Antifungal Drug R&D Comes of Age

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I will share these slides via my newsletter/blog

Please note these details!
Agenda

• Introduction

• What does it take to invent & deliver a new drug?

• Evolving regulatory paradigms

• Evolving payor paradigms

• Summary

• Resources
Thank you!

• I am honored to have been asked to give this talk
• I have been a student of mycology for 33 years!
  • Many beloved mentors: Jack Bennett, Elias Anaissie, Bill Dismukes, Jack Edwards, June Kwon-Chung, Jacky Sobel, David Stevens, Gail Triggs, Doug Webb, Temple Williams
• I have followed a somewhat winding career path
  • 1987-2002: Academic medicine (99% antifungal)
  • 2003-present: Development within regulated Industry
    • Antibacterial then antifungal
  • As this is part of what makes me qualified to discuss this subject, a bit more detail is helpful...
Qualifications: A continuous focus on drug development!

Drug Development History, (A)cademia & (P)harma: Antifungals

- Pre-clinical: Micafungin (A)
- Phase 1: Micafungin (A)
- Phase 2: Anidulafungin (A), Caspofungin (A)
- Phase 3: Fluconazole (A), Voriconazole (A), Anidulafungin (A), Caspofungin (A)
- Marketed: Olorofim (F901318, P)
Qualifications: A continuous focus on drug development!

Drug Development History, (A)cademia & (P)harma:

Pre-clinical
- Micafungin (A)

Phase 1
- Micafungin (A)
- Anidulafungin (A)
- Caspofungin (A)
- Olorofim (F901318, P)
- AA139 (P)
- Ceftazidime-avibactam (P)

Phase 2
- Ceftaroline-AVI (P)
- Ceftazidime-avibactam (P)
- Aztreonam-avibactam (P)

Phase 3
- Fluconazole (A)
- Voriconazole (A)
- Anidulafungin (A)
- Caspofungin (A)
- Olorofim (F901318, P)
- AA139 (P)
- Ceftaroline-AVI (P)
- Ceftazidime-avibactam (P)
- Aztreonam-avibactam (P)
- Meropenem (P)
- Ceftazidime-avibactam (P)
- Daptomycin (China, P)

Marketed
- Fluconazole (A)
- Voriconazole (A)
- Anidulafungin (A)
- Caspofungin (A)
- Meropenem (P)
- Ceftazidime-avibactam (P)
- Daptomycin (China, P)
With that in mind...

• This talk will be tour of the ideas I find most relevant to developing novel therapeutics

• The focus will mostly be from mid-Discovery to Registration: The very early stages of target discovery will be covered only incidentally

• The topics are
  • Biased by my personal experience and lessons learned
  • Often drawn from the antibacterial world – there are more similarities than differences between antifungals & antibacterials

• For avoidance of doubt, note that I work with a company that has novel antifungal in Phase 2 (F901318, olorofim)
  • Details on it were shared at the pipeline session yesterday
  • I will draw on a lesson from its development program, but only with the intent of showing how this idea can be generalized
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• What does it take to invent & deliver a new drug?
  • A focus on Unmet Need
    • Multiple disciplines: Biology, MedChem, Tox, CMC, PK-PD

• Evolving regulatory paradigms

• Evolving payor paradigms

• Summary

• Resources
Unmet Need

• Every product needs a clear value
  • This is true of everything, not just antimicrobials
• But, making good on this can be subtle
  • How do you prove its advantages in the clinic?
  • Harder than you’d think ... and we’ll come to that
• The best advantages are durable & visible
  • Novel mechanism: Not required, but a great start
  • Oral: So few things do this!
  • Spectrum and low frequency of (mutation to) resistance
  • Drug-like properties: Plays well with other drugs and with key body systems
Unmet Need in Mycology: Abundant!

• Novel mechanisms: *We have so few on the market*
  • Amphotericins, azoles, candins, terbinafine, 5-FC
  • Exciting: Several novel mechanisms are in the clinic now

• Oral: *As yet, only the azoles, terbinafine, and 5-FC*

• Spectrum: *Resistance is seemingly everywhere!*
  • *Candida*, esp. *C. auris*: Azoles & candins
  • *Aspergillus*: Azoles & amphotericins (the cryptic species have turned out to be very interesting)

• And then there are the places where current agents struggle in one way or another
  • E.g., we still can’t always cure coccidioidomycosis!

• I could go on, but a picture tells a thousand words...
Fisher, 2018

• Shown at right is the rate of antifungal resistance over time for plant and human products.
• Darker = more resistance

• Resistance advances!

1. Fisher et al., Science 360:739–742, 2018
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Many Disciplines in Drug R&D

• Biology, MedChem, Tox, CMC, ADME, PK-PD, Regulatory, Clinical Operations ... a long list
  • It takes a substantial team to create a new drug!

• Being selective, I’m going to look at Discovery Biology (briefly) and then at Tox, CMC, PK-PD, and Regulatory in more detail
Biology: The role of Academia

Drakeman 2014¹: Origins of priority review NMEs, 1998-2012

<table>
<thead>
<tr>
<th>Sector</th>
<th>NBEs</th>
<th>NCEs</th>
<th>Fast track</th>
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<tr>
<td>Biotech</td>
<td>24 (92%)</td>
<td>65 (48%)</td>
<td>49 (70%)</td>
</tr>
<tr>
<td>Pharma</td>
<td>2 (8%)</td>
<td>71 (52%)</td>
<td>21 (30%)</td>
</tr>
<tr>
<td>Totals</td>
<td>26</td>
<td>136</td>
<td>70</td>
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In short, small companies (often launched from academic insights) really power the pharmaceutical industry.

But, the move from Biology to Pharmaceuticals is a big leap!

NME = New Molecular Entity; NBE = New Biological Entity; NCE = New Chemical Entity
Toxicology: Key idea #1

• You need to study supratherapeutic exposures of new agent and its metabolites in 2 animal species

• Serious fungal infections often require prolonged therapy: your studies must run for long periods
  • 0-90 days of exposure: day-for-day coverage in man
  • 180 days: (generally) enough for indefinite exposure

• Metabolites can be tricky. You can try to predict human metabolites but you don’t know until Ph1
  • Sometimes you have to do additional studies
  • Forewarned is forearmed. Be sure your investors know!
Toxicology: Key idea #2

• Don’t panic! *Everything* has toxicity

• Your job is to triangulate three things
  • Exposure that you think required (PK-PD! See next)
  • The nature of the toxicity (monitorable? reversible?)
  • The Unmet Need you are addressing

• This is your first look at benefit-risk (B-R)!
  • B-R needs be B >>>>>>> R for vaginal candidiasis
  • B-R can be B ≥ R for (say) curative therapy of CNS cocci

• Advice: Have a PK-PD expert & a medic on your toxicology team
  • CARB-X + GARDP workshops this year on toxicology
  • Watch my newsletter for access to same
CMC: Chemistry, Manufacturing, & Controls

• How does a molecule become a physical medicine (tablet, injectable, etc.) to give to a human?

• I knew *nothing* about this before joining Industry

• You must plan for
  • Early materials for preclinical studies
  • GMP (Good Manufacturing Practice) materials for human studies
  • Sufficient quantity at scale & on stability for Ph3 and registration

• This is a science unto itself
  • In parallel with the IND/MAA (you’ve heard of those), you also file an IMPD (Investigational Medicinal Product Dossier) of equal length

• Advice: **Start early!** Have a CMC guru on your team
  • Great CARB-Xed + GARDP workshop from 2017 on this:
  • Search for “amr.solutions 2017 bootcamp”
PK-PD: Overview

• PK-PD (pharmacokinetics-pharmacodynamics) is now a key element of antibacterial programs
  • Strong PK-PD is the reason a smaller trial program is acceptable proof of drug utility

• Antifungal PK-PD has lagged a bit
  • Fewer agents; Effect measures (esp. moulds) harder to validate

• But, significant progress has been made\(^1\)
  • MIC methods standardized & at least as good as antibiotics
  • *Candida*: PD targets now known for azoles & candins
  • *Aspergillus*: Galactomannan and quantitative PCR as endpoints
  • Other tools: Beta-D-glucan, for example

• For a novel product, the hard part is defining a PD target that has meaning

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PK-PD: Defining a PD target

• Known class (e.g., newazole, new carbapenem)
  • You can lean on precedent
  • Compound class predicts PD parameter & approximate target value

• Novel class: This gets interesting!
  • It is typically true in animal model that you can push drug exposures to levels producing 100% effects on your endpoint of choice
  • Those exposure may not be needed in man
  • Those exposure may even be unattainable in man

• So, how much PK-PD is enough?
  • W. Hope (ECCMID 2018): It’s enough when “I would be prepared to be the first person to administer a new compound to a patient”
  • There’s a fair bit written on this, but one idea that has helped me a lot has been the emerging idea of cross-class benchmarking...
PK-PD of new anti-mould agent

Activity includes Aspergillus spp.

- **What is the PD parameter?**
  - How do we analyze?
- **Answer:**
  - Dose-fractionation in neutropenic mouse model of pulmonary aspergillosis
  - Galactomannan response (y-axis) vs. time (x-axis)

- **Results:** Control in Panel A. Same total dose in Panels B-D
  - **PD parameter:** Must be time > threshold
  - **Summary effect metric:** Area-Under-the-GM-Curve

OK, so what exposure is needed?¹

Novel agent

• Above, see AUC-GM-Curve vs. Cmin:MIC for 8 isolates
  • 4 (each) azole-S and –R strains
• How much is enough?
  • Animal model ≠ human illness
  • Arbitrary intensity & response

OK, so what exposure is needed?\textsuperscript{1}

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Posaconazole as a benchmark

- Posa’s AUC vs. AUC-GM
- Same animal strain
- Same lab
- Same infection model

OK, so what exposure is needed?\textsuperscript{1}

**Novel agent**
- Above, see AUC-GM-Curve vs. Cmin:MIC for 8 isolates
  - 4 (each) azole-S and –R strains
- How much is enough?
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**Posaconazole as a benchmark**
- Posa’s AUC vs. AUC-GM
- **Human data** show strong response at AUC\textsubscript{24} of 30-47 mg·h/L (Walsh CID 2007, 44;2-12)

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OK, so what exposure is needed?\textsuperscript{1}

Novel agent

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- How much is enough?
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Posaconzole as a benchmark

- Posa’s AUC vs. AUC-GM
- Human data show strong response at AUC\textsubscript{24} of 30-47 mg\(\cdot\)h/L (Walsh CID 2007, 44;2-12)
- At 95% upper bound on human exposures, 27% drop in GM AUC

OK, so what exposure is needed?\textsuperscript{1}

Now, work backwards for NEW

- 27% drop is at $C_{\text{min}}:\text{MIC} \sim 9$
- This, in turn, yields an efficacy target of $C_{\text{min}}$ of 0.1-0.3 mg/L
- Exposures \textit{in} this range should equal the effect of the maximal posaconazole exposure

Similar results with...

- Rabbit model
- Survival as an endpoint
- Histopathology as an endpoint
- For more detail: Hope 2017\textsuperscript{1}

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  • Preview: A fungal case-study
  • Lessons from antibacterial development

• Evolving payor paradigms

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Applications in Mycology

• Isavuconazole’s registration program
  • 1x NI RCT*: ISA vs. voriconazole in (azole-susceptible) Invasive Aspergillosis (IA)
  • 1x salvage: Open-label study for mucormycosis
    • Control groups drawn from literature and Fungiscope

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• Why this pair of studies?
• What is the relevance of a study in azole-susceptible infections?
• Why not just study difficult infections?

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Trial Design 101: Two study designs – everything reduces to one of these

• Superiority studies
  • X vs. Y, with an aim to show X beats Y
  • TEST vs. placebo or TEST vs. Standard of Care
  • Preferred design – result is unambiguous
  • Everybody likes the idea of Better

• Non-inferiority (NI) studies
  • X vs. Y, with an aim to show X ≈ Y
  • Messy, harder to do accurately, confusing

• But, we (almost) always use NI for new antibiotics
  • Why?
The paradox of antibiotics

• We want new drugs for bad bugs
  • The superiority of NEW is easily shown in the lab on the basis of MIC testing or in animal models of infection

• But, asking for clinical data leads to a problem
  • Trials must (usually) be designed to avoid superiority
  • Instead, we must use non-inferiority designs showing similar activity relative to another active agent

• Example: Limb-threatening infection due to MRSA*
  • It is not ethical to randomize to methicillin vs. NEW
  • Must instead do something like vancomycin vs. NEW
  • Must NOT enroll if resistant to NewDrug or comparator

*MRSA = Methicillin-resistant Staphylococcus aureus
This idea is very, very hard

• Non-life-threatening illness (e.g., migraine)
  • Delayed effective therapy is not dangerous

• Cancer: Placebo is (usually) not possible, but there is always room to improve on 5- or 10-year survival

• Infections: We routinely produce Cure of potentially fatal illness
  • And, it’s hard to improve on Cured

• But, the idea of non-inferiority is confusing
  • “We want a better drug.”
  • I get it, but insisting on clinical superiority before approving new agents means progress only when/if the pipeline (again) becomes inadequate

• Next 2 slides: Let’s discuss in two other ways
In Infection, superiority means something bad has happened: Plazomicin and CRE

- In 2012-13, colistin was the only alternative for CRE. A study of plazomicin vs. colistin-based SOC for CRE was plausible.
- Plazomicin wins, but efforts to control CRE made it very hard to find cases & enroll (note small N). Cost was $1m/case!
- And, 40% mortality is not good!
- Future studies will need to use plazomicin (or one of the other new agents with comparable data) as the comparator.


1. CRE = Carbapenem-resistant Enterobacteriaceae
2. SOC = Standard of Care
But, superiority trials are used in other areas! Tell me again: *Why not in Infection?*

<table>
<thead>
<tr>
<th>1. Durable cure is routine</th>
<th>Migraine</th>
<th>Cancer</th>
<th>Infection</th>
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<td>No</td>
<td>Yes</td>
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<table>
<thead>
<tr>
<th>2. Placebo is routinely acceptable</th>
<th>Migraine</th>
<th>Cancer</th>
<th>Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<table>
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<tr>
<th>3. Transmissible resistance arises → new agents always needed</th>
<th>Migraine</th>
<th>Cancer</th>
<th>Infection</th>
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</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>Yes</td>
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</table>

<table>
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<tr>
<th>4. New agents are really for use...</th>
<th>Migraine</th>
<th>Cancer</th>
<th>Infection</th>
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</thead>
<tbody>
<tr>
<td>Today</td>
<td>Today</td>
<td></td>
<td>Tomorrow¹</td>
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</table>

**Points 1 & 2:** Superiority is routinely used in some areas not but others
- *Migraine (non-life-threatening example):* Placebo with rescue is possible
- *Cancer:* Durable cure is not routine and continual improvement (e.g., improve 5- or 10-year survival) is hence possible. Also, resistance is not transmissible.
- *Human Infection:* Placebo not usually acceptable & it’s hard to improve on Cured!

**Points 3 & 4:** We need to develop new anti-infectives despite this limitation
- There are negative Public Health issues if superiority is (or becomes) possible!

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1. This points to part of the reason why new antibiotics suffer from several forms of market failure. For more on this, see the DRIVE-AB report, various blogs on John’s website, and any of Kevin’s various publication (the 11 Apr 2018 op-ed in *STAT News* is a very good place to start: [https://www.statnews.com/2018/04/11/innovation-new-antibiotics-fight-superbugs/](https://www.statnews.com/2018/04/11/innovation-new-antibiotics-fight-superbugs/)).

Solution: The (emerging) 2-study path for new traditional antibiotics

- 1x NI RCT* vs. a good comparator
  - UDR (Usual Drug Resistance) setting: both agents are predicted to be active
  - Done in one of the major indications (cUTI, cIAI, etc.)
- 1x salvage study for highly Resistant pathogens
  - Randomized vs. Best-Alternative Therapy (BAT) if possible, Open-label if N too small for this
- Example: Plazomicin initial registration program
  - NI RCT: 1x complicated UTI NI RCT vs. meropenem
  - Salvage: 1x study in CRE vs. colistin (prior slide)

About narrow-spectrum agents...

• This is the concept of “Tier C” pathways\(^1\)
  • Rare pathogens, (only) MDR pathogens, rare diseases
  • Small trial programs, just barely (or not) powered

• Can this be done? Yes, but it’s not an easy out
  • Do not think of this as simpler, faster, or cheaper
  • It’s not (just) a regulatory hurdle – the strength of evidence will become frustrating

• See recent IDSA whitepaper and FDA workshops
  • My blog notes: 13 Apr 2017 + 5 May 2017 workshops

Agents that Augment

• Example: Virulence inhibitor or such
  • Not sufficient alone: Must also give an active agent (e.g., toxin inhibitor + active 2nd agent)

• Distinctive hurdles
  • **Base therapy needs to work**
    • Might protect a base therapy from emergence of resistance but doesn’t solve existing resistance problems
  • **Dose: Lack of an MIC → harder to apply PK-PD**
    • If the PK-PD rationale has gaps, it may become harder to validate dose/exposure logic
  • **Superiority problem: Must show NEW + OLD > OLD**
  • **May need a novel endpoint to show value**
Superiority & Endpoints

- Ultimately, must study NEW + SOC vs. SOC
  - We will want to see that NEW + SOC is superior to SOC
  - And this superiority must be grounded in how the patient feels, functions, or survives

- Are there settings where this might be possible?
  - Endocarditis is a good candidate: more rapid bloodstream clearance might have a measurable clinical effect
  - Chronic infections (many fungal infections!) may also offer scope for showing improvement

- **Endpoints**: Would different endpoints help?
  - How would you show a clinical benefit for reduced rate of onset of resistance? Can you show this at a community level?
  - A challenging question! Whatever is proposed must be compelling.

- Finally, know that this is not a regulatory problem per se
  - The agencies are simply the first to point out the issue
  - Why should I use this? Why should I pay for this?
Applications in Mycology

• Isavuconazole’s registration program
  • 1x NI RCT*: ISA vs. voriconazole in (azole-susceptible) Invasive Aspergillosis (IA)
  • 1x salvage: Open-label study for mucormycosis
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Applications in Mycology

• Isavuconazole’s registration program
  • 1x NI RCT: ISA vs. voriconazole in (azole-susceptible) Invasive Aspergillosis (IA): UDR* setting. N = 123 vs. 108
  • 1x salvage: Open-label for mucor: N = 37
    • Control groups drawn from literature and Fungiscope
  • For both, similar efficacy to control

• Why this pair of studies?
• What is the relevance of a study in azole-susceptible infections?
• Why not just study difficult infections?

*UDR = Usual Drug Resistance
Applications in Mycology

• Isavuconazole’s registration program used this idea
  • 1x NI RCT*: ISA vs. voriconazole in (azole-susceptible) Invasive Aspergillosis (IA): UDR setting. N = 123 vs. 108
  • 1x salvage: Open-label for mucor: N = 37
    • Control groups drawn from literature and Fungiscope
  • For both, similar efficacy to control

• Future agents will likewise apply these tools
  • ISA: Advantages are real but hard to show clinically
  • There may a little more scope for showing superiority with antifungals, but it is generally a tough road
  • Requiring clinical data on superiority for every future drug creates a Catch-22 that must be avoided

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  • Have you used a fire extinguisher today?
  • Unmet Need revisited

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Current economic model is broken

• Current approach to antibiotics
  • Everyone is delighted to have a new antibiotic
  • 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
  • It is not financially rational to do antibiotic R&D

• Problem: Current pay-per-use model reimburses for only a piece of the value
Pop Quiz #1: Have you used a fire extinguisher today?
Pop Quiz #1: Have you used a fire extinguisher today?

Actually, we can get more concrete. Are you using a fire extinguisher right now?
Antibiotic benefits go beyond simple use

*But, we don’t (yet) have an agreed way to capture that value*

- **Enabling value:** Many surgical and medical procedures rely on prophylaxis with effective antibiotics.
- **Option or insurance value:** We may want to have an antibiotic in reserve before we really need it, so it’s ready if resistance arises or worsens.
- **Diversity value:** Having multiple antibiotics may reduce selection pressure and delay resistance.

**Antibiotics are the fire extinguishers of medicine!**
The Fix: New Incentive Models

• Three major reports\(^1\)
  • DRIVE-AB, UK AMR Review, Duke-Margolis paper
  • Links below or, search “john rex amr blog davos”

• Recommendation: Two types of incentives
  • Push: More grants and coordination of grants
    • We’re doing this: CARB-X, Novo’s REPAIR, NIAID, etc.
  • Pull: Market entry rewards & Long-term continuity

• The two *Pull* ideas require a bit of explanation

Pull #1: Market Entry Reward (MER)

• How do we separate usage from payment?

• Essence of the solution
  • A defined sum of money (a MER) is given on registration of an interesting new antibiotic
  • The MER is independent of volume of use

• The company still sells the drug
  • But, the company does not actively market
  • There may be other stewardship / access requirements
  • Fundamentally, the MER is intended to provide (most of) the financial reward

• A picture is helpful…
MER, illustrated. This is one pattern

Partially de-linked MER


2018-07-03 - JH Rex - ISHAM - Antifungal R&D comes of age
Pull #2: Long-term continuity model

The problem of off-patent & forgotten antibiotics
Pull #2: Long-term continuity model

The problem of off-patent & forgotten antibiotics

“In conclusion, despite the ongoing bacterial resistance crisis, the situation regarding the availability of ‘forgotten antibiotics’ has worsened since 2011.”
Why is this? Pop quiz #2

• What does it cost per year to maintain the plant that makes a sterile injectable so that you can make at least 1 vial per year?

• Please consider
  • Cost for the building
  • Cost for the staff
  • Cost for record-keeping
  • Etc.
Long-Term Continuity Model

• **Idea:** Use a long-term procurement process for antibiotics with fragile supply chains
  - Contract for 10-year supply of a drug
  - Good test cases would be “access” antibiotics on WHO’s Essential Medicine List (e.g., benzylpenicillin)

• **Beneficial side effect:** Testing a long-term supply continuity model can also test the aspects of implementation of a MER
Putting it together

• There are still many puzzles to be solved and we don’t (yet) have a viable MER model
  • What is the value of a new antibiotic?¹
  • Do all antibiotics have the same value?²
  • Who will pay? How will payment be delivered?

• I am hopeful (there are serious discussions in US and EU), but I am also realistic
  • I assume the future market will be a mixture of the current model (pay per fire) and a MER model

• What does this mean for you?

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Implication: Novelty above all

- Fire extinguishers come in different categories
  - You only need one of each!
- Incremental extensions
  - Some of this is OK
  - But, it will only go so far
- Easily articulated scientific value is the best path to economic value
  - Novel mechanisms
  - Novel molecular basis of resistance
  - Addressing strong Unmet Need
- And, this is true both in the current market model and any MER-based future model. Not all products will earn a MER!
Implications for Medical Mycology

• The focus in the prior work (DRIVE-AB, etc.) has been 99% on antibacterial compounds
  • The only fungus-focused elements are in the US
  • The GAIN Act\(^1\), QIDP\(^2\), and LPAD\(^2\) all recognize the Unmet Need for fungi
  • Current discussions in the US on other incentives also include (by extension) the fungi

• We need to keep building awareness of the fungi
  • Developed countries in Europe and Asia (and societies within them!) need to develop incentives
  • Involvement with lobbying groups is way to contribute

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1. GAIN: Generating Antibiotic Incentives Now, the 2012 legislation in the US that created the QIDP designation
2. QIDP: Qualified Infectious Diseases Product, a designation that gives a product additional exclusivity as well Fast Track and Priority Review status
3. LPAD: Limited Population Pathway for Antibacterial and Antifungal Drugs, the Act in which Congress emphasized the need to products that (a) treat a serious/life-threatening bacterial or fungal infection, (b) target a clinically relevant and limited population, and (c) address an unmet need.
Agenda

• Introduction
• What does it take to invent & deliver a new drug?
• Evolving regulatory paradigms
• Evolving payor paradigms
• Summary
• Resources
Summary perspective & advice

• Start early and ensure expertise in key areas
  • CMC, PK-PD, Tox, and regulatory

• Study the antibacterial literature
  • Attend (or at least listen to) as many FDA Advisory Committees as possible
  • The isavuconazole AdComm is a good place to start
  • Attend the major meetings, especially the ASM-ESCMID development meeting series (#3 is in Lisbon this year)

• Focus on strong approaches to Unmet Need
  • Don’t waste your time on minor improvements

• My newsletter is a good way to hear about events
  • [http://amr.solutions](http://amr.solutions)
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Read, Listen, & Learn

• FDA guidances
  • The full collection: [ucm064980.htm](http://ucm064980.htm), with a focus on this group: cIAI: [ucm321390.pdf](http://ucm321390.pdf); cUTI: [ucm070981.pdf](http://ucm070981.pdf); Nosocomial pneumonia: [UCM234907.pdf](http://UCM234907.pdf); Skin infection: [UCM071185.pdf](http://UCM071185.pdf);
  • LPAD: [UCM610498.pdf](http://UCM610498.pdf)

• FDA Advisory Committees: Attend or listen by webcast to *every AdComm*. These are free master classes. I can’t emphasize this one strongly enough.

• EMA guidances
  • Core antibacterial guidance: [WC500003417.pdf](http://WC500003417.pdf)
  • “The addendum”: [WC500153953.pdf](http://WC500153953.pdf)
  • PK-PD: [WC500210982.pdf](http://WC500210982.pdf)
  • Pediatric antibacterials: [WC500247102.pdf](http://WC500247102.pdf)

• Papers

Thanks for listening!

Antifungal Drug R&D Comes of Age

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I will share these slides via my newsletter/blog