saving" should actually be shown to save lives in adequate and well-controlled studies in patients. FDA's own guidance on expedited approval programs states:

> **"**Accelerated approval [based on surrogate endpoints] is generally less useful in more acute disease settings in which therapy is intended to provide a more near-term clinical benefit. In such settings, even if there are potentially predictive surrogate endpoints or intermediate clinical endpoints, there may be little or no time advantage for studies evaluating a surrogate or intermediate endpoint compared to studies evaluating the intended clinical benefit."[8]

Approval for chronic diseases based on outcomes that are not patient centered, such as microbiological testing of sputum cultures in tuberculosis, should include a "sunset provision." If confirmatory studies based on patient centered outcomes like decreased deaths are not done within a specified amount of time then approval should be automatically withdrawn. Companies should be required to keep open expanded access programs while further work is done to gain full approval.

Work in ongoing through the Foundation for the National Institutes of Health (FNIH) to improve the outcomes assessments in clinical trials in infectious diseases and move away from poorly defined outcomes based on clinician judgment and/or laboratory testing to more patient centered outcomes.[9] Companies should be given incentives to develop drugs using patient centered outcomes.

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[7] FDA Drug Safety Communication: FDA warns of increased risk of death with IV antibacterial Tygacil (tigecycline) and approves new Boxed Warning. http://www.fda.gov/drugs/drugsafety/ucm369580.htm **FDA Drug Safety Communication: FDA approves label changes for antibacterial Doribax (doripenem) describing increased risk of death for ventilator patients with pneumonia.** http://www.fda.gov/Drugs/DrugSafety/ucm387971.htm

[8] US Food and Drug Adminustration. Guidance for Industry. Expedited programs for serious conditions - drug and biologics. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

[9] Talbot GH, Powers JH, Fleming TR, et al. Progress on developing endpoints for registrational clinical trials of community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections: update from the Biomarkers Consortium of the Foundation for the National Institutes of Health. Clin Infect Dis. 2012; 55: 1114-21.

4. **Studies should be adequate and well-controlled studies in patients with wel-defined serious and life threatening disease under study, not based solely on test tube tests, animal models or mathematical modeling:** Recent antibiotic studies have shown increased deaths or decreased cures in patients who received new antibiotics compared to older drugs already proven safe and effective in treating serious infections. These new drugs had promising test tube tests, animal models and mathematical modeling but they still resulted in worse outcomes for patients. Therefore concerns about the use of test tube tests, animal models and mathematical modeling are not merely theoretical but have resulted in real harms for patients who already have effective therapies. This type of preliminary information is not "confirmatory evidence". Increased deaths have occurred more often in the sickest types of patients. Since patients with disease due to resistant pathogens tend to be older, sicker, have more concomitant disease and receive more medications, they are most likely to be harmed by ineffective drugs. Doing studies to show a new drug is a little less effective in patients who are relatively less sick with disease due to susceptible organism and then extrapolating improved benefit to unstudied types of sicker patients with resistant pathogens is not logical or scientifically supported by these same studies showing harm in sicker patients. FDA has several warnings on it's website concerning these drugs.[10]

   A study by the Agency for Healthcare Research and Quality of over 1700 studies showed a lack of evidence that mathematical modeling resulted in better patient outcomes. Therefore it is scientifically inappropriate to rely on such methodology as "predictive" of improved effectiveness in patients in lieu of clinical trials in patients with the disease under study.[11]

   Dr. Finland warned of this same problem of accepting new drugs as effective and safe based on preliminary information before they are studied in patients:

   > "Clinical investigators and authors of medical and scientific publications [have] the duty to protect the medical profession and the public against the abuse of preliminary scientific information and against the improper and premature exploitation of conclusions based on inadequate data."[12]

5. **Focusing studies on well-defined patients with disease due to resistant pathogens will allow for smaller studies:** Non-inferiority studies usually are larger than studies designed to show improved effectiveness (superiority) of new therapies. The number of patients needed to show a test intervention is effective is based on how much more effective the new therapy really is: therapies with greater effectiveness need a smaller sample of patients and less effective therapies require a greater number of patients to study. Prioritization should be given to the most effective

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[10] FDA Drug Safety Communication: FDA warns of increased risk of death with IV antibacterial Tygacil (tigecycline) and approves new Boxed Warning.
http://www.fda.gov/drugs/drugsafety/ucm369580.htm
FDA Drug Safety Communication: FDA approves label changes for antibacterial Doribax (doripenem) describing increased risk of death for ventilator patients with pneumonia.
http://www.fda.gov/Drugs/DrugSafety/ucm387971.htm

[11] Agency for Healthcare Research and Quality. Pharmacokinetic/pharmacodynamics measures for guiding therapy in nosocomial pneumonia. http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=1598&pageaction=displayproduct

[12] Finland. The New Antibiotic Era. Ibid.

interventions, and "limited datasets" for less effective drugs will only hide their lack of effectiveness. The earliest studies in infectious diseases in patients who lacked effective therapies required few patients because the drugs were highly effective in decreasing deaths in the studied patients.[13]

The size of a clinical study also has ethical implications for clinical research studies. The Institute of Medicine monograph on Small Clinical Trials points out that the sample size of a study:

> "A critical aspect of clinical trial design is determination of the sample size needed to establish the feasibility of the study (i.e., sufficient statistical power). The number of participants in a clinical trial should always be large enough to provide a sufficiently precise answer to the research question posed, but it should also be the minimum necessary to achieve this aim. A proposed study that cannot answer the question being asked because the necessary sample size cannot be attained should not be conducted on ethical grounds. That is, it is unacceptable to expose patients or research participants to harms even inconveniences if there is no prospect that useful and potentially generalizable information will result from the study"[14]

6. **New therapies can only be studied and used in practice with appropriate diagnostics**: The lack of diagnostics that not only select patients with a specific disease but also select patients who will benefit from specific new therapies is long overdue in infectious diseases. Empirical therapy exposes patients to excess harm. Approving drugs based on "limited datasets" and then using the drugs widely without ability to focus therapy on patients who benefit will also result in excess harm. Currently there is no incentive for drug companies to develop diagnostics as empirical usage spurs excess sales and increased profits. Any incentives for new antibiotics should be limited to those drugs that can provide patients characteristics and diagnostic testing in real world clinical practice that allows for selection of patients who benefit form new interventions.

7. **Clinical trials transparency is needed to better inform patients, clinicians and drug developers:** Complete release of all clinical trials and preclinical information is needed. We can learn from both successes and failures of previous development programs to avoid repeating past mistakes. Clinicians should be able to access all information about drugs approved through both expedited and standard reviews in order to assess how the study design affects the reliability of the study results and to evaluate how the results apply to their particular patients.

8. **FDA labeling should accurately reflect the benefits and harms and the types of patients studied, how clinicians should select those patients and the information used as the basis for approval:** FDA does not regulate the practice of medicine but FDA does regulate what drug companies can advertise to practicing clinicians. Drug companies should not be allowed to advertise that their drugs are safe and effective in patients with disease due to resistant pathogens

[13] Colebrook L, Kenny M. Treatment of human puerperal infections, and of experimental infections in mice, with prontosil. Lancet 1:1279-1286.
[14] Institute of Medicine. Small Clinical Trials: Issues and Challenges. http://www.iom.edu/Reports/2001/Small-Clinical-Trials-Issues-and-Challenges.aspx

unless they have performed adequate and well-controlled studies in those patients. Clinicians are often forced to make treatment decisions without evidence not because we wish to do so but because the evidence is not available. FDA approval of new antibiotics based on assumptions from test tube tests, animal models and mathematical modeling removes any incentive for drug companies to do appropriate studies in patients with resistant disease. FDA labeling informing patents and clinicians that a drug has not been studied properly does not help either patients or clinicians, and reserving a drug for those in whom the benefits outweigh the risks requires evidence about which patient experience those benefit and harms.

FDA labeling should remove the statement instructing clinicians to administer antibiotics when infections are "suspected". Rather than focusing usage of antibiotics, this statement allows drug companies to advertise their drugs for empirical usage. What clinicians need is better diagnostics to focus usage so we can prescribe new therapies to patients who actually need them and withhold them from patients who do not need them.

FDA labeling for any drug approved under expedited pathways should include wording as already specified in 21 CFR201.57 that the drug has not been shown to be effective for other diseases not studied.

9. **Stewardship of antibiotics and tracking of use needs to accompany any program for approval of new antibiotics**: We need information on how and when antibiotics are used in both animals and human, what they are used for and how much is used. Appropriate stewardship programs are needed to use drug appropriately since CDC data shows antibiotics are still used inappropriatel y in both inpatient and outpatient settings.[15] FDA should require a Risk Evaluation and Mitigation Strategy (REMS) that can take various measures to ensure appropriate use. These measures might include limiting prescribing and dispensing to certain trained providers or certified institutions, requiring administration in specific healthcare settings, or enrolling treated patients in a registry for monitoring follow-up outcomes.

10. **If the economics are broken, fix the economics but improve the science**: Drug companies complain they do not make enough money on antibiotics. However, putting patients at risk so that companies can get more return on investing in antibiotics is not an appropriate response. The standards for antibiotic approval should be improved rather than lowered, and approval should be based on actual evidence from adequate and well-controlled trials in patients with resistant infections rather than on guesses from test tube tests, animal studies and mathematical modeling. Strategies such as de-linkage of antibiotic sales from usage may provide companies with sufficient return while appropriately reserving and preserving antibiotics. Patients, clinicians and payers are not willing to pay more for antibiotics that do not have added value on patient outcomes. A recent study showed almost half of antibiotics approved since 1980 have been discontinued from the market not due to resistance but due to lack of added benefit compared to older drugs.[16] This shows the bottleneck is not regulatory approval but lack of added value.

[15] Centers for Disease Control and Prevention. Improving antibiotic use among hospitalized patients. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6309a4.htm?s_cid=mm6309a4_w

[16] Outterson K, Powers JH, Seoane-Vazquez E, et al. Approval and withdrawal of new antibiotics and other antiinfectives in the U.S., 1980-2009. J Law Med Ethics. 2013; 41: 688-96.

New treatments for infectious diseases should be based on added value on patient outcomes to make any increase cost of new drugs worthwhile. Approval of drugs that are less effective than current options increases the costs to the health care system by delaying administration of effective treatments to patients, and waste resources that could be put towards developing more effective therapies. Incentives should be provided not just for more antibiotics but other therapies such as monoclonal antibodies, bacteriophages, lysins, interventions that modify patients' immune response to disease, etc. These therapies may increase and preserve the effectiveness of antibiotics and may be less susceptible to the development of resistance.

11. **Antibiotic susceptibilities should be based on patient outcomes data, not mathematical modeling alone, without conflicts of interest:** Determining the very definition of "antibiotic resistance" is based upon the fact that patients have worse outcomes from "resistant" infections. Therefore any changes to susceptibility criteria need to be based on evidence of worse outcomes in patients by comparing patients with similar severity of illness across susceptibility criteria. FDA should obtain clinical evidence from multiple sources including other government agencies and hospitals already performing such evaluations of part of quality improvement and stewardship programs. Clinical studies show that changing susceptibility criteria based on mathematical modeling in the absence of patient outcomes data will increase "apparent resistance" but not change patient outcomes, resulting in shifting of antibiotic usage to other drugs that may be less well tested, more toxic and more expensive.[17] FDA acceptance of unverified information from organization with obvious conflicts of interest including charging drug companies membership fees and including drug company employees on susceptibility committees does not serve the public health. Disclosures of conflicts of interest are insufficient to address these conflicts.

    Dr. Maxwell Finland and his colleagues had to grapple with the same challenging issues we do today with antibiotic resistance. We can take the example of clinician investigators from a time when there was as great or greater unmet medical need for improved effectiveness in infectious diseases therapies as we have today. Dr Finland pointed out our obligations to patients to develop and prescribe better therapies which improving their lives as our primary goal:

    > "We would be remiss in our duties as physicians, teachers, and investigators were we to encourage, adopt, and recommend the use of new agents that we cannot consider to be as good as, or no better than, those previously shown to be good, even if they are legally certified."[18]

    Physicians want new therapeutic options for our patients and we depend on the FDA to ensure that new therapies are both safe and effective before they become available for general use. **We offer the National Physicians Alliance FDA Taskforce as a resource for you when specific legislative pertinent to our focus arise**. We offer this comprehensive pathway to provide a constructive way forward to address the issues of antibiotic resistance. Please visit our website http://npalliance.org/fda-taskforce/ for further information. **Contact: npa@npalliance.org**

[17] Tamma PD, Wu H, Gerber JS, et al. Outcomes of children with enterobacteriaceae bacteremia with reduced susceptibility to ceftriaxone: do the revised breakpoints translate to improved patient outcomes? Pediatr Infect Dis J. 2013; 32: 965-9.
[18] Finland. The New Antibiotic Era. Ibid.