

A Pivotal Point in Time:

What Do We Need,

What Should We Be Doing,

Who Should Be Doing It?

Antibiotic R&D 3.0: *Let's all row the boat together...*

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19 Nov 2019 – FDA-IDSA-NIH-Pew Workshop

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Slides happily shared

*With thanks to Kevin Outterson
and Helen Boucher for constructive
critiques of this deck.*

Antibiotic R&D 3.0: *Let's all row the boat together...* *... and in the same direction*

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We meet at a pivotal point in time

- We have poured substantial resources into preclinical and Phase 1 work: CARB-X, etc.
 - *And there is progress!* There are signs in the early pipeline of some very interesting, innovative products
- But all will collapse due to two intertwined issues:
 - New antibiotics don't get used
 - Some of the new agents are not really that interesting
 - Even the good ones are perceived as “only non-inferior”
 - Guidelines are out of date by YEARS
 - Stewardship is based both on cost and utility
 - The payor model is broken
 - Antibiotics are the fire extinguishers of medicine!
 - We need to stop paying for them solely on a per-fire basis



We can't fix it all at this workshop

- In scope
 - The type(s) of trials we conduct for (new) antibiotics
 - The type of data we can *realistically* get
 - How those data should be reported in labeling
 - How the ID community talks about those data
 - How guidelines can / should handle those data
- Out of scope
 - Payor models
- Also out of scope: “Oh, I just don't like X or Y”
 - Unless you propose something else *that can actually be done predictably in the real world*, you are not helping

Rant over! Let's think big picture

We've come a long way...

- Antibiotic R&D v1.0: 1950 to ~2005-6
 - Generally easy to see the value of new drugs
 - Weaknesses in pivotal designs gradually become obvious, especially for upper respiratory infection
- Antibiotic R&D v2.0: 2007-2019
 - Ketek hearings in Congress during 2007
 - Rapid refinement of non-inferiority designs for major indications → clear roadmaps for skin, UTI, etc.
 - Single pivotal trials become acceptable for approval
 - Substantial harmonization between EMA and FDA

And now: Antibiotic R&D v3.0!

1. LPAD as a springboard
2. From that springboard, R&D v3.0 needs to build on v2.0 to address several really hard problems
3. The idea of superiority designs as a consistently viable path is a mirage that must be swept away
4. This is not (just) a regulatory problem – the entire community must collaborate to move us forward
5. Suggestions for next steps
6. Closing thoughts

1a. What is LPAD?

- LPAD: Limited Population Antibacterial and Antifungal Drug. *Really should be called LPAAAD!*
 - Concept: Physicians and patients will accept greater uncertainty for serious diseases with unmet needs
- In brief...
 - Streamlined approaches based on severity, rarity, and prevalence: single trials, wider non-inferiority margins
 - **But**, not a license to run riot: Must still meet the standard of substantial evidence of efficacy based on adequate and well-controlled clinical data
 - **Also**, labeling must make clear the limited population that is appropriate given the unmet need

1b. LPAD as a springboard

LPAD's two key gifts to us...

1. The idea of LPAD itself

- The very name is a clear reminder that patients & physicians make different risk-benefit decisions when options are limited
- And, LPAD defines settings in which this is true

2. A way to mark LPAD-approved drugs as different

- LIMITED POPULATION: “This drug is indicated for use in a limited and specific population of patients.”

Combined with robust stewardship programs and CDC's ongoing surveillance, we can be comfortable that LPAD agents would be used wisely

2. The hard problems that remain

- Antibiotic R&D 3.0 needs to address these issues
 - a) Communicating the value of standard NI trials
 - b) Developing for rare and/or resistant pathogens
 - c) Developing for less common infections
 - d) Adequate quanta of data for labeling for (b) and (c)
- Issues (b)-(d) reduce to study size and how we think about “substantial evidence of efficacy based on adequate and well-controlled trials.”
- Importantly, $\alpha = 0.05$, 10% margins, specific endpoints, and concurrent randomized controls are not legal requirements
- We are permitted to consider risk-benefit

3. Superiority is not the answer

- Antibiotics *cure* ... and you can't improve on cured
- If it's easy to run a superiority trial, something terrible has happened in public health
 - Resistance must be so common good choices do not exist
 - Except for the very mildest of infections, a superiority result means someone has gotten hurt (or possibly died)
- We want antibiotic superiority trials to be impossible
 - And if superiority is possible due to a gap, successful use closes the path to repeated superiority studies
- Instead, non-inferiority must (will) be our main tool
 - Modern NI designs are proven sensitive to drug effects
 - These designs enable drugs to be developed now
 - We must be very clear about this in our public documents

4. Not (just) a regulatory problem

- It's easy to be critical and ask for more: We all do it
- The agency is just the first group to do this...
 - Academia & journal editors: *Oh, the trial is too small*
 - Payors: *I expected superiority data!*
 - Physicians: *I'll wait for the guidelines to change*
 - Patients: *Non-inferiority sounds so dodgy*
- This is a communication and education problem
 - Confusion and debate on the scientific principles^{1,2}
 - We need to clarify this in public
- Non-traditional agents face similar issues³

1. Rex JH et al. Progress in the fight against multidrug-resistant bacteria 2005-2016: Modern non-inferiority trial designs enable antibiotic development in advance of epidemic bacterial resistance. *Clinical Infectious Diseases*. 2017;65:141-6.
2. Powers JH et al. Studying new antibiotics for multidrug resistant infections: are today's patients paying for unproved future benefits? *BMJ*. 2018;360:k587.
3. Rex JH et al. Designing development programs for non-traditional antibacterial agents. *Nature Communications* (in press), 2019.

5. Suggestions (1 of 4)

Fundamentals: Be cognizant of labeling regulations

- 21 CFR 201.57(c)(15), Clinical Studies Section: For drug products other than biological products, any clinical study that is discussed in prescription drug labeling that relates to an indication for or use of the drug must be **adequate and well-controlled** as described in 314.126(b) and must not imply or suggest indications or uses or dosing regimens not stated in the "Indications and Usage" or "Dosage and Administration" section.
- Those are the regulations

5. Suggestions (2 of 4)

Use LPAD to its maximum; supplement as needed

- Convene working groups (FNIH?) to create credible ways to work with the available data
 - Engage with trade-offs: starting with BSI is so very risky
 - Starting from a standard indication is a much better bet!
- As part of this, think carefully about what defines “adequate and well-controlled clinical data” for antibiotics in different settings
 - **Adequate?** Remember that patients and physicians will accept different trade-offs in settings of unmet need
 - **Well-controlled?** No argument about the need for controlled data, but we should be flexible on **well**
 - 100 patients = \$10m and several years of work
 - External controls are legitimate controls and should be used

5. Suggestions (3 of 4)

Agency, societies, and journals: Spread the word(s)

- Superiority trials are not a reliable way forward – we do all we can to make them impossible to run!
 - I tire of hearing “A superiority trial can be much smaller.”
 - That’s true, but not helpful: It is not a path forward
 - This is not migraine: superiority with a modern anti-infective usually means people in the control arm died
- Non-inferiority is a not a synonym for “worthless”
 - Data we do have should be shared
- Guidelines must be continuously updated
 - Example: Use of colistin must come to a screeching halt

5. Suggestions (4 of 4)

Industry: Focus on novelty and unmet need

- There is a need for a different reimbursement mechanisms (Pull incentives) for new antibiotics
 - This is not a discussion for today: pull incentives are needed but are not within the purview of the FDA
 - Rather, this meeting is about tools available to this group. My comments address necessary (but not sufficient!) conditions for a healthy antibiotic ecosystem
- That said, novelty and unmet need will be the key to selecting products to receive incentives in any future Pull mechanism
 - QIDP is really not enough
 - Focus on products that can really move the needle!

6. Closing thoughts

- At heart, I'm a doc who moved into Industry in 2003 because of the problem of AMR
 - As a university-based Infectious Diseases physician, I had begun to see truly untreatable infections
- Since then, I've had the opportunity to walk all sides of the challenge of antibiotic R&D
 - Fund raising within large & small companies. Lyophilizer failures shutting down supply chains. Corporate decision-making. The pressure of time.
- Tradeoff-free solutions to AMR don't exist
 - If they did, we'd all be using them
 - Since they don't, we as a community need to find pragmatic solutions to real-world problems
 - We need to do this NOW and preferably by 1pm today!