



Richard Bruno's FDA Testimony: Antibiotic Ceftazadime-Avibactam (CAZ-AVI)

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Hi I'm Richard Bruno, resident physician in the combined family & preventive medicine program at MedStar Franklin Square and Johns Hopkins in Baltimore. I am here today representing the National Physicians Alliance of over 15,000 physicians representing multiple specialties that promotes high quality care. I serve on our FDA task force. I have no financial interests in Cerexa, Inc.

I would like to start by *commending* the FDA's efforts to apply judicious scrutiny of pharmaceuticals and devices that have the power to help or harm patients. Your vigilance protects and helps heal millions of Americans, and I *very* respectfully thank you for the opportunity to speak today.

Story

My story is borne out of the frustrations I am seeing in the Baltimore area with more and more community-acquired MRSA infections. I *recently* saw a 3 month old child with a red, painful, pus-filled skin abscess on his back, which previously would have been treated effectively with oral antibiotics, but for this unfortunate child and his parents, required hospitalization and IV vancomycin. His infection resolved because we still *have* effective medicines, but had it *been* resistant to vancomycin (and it's likely that day is coming), I would have wanted a more effective drug that had been tested in patients *with* this condition, *not* one that that was merely non-inferior.

We have *time* to do the appropriate studies, and we *should* be doing them, because **no child deserves to be exposed to increased harm** by *less* effective and *poorly* studied antibiotics.

Stewardship

At the National Physicians Alliance one of our core tenets is good stewardship of medicines, including the appropriate use of antibiotics. We believe that current and future patients who already *have* safe and effective treatment options should *not* be placed at increased risk from less effective therapies. Doing so, would *violate* the principle of **Justice** in the Belmont Report of 1979 regarding the equitable distribution of the benefits and *risks* of clinical research, because those who *bear* the risk in these studies are not also benefiting.

It is our belief that these non-inferiority studies that are being used to investigate the effectiveness of ceftazadime-avibactam are **exploiting research subjects** without an unmet medical need in order to *extrapolate* the drug's effectiveness for those who do. I can tell you from reading through the *scant* precursory Phase III study data comparing ceftazadime-avibactam to meropenem in complicated intra-abdominal infections, that the drug does *not* look that great—in fact, they would make me want to prescribe the meropenem!

I can also assure you that simply placing a warning in the FDA labeling about a drug being studied in “limited population” is unlikely to impact appropriate use in practice *or* protect other populations.

Approval process

As the National Physicians Alliance we *implore* the FDA to base the approval of new drugs for patients with unmet medical needs on **superiority studies** that *enroll* patients who have unmet medical needs. When we rely on **non-inferiority study** designs, we can at best only rule out how much *worse* a new therapy might be compared with an older drug that already *meets* the medical need of the patient population studied.

//Fortunately, there are laws, legal precedence, and current US federal regulations to support this stance, dating back to 1970 when the Upjohn Pharmaceutical Company sued the Secretary of Health Robert Finch and FDA Commissioner Herbert Ley, Jr for *withdrawing* combination antibiotic drugs based on their shown lack of safety and effectiveness, and setting precedence that *in vitro* testing, animal models, and pharmacodynamic modeling are *not* substantial evidence for obtaining drug approval.

We also strongly suggest that the **outcomes** studied in these clinical trials should be *direct* measurements of irreversible morbidity or mortality, or *patient-centered* outcomes, *not* subjective clinical response or microbiology.

We were very supportive of the New England Journal of Medicine article published this week by three FDA staff physicians Drs Edward Cox, Luciana Borio, and Robert Temple on randomized clinical trials for Ebola therapies

arguing that *everyone* deserves appropriately studied drugs, and that “those with bacterial diseases deserve no less.”

Conclusions

In conclusion, we believe that an unmet medical need is *not* a reason to accept a lower standard of evidence from clinical trials for potential new therapies.

Approving drugs for more indications with less data is dangerous and it won't help current or future patients.

Non-inferiority studies should *not* be relied upon for new approvals.

And we request that the FDA require adequate and well-controlled studies for the approval of a new antibacterial therapy in nearly all instances.

OPEN PUBLIC TESTIMONY SPEAKERS:

- Anna Mazouko, natl Ctr for health research. Alliance for stronger FDA. Expose Unnecessary risks. Concerns for the minimal data presented today. Wait until phase III complete before making decision. Mentioned Upjohn v Finch so I dropped it.
- Amanda Jessig. Inf dz soc america. No industry funding. No position on FDA approval of any specific product. Bad bugs, no drugs report. 10x20 initiative. Want 10 new drugs in next 20 yrs. so far 4 new drugs. Gain act. Grave need of Abx to fight Gm neg bacteria. CRE is urgent threat. 9000 infections last year. Even colistin resistance occurring. \$21-34B cost of Abx resistant bact inf. Abx are a gift. Moral obligation to ensure robust Abx pipeline.
- Margaret Swetz. Father had prostate biopsy, developed esbl E. coli inf. tho rare, For someone so close as family member is a big deal. Admitted. Released. Admitted again with sepsis. Released. Received home infusions of Abx. Still recovering. Abx today do not match current needs of pts.
- Jason Gallagher. Soc Inf dz pharmacists. Consultant with pharma, incl Cerexa. Pharmacist at temple. Seeing CRE infections and high levels of resistance. Support innovative new products. Alt drugs not good. 29y woman with urosepsis, Vancouver/zosyn, Kleb. Erb/imi. Resistant to colistin. With Cerexa and FDA approval, Used compassionate use caz-avi. N=1 doesn't constitute basis for approval.
- Jerome Schentag. Prof at buffalo. Labeling of certain pops will help. Past 4 ndas have been NI. Need to make phase IV better. Can do several

superiority studies in time/cost of one NI study. Doing need randomization.

AIDAC VOTING

- Question 1: has applicant demonstrated substantial evidence of safety and efficacy of caz-avi for cIAI?
 - Dr Alan Magill: what is the delay here? when will they be able to submit more complete phase III data? 505b2 application: risk/benefit-need-promise
 - Cerexa person: Planned sNDA late 2015, PDUFA mid-2016. they have enough data on caz-resistant pathogens.
 - Dr Edward Cox: this is for approval not accelerated approval.
 - Magill: whether sNDA will be submitted in future should not bear on decision today
 - Dean Follmann: do you have phase III data? what would you do with it if you had it?
 - Cox: results of trial even after approved could have impact on indications.
 - Debra McCall: would any docs on this cmte be comfortable prescribing this med?
 - Moore: If carbapenem-resistant bug then yes... [then he kind of changed his answer], would have to weigh options, but wouldn't exclude it. then asked if there are any pediatric data
 - Cerexa: no IRB would approve that but will be investigating in future once good safety/eff data
 - VOTE: 11 to 1 (Dekker only no), Follmann thought sponsor did good job of presenting data. McCall qualifies her vote is a "yes, but" and wants to see phase III data. Andrews: concerned and wants another tool in toolbox, wants labeling to exclude renal pts with "super red flags," thinks it's ironic that as kidney function improves, can use drug. Waterman voted "yes" despite data yet to be analyzed. secondline treatment or last-line treatment. Dekker: difficult vote, half in favor half against, he is med microbiologist, understands critical need, this is vote for limited use labeling given just data. concerned by safety signal. wants to see clinical data from phase II/III, even if gets label still will be used like meropenem. Parise: phase III data sufficient for unmet medical need. struggle with labeling with renal impairment. if i were clinician i would prescribe. cappelletty: 2.5g dosing makes sense from PK/PD basis, concern for pseudomonas isolates. would like to see reduced functionality in renal pts addressed, CRRT data. Magill: unmet med need, many pts

out there who would benefit from this drug, but with significant hesitations and reservations, can't translate limited use into actual use. need to add resistance as important as safety and efficacy. this is monotherapy for beta lactams, gonna lose avibactam very quickly if you don't get dose right. Ostrosky wants specific label "hasn't been studied adequately." Moore: feels bad for clinicians who are limited in what they can prescribe. circumspect to rush to judgment about drug where all data not it. Reller: how we approach over the next year or two as more data available: label should read <when limited or no avail treatments>, exclude renal function <50. FDA should reconsider label and indications as Phase III data emerge, probably need another hearing. How to address limited use in practice is beyond purview of this panel.

- Question 2: has applicant demonstrated substantial evidence of safety and efficacy of caz-avi for cUTIs incl pyelo?
 - no discussion
 - VOTE: 9-3 (Nos: Dekker, Follmann, McCall).
- Question 3: has applicant demonstrated substantial evidence of safety and efficacy of caz-avi for gm neg (HAP/VAP)?
 - VOTE: I LEFT before vote

Full report: <http://www.sac-tracker.com/aidac-20141205-rw>