

Developing new antibacterial products: Perspectives on giving new therapies the best chance

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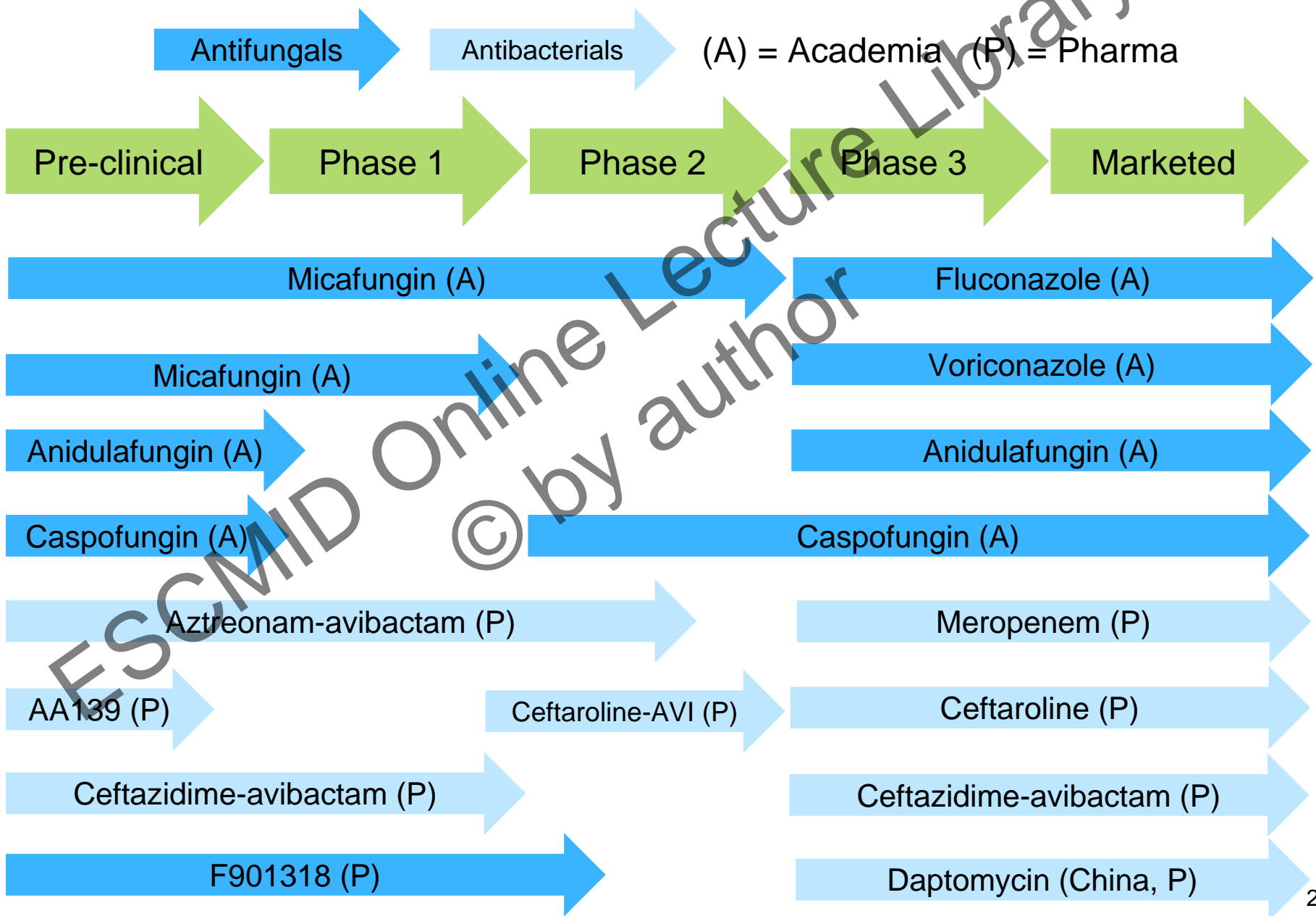
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Drug development history



To finish first,
first you must finish

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Agenda

To finish first, first you must finish

- Pathways to registration:
 - Five key ideas
- The future of the economics of antibiotics
 - What kind of product(s) will best succeed?
- Common mistakes
- Conclusions

Pathways to registration

- If you seek to develop a new therapy, there are several (sometimes overlapping) ideas to understand
 1. Nomenclature: UDR vs. MDR/XDR
 2. Superiority vs. non-inferiority
 3. Non-inferiority: Tier B/C and LPAD-like ideas
 4. Narrow-spectrum agents: Pathogen-focused labeling
 5. Taking UDR-focused trial networks
- Let us now consider these themes...

1. Nomenclature: UDR vs. MDR/XDR

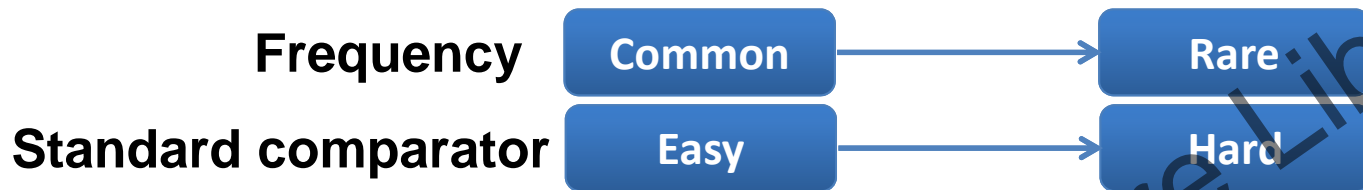
- Useful categories of bacteria:
 - WT: Wild-type. *May well now be pretty rare*
 - UDR: Usual Drug Resistance¹
 - MDR: Multi-drug resistance
 - XDR: Extensive multi-drug resistance

Or, perhaps RDR (rare DR)?
- This is a continuum with implications for trial design
 - UDR: Many easy choices. **Easy to choose a blinded comparator.**
 - MDR: Harder – may need 2nd-line drug.² **Single comparator is harder**
 - XDR: Needs a difficult or unusual drug.² **Comparator must be ad hoc.**
- Today's UDR can be tomorrow's MDR (and vice versa)
 - Consider MRSA: It's been UDR, then MDR³, it's now seen as UDR
- If an organism is S(usceptible) to the novel test agent...
 - Response is independent of being UDR, MDR, or XDR **to other drugs**

¹This may or may not be the same thing as wild-type. See McDonnell, Rex, et al, Efficient Delivery of Investigational Antibacterial Agents via Sustainable Clinical Trial Networks, Clin Infect Dis (in press), 2016. ²Or combination of drugs.

³When MRSA emerged after the introduction of penicillin, it was the nightmare MDR bug. Vancomycin made it UDR.

UDR vs. MDR/XDR



	UDR	MDR	XDR
NEW DRUG	S	S	S
Approved Drug #1	S	S	S?
Approved Drug #2	S	S	R
Approved Drug #3	S	S	R
Approved Drug #4	S	R	R
Approved Drug #5	S	R	R
Approved Drug #6	S	R	R
Approved Drug #7	R	R	R

Activity of NEW DRUG is independent of being UDR, MDR, or XDR to other drugs.



With adequate PK, efficacy vs. UDR predicts efficacy* in MDR or XDR.

**Efficacy against the infection, that is ... the antibiotic can't reverse the underlying disease that may have put the patient at risk for the infection.*

Why does this matter?

- It's ***much*** harder to do prospective, randomized, registration-quality studies in patients with infections due to MDR/XDR isolates than due to UDR isolates
- AZ data: At least twice as slow and twice as costly
 - Patients must present at a study site as referral is hard
 - Transferring a patient with an MDR/XDR infection is not popular
 - Sites work hard to make MDR and XDR rare!
 - No site wants to be a Center of MDR/XDR Excellence!
 - Chasing MDR/XDR is very frustrating: Lasagna's Law¹ in action
- Achaogen: Pivotal trial in CRE was not possible
- (R)are DR: And, we *want* MDR/XDR rates to be low!!
 - If it's easy to recruit MDR/XDR, something is very wrong

¹Louis Lasagna: "The incidence of patient availability sharply decreases when a clinical trial begins and returns to its original level as soon as the trial is completed." <http://www.pmean.com/11/lasagna.html>

2. Superiority vs. Non-inferiority

- Problem statement: New antibiotics are mainly developed using non-inferiority (NI) comparisons vs. existing agents in the setting of UDR pathogens. Why? Overlapping issues...
 - New antibiotic trials must (usually) be designed to avoid superiority
 - Must NOT enroll if resistance is known/likely to TEST or comparator.
 - Very unlikely to see superior efficacy over a fully dosed modern comparator when pathogen is susceptible to same
 - Very hard (rare) to be superior on toxicity (short-term dosing)
 - (R)DR: MDR/XDR are rare (we hope)
- Superiority is a high-stakes gamble for a novel agent
 - If your primary aim is superiority and the study fails, you cannot retreat to a claim of non-inferiority.
 - But if you see superiority in a NI study, you can claim that result

3. Simpler pathways: LPAD* & Tier B/C

- We've spent 5+ years discussing simplified pathways
 - Consensus that PK-PD-based dose selection should make it possible to register on (somewhat) smaller datasets
- But, actually doing this is hard
 - LPAD is/was an idea to fix some of the issues by (in the US) legislation to create a special pathway for antibiotics
 - Approval would be based on a combination of types of data plus safeguards to focus use in the limited populations where benefits exceed risks
- LPAD legislation seems (right now) low probability
 - What we have now is a practical implementation of the Tier B idea proposed 2012-13 along with a partial implementation of Tier C (see subsequent slides)

*LPAD = Limited Population Antibacterial Drug

Pathogen-focused development

This mental schema was developed 2012-13

Tier A

Traditional Development:

Two well-controlled, adequately powered Phase III studies per body site

Focused on body sites of infection

Tier D

The “Animal Rule:”¹

When studies in humans are unethical: Approval on human safety studies + preclinical (non-human) efficacy studies

Focused on infectious agent

Rex et al. Lancet Infect Dis 13: 269-75, 2013.

¹In the US, defined in 21 CFR 314.600–650. No specific equivalent exists in the EU regulatory framework, but the idea is discussed in Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. CPMP/EWP/558/95 rev 2. London: European Medicines Agency, 2011.

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Tier B & C:
Progressively more pathogen-focused development as a middle path

Tier D

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Tier B/C Development Programs¹

- **Tier B:** Two treatment studies (one large, one small)
 - *Drug has spectrum that covers an entire syndrome*
 - Standard P3 study of Drug B vs. standard comparator at standard body site
 - Focused on UDR pathogens: No MDR or XDR
 - Provides good view of safety & efficacy of Drug B
 - Open-label salvage study of Drug B for MDR/XDR pathogens
- **Tier C:** Combination of small studies
 - *Drug is narrow-spectrum, perhaps only one organism (e.g., Pseudomonas)*
 - Prospective, randomized, (open-label?): Drug C vs. BAT² across multiple body sites. N at most a few 100. **Limited expectation of statistical testing**
 - Open-label salvage study for MDR pathogens (no BAT exists)
 - Observational study of (inadvertent) ineffective therapy for the target pathogen (estimates placebo response)³

¹Detailed examples are available. ²BAT = **Best Available Therapy, standardized insofar as possible**. ³There is no easy way to provide a good control group: Ineffective therapy does not mean no therapy and also might quickly be replaced with active therapy. One might also use modern data (pharmacometric estimates of placebo response rates: AAC 56:1466, 2012), pharmacometric analyses with the new drug, or historical estimates of true placebo response rates.

The good news: Tier B works

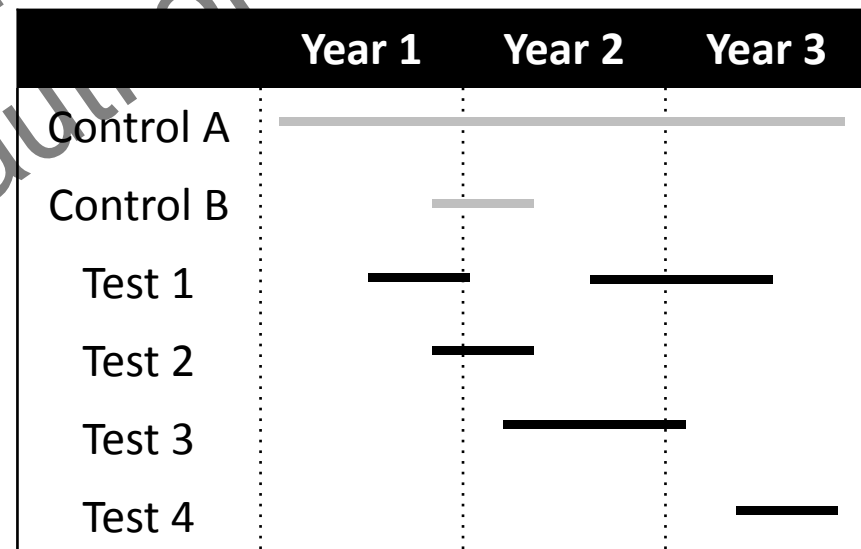
- Antibacterial guidances from FDA & EMA (both from 2013) describe Tier B as acceptable
- Candidate drug must convincingly address an unmet need
- Label likely to include language of this form:
 - “... use of this drug should be limited to patients with limited treatment options”

4. But, we're not there (yet) with Tier C

- EMA: Clearly defined as an idea in the guidance
 - An indication for “treatment of infections due to X” is possible and has been granted **in parallel** with standard indications
 - In theory possible as the **one & only** indication, but not yet seen
- FDA: This is a sticky point
 - Statutory requirement for “substantial evidence based on adequate and well-controlled investigations”
- In truth, we're all frustrated by this – we all want clear data
 - A registration without clear data would be a Pyrrhic victory
- Pragmatic translation: For a single-pathogen (Tier C) drug,
 - Non-Inferiority: Build largest dataset you can at plausible body site(s) & justify wide margins. Gain experience with XDR pathogens.
 - Superiority: Always acceptable (but see above)
- More work is underway on a path here

5. Now in development: A UDR-focused trial network

- UDR = Usual Drug Resistance
 - Non-inferiority study of standard infection (e.g., cIAI), vs. a standard comparator: Enables reliable drug registration
- Test agents can enter or leave at different times
- Control data can be shared
- Costs and time are reduced as much as 40%
- Studies of MDR/XDR should be done separately by the sponsor



McDonnell, A. M., J. H. Rex, et al. (2016). "Efficient Delivery of Investigational Antibacterial Agents via Sustainable Clinical Trial Networks." *Clinical Infectious Diseases* 63 (Suppl. 2): S57-S59.

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Current economic model is broken

- Current approach
 - Everyone is delighted to have a new drug
 - But, use is delayed and deferred in effort to preserve new antibiotic
- Stewardship perspective: Entirely rational
- Economic perspective: A financial loss
 - Many analyses show same thing: Not financially rational to do antibiotic R&D
- Problem: Current pay-per-use model reimburses for only a piece of the value

What's a fire extinguisher worth?

- Fire extinguisher: 2 roles
 - Put out fires
 - **Be on hand to put out** fires
 - Keeps everybody safe!
- Antibiotics: 2 uses
 - Treat infections
 - Know that you **could** treat!
 - Keeps everybody safe!



Antibiotics are the fire extinguishers of medicine!

Buzzword: Delinkage

- Must find economic models that separate reward from usage
- DRIVE-AB (ND4BB): Options actively being developed & piloted
- Ideas such as
 - Lump sum access fees
 - Insurance-like models

- Jan 2016 Davos Declaration
- 100 companies, 13 trade groups
- Ready to work in partnership with leading countries to deliver sustainable solutions to meet this global challenge.
- We seek proposals that (a) support reduction in the link between financial revenues for new antibiotics and the amount they get used while (b) mitigating the financial risk for both developers and health systems.
- <http://amr-review.org/industry-declaration>

Implication: Novelty above all

- Fire extinguishers come in different categories
 - You need one of each!
- Incremental extensions
 - Some of this is OK
 - But, it will only go so far
- Strong scientific value is best path to economic value
 - Novel mechanisms
 - Novel molecular basis of resistance

KNOW YOUR FIRE EXTINGUISHER

CHOOSING THE RIGHT EXTINGUISHER CAN PREVENT PROPERTY DAMAGE AND SAVE LIVES

Extinguisher Type →	Water	Foam	CO ₂	Dry Chemical
Type of Fire ↓				
A Paper, Wood & Plastic	✓	✓	X	✓
B Flammable & Combustible Liquids	X	✓	✓	✓
C Electrical Equipment	X	X	✓	✓

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(Lack of) Dose justification

- PK-PD! You can't do too much!
- One animal model + one isolate = inadequate
- You need clear data on the PD driver, clear data on a target PD index magnitude
- Such preclinical data allow you to conclusively prove you have a dose that gives the right exposure
 - And then prove to yourself **before Phase 3** that you can get that exposure **in the target population**

(Mis)Reading Regulatory Feedback

- For Phase 1 and Phase 2 studies...
 - Agencies only say “NO!” if you are likely to injure someone
 - Designs that use exploratory endpoints for dose-finding are acceptable BUT acceptance of same does not endorse those endpoints for pivotal trials
- Following regulatory advice is an under-used strategy
 - Go talk to the Agencies. They really will make time to help
 - Listen closely!
 - It is so tempting to hear what you want to hear
 - Pay close attention when you hear the words “... sponsor risk ...”

(Unrealistic) Expectations #1 & #2

- Expecting superiority over a fully dosed comparator
 - This really should be rare
 - Must avoid designs that deliberately enroll subjects whose infection is likely due a comparator-resistant isolate
 - Unless, of course, there are actually no other options because we've failed as a community to stay ahead of this problem...
- Chasing the really hard indications first
 - Endocarditis? Bacteremia? Osteomyelitis?
 - There may be a path here, but you must first understand general safety and pharmacology
 - Do one of the basic indications to get started!

(Unrealistic) Expectation #3

- “We want to be labeled for treatment of *CRE*”
 - This does not happen!
- Instead, your drug will be indicated for
 - Treatment of Infection X
 - caused by strains of Y
 - that are susceptible to *your drug*
- Especially across compound classes, resistance to one drug does not have a 1:1 linkage to susceptibility to another drug

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Key points

- Seek novelty!
- Get it registered! *To finish first...*
 - Justify the dose: LOTS of preclinical PK-PD data
 - Double-check the PK in the target population!
 - If at all possible, do a standard NI study for a standard indication vs. a strong comparator
 - Do the standard NI study in the UDR setting
 - Seek MDR on the side – don't make this pivotal
- Keep it simple!
 - Required # of miracles should be less than one

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