New agents for aspergillosis: Development pathways and economic pull

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Disclosures

- AstraZeneca Pharmaceuticals
  - Senior VP and Head of Infection, Global Medicines Development
  - Shareholder
  - No antifungal agents under development
- F2G, Ltd
  - Non-Executive Director, shareholder, and consultant
  - Preclinical antifungal pipeline
- Advent Life Sciences (investor in F2G)
  - Consultant

Four themes in 25 minutes

1. Is there a reason for new antifungal agents?
   - Yes. Gaps exist in resistance, spectrum, & safety
2. Does the current pipeline cover these needs?
   - In part, but only in part
3. How will future antifungals be developed?
   - Lessons from the world of antibacterial agents
4. Economics: Will anybody do this work?
   - I think so: the economics are changing

Theme One

Is there a reason for new antifungal agents?

"There is an increasing need for antifungals due to the growth of susceptible populations, limitations of the activity spectrum or tolerability of current antifungals, and the development of antifungal resistance"

Ostrosky-Zeichner et al. Nature Rev Drug Disc 9: 719-27, 2010.

Susceptible populations

- Multiple recent population-based estimates
  - Brazil: Beathgen et al., P1042, ECCMID 2013
  - India (aspergillosis): Chakrabarti et al., P1045, ECCMID 2013
  - India (mucormycosis): Chakrabarti et al., P1044, ECCMID 2013
  - China: Zhu et al. P1041, ECCMID 2013
  - US: Wilson et al. ValueHealth 5:26-34, 2002
  - Global (cryptococcoccal meningitis): Park et al. AIDS 23:525-530, 2009
  - Global (ABPA): Denning et al. Med Mycol 51:361-70, 2013
  - Global: Anonymous, 2011 estimates by Fungal Research Trust (http://www.fungalinfectiontrust.org/fungaldis.html)
  - Global: Brown et al. Sci Translat Med 4:1-9, 2012
- Rounding and averaging to estimate annual global burdens
  - Allergic bronchopulmonary aspergillosis: 5-6m patients
  - Invasive aspergillosis: 0.4m patients
  - Esophageal & invasive candidiasis: 0.5-4m patients
  - Oral/vaginal candidiasis: >10m patients
  - Cryptococcosis (meningeal): ~1m
- Orphan drug-like frequency! (EU: 5 per 10,000; US 200k total)

Spectrum and Resistance

- Resistance now increasing
  - Echinocandins: some resistance reported in albicans, parapsilosis, tropicalis, guilliermondii, but …
  - The big problem is *C. glabrata*! Azoles long marginal but now seeing dual echinocandin (>10% rate!) and azole resistance
  - Azoles and *Aspergillus*: Regional emergence of resistance
- We have never had good therapy for some fungi
  - *Scedosporium* spp. (often R, esp. *S. prolificans*)
  - *Coccidioides immitis* (we suppress but often do not cure)
  - … and more, especially in immunosuppressed hosts

Candida and echinocandins. Focus on glabrata: ★Alexander et al. Clin Infect Dis 56:1724-32, 2013; Ostrosky-Zeichner Clin Infect Dis 56:1733-34, 2013 (editorial); Beyda et al. Ann Pharmacother 46:1086-96, 2012. Lewis et al. AAC 57:4559–61, 2013. **Azoles and Aspergillus:** van der Linden et al. Clin Infect Dis 57:513-520, 2013; Denning & Bowyer Clin Infect Dis 57:513-521-2, 2013 (editorial). ★ Anonymous. ECDC Technical Report 2013 (doi 10.2900/76274). **Scedosporium:** Cuenca-Estrella et al. J Antimicrob Chemother 43:149-151, 1999. Lin et al. Clin Infect Dis 56: 1838-1839, 2013. **Cocci:** Nguyen et al. Clin Microbiol Rev. 26:505-25, 2013. **Moulds in the immunosuppressed:** Safdar Clin Infect Dis 57:94-100, 2013.

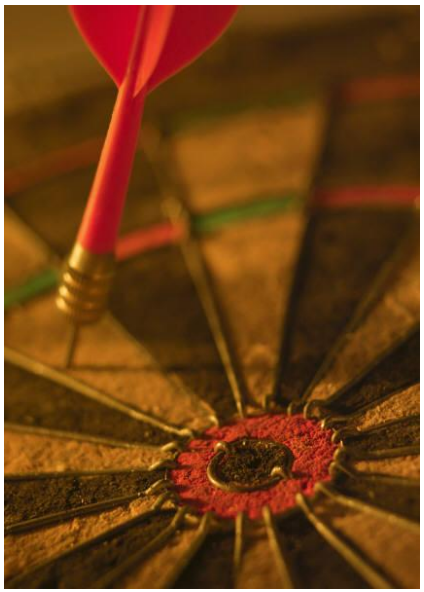
Use & Tolerability

- Only IV
  - Amphotericins
  - Echinocandins
- Drug-drug interactions
  - Azoles (e.g., voriconazole and cyclophilin inhibitors)
- Toxicity
  - Amphotericins
  - Voriconazole with chronic use
- As an aside: Therapeutic drug monitoring, better diagnostics, and earlier therapy…
  - … would help us get the maximal value out of the agents we do have
  - More on diagnostics a bit later

Theme Two

Does the current pipeline hit the mark?

Only in part



Current pipeline (1 of 2)

- Based on industry pipeline reports and recent meeting abstracts, these have shown some form of recent activity suggesting ongoing work (apologies if I've missed one!)
  - 3 CYP inhibitors: albaconazole, isavuconazole, VT-1161/1129
  - 2 glucan synthesis inhibitors: SCY-078 (formerly MK-3118), ASP-9726
  - 1 chitin synthesis inhibitor: nikkomycin Z
  - ~5 agents with a variety of other mechanisms of action
    - MGCD290: Inhibits HDAC (histone deacetylase. JCM 47:3797-804, 2009
    - T-2307: MOA – disrupts yeast mitochondrial function. AAC 56:5892-7, 2012
    - E-1210 : inhibits glycosylphosphatidylinositol (GPI) synthesis. IDrugs 13:746-8, 2010
    - Iliocin H: inhibits mitochondrial cytochrome bc1 reductase. 52nd ICAAC, Abstract F-810
    - FG-3622 / F3 series: Undisclosed MOA. http://www.f2g.com/05_Sep_2012.htm

To create this list, I reviewed TrialTrove, Citeline, IDSA (2011, 2012), ECCMID (2012, 2013), and ICAAC 2011-3. See also Ostrosky-Zeichner et al. Nature Rev Drug Disc 9:719-27, 2010.

Current pipeline (2 of 2)

- Only 6 agents appear to be at or beyond Phase 1
  - The 3 CYP inhibitors, SCY-078, MGCD290, and T-2307
- The most advanced agent is isavuconazole
  - In Phase 3 with a trial program focused principally on invasive aspergillosis and candidiasis.
- Antibody-based approaches
  - Recent activity in vaccines for candidiasis (NovaDigm, Pevion), most advanced compound is in ~Phase 2a
  - Steady flow of preclinical ideas
  - Hard to judge likelihood of progression of these products

Analysis

- Small molecule agents in the clinic:
  - These do offer value (e.g., reduced cross-resistance, oral administration of an IV class)
  - But, most are similar to known agents and may have some of the same limitations
  - The most advanced do not have a novel MOA. This is frustrating to see
- As for the preclinical compounds
  - Novel MOA compounds, but they may or may not progress
  - The usual rule of thumb is to estimate < 10% chance of success for any given molecule

Theme three

How will future antifungal agents be developed?

The paradigm gap

Lessons from the world of antibacterial agents

New pathways for antibiotics for highly resistant pathogens:

The fundamental role of PK-PD in Tier B and Tier C development programs

THE LANCET Infectious Diseases 13:269-275, 2013

A comprehensive regulatory framework to address the unmet need for new antibacterial treatments

John H Rex, Barry I Eisenstein, Jeff Alder, Mark Goldberger, Robert Meyer, Aaron Dane, Ian Friedland, Charles Knirsch, Wendy R Sanhai, John Tomayko, Cindy Lancaster, Jennifer Jackson

The paradigm gap

- For registration, we traditionally expect
  - Two substantial trials per indication (e.g., two UTI trials)
  - Typical size & cost/trial: ~1,000 patients, ~$50-70m
- This presumes ready availability of substantial numbers of patients with the target disease
- But, what if the target disease includes requirement for a specific less common pathogen or type of resistance?
  - Less common pathogen: *Pseudomonas*
  - Emerging form of resistance: KPC or Metallo-ß-lactamase
- When only limited clinical data are possible, current paradigms give no easy way forward
  - Waiting for widespread resistance means we can't anticipate the epidemic

The antibiotic paradigm gap
Existing regulatory framework

Traditional Development:

Two well-controlled, adequately powered Phase III studies per body site to demonstrate safety and efficacy

Focused on body sites of infection

The "Animal Rule:"[1]

For cases when studies in humans are unethical; Approval based on human safety studies and preclinical (non-human) efficacy studies

Focused on infectious agent

1. In 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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Pathogen-focused development as a middle path

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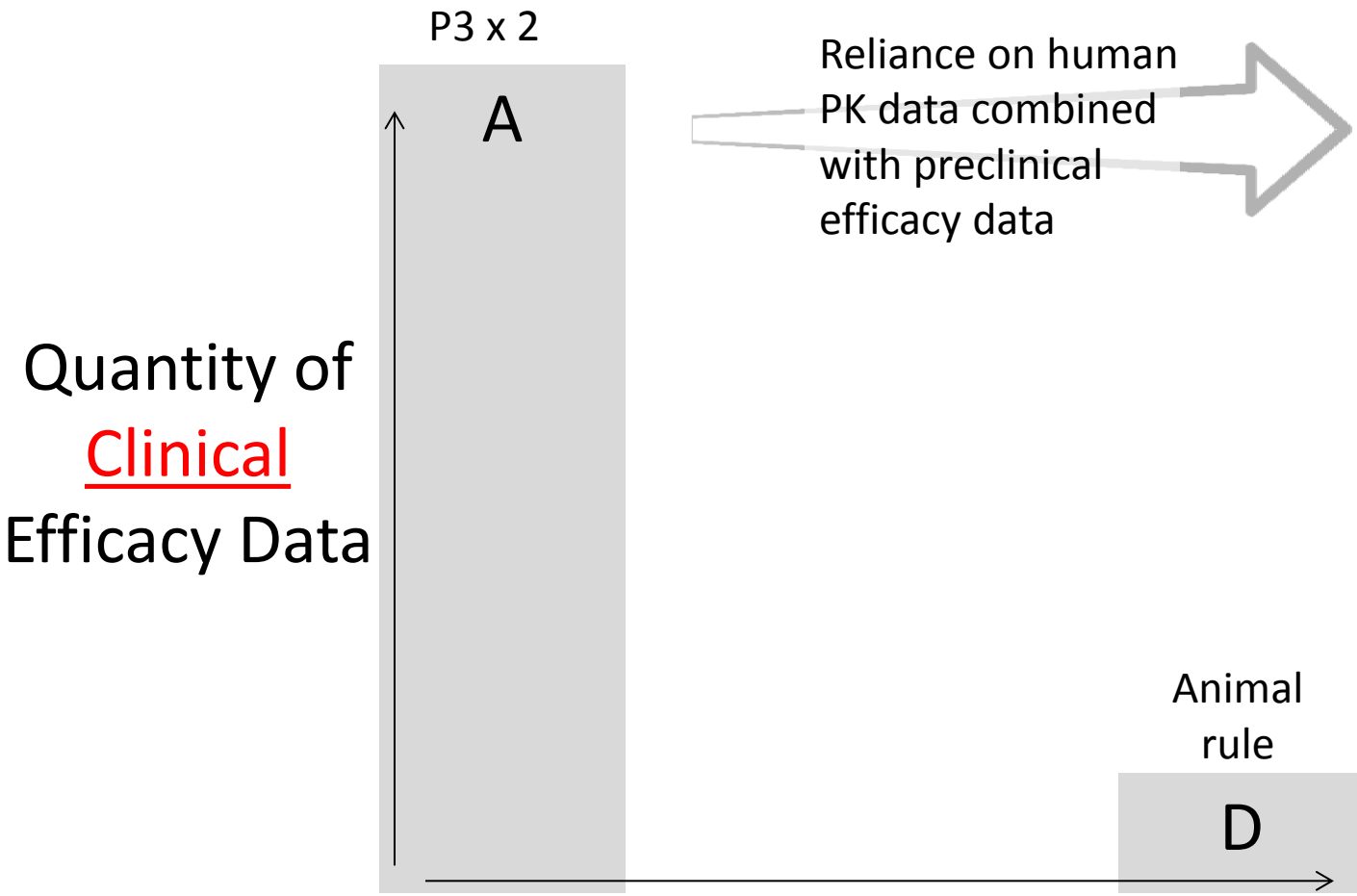
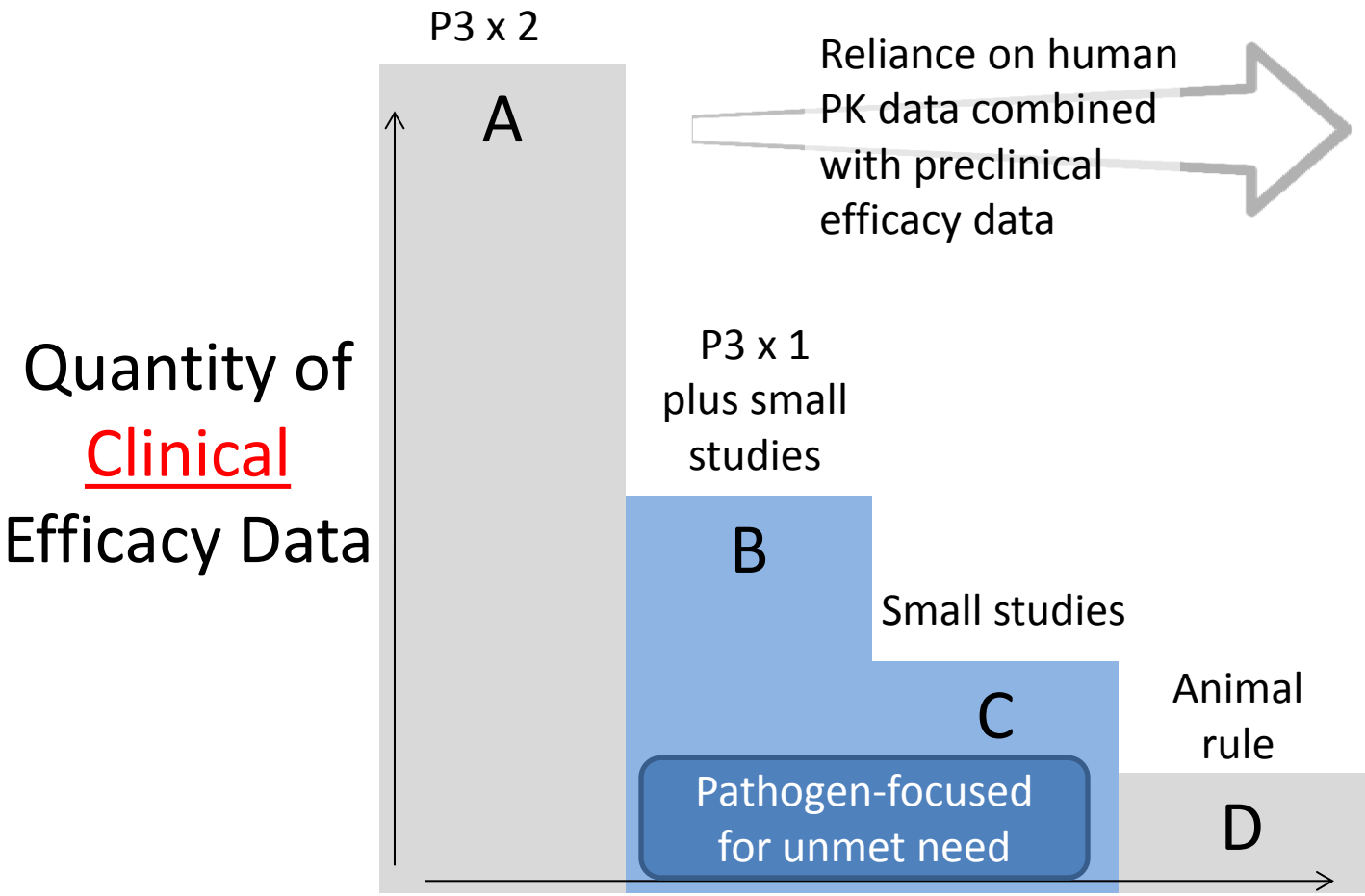
An approach: Four Tiers



Acceptance of smaller clinical datasets (often merged across body sites) in response to unmet medical need

Four Tiers: *B & C are new*



Acceptance of smaller clinical datasets (often merged across body sites) in response to unmet medical need

Tier B & C Overview: Preclinical

Attribute	Tier B	Tier C
Example spectrum	**Broad** with MDR pathogen coverage	**Narrow** MDR pathogen coverage
Example target pathogen	MDR Enterobacteriaceae (also covers if non-MDR)	*Pseudomonas aeruginosa* **only**
Challenge in studying MDR pathogen in large numbers?	Yes	Yes
Detailed insight into:		
Microbiology including mechanism of action and resistance?	Yes	Yes
Animal models that mimic human disease?	Yes	Yes
Exposure-response in animals?	Yes	Yes

Tier B & C Overview: Clinical

Attribute	Tier B	Tier C
Detailed PK/PD justification of dose selection in humans[1]	Yes	Yes
Can do "standard" P3 study vs. *susceptible* organisms?	Yes[2]	No
Randomized comparative data generated?	Yes (single body site, vs. standard comparator)	Yes (multiple body sites, vs. BAT[3])
Able to do "usual strength" statistical inference testing?	Yes, but only in the standard P3 study	No
Pooling of data across infection sites proposed?	Yes	Yes
Reliance on a totality-of-evidence approach?[4]	High	Even higher

[1]Mechanism of action understood, animal models reasonably mimic human disease at relevant sites, exposure-response in the animal studies informs human dose with adequate margin, PK known in healthy volunteers and relevant patient groups. [2]This provides relevant efficacy data if MDR pathogens have same susceptibility to new agent as do non-MDR pathogens. [3]BAT = Best Available Therapy, standardized insofar as possible. [4]All drug reviews consider the totality of evidence, but the reliance on such things as PK-PD predictions and pooled responses across sites will be very high here.

Tier B/C Development Programs[1]

- **Tier B:** Two treatment studies (one large, one small)
  - Standard Phase 3 study of Drug B vs. standard comparator at standard body site vs. ordinary (mostly wild-type) pathogens
    - No expectation of enrolling any MDR pathogens!
    - Provides general data on activity of Drug B
  - Open-label salvage study of Drug B for MDR pathogens
- **Tier C:** Two treatment studies + one observational study
  - Prospective, randomized, open-label study of Drug C vs. BAT[2] across multiple body sites. N ≅ a few 100
  - Open-label salvage study for MDR pathogens (no BAT exists)
  - Observational study of (inadvertent) ineffective therapy for the target pathogen (this estimates placebo response rate)[3]

[1]Detailed examples are available. [2]BAT = Best Available Therapy, standardized insofar as possible. [3]There 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.

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

What is the status of these ideas?

- EMA: Final addendum[1] released 24 Oct 2013
  - Clearly describes Tier B & C as acceptable pathways
  - A Tier C variant using external controls is also described
- FDA: Draft "Unmet Need" guidance[2] released July '13
  - It is less detailed than the EMA addendum, but signals significant flexibility and a desire for dialogue
  - Recent specific interactions have shown that Tier B- and Tier C-like programs can be acceptable
- In short, all conversations point to the same ideas
  - Careful PK-PD work can point to a dosing regimen
  - The registration program can take many forms

[1]EMA/CHMP/351889/2013; Committee for Human Medicinal Products (CHMP); Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. [2]DHHS/FDA/CDER: Guidance for Industry Antibacterial Therapies for Patients With Unmet Medical Need for the Treatment of Serious Bacterial Diseases

Is this relevant to antifungals?

- I think so. Antifungals have long
  - Been registered with a single pivotal trial per indication
  - Accepted some degree of mixed body site data
  - Thus, effectively been Tier B-ish
- But, what do you do for
  - A mould-only agent?
  - An agent focused on MDR strains of *C. glabrata*?
  - Something really narrow (a monoclonal)
- Tier C-like programs look like the answer to me
  - And PK-PD becomes critical. Fortunately, we're now seeing ways to make this work as well.

Diagnostics (1 of 2)

- Microbiologically-proven patients are needed
  - Culture is slow: We must enroll before result is known
  - If only 50% of patients are qualified…
  - Then 50% (half the study) aren't fully evaluable
  - So, are we still dependent on culture?
- If a (rapid) test moves us from 50 to 75% evaluable...
  - Test might rule in or rule out – doesn't matter
  - Test need not make a diagnosis, it only needs to increase likelihood of a positive culture or other definitive result
  - Study size goes down 1/3rd: we save cost & time
- And the MSG has been working on this…

Diagnostics (2 of 2)

- MSG took this to FDA. On January 7, 2013, the FDA responded with the following advice:[1]
  - "We currently believe that galactomannan results on samples obtained prior to the initiation of anti-fungal therapy can be used to classify a subject enrolled into an aspergillosis treatment trial as having probable invasive aspergillosis under the following conditions:
    - Specific rules given for GM testing in serum, BAL; nature of the at-risk group (heme malignancy or HSCT) and a few other details
- This is a major step forward
  - Well done to all who participated in this work!

1. The Mycoses Study Group, Summer 2013 Newsletter

Diagnostics are not endpoints

- Another lesson from the antibacterial arena
  - Endpoints must be grounded in how a patient feels, functions, or survives
  - No one has ever said “Doc, please reduce my plasma galactomannan levels!”
  - They say “Doc, make me feel better”
  - Surrogate markers *are* possible (e.g., HIV viral load) but require a lot of documentation
- Mortality or another clinical response endpoint will be our tools for the near-term
  - I think this is workable

Newsflash: 30 Sep 2013 (1 of 2)

- 30 Sep 2013: Basilea Pharmaceutica AG (SIX:BSLN) and partner Astellas Pharma Inc. (Tokyo:4503) said
  - "once-daily isavuconazole met the primary endpoint of non-inferiority to twice-daily voriconazole in reducing all-cause mortality from baseline to day 42 (18.6% vs. 20.2%)
  - in the Phase III SECURE trial to treat invasive fungal disease
  - caused by *Aspergillus* species or other filamentous fungi.
- The partners said the pre-specified non-inferiority margin was 10%.
- The double-blind, international trial enrolled 516 patients."

Newsflash: 30 Sep 2013 (2 of 2)

- Let's do some back-calculating
  - N = 258/arm (516 total)
  - Mortality rates of 48/516 (18.6%) and 52/258 (20.2%)
  - Difference = -1.6%, 95% CI = -8.4 to 5.3%
  - Easily within 10% no matter which drug yielded which point estimate
- Is a 10% non-inferiority margin supported? YES
  - At 6 weeks (and reading off Fig. 2 from the 2002 NEJM Herbrecht voriconazole vs. amphotericin B paper), I estimate survival rates of
    - 80% (115/144) vs. 65% (86/133). Delta = 15%, 95% CI = 5% to 26%.
  - At 12 weeks, we have the actual data:
    - 102/144 (71%) vs. 77/133 (58%), Delta = 13%, 95% CI = 2 to 24%
  - If we take AmB to be placebo, we can support a 10% margin
  - That's very conservative as AmB is better than placebo → no discounting needed on margin

Theme Four

Economics: Will anybody invest in this area?

"We can't make companies do this work.
We have to make them want *to do this work."*

-- Brad Spellberg

Drug development is slow & costly

- Typical estimates are ~$1b for a new compound
  - Lots of failures then one finally makes it
  - You need a lot of economic pull to overcome this!
- All the discussion about antimicrobial resistance has heightened global awareness and understanding
- As a result, economic change is in the wind
  - US: 2012 FDA renewal act (FDASIA) contains the GAIN Act granting 5 years of extended exclusivity for qualified antibacterial and antifungal agents
  - EU and US (NIAID, BARDA): Significant investment in support of small-medium enterprise work on new antimicrobial agents

The elements of success

- The development plan must show
  - A clear unmet medical need
  - A way to know which patients have that need (GM assay!)
  - Data on an outcome in those patients that matters to them
  - Outcome data without effective therapy
- With these elements
  - Approval becomes possible
  - Reimbursement should be appropriate
  - Value-based pricing is increasingly seen as reasonable

- Planning for this must begin before Phase 1!

Value-based pricing: Antibacterial

- What's a drug worth?
  - Imagine a new drug for MDR *Acinetobacter*
  - Take US estimates of case rate & excess cost/case
  - Assume new agent provides effective therapy that restores 8 years of life at a quality of 0.6
  - Assume also that it reduces cost of care by 50%
- With these conditions, we[1] estimated that
  - At $10K/course the cost/life-year saved was ~$3K
  - At $10K/course, the cost/QALY was ~$5K

[1]Spellberg and Rex, *Nature Reviews Drug Discovery* 12:963-963, 2013.

Value-based pricing: Antifungal

- Imagine a new drug for *Aspergillus* spp.
  - Assume efficacy similar to voriconazole
  - Don't assume cost savings: it is just an effective alternative
    - Of course, activity vs. azole-resistant isolates would add value
  - Assume ~5 years of life saved when effective
    - This is a weighted average across various at-risk patient groups
- We[1] estimate these costs & values:
  - At $10K/course, cost is $8K/life-year saved
    - At $25K/course, cost is $20K/life-year saved
  - At quality of 0.6, this is $13K/QALY (or $33K/QALY)
    - These costs are well within usual $50K/QALY benchmark
  - Key value is life years saved: a very patient-centric metric

[1]Work in progress, Denning, Spellberg, and Rex

Summary

Our head is round so that our thinking can change direction (Francis Picabia)

Summary

- We need new choices
  - Susceptible populations, spectrum, resistance, tolerability, ease of use
- The current pipeline is very slender
- New agents are developable
  - Ideas can be taken from antibacterials
- The economic puzzle will be addressed
  - New agents offer can real value
  - We are going to evolve our economic view

Thank you!

Many thanks to the organizers for this opportunity to be with you today and share these thoughts