Working to Reduce Conflict of Interest at the FDA
May 29, 2014 - Call Notes

**Featured Speaker:** John H. Powers, MD FACP FIDSA,
Associate Clinical Professor of Medicine, George Washington University School of Medicine
University of Maryland School of Medicine

**Welcome and Introductions:**
Welcome to this bi-monthly Conflict-free Leadership call hosted by the National Physicians Alliance as part of its Unbranded Doctor project, which takes place under the Partnership to Advance Conflict-free Medical Education, PACME, grant. I am Rachel DeGolia, facilitator for this call and a board member of the National Physicians Alliance. In my day job, I direct the Universal Health Care Action Network.

The PACME grant is the result of a state Attorney General settlement regarding the inappropriate marketing of the drug Neurontin. Partners for the grant include the National Physicians Alliance, American Medical Student Association, Community Catalyst and the Pew Charitable Trust. The goal of the project is to reduce conflicts of interest (COI) created by the pharmaceutical industry in the medical profession and medical research. The partners on this grant promote a number of approaches to raise awareness of the issue and to build leadership in the medical profession to eventually eliminate some conflicts.

We have a good mix of physicians and medical students on the call tonight from around the country, including at least the following states: CA, DC, IL, MD, NY, OH, OR, TX, VA, WA and WI.

Our topic tonight is Working to Reduce Conflict of Interest at the FDA. Our featured speaker is Dr. John Powers, Associate Clinical Professor of Medicine at George Washington University School of Medicine. John formerly was the Lead Medical Officer for Antimicrobial Drug Development and Resistance Initiatives in the Office of Antimicrobial Products, Center for Drug Evaluation and Research, at the US Food and Drug Administration where he was responsible for issues related to clinical trials and policy in antimicrobial research. Prior to joining the FDA, John was assistant professor in the Division of Infectious Diseases at the University of Maryland School of Medicine and he still is on the faculty there as an Assistant Clinical Professor of Medicine. John also actively sees patients weekly in clinic and attends on the infectious diseases service.

Tonight John will discuss the work of the NPA’s Task Force on the FDA, including current efforts related to conflicts of interest and antibiotics.

Joining John in responding to questions and participating in the discussion will be Reshma Ramachandran is a fourth year medical student at Brown Medical School and 2nd year Masters in Public Policy student at the Harvard Kennedy School. In 2012, she was the American Medical Student Association PharmFree Fellow and is currently working in China with the Harvard Global Health Institute on increasing access to biologics. Reshma will share information about additional resources and new tools designed to reduce conflicts of interest at academic medical centers and in the medical profession.
Now a few words from Ann Woloson, Director of Education for the NPA.

Ann Woloson: A quick reminder about resources from the Partnership for a Conflict-Free Medical Education (PACME) project. These conference calls and our Grand Rounds are archived at www.npalliance.org/conflict-free, including information on the AMSA Pharm-Free Scorecard, the Physician Sunshine Payment Act, ghost-writing and much more.

Rachel: Now I am pleased to welcome Dr. John Powers to tell us about the work of the NPA’s Task force on the FDA including their efforts to reduce conflicts of interest and inappropriate use of antibiotics.

John Powers: My slides for this talk will be emailed to all participants. I would like to give a little history of the NPA FDA Task Force, the goals of the group and some of our current work that relates to conflict-of-interest. The NPA Executive Director, Jean Silver-Isenstadt, was involved with an informal coalition, the Patient and Consumer Coalition, that was working on issues relating to the FDA. So, NPA decided to form a task force to address the growing number of issues regarding the efficacy and safety of medical interventions, including drugs, biologics and devices. Find information on the NPA FDA Task Force at www.npalliance.org/npa-fda-taskforce. The chairs are Lisa Plymate, a general internal medicine and geriatrician in Seattle, and Reshma Ramachandran. The mission of the group is “To educate and empower a multispecialty group of NPA members, free of conflict-of-interest, to provide unbiased expertise in evaluating and responding to the FDA regulatory process in a way that maximizes meaningful clinical outcomes for our patients.”

The guiding principles of the NPA FDA Task Force are:

- We believe the nation’s food supply should be kept safe for immediate consumption and should also cause no harm to our population over time. The first letter is “food” in the FDA’s title.
- We believe that drug, biologic and medical device regulation should be based in transparency, integrity and accountability, firmly grounded in scientific evidence and driven by public health interests. Some of our current efforts are directly addressing this principle.
- We strongly support the development of meaningful new treatment options and recognize the need to improve the efficiency of clinical trials to expedite obtaining clinically relevant information. We’re all for getting the best information in an expedient way, but in ways that help patients and not just making more money for pharmaceutical companies. They can do well by doing good for patients at the same time.
- We believe that the process used to approve these options should be based on substantial evidence from adequate and well-controlled clinical trials regarding both safety and efficacy of products and procedures. That is the legal standard that is in the Food, Drug and Cosmetic Act.
- Finally, as providers, we believe that the FDA regulatory process, including policies on dissemination of information by the FDA, pharmaceutical and device manufacturers and researchers, should allow us to make informed clinical decisions in a way that optimizes patient health and safety.

I want to quote a paragraph from Lisa Plymate’s blog post a few months ago – it explains the whole idea behind this group in one simple paragraph:

“In recent years, physicians have found themselves in growing tension with the pharmaceutical industry as our respective interests do not always coincide and in some cases directly conflict. Yes, physicians want real innovation. We need better diagnostic tools and we want truly novel drugs. We want to work with PHARMA, the NIH and the FDA to encourage development, but we must always assure to the best of our abilities that drugs are thoroughly tested before being released to the public. We want to offer our patients, especially those with novel disorders or fatal, disabling diseases, real hope, but not false hope. We must step up to defend the regulatory rigor of the FDA. Drug and device companies may see regulation as a roadblock to discovery and growth. We see regulation as a critical line of defense for public health. Well done, scientific regulation provides the best pathway to achieve real and lasting innovation. As physicians, we want to know we can trust the label, “FDA approved.”
Some of our recent work includes letters to the FDA and Congress regarding a number of issues and comments on FDA guidances, including a number relating to antibiotics. Some of our members have presented at public hearings of FDA advisory committees, including one on how antibiotic resistance is defined and one on skin infections, and felt they had a bit impact on the discussions. One was quoted in Wall Street Journal. We have published several NPA blog posts and our monthly conference calls. feature guest speakers for the first 20 minutes to provide learning sessions regarding a FDA regulatory topic.

Recently we’ve been working on legislative issues regarding antibiotics. Most people realize that effective antibiotics have had a huge impact on public health and decreased morbidity and mortality starting in the 1930’s. What is less well known is that in the ‘40’s and ‘50’s antibiotic studies were the first to employ methods to decrease bias. However, in the 1980’s, multiple antibiotics started to be approved by comparing one antibiotic to an older one whose effectiveness was not clear to begin with. At least 60 new drug applications submitted to the FDA were approved for self-resolving illnesses such as ear infections in children, sinusitis in healthy adults, and bronchitis. So, these drugs were never proven to be effective in the first place, and not only do they cause side effects, but they have a big impact on spreading antibiotic resistance.

It is clear there is an intrinsic link between pharmaceutical companies wanting to sell more drugs, and inappropriate use of antibiotics and the spread of antibiotic resistance. Drug companies are saying they need incentives to make new antibiotics because they don’t make enough money off current antibiotics despite the current antibiotic market being between $27-42 billion per year. What’s happening is that the drug industry and groups linked to them are lobbying the FDA to lower the standards for approval of antibiotics despite recent drug trials showing an actual increase in mortality for new antibiotics compared to older antibiotics. There is, in truth, an unmet medical need for patients with antibiotics resistance, but the FDA has allowed the new drugs to be less effective than the older drugs and assume they’ll be superior with these patients. So, we are putting these patients at risk.

The industry is also calling to allow animal studies and pharmacological modeling instead of actually doing randomized trials in patients with disease. It has been proven again and again that these are not reliable measures of whether a drug is effective in patients.

Another issue is that the drug companies are pushing for outcome measures in studies to be based on laboratory tests, such as killing bacteria in a test tube, instead of patient outcomes such as death, disability or improvement in systems. What is remarkable about this is that effective antibiotics have been shown to decrease death with very small sample sizes.

The drug companies are also calling for “limited approval,” and it is unclear what that means, whether they are calling for very small data sets to approve a drug, or to approve it for a small subset of patients. Antibiotics are probably the worst place to try to limit drug usage because we already know that 50% of antibiotics are used inappropriately and there is a lack of rapid, accurate diagnostics for most infections - they are used imperically in a large number of cases.

It’s stunning that this is happening in a setting in which recent antibiotics are actually increasing mortality compared to older drugs. [See examples in his slides] For example, a drug that caused a five-fold increase in mortality when it was added to already available therapies was approved by the FDA which labeled its use to “reserve it for appropriate patients.” It is unclear what patients those would be.

What happens over and over with these antibiotics is that they are seen to fail in sicker patients. In healthier patients, they are seen to be “non-inferior.” For all of these drugs, they are not studied to show improved effectiveness, but to show how much less worse they are than the older drugs. This does not make sense to do studies in this way and puts patients at risk. It is ethically questionable. We are then extrapolating that these drugs will be effective in populations that really need them.
There have been several recent legislative initiatives to lower the threshold for antibiotics approval even further. The GAIN Act – Get Antibiotic Incentives Now – was passed as part of the FDA legislation in 2012 and gives extended protection from generic drugs to any antibiotic active in the test tube against a long list of pathogens. This means that any new antibiotic gets a priority review, that means faster, and 5 to 7 years protection against generic drugs.

The ADAPT bill would change the standard to allow antibiotics to be approved based on test tube tests, which has been shown it does not predict benefits for patients, and “limited data sets” and “alternative end points.” This bill also outsources defining antibiotic resistance in the test tube to an outside group that includes drug company employees as its members. We are gravely concerned that this would essentially allow the drug industry to regulate itself. If they change the definition of antibiotic resistance, it will make it appear that older drugs are less effective and shunt physicians toward newer, less effective, more toxic drugs with no evidence that those drugs are better. A John Hopkins study showed that these definitions being promoted could raise the apparent antibiotic resistance in the hospital by 300% with no benefit to patients at all.

Another bill being promoted, DISARM, would force hospitals to pay premium prices for antibiotics that are not better than current drugs. This would raise the price from $800 to $30,000 for a course of antibiotics. We will ask patients to foot the bill for drugs that are no better than older, less expensive drugs.

We are planning a day at Congress on June 12th to show Members the data on these issues, and we have started a letter-writing campaign. We are planning a meeting this fall to discuss appropriate design for clinical design for antibiotics trials and a white paper.

Our concern is not just about antibiotics. They are a poster child for what is coming up in other therapeutic areas. The pharmaceutical industry is trying to promote these same ideas of limited approval for diabetes and cancer drugs as well. People widely assume that all antibiotics are effect when, in fact, they are not. This raises important issues about medical professionalism as well. How does this conform to the principle of first, do no harm, if we are enrolling patients in studies where the prime goal is to show how much worse a new drug is compared to an old drug?


Rachel: Now I invite Reshma to share with us to provide an initial response to John’s remarks and tell us about some additional resources available to medical students and physicians to address conflicts of interest in the institutions where you are. We hope that everyone on the call will take away information and inspiration that enables you to act on what you learn today.

Reshma Ramachandran: The Task Force has been instrumental in giving us information about the clinical trials, but also the ethical issues involved in prescribing antibiotic drugs – it has been eye-opening. As John said, a group of us from the Task Force will be going to talk to Congress to talk about legislation. We are very concerned that the ADAPT bill in particular may be pushed very quickly. It has already garnered some support from the AMA and APHA and there is misinformation about the bill being put out to the public. We will talk with Congress about what needs to be included in the bill – they talk about “unmet medical needs” which is not defined in the bill. We want to urge Congress to focus on patients rather than the drugs themselves, and to support having better and robust trials to determine the effectiveness and safety of the drugs rather than incentivizing companies to lower standards to get the rugs to market more quickly.

We have a great group on the Task Force, but we need more members and other types of physicians, especially oncologists. We are usually the only professional physicians group asking these questions about what the
evidence is for approving these drugs. There are consumer groups doing this, but we need more physicians to join the Task Force to take up these issues with Members of Congress in their districts as well as in DC. We need better antibiotics, not just more. We are looking for physician voices to advocate both formally and informally – please contact us!

We have monthly blog posts on the NPA website about what issues we’re addressing, and out monthly calls are a great way to learn about these topics. We are always open to new topics, too. The more we get Congress to pay attention to the need for better trials and better antibiotics, the better it will be for our patients.

Contact any of us for more information about the Task Force and the issues it’s working on:

John Powers: jpowers3@aol.com
Reshma Ramachandran, FDA Task Force Co-Chair: reshmagar@gmail.com
Lisa Plymate, FDA Task Force Co-Chair: lisaplymate@comcast.net

Q: How does the Task Force decide its priorities?

Lisa Plymate: We have information sessions with good speakers who motivate us and we pick up on issues we see in journals or the media. We focus on topics people find most interesting and where we have some expertise. This is why we are particularly interesting in recruiting an oncologist – because we want to look at some of the oncology drugs - but we also are interested in finding a cardiologist and other specialists. We do have an endocrinologist, someone in rehab medicine, primary care and physicians from other backgrounds. We appreciate whatever anyone brings to the table. We don’t have grants to support us right now, but are hoping to find funding to get staff report in the future.

Q: Does the CDC have anything to say about these less effective, less safe antibiotics John talked about?

John: Great question! Having working at FDA before my current job, I can say that the CDC and the FDA work differently. Unfortunately, the CDC has their own biases. However, they have been instrumental in trying to address the inappropriate use of antibiotics with their “Get Smart” program, but it has been chronically underfunded. How the trials are designed is strictly an FDA issue and the CDC does not get involved in that.

Q: Has the Task Force reviewed the ethical dimensions of cost related the new Hepatitis C drugs?

Lisa: We’ve discussed this because we’ve seen a lot of national media on it. Public Citizen and other groups have been working on this, but we have not.

John: We are addressing this in a related way via the DISARM bill which is trying to codify what this drug is trying to do. That is forcing patients and payers to pay much higher prices for these drugs than in the past. The high price of that Hepatitis C drug is being justified by the drug company because they say they are saving lives and decreasing hepatic cancers. In fact, the outcome measure of that study was that it decreased the amount of Hepatitis C in the blood and they did not directly evaluate if they stopped any of the bad outcomes in patients. So, that gets to the issue we address in our Task Force which is, measure what you say rather than inferring benefits based on laboratory tests.

Q: How can a clinical trial be ethically structured in the sickest patients where there are existing drugs and you offer them a study with an unproven medicine?

John: The basics of research is that you should offer the patient the potential for benefit. That new intervention should have some added benefits above and beyond currently available therapies based on pre-clinical and early clinical information. This important ethical dimension is completely ignored in these non-inferiority trials.
The Task Force hypothesizes, because there are no studies yet, that patients don’t really know what they are signing up for with these studies. Thus, you’re sick in the hospital and you sign up for a study comparing new antibiotic A to old antibiotic B, and you don’t really know that the primary goal is to prove that new antibiotic A is only 15% worse than you could have gotten otherwise.

Added benefits could include less side effects as well as improved effectiveness, but you are still talking about an added benefit for patients.

Q: Are you familiar with the FDA’s conflict of interest (COI) waiver process and how often is it used?

John: In 2007, the FDA Amendments Act limited the amount of waivers that FDA could grant for COI on the advisory committees. In 2008, the industry pushed back to allow more people to get on the committees who had COIs. They advocate that somehow people aren’t qualified to be on those advisory committees if they don’t have a COI. I believe this borders on the ridiculous. But now the FDA is empowered to add more, not less, conflicted people on the advisory committees based on the 2012 law.

Reshma: One case related to this regards a physician who was on the FDA’s skin infection drug approval committee who went to an industry-funded event to tell them how to get their drugs approved quickly. This was a public event, but she did not report this as a COI in her academic setting. She was called out for this and released a statement apologizing for not disclosing it and indicating she would not participate in such events in the future. So, people are paying more attention to people on the FDA approval committees as to the conflicts that are disclosed or not.

Lisa: All of this is complex. We try to limit ourselves to issues related to the FDA as our court of last resort to try to preserve their basic function as a regulatory agency. We have two other members, in addition to John, who worked at the FDA for many years who help us understand how the FDA works.

Q: Please repeat where this work is found on the NPA website and how people might get involved locally.

Becky: Go to the Projects tab and get to the FDA Task Force to find all the information about their work and membership.

Lisa: We taped all our information talks and posted them on the website.

Rachel: We thank our speakers for the information they shared to night and everyone who listened in. Watch your email for notice of our next Conflict-Free call. Recordings and notes of past calls are archived online at http://npalliance.org/conflict-free/

Again, for more information about NPA and this project, visit the NPA Unbranded Doctor website at: npalliance.org/conflict-free. For more information on the AMSA PharmFree Scorecard, visit http://www.amsascorecard.org/.

The NPA is a proud partner in the Partnership to Advance Conflict-free Medical Education (PACME), a three-year initiative to identify and promote best practices aimed at reducing conflicts of interest with the pharmaceutical industry. Key partners in the PACME initiative include the National Physicians Alliance, the American Medical Student Association, Community Catalyst, and the Pew Charitable Trusts.

This partnership and related materials were made possible by a grant from the state Attorney General Consumer and Prescriber Education Grant Program which is funded by the multi-state settlement of consumer fraud claims regarding the marketing of the prescription drug Neurontin.

Learn more at www.npalliance.org/conflict-free