



***NPA FDA Task Force Testimony  
Before the Anti-Infective Drug Advisory Committee***

***December 4-5, 2014***

**John Fratti's Testimony:**

My name is John Fratti. I appreciate the opportunity to provide my testimony here today and for all the work the FDA has done in attempting to improve non-inferiority clinical trials. I am a former pharmaceutical sales representative. I worked in industry for seven years and sold the antibiotic Ceftin. I speak before you today, however, as a patient, a patient whose life was dramatically altered by an antibiotic. Over nine years ago I was prescribed Levaquin, an antibiotic in the fluoroquinolone drug class. I suffered severe injuries to my central and peripheral nervous system along with damage to my tendons. Prior to my disability, I was healthy, active, and had earned my MBA degree. Now I require multiple pain medications in order to be somewhat functional. In evaluating new antibiotics and in deciding what evidence we need for FDA approval, I ask you to keep the patient's needs at the center of your considerations.

On the basis of noninferiority trials, Levaquin received FDA approval in December of 1996. Many of the Levaquin clinical trials submitted to the FDA, upon which its approval was based, were considered significantly flawed in protocol design and protocol implementation, as posted on the FDA website. Non-inferiority trials often fail to meet basic quality criteria, report biased and misleading conclusions, and are unduly influenced by commercial sponsors.

FDA approved over 60 New Drug Applications for sinusitis, bronchitis, and ear infections in children based on non-inferiority trials, which could not differentiate the new drug from placebo, yet these same drugs increase side effects for patients and spread antibiotic resistance.

In addition, as a former drug rep, I believe certain antibiotics have the potential to be promoted off-label. It is also important to note that more than 3,000 fluoroquinolone-associated deaths have been reported to the FDA since 1997. And more than half of the fluoroquinolone antibiotics that were once on the market have now been removed.

If Levaquin or other widely prescribed fluoroquinolones such as Cipro or Avelox are the only available antibiotic class to keep people alive, then they should show superiority in effectiveness to older less effective drugs. However, for patients with other safer options for serious infections that do not cause the potential severe and long-term disability associated with fluoroquinolones, there is no need for patients to accept increased risks.

It is often stated by pharmaceutical companies and others, that patients with 'unmet medical needs', are willing to take risks, to try new drugs without knowing whether they will be effective or not. Are these patients giving their informed consent in the case of non-inferiority trials, to possibly taking a drug that may be 10-20% less effective than currently available drugs? Do they know they are being put at risk for some potential untested and hypothetical "future benefit"?

In closing, I stand before you as one who could have taken a better-tested drug with fewer side effects, and I can assure you I would not choose – nor would I recommend any other patient choose – to be in such a trial. I made this difficult trip here today to raise awareness about non-inferiority clinical trials and to prevent others from suffering a similar fate to what I have gone through. Thank you for your time and consideration.

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### **Susan Molchan's Testimony:**

I appreciate the opportunity to speak about my concerns for what I see as pressure to approve drugs that won't effectively treat infections including those due to resistant organisms, and that will undoubtedly release drugs about which we'll have much less safety information.

Today, I'm speaking as a physician in practice, though I spent much of my career in clinical research at the NIH, and 5 years at the FDA, so I have a lot of respect for the work and the people of the agency.

While we always have preclinical evidence—all the good things listed on this 1<sup>st</sup> slide-- from animal and test-tube studies that a drug has activity against targets, for our discussion at hand, microbes, time after time we've seen that this doesn't translate to our hopes for treating disease in people.

Recent examples of antibiotics that have looked promising from pre-clinical and early, small studies in humans but then failed when used in sick patients include the 6 antibiotics listed here.

The 1st three examples: daptomycin, doripenem, and tigecycline, are all approved drugs—for infections in skin, or the urinary tract, or the abdomen. During trials though, they were found not to be effective for various types of pneumonia. This makes a point about one of the discussion points for this meeting--pooling various body sites into a single study of a drug.

Why were these drugs ineffective for pneumonia? In the case of daptomycin later animal studies performed after clinical trials showed that the drug interacted with surfactant in the lungs, inhibiting its bactericidal activity.<sup>1</sup>

Not only may the dose of the test drug be different in the lung or the abdomen or skin structures, but so may the dose of the comparator drug. Pooling outcomes across different body sites, combining infections with different natural histories and patient populations, could well create, as articulated in this review article I like on composite outcome measures, an “exaggerated perception on how well interventions work,”<sup>3</sup>

Tigecycline was granted priority review as a new IV antibiotic to treat MRSA and other resistant organisms. It was approved in 2005. The black box warning came in 2010, indicating that it increased the risk of death compared to older drugs. The drug may have been noninferior in trials, but when used in really sick patients, who weren’t included in pivotal trials, it was more likely to be fatal. A point coming from this is that that non-inferiority in less sick patients doesn’t translate into superior or adequate outcomes in sicker patients with resistant disease.

Tigecycline was approved based on trials with noninferiority margins of 15%, which was wider than the more traditional 10%. Later analyses of the data indicated that if larger trials with smaller noninferiority margins had been used, its mortality disadvantage and higher noncure rates would have been revealed sooner<sup>4,5</sup>.

Once approved tigecycline itself was used as a comparator in a noninferiority trial, potentially perpetuating a downward spiral of standards for efficacy.<sup>4</sup> Along with perhaps the undesirable spin-off of more post-approval black boxes? There’s that little guy digging his own hole—a point about him is coming . . .

What was the result of decades of non-inferiority studies?: One is that over a 20 year period from 1980-2009 half of the antibiotics approved were discontinued.<sup>7</sup> Of 61 NME antibiotics approved during these years, 26 were withdrawn. Six were withdrawn for safety reasons (all fluorquinolones). The others, all essentially “me-too” drugs, were not any better than older products, generally cost more, and simply weren’t selling.

We’ve been digging a hole so to speak, and we need to stop digging and change course in some of the ways recommended in the *National Strategy on Combating Antibiotic Resistant Bacteria* report for example. Piling up a list of antibiotics and approvals similar to those we’ve had over the past 25 years is not part of that strategy. It’s not about numbers approved, it’s about clinical impact, about making a real difference.

Across clinical research, an increasing emphasis is being put on patient centered outcomes. Patients and physicians look to the FDA to center on what matters to patients as well.

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## Joseph Brodine's Testimony:

At its inception in the Pure Food and Drug Act of 1906, the FDA's first purpose was to protect the American public from unsafe medical treatments. Providers and patients are more than just grateful to the FDA for serving this function; we are **dependent** on the FDA to above all, protect patient safety. My name is Joseph Brodine, and I am a medical student who took one of my exams a day early so I could be here today to advocate on behalf of my future patients. I am also a former registered nurse with more than a decade of clinical research experience. I came because I am alarmed by the trajectory of changes to antibiotic approval standards. The need for the FDA to expedite innovation is clear, but efforts to accelerate the approval process may imperil patients. Clearly the agency is being pushed by recent legislation to fast-track drug approvals to combat problems of drug resistance. It will be prompted further if Congress passes the *Antibiotic Development to Advance Patient Treatment Act*, that would allow surrogate endpoints (such as mathematical modeling and in vitro studies) to substitute for clinical outcomes of real patients. Such measures would undoubtedly diminish the safety assured by the review process, much as the current prevalent use of non-inferiority trial designs may have already posed a risk to current study participants and future patients.

Today the Committee is discussing clinical trial designs for patients with infections for which there are limited or no therapeutic options. As a clinician, I urge the FDA to keep the patient at the core of their approval process. Are patients who serve as study participants in drug trials being asked to test an **appropriate** hypothesis in a **non-inferiority trial**? In a non-inferiority design, an unknown study drug is tested against a known comparator in order to determine if the study drug is "not inferior to an unacceptable extent."<sup>4</sup> Is it ethical to expose a study patient to the harms of an unknown drug with no known chance of deriving **added** benefit?<sup>5</sup> The patients I enrolled into HIV and brain tumor treatment trials invariably asked me if the study drug would help them; it is a fundamental concern of a sick person seeking to be well that participating in drug research will have added benefits for them—a concern that FDA leadership must keep foremost in their guidance to the drug industry.

It seems that non-inferiority studies ask the wrong question, and have provided answers that cannot be appropriately applied to the patients with the greatest unmet medical needs. Study sample populations should represent the intended recipients of the approved therapy. If new drugs are studied only in patients with susceptible disease who are less critically ill than patients with resistant disease, how will physicians know what to expect from the drug when considering its use in a critically ill patient? A meta-analysis of 14 comparative clinical trials published last year showed a 50% mortality rate in patients with Ventilator Associated Pneumonia who received tigecycline versus 7.7% in the comparator group.<sup>6</sup> Tigecycline was approved based on non-inferiority studies despite increasing mortality compared to older drugs.

New drug research and approval should aim for superior efficacy compared to current standard treatments in order to address antibiotic resistance. History shows this is to be possible. When I worked with HIV patients, they would recount the limitations of therapy at the advent of HAART: AZT was administered 400 mg every four hours day and night. Improvements in quality and quantity of life were gained from research built on superiority trials in the sickest patients. The FDA should streamline and augment its approval process for greatly needed novel therapies in ways that actually add more effective and safer drugs to our armamentarium. We need innovation, and innovation should mean drugs are *superior*, not '**non**-inferior'. We need studies that focus not just on surrogate endpoints but on patient centered endpoints like overall survival and functional improvement with meaningful quality of life. We must develop rapid diagnostics to identify drug susceptibilities. We must establish a system for sharing clinical trial data to form accurate historical control datasets and make these data-sets public so treatment decisions can be based on the most complete information. Finally, we should encourage comparative efficacy designs that aim to demonstrate *superiority*; drugs that are truly superior actually require fewer study patients than those used in non-inferiority studies. These suggestions originated from stakeholders, academia, and the FDA's own guidance for industry documents.<sup>9</sup> Most importantly, these mechanisms are consistent with the FDA's mandate to "guarantee...safety and effectiveness" for the many patients of today and the countless patients of tomorrow.<sup>10</sup>

<sup>1</sup>Powers JH. Noninferiority and equivalence trials: deciphering 'similarity' of medical interventions. *Stat Med.* 2008;27:343–52

<sup>2</sup><http://www.fda.gov/NewsEvents/Testimony/ucm415387.htm>

<sup>3</sup><https://www.congress.gov/113/bills/hr3742/BILLS-113hr3742ih.pdf>

<sup>4</sup><http://www.fda.gov/downloads/Drugs/.../Guidances/UCM202140.pdf>

<sup>5</sup>Emanuel EJ, Wendler D, Grady C. What Makes Clinical Research Ethical?. *JAMA.* 2000;283(20):2701-2711.

<sup>6</sup>All-cause mortality imbalance in the tigecycline phase 3 and 4 clinical trials McGovern, Paul C. et al. *International Journal of Antimicrobial Agents*, Volume 41, Issue 5, 463-467

<sup>7</sup>Nambiar S, Laessig K, Toerner J, Farley J, and Cox E. Antibacterial Drug Development: Challenges, Recent Developments, and Future Considerations. *Clinical Pharmacology & Therapeutics* 96, 147-149 (August 2014) | doi:10.1038/clpt.2014.116

<sup>8</sup>World Economic Forum. *Global Risks 2013*. 8 ed. Geneva, Switzerland: World

Economic Forum, 2013. Available at <http://www.weforum.org/reports/global-risks-2013-eighth-edition>.

<sup>9</sup><http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm359184.pdf>

<sup>10</sup>21 CFR 312.80, subpart E, Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses

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## **Reshma Ramachandran's Testimony:**

### **SLIDE 2**

Good Afternoon! My name is Reshma Ramachandran and I will be speaking on the behalf of the National Physicians Alliance FDA Task Force as the Task Force Co-Chair. The National Physicians Alliance is an independent, multispecialty physician organization dedicated to promoting evidence-based medicine and advocating first and foremost for the interests of our patients and public health. I am also a final year joint medical and public policy student at Brown Medical School and Harvard Kennedy School. Thank you for the opportunity to speak to you today.

### **SLIDE 3**

I echo my colleagues in saying that the FDA must not compromise safety and efficacy in favor of a streamlined or expedited antibiotic approval process. Doing so would only undermine the FDA's mission in protecting the public health by assuring our patients and ourselves as clinicians of the safety, efficacy, and security of all drugs including antibiotics. We agree that new antibiotics are needed, but the bottleneck is not regulatory.

### **SLIDE 4**

Dating back to 1964, antimicrobials have had the highest rates of regulatory agency approval compared to any other therapeutic class. Data from the pharmaceutical industry has also shown there is only a 7% yield from screening promising antibiotic drug compounds which is less than one-tenth of the yield for finding promising drugs in all other therapeutic areas. This only indicates that the bottleneck is well before clinical trial testing. Not only that, but the time in clinical development for anti-infectives is among the shortest compared to other therapeutic classes.

### **SLIDE 5**

Additionally, shortening clinical trials will not stimulate antibiotic innovation. The Eastern Research Group modeled various incentives for the U.S. Department of Health and Human Services and found that shortening these trials or changing approval standards would not make a difference economically for drug companies unless they cut clinical trial lengths by 75%. This would be impossible without severely compromising patient safety.

## **SLIDE 6**

As noted by the examples in Dr. Susan Molchan's talk earlier, standards of approval of new antibiotics are already low and already use too few patients in clinical trials. This has resulted in FDA approval of these new drugs actually causing more deaths in patients than existing treatments. As a physician-in-training, I cannot advocate in good faith for this sort of uncertainty especially if it may cost my patients' lives. Also, these regulatory mistakes could instead have a chilling effect on drug R&D.

Instead, we ask that the FDA provide incentives only for antibiotics that address unmet medical needs, studied in patients with these unmet medical needs, and actually demonstrate added benefits for these patients. Both patients and clinicians want drugs that will improve efficacy and/or decrease harm. Current legislation in Congress – namely, the ADAPT or Antibiotic Development to Advance Patient Treatment Act fails to target incentives to developing truly novel antibiotics rather than me-too products. The withdrawal rates of antibiotics from the market is already more than three times as high than that of non-antibiotics as these drugs appear to be just not effective enough to compete with existing regimens.

## **SLIDE 7**

The FDA approval process should not be undermined, but strengthened. In regards to the tiered approval approach, we agree with the FDA that Tier C and D are not sufficient to meet FDA's requirements for demonstration of safety and effectiveness. We also think that the Tier B approach of one phase 3 body site trial with inference testing demonstrating effectiveness and safety in that body site along with descriptive studies receiving the investigational drug would not be sufficient either. Extrapolating non-inferiority in one patient group to show superiority in another patient group is not valid. There have been many examples of drugs including ones already mentioned today that were shown to be non-inferior in less ill patients, but then showed mortality in sicker patients. This clearly shows that patient factors are equally as or even more important than organism factors. Besides this, using descriptive studies are not adequate or well-controlled themselves and will not become so just because of a non-inferiority trial in a different group of patients. In 1970, in the case *Upjohn v Finch*, the court (WHICH COURT) actually rejected the standard of case studies as being

substantial evidence for drug efficacy in addition to relying on in vitro and animal data.

## **SLIDE 8**

Instead, we ask that the FDA approve antibiotics based on a single superiority study with patient-centered outcomes in patients with a single type of disease. If the drug is effective, fewer patients are needed. Additionally, the FDA should remove financial conflict of interest in setting standards for antimicrobial susceptibility. The process for determining these standards should be transparent, independent of financial COI, and be based on patient centered outcomes such as survival, function, and mortality.

Only 3 of the current members of the Clinical and Laboratory Sciences Institute Antimicrobial Susceptibility Subcommittee reported no financial COI. In 2010, the Clinical and Laboratory Sciences Institute lowered antibiotic resistance breakpoints for ceftriaxone, which would have led to a 300% increase in the number of infections that are classified as antibiotic resistant. This would have prompted physicians to prescribe newer, broad-spectrum antibiotics for these cases even though studies have shown that this change in prescription practices would have offered no improvement in clinical outcomes. Changing these standards for antibiotic resistance could lead to greater resistance from inappropriately prescribed and increased use of broad-spectrum antibiotics that should be reserved for infections for which they are effective.

The National Physicians Alliance asks that the FDA continue to uphold its mission to provide us as clinicians and our patients assurance that the drugs the agency proves are truly safe and effective by approving these drugs based on sound scientific evidence, rather than allowing for further uncertainty

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