

Developing antibacterial drugs for unmet need and so that we stay ahead of the epidemic: Points to consider for developers

John H. Rex, MD

SVP & Chief Strategy Officer, AstraZeneca Pharmaceuticals

Non-Executive Director & Consultant, F2G Ltd.

Non-Executive Director & Consultant, Adenium Biotech ApS

Operating Partner and Consultant, Advent Life Sciences

Expert-in-Residence, Wellcome Trust

Scientific Advisory Board and/or Consultant: Macrolide Pharmaceuticals, Spero

Therapeutics, Polyphor Ltd., and Allecra Therapeutics GMBH

john.rex@astrazeneca.com; john.h.rex@gmail.com

Slides happily shared – just drop me a note

Disclosures

- This presentation does not contain any product-specific information so I have no specific disclosures to make
- But, and as noted on the title slide, I am employed in the pharmaceutical industry. I also have equity in pharmaceutical companies and provide consultative support and advice to various pharmaceutical companies
- So, please do be clear on my bias:
 - As a board-certified internist and ID specialist, I am terrified by the problem of antimicrobial resistance.
 - I firmly believe that we need new therapeutic options, I believe that a combination of public and private investment is required for these to be created, and I am working hard to ensure that this happens

Agenda

- 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. UDR-focused trial networks (*see talk by Joe Larsen*)
- 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 Resistance¹
 - MDR: Multi-drug resistance
 - XDR: Extensive multi-drug resistance
- 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 vs. 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.

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: It's twice as slow and costs twice as much
 - Patients must present at a study site as referral is hard
 - Infections move rapidly – therapy must start *now*
 - 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
- And, we *want* MDR/XDR rates to stay 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

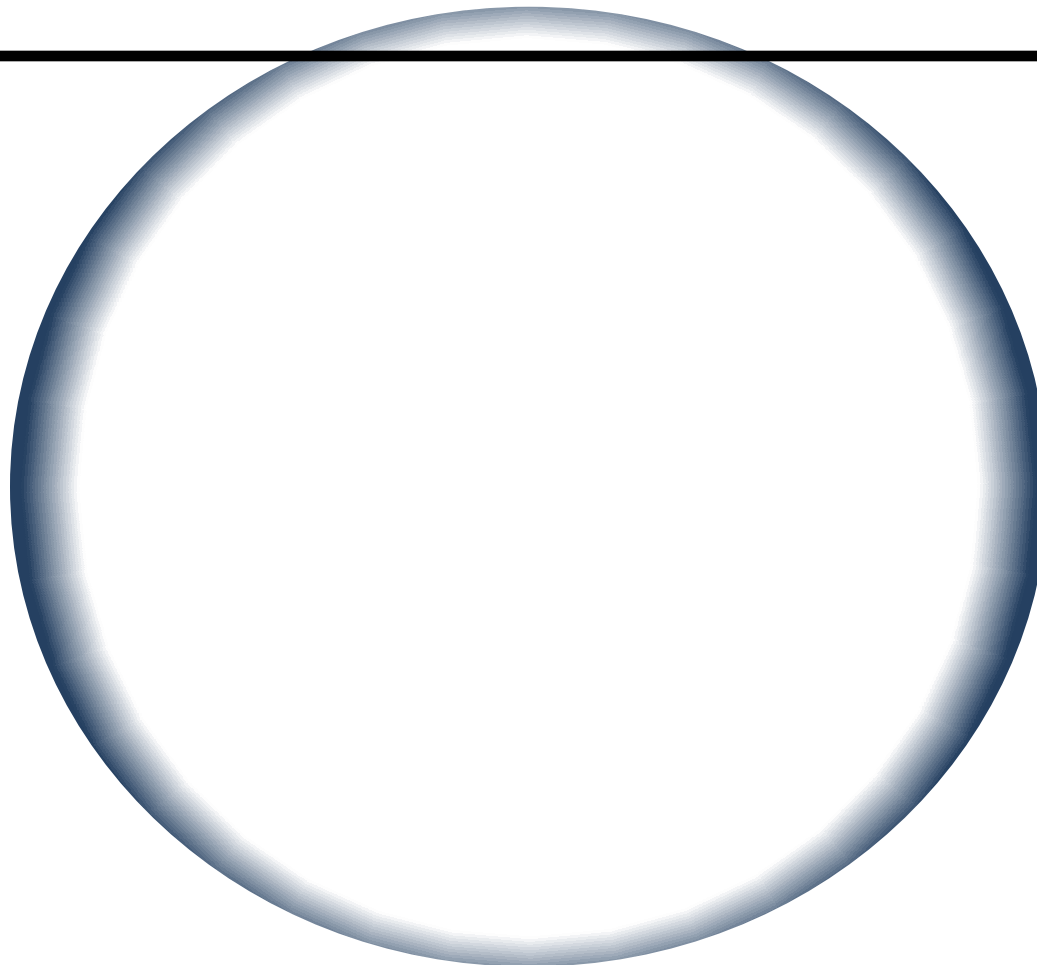
- Problem statement: New antibiotics are mainly developed using non-inferiority (NI) comparisons vs. existing agents in the setting of UDR pathogens. Why? Overlapping issues...
 - New antibiotic trials must (usually) be designed to avoid superiority
 - Must NOT enroll if resistance is known/likely to 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)
 - MDR/XDR are rare (we hope)
 - This setting requires customized comparators – lots of heterogeneity
 - We will be very unhappy if these patients are easy to enroll!
- 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)

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**

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.

Rex JH - 2016-07-19 - Unmet Need Workshop - Implications for Developers

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

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

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 study of Drug C vs. BAT² across multiple body sites. N at most a few 100. **Limited ability to do 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:
 - “... in patients with limited treatment options”

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

The problem of pathogen-focused labeling

- About that limited ability to do statistical testing...
- FDA: This is a sticky point
 - Statutory requirement for “substantial evidence based on adequate and well-controlled investigations”
- EMA: Willing to consider but not clear if it can be standalone
 - An indication for “treatment of infections due to X” is possible and has been granted in parallel with standard indications
 - Not clear if a drug could get this as its one & only indication
- Translation: For a single-pathogen (Tier C) drug,
 - Non-Inferiority: Build largest dataset you can at plausible body site(s) & justify wide margins. Possibly forgo (initial) US registration.
 - Superiority: Always acceptable (but see above)
- **Further discussion on this tomorrow!**

Disambiguation: Pathogen-focused

- The phrases “Tier C” & “pathogen-focused pathways” can confuse and might be taken to be any of:
 1. Truly narrow: *Acinetobacter* only
 2. Broad-spectrum, including a rare pathogen (*Acinetobacter*)
 3. Any spectrum, developed to focus on MDR/XDR variants in that spectrum (e.g, active vs. Enterobacteriaceae) and seek to develop for carbapenem-resistant strains (CRE)
- “Pathogen-focused pathways” really only means #1
 - For #1, see discussion tomorrow
 - For #2, do Tier B plus a small study for the rare pathogen
 - For #3, see #2. Chasing MDR/XDR is high-risk. Develop for UDR while collecting a few MDR/XDR on the side

Agenda

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

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

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

KNOW YOUR FIRE EXTINGUISHER				
CHOOSING THE RIGHT EXTINGUISHER CAN PREVENT PROPERTY DAMAGE AND SAVE LIVES				
Extinguisher Type →				
Type of Fire ↓	Water	Foam	CO ₂	Dry Chemical
A Paper, Wood & Plastic	✓	✓	X	✓
B Flammable & Combustible Liquids	X	✓	✓	✓
C Electrical Equipment	X	X	✓	✓

Agenda

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

(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, and clear proof of how you'll produce the required exposure in man
- **Use preclinical data to conclusively prove you have a dose that gives the right exposure**
 - And then prove 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

Agenda

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

Key points

- Seek novelty!
- Get it registered!
 - Justify the dose: LOTS of preclinical PK-PD data
 - 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