

Barriers to New Antibiotic Development

The Perfect Storm
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Disclaimers

- I make my living by consulting
 - Large PhRMA
 - Biotech
 - Academics
- “Active” member of IDSA.
- I am NOT a statistician!
- Mostly working on antibiotics, occasionally antiviral drugs.
- A recent client list can be found on my website.
- The views I present today are my own.

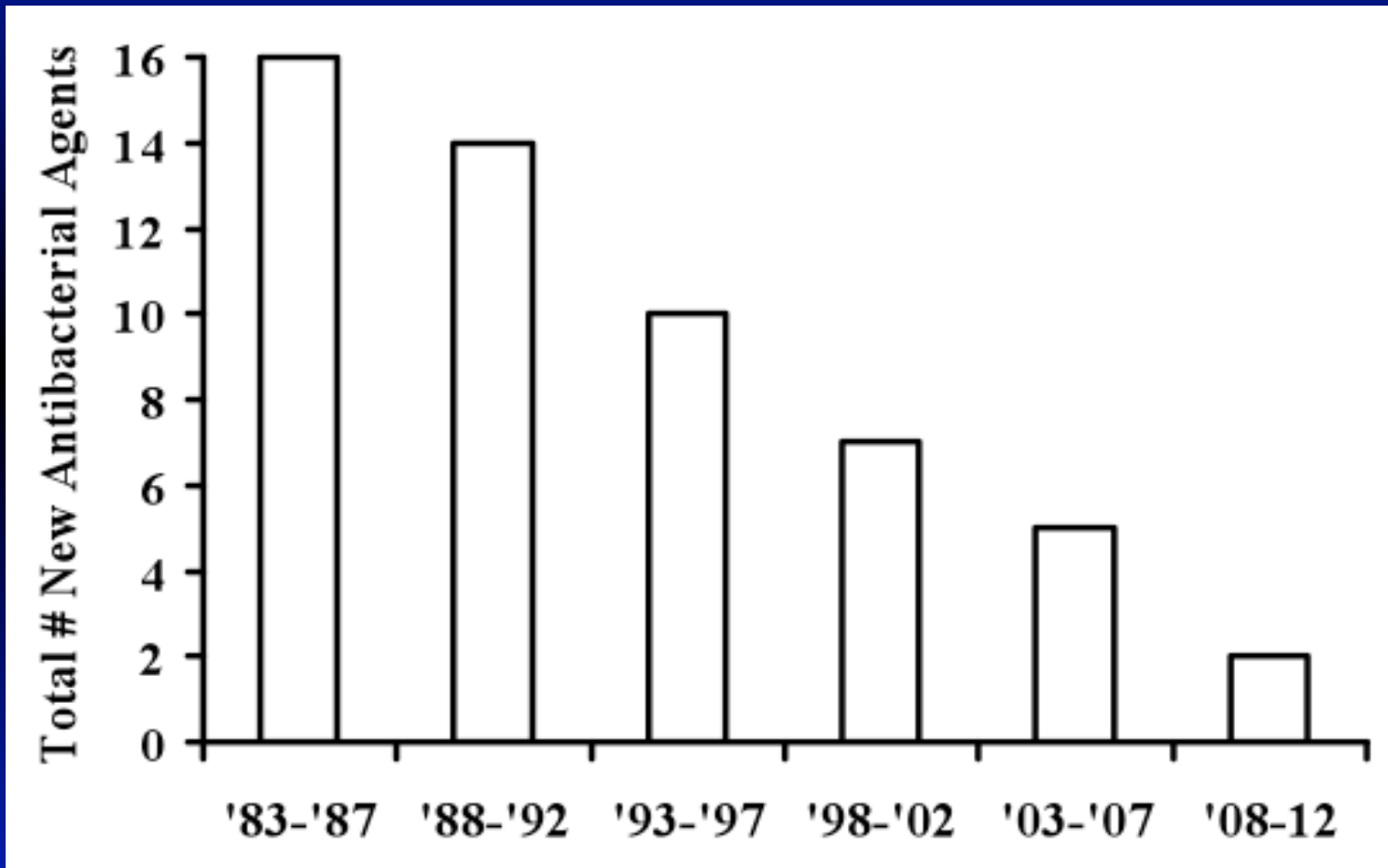
Appropriate Attire to Give This Lecture



Outline

- Resistance is global
- Our antibiotic pipeline, especially for Gram negative infections, is paltry.
- The FDA is a major roadblock.
- The US market is declining while pharmemerging markets are growing.
 - The US will soon be irrelevant.
 - New and needed antibiotics will be available in Beijing but not Washington.
- We need
 - FDA reform
 - novel trial designs.

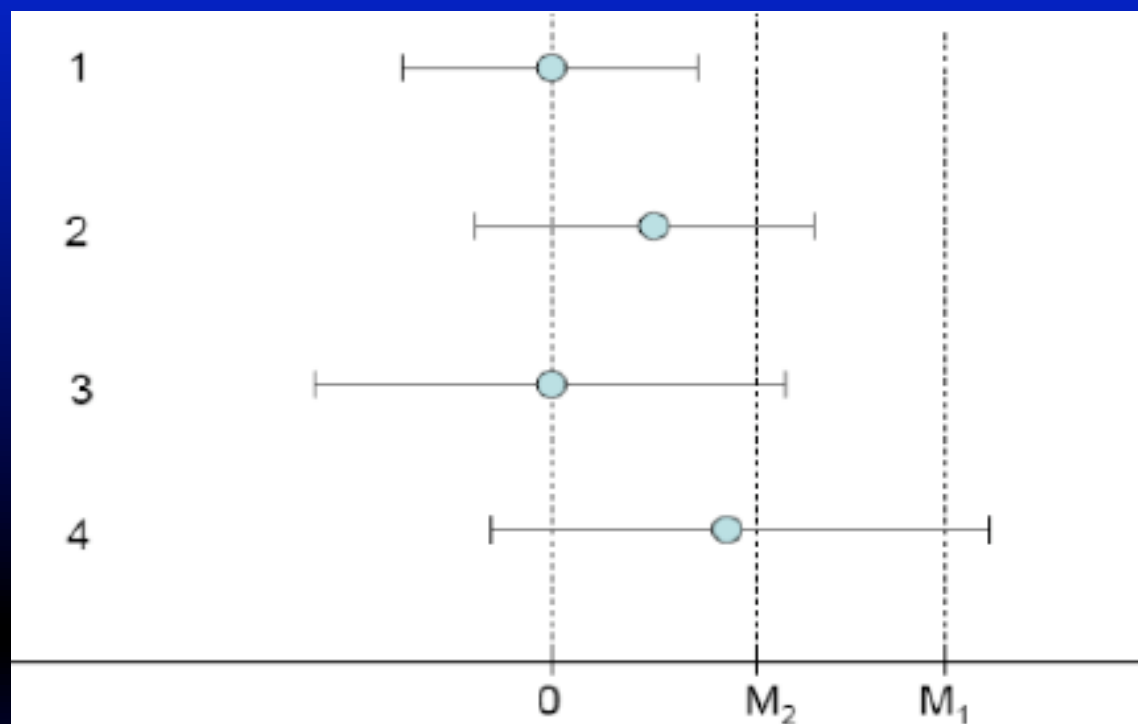
FDA Antibiotic Approvals 1983-2012



Boucher, H at Pew charitable Trust Meeting

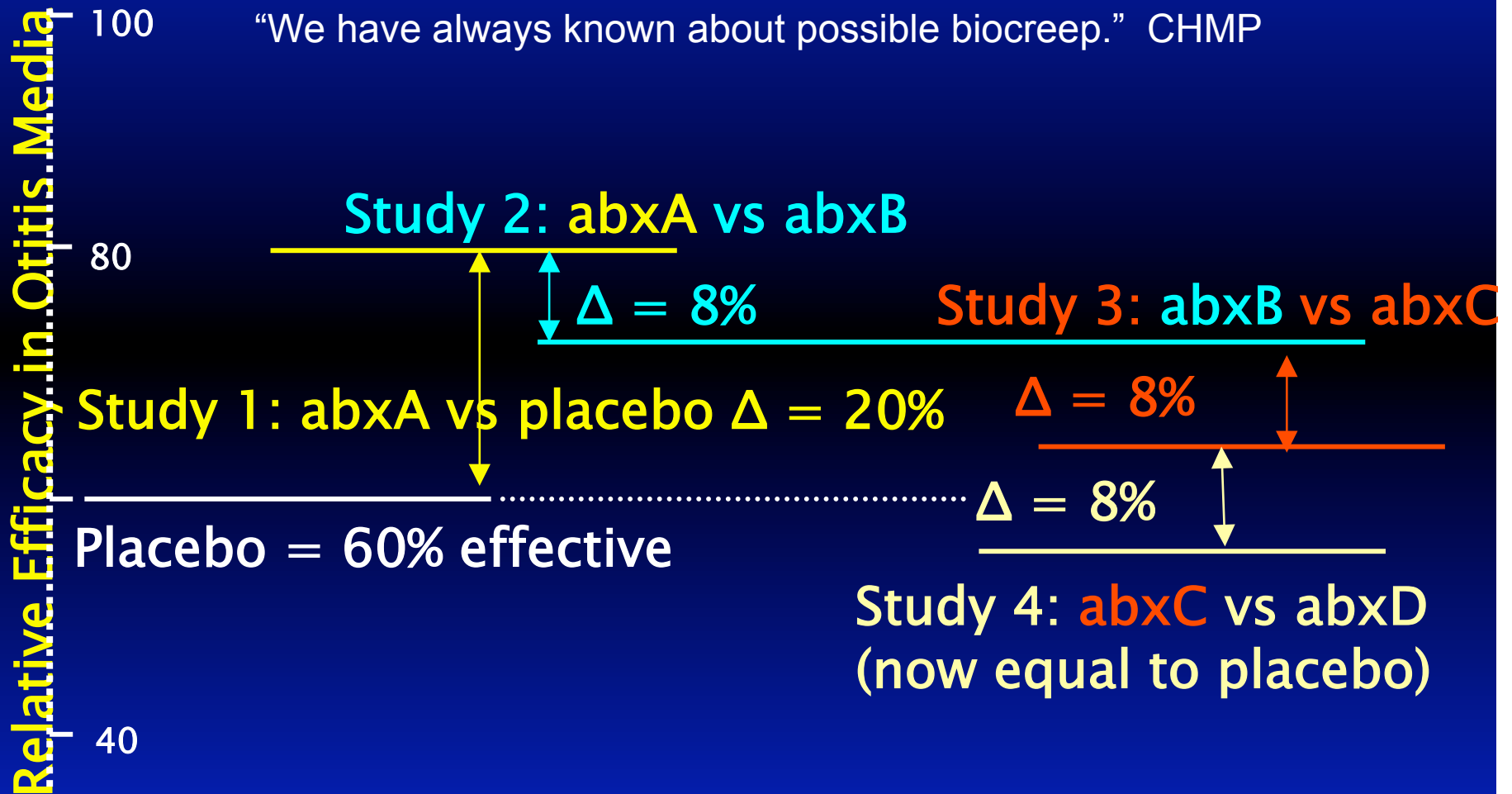
The Basis of Non-Inferiority

- A non-inferiority trial ASSUMES that the control antibiotic (directly or indirectly) has been shown to be superior to placebo.
- The treatment effect = control – placebo.
- The NI margin can never be greater than the treatment effect.
- To justify their NI margins, the FDA has used data from the pre-antibiotic era, or has used modern data where treatment has been inadequate, to determine a treatment effect.



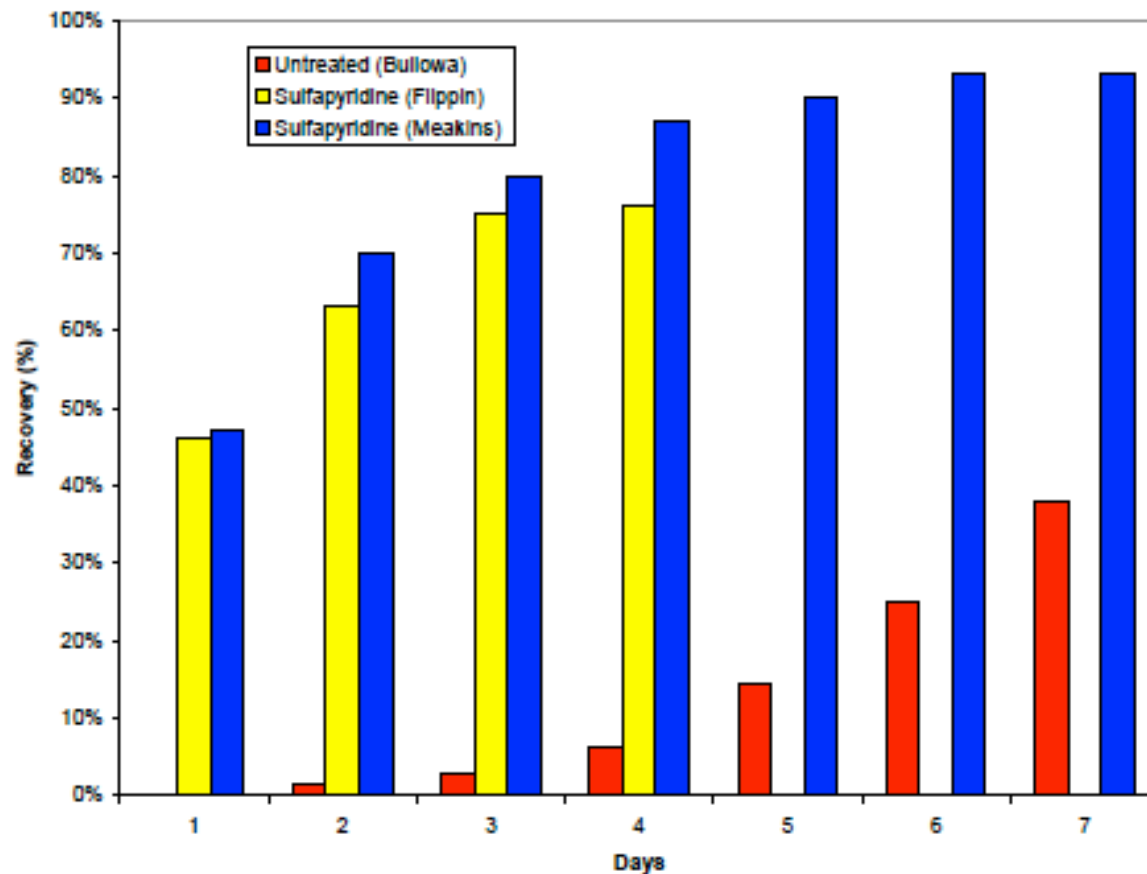
1. C-T point estimate = 0 and upper bound of 95% CI < M_2 , indicating test drug is effective (NI demonstrated).
2. Point estimate of C-T favors C and upper bound of 95% CI < M_1 but $326 > M_2$, indicating effect > 0 but unacceptable loss of the control effect.
3. Point estimate of C-T is zero and upper bound of 95% CI < M_1 but it is slightly greater than M_2 . Judgment could lead to conclusion of effectiveness.
4. C-T point estimate favors C and upper bound of 95% CI > M_1 , indicating 330 there is no evidence of effectiveness for test drug.

Non-Inferiority Trials and Bio-Creep



Approval based on a $\pm 10\%$ delta
John Bradley, UCSD

Antibacterial Treatment Effect on Clinical Recovery of Pneumococcal Pneumonia*



*Adapted from Bullowa (1937); Meakins and Hanson (1939); and Flippin, et al. (1939)

FDA Discounting

- To calculate the NI margin – once they have defined a treatment effect – the FDA then estimates the 95% confidence interval around this effect and selects the lower bound.
- They then apply an arbitrary discount to be sure that the NI margin does not exceed a treatment effect. (???)
- In this way a treatment effect of 50% always leads to an NI margin of 10%.

Tigecycline example

Indication	Cure Rate	90% Power 10% delta	90% Power 15% delta
CAP (Total Number for 2 Studies) 70% evaluability	85%	1532	688
Skin (Total Number for 2 Studies) 60% evaluability	80%	2248	1000
IAI (Total Number for 2 Studies) 60% evaluability	70%	2948	1316
HAP (Total Number for 1 Study) 60% evaluability	65%	1598	710
TOTAL		8326	3714
		80% Power 10% delta	80% Power 15% delta
TOTAL		6226	2770

Decreasing from 90% to 80% power doubles the risk of a false negative result when the agent is actually not inferior (thanks to M. Wible)

Multiple Indications and Multiple Trials: Implications for Program-wise Error Rate

A total of 300 evaluable patients (150 each arm) are needed to have a 90% chance to declare non-inferiority based on a -15% margin and a control cure rate of 80% .



If the approval is based on 2 independent trials, the chance of approving a drug that is truly 10% inferior than the control is $< 0.18 \times 0.18 = 0.032$. If we have 3 trials, the chance is < 0.006 .

Christy Chuang-Stein, Ph.D.

PhRMA – why do this?

Table 6-3. Net present value (lifetime earnings minus lifetime costs) of drugs.

Net Present Value (NPV) of Drugs 1990-94

	Mean NPV
All Drugs	\$0.8B
Antibiotics	\$1.1B
Statins	\$15B
SSRI anti-depressants	\$11B

Consolidation within the pharmaceutical industry 1980-2003.

2003 Pharmaceutical Company

Number of original companies since 1980

Aventis ¹	17
Bristol-Meyers-Squibb	8
Glaxo Smith Kline	12
Novartis	7
Pfizer	12
Wyeth ²	14
Total	70

1. Now Sanofi-Aventis

2. Now Pfizer

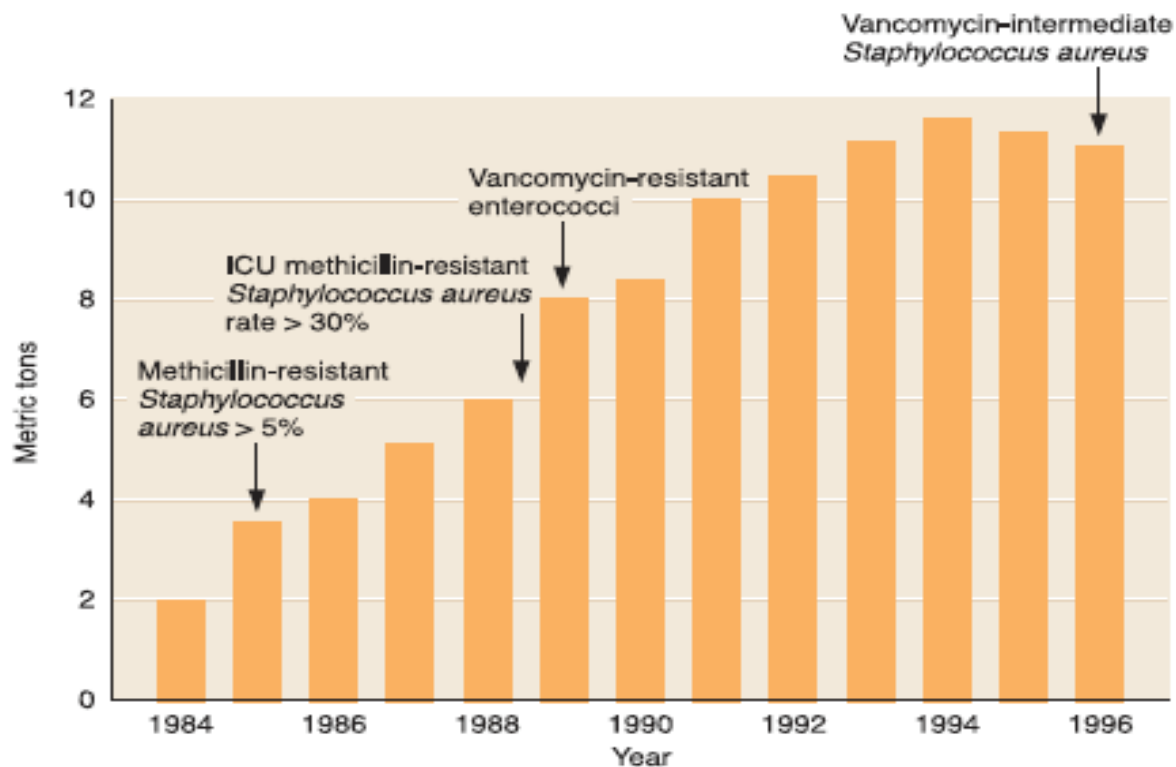
Biotech needs Large Pharma

Large PhRMA Actively Pursuing Antibiotic R&D 2011

- Astra-Zeneca
- GSK
- Sanofi-Aventis
- (Novartis)
- (Merck)

Biotech

- Cannot pay for ph 3
 - M&A
 - IPO
 - License
- Fewer Pharma partners = less opportunity = less interest by investors = less antibiotic R&D



Resistance creates markets, use creates resistance. Vancomycin use in the United States, 1984–1996.

Synercid - 1999

Linezolid – 1999

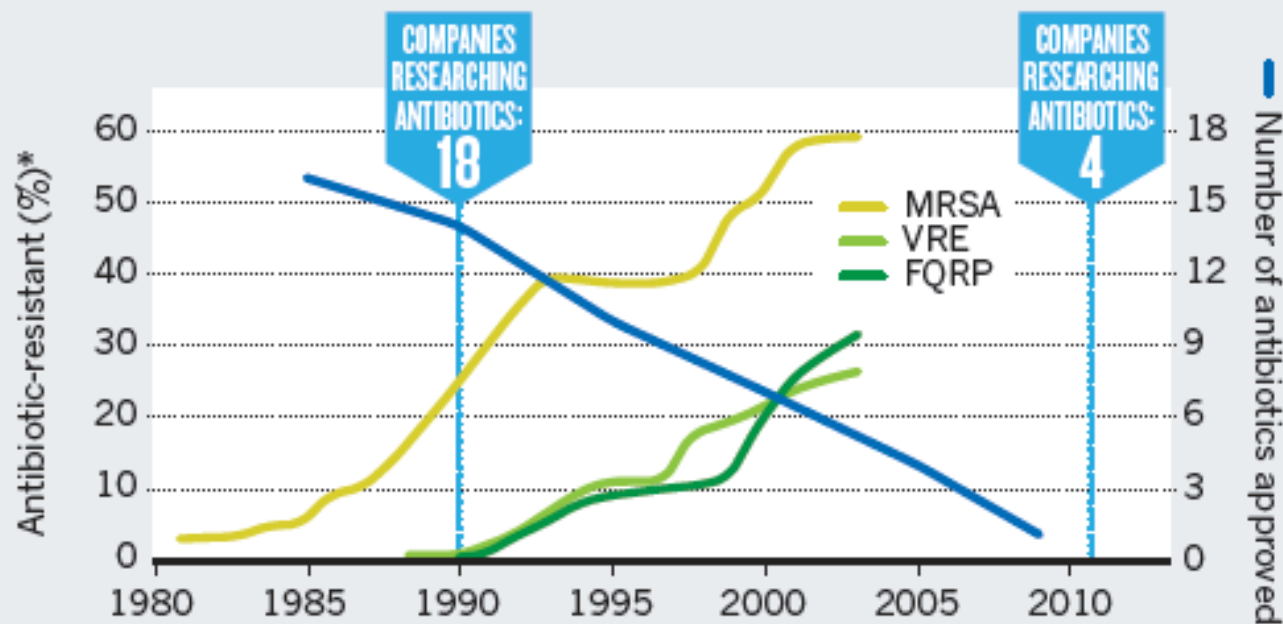
Daptomycin – 2003

10-14 years will seem short if things don't change.

The Perfect Storm

A PERFECT STORM

As bacterial infections grow more resistant to antibiotics, companies are pulling out of antibiotics research and fewer new antibiotics are being approved.



*Proportion of clinical isolates that are resistant to antibiotic. MRSA, methicillin-resistant *Staphylococcus aureus*. VRE, vancomycin-resistant *Enterococcus*. FQRP, fluoroquinolone-resistant *Pseudomonas aeruginosa*.

Antibiotic discovery is hard!
The ROI is average at best.
The regulatory environment (US) is hostile.

The Low Point

- At the 2010 ICAAC, Mark Goldberger, former Director ODE IV at FDA, stated that our letter, Shlaes and Moellering, entitled, The FDA and the End of Antibiotics, 2002, was the low point in FDA-industry relations on antibiotics.
- Little did he know . . .

The Ketek Scandal

- David M Shlaes, Robert C Moellering. Telithromycin and the FDA: implications for the future. Feb 2008 *The Lancet Infectious Diseases*, Vol. 8 No. 2 pp 83-85.
- In 2006, US marketing approval for telithromycin (Ketek) for otitis, sinusitis and ABECOPD was withdrawn.
 - Rare but serious liver tox.
 - They had not proven efficacy via placebo-controlled trials as is now required but was not required when S-A developed the drug.
- In the wake of the Ketek scandal of 2006, congress piled-on on the FDA demanding answers as to how such a drug could have possibly been approved.
- The results of this unnecessary scandal have been
 - a loss of critical FDA personnel and a subsequent lack of leadership at the FDA.
 - consistent interference in FDA's efforts in the critical area of clinical trials for new antibiotics (GAO report)
 - constant and unpredictable waffling by the FDA along with an antibiotic approval record that will leave our critical antibiotic pipeline in imminent danger for at least the next decade.

FDA Guidance requiring infeasible trial designs

- ABSSSI – design is feasible – endpoint clinically irrelevant.
- AOM, ABS, ABECOPD – all require placebo controlled trials.
- CABP – proscription against prior antibiotics and stringent NI margin – especially for oral drugs. Clinically irrelevant endpoint.
- HABP/VABP – mortality endpoint, stringent NI margin and proscription against prior antibiotics.
- cUTI - proscription against prior antibiotics and stringent NI margin

Indications for Anti-infectives

Clinical Trial Feasibility, Market Attractiveness, and Medical Need for New Antibiotics

Indication	Are Trials Feasible	Market attractive	Medical Need for New Antibiotics
Skin infections	Yes	Yes	For oral drugs
Community-acquired pneumonia	No	Yes	Not at this time
Hospital acquired pneumonia	No	Yes	YES
Ventilator associated pneumonia	No	Yes	YES
Intra-abdominal infections	Yes	Moderate	Moderate - for resistant pathogens
Urinary tract infections	NO	Maybe	YES - for resistant pathogens
Bone and Joint infections	No	Maybe	For oral drugs
Heart valve infections	No	No	Not at this time
Fever in neutropenic patients	No	Yes	For resistant pathogens
Otitis media	No	Yes	Not at this time
Acute bacterial exacerbations of chronic bronchitis	No	Yes	Not at this time
Acute Bacterial Sinusitis	No	Yes	Not at this time
Pharyngitis	?	No	No

FDA Trial Design Agreement (SPA) Untrustworthy

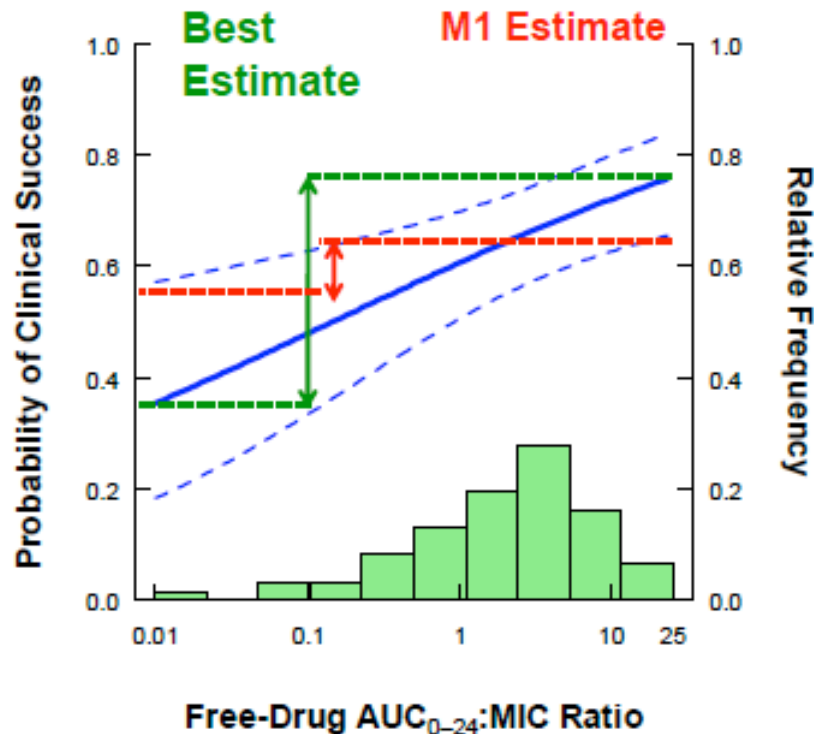
- After trials have been initiated or even completed based on a design agreed between the sponsor and the FDA, the FDA allows themselves the prerogative of changing their trial design requirements.
 - They have exercised this prerogative on several occasions.
 - Companies have gone belly up or abandoned antibiotic R&D as a result.

The IDSA Steps Up

During a recent policy meeting, representatives from the few pharmaceutical companies still investing in antibiotic R&D said they plan to focus their future efforts on European, Asian, and Latin American markets and not on the United States. The primary reason for this shift: the regulatory environment. For more than a decade, FDA's antibacterial human drug review process has been fraught with uncertainty that has shaken the foundation of the nation's antibacterial pharmaceutical industry. FDA has failed to fully appreciate, prioritize, and address the unique challenges facing antibiotic development, and the lack of a clear antibiotic approval pathway, coupled with economic disincentives, has brought antibiotic development to its knees. Companies need consistency, feasibility, predictability, and timeliness in order to make investment decisions. FDA has made it difficult, if not impossible, for companies to plan new investments in the antibiotics area first by throwing out existing rules without having new guidelines available to replace them and more recently by proposing new requirements that have been deemed infeasible both by industry and by independent infectious diseases physician experts. While FDA must periodically update the rules for approving new drugs to keep pace with the advancing science, they also must provide an approval pathway that works.

How can we get to relevant endpoints?

Best Estimates of Treatment effect



Ambrose PG, Hammel JP, Bhavnani SM, Rubino CM, Ellis-Grosse EJ, Drusano GL. A Bayesian Pharmacometric-Based Approach to Facilitate Critically Needed New Antibiotic Development: Overcoming Lies, Damn Lies and Statistics. *Antimicrob Agents Chemother.* Awaiting Disposition.

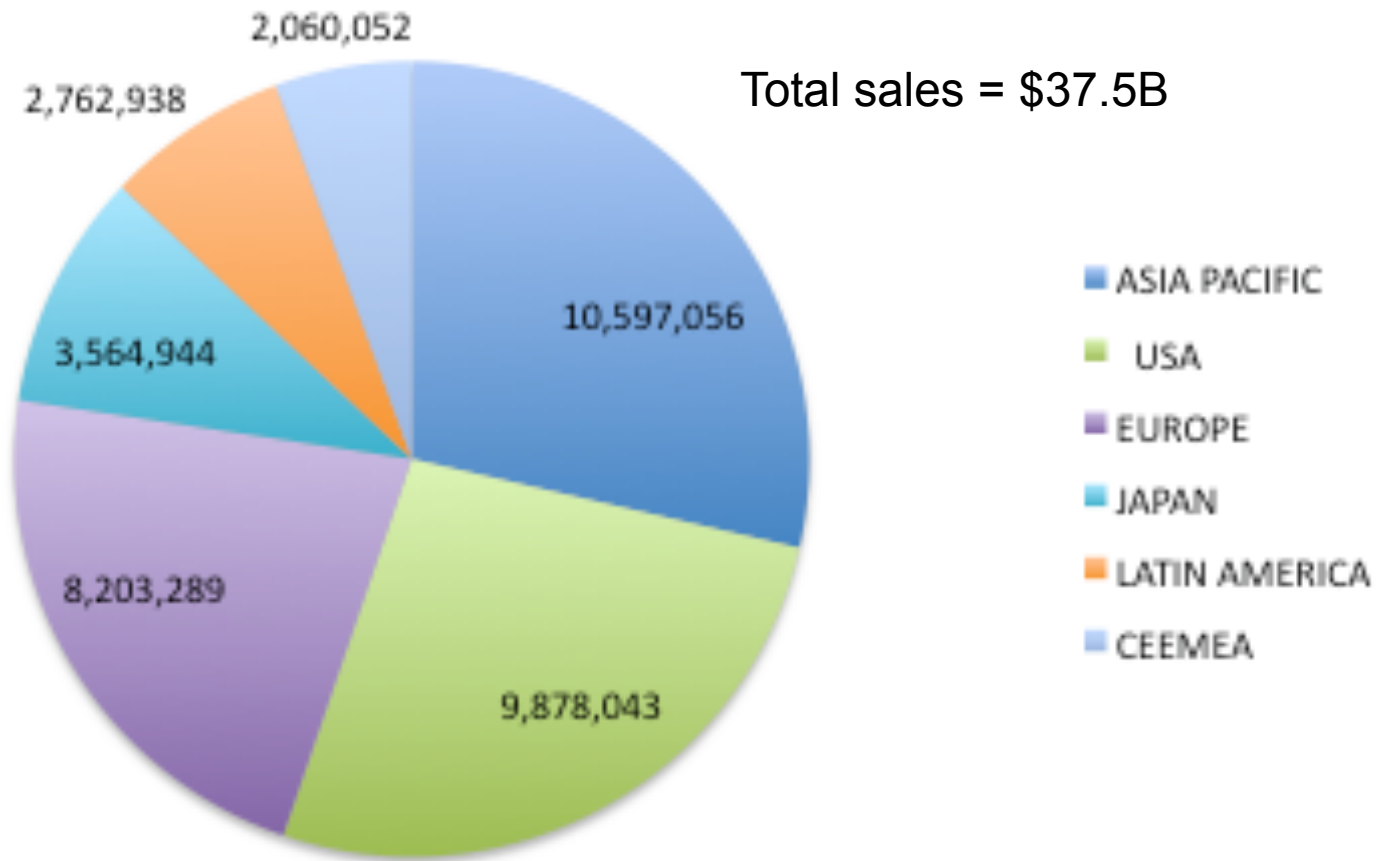
Estimates of Treatment Effect

Method	Endpoint	Estimates of Effect		
		Best	M1	ICPD M1*
Frequentist	Microbiological	0.655	0.004	0.166
	Clinical	0.672	0.043	0.211
Bayesian	Microbiological	0.468	0.074	0.301
	Clinical	0.405	0.085	0.314

* 95% lower bound of treatment effect based upon 1000 bootstrap analysis

Ambrose PG, Hammel JP, Bhavnani SM, Rubino CM, Ellis-Grosse EJ, Drusano GL. A Bayesian Pharmacometric-Based Approach to Facilitate Critically Needed New Antibiotic Development: Overcoming Lies, Damn Lies and Statistics. *Antimicrob Agents Chemother.* Awaiting Disposition.

Antibacterial sales 2010

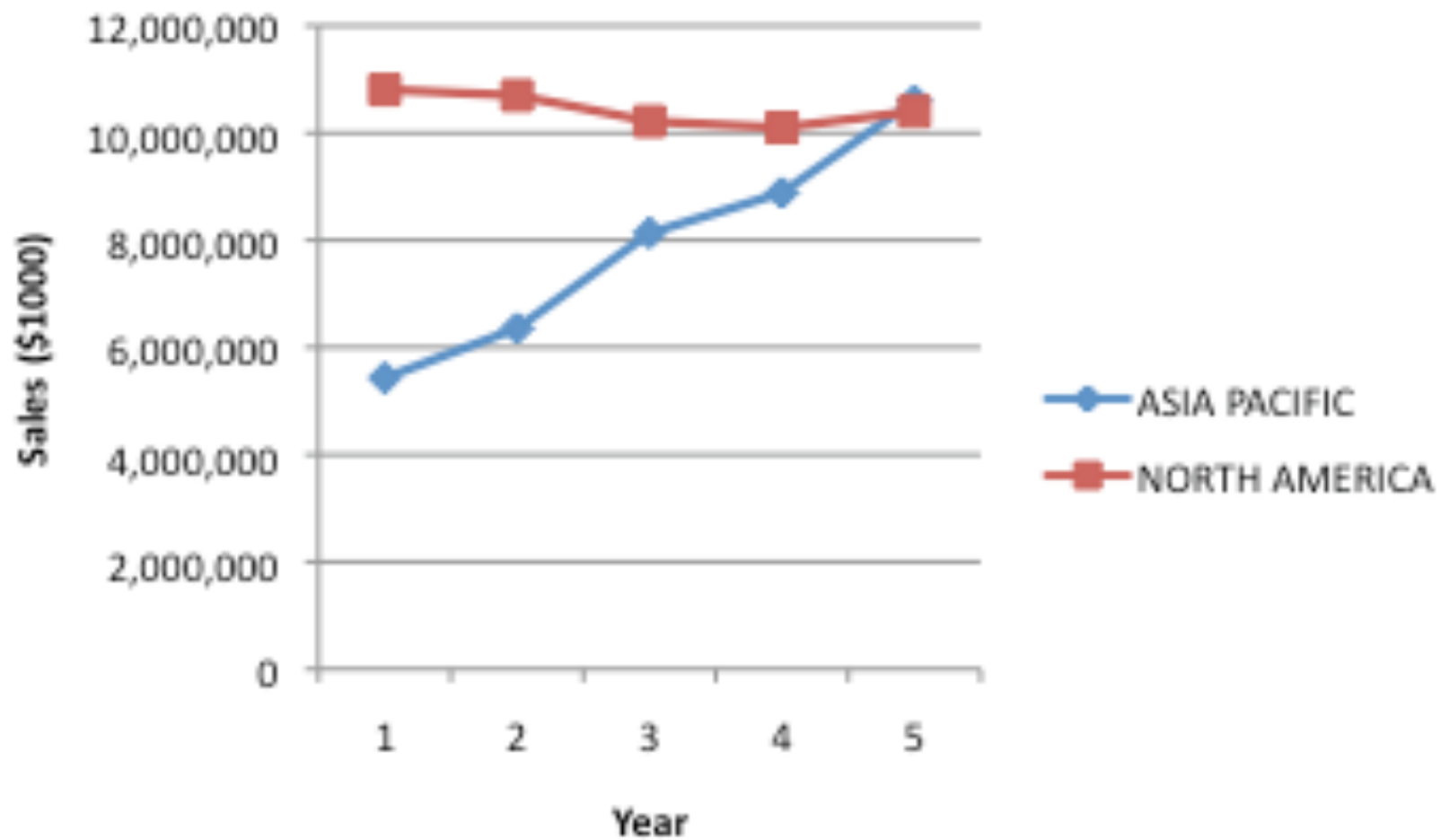


Pharmaceutical Markets

- Growing markets
 - Pharmemerging markets (China, India, Brazil, Russia, Mexico, Turkey, S. Korea)
 - Rest of World
- Stagnating (but LARGE) markets
 - US
 - Europe
 - Japan

Pharmaceutical and Antibiotic Market - US Share





Drivers of Lack of Growth in US

- Generic Intrusion + Lack of New Products
- Generic Intrusion + Lack of New Products
- Generic Intrusion + Lack of New Products
- Generic Intrusion + Lack of New Products

New Trial Designs

for drugs with activity against highly resistant strains

- Low Quantity, High Quality – Mark Goldberger, FDA, 2002.
 - IDSA - ***Special Population Limited Medical Use*** (SPLMU)
- Superiority
 - Historical controls
 - Active controls
 - Active plus optimized standard of care vs. SOC + placebo.
- Compassionate use
- Conditional approval

Top 5 Priorities to Rejuvenate Antibiotic R&D

- FDA REFORM
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- FDA REFORM

Backup Slides

FDA vs. EU

- FDA –

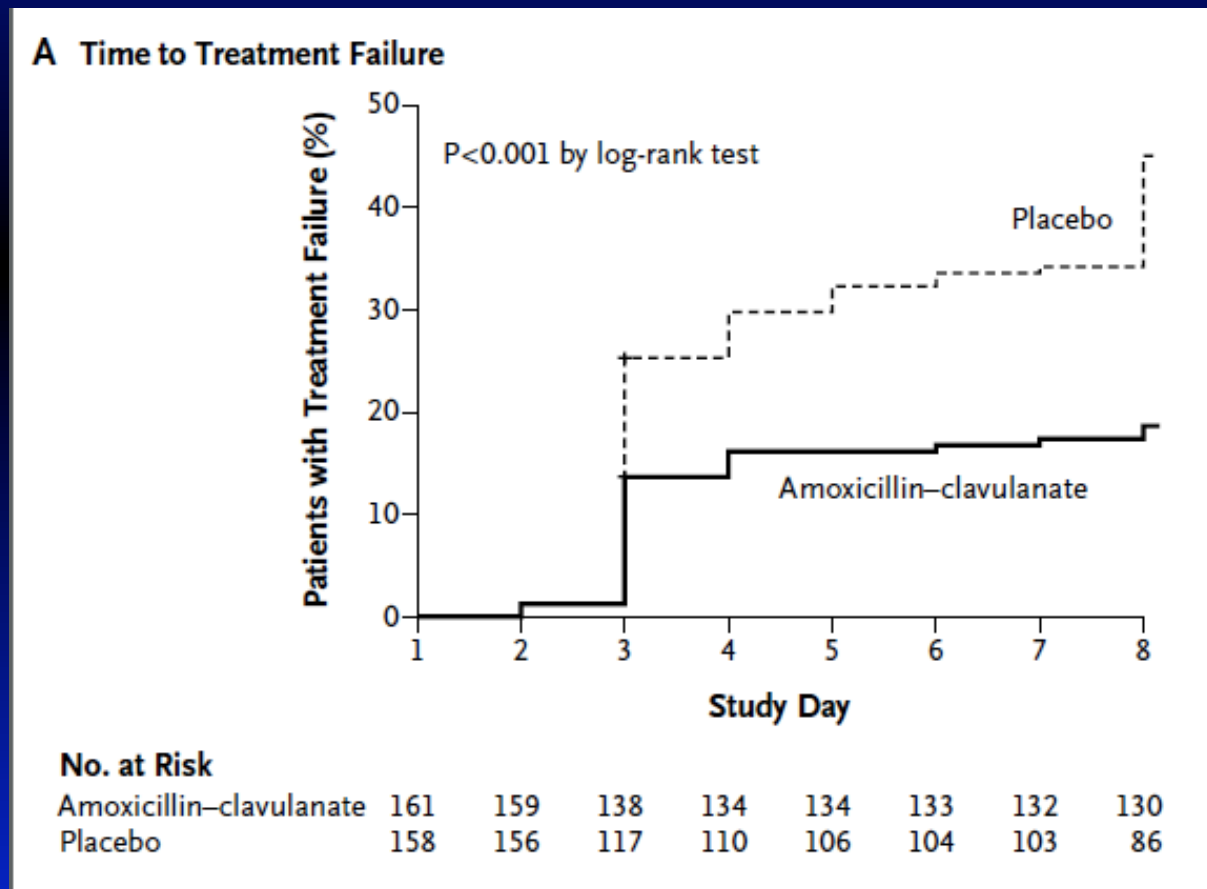
- Guidance for each indication.
- Establishes own breakpoints – can conflict with CLSI, EUCAST.
- Good communication possible and encouraged.
- No link between regulatory process and price.
 - May change with Medicare

- EMEA

- General guidance – lots of room for novel approaches.
- Communication encouraged but difficult – formal process – both sponsor and CHMP “obliged” by decisions.
 - Most sponsors use individual country agencies for communication.
- Breakpoint - Individual countries decide
 - New process exists to allow EUCAST review of proposed breakpoints for EMEA.
- Regulatory decisions linked to pricing by individual countries.

Otitis Media – middle ear infection of childhood

- 2 very recent studies – 3-5 years to complete.



DRAFT Guidance CABP 2009

- Efficacy population – microbiologically documented.
- NI margin – oral drugs – 10%.
- No prior antibiotics allowed.
- Assume – 90% power, 85% cure, 85% clinical evaluability, 25% microbiologically documented.

Total enrolled

CE 0.85

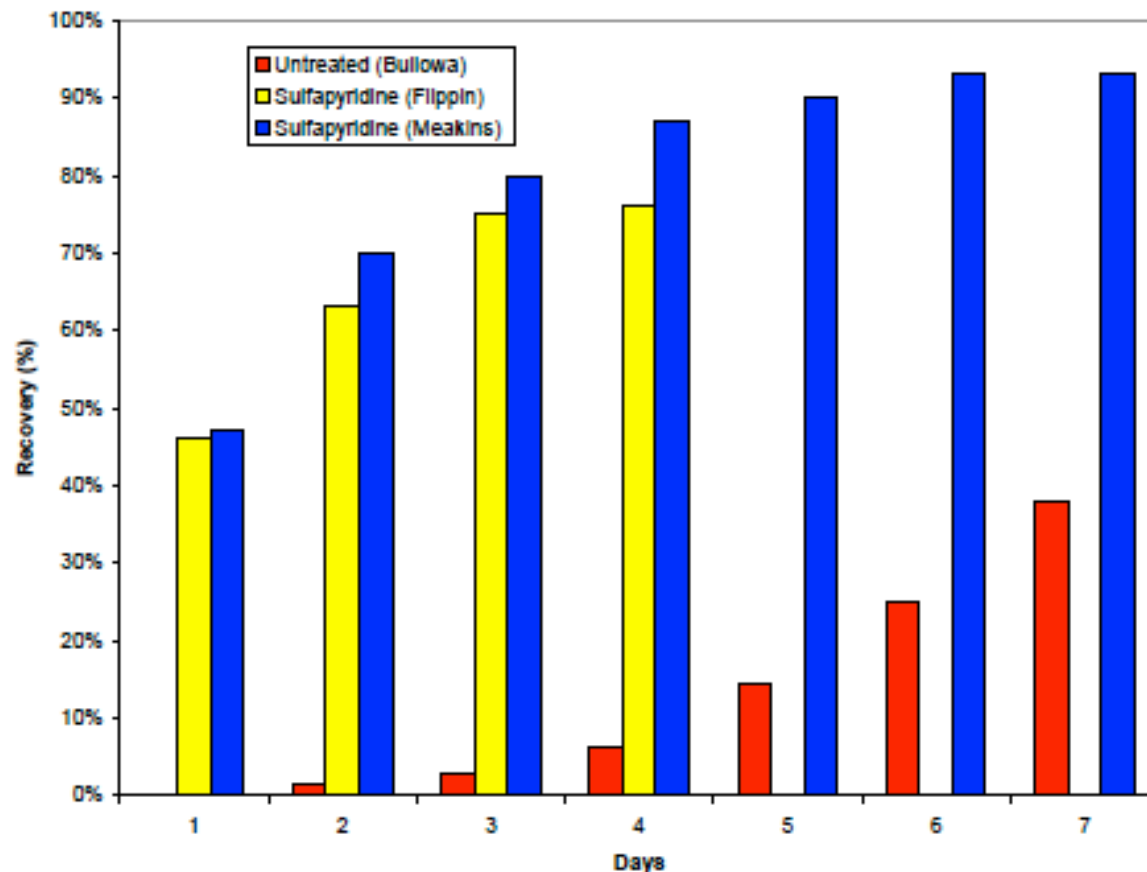
ME 0.25

2524

Total of 2 trials

5048

Antibacterial Treatment Effect on Clinical Recovery of Pneumococcal Pneumonia*



*Adapted from Bullowa (1937); Meakins and Hanson (1939); and Flippin, et al. (1939)

Early Endpoints required!

CABP Guidance

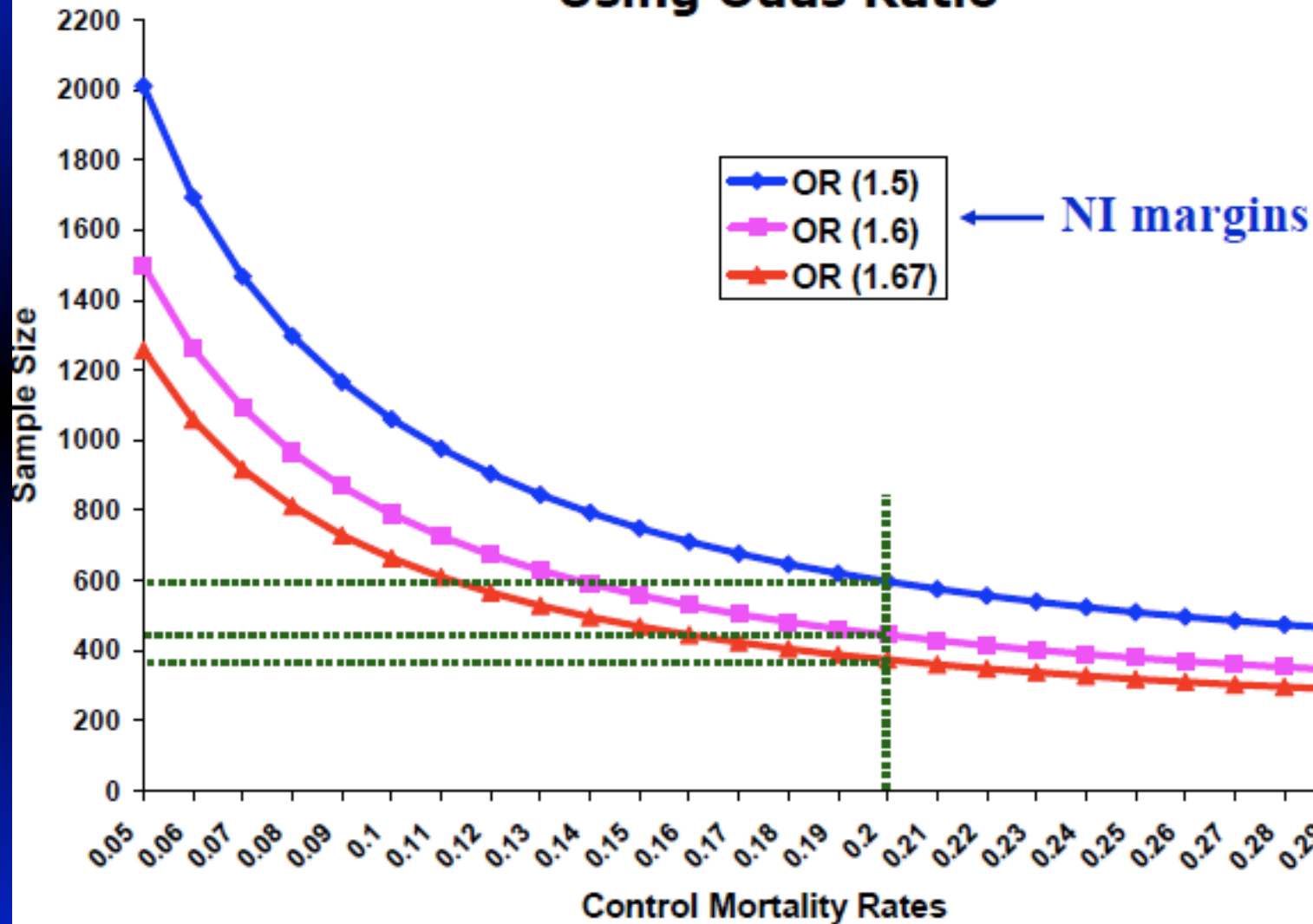
- Community acquired bacterial pneumonia – under revision in response to an uproar from stakeholders over trial feasibility and relevance of endpoints.
- At a recent AIDAC meeting the FDA proposed a series of feasible designs for IV or IV-oral antibiotics. The allowance of at least limited prior antibiotic use will provide for at least some US patients to be enrolled in these trials. Oral antibiotics remain in limbo.
- The proposed endpoints, based on historical studies, are thought to be clinically irrelevant by many.
- The more relevant endpoint of cure at TOC could be justified using pharmacometrics to establish a treatment effect and therefore a non-inferiority margin.

HABP/VABP Endpoint - Mortality

- An area of high medical need.
- The FDA has identified a body of literature that compares mortality rates after adequate vs. inadequate therapy.
 - Similar data for clinical outcome is not available.
 - Therefore – the endpoint is mortality at 28 d.
- 28 d mortality in the context of a HABP/VABP trial is a confounded variable that depends as much on comorbidities as it does on pneumonia.
- A more appropriate endpoint based on clinical outcomes could easily be justified using pharmacometrics – why don't we take advantage of this for M1 and M2 calculations?
- Once again – prior antibiotics are prohibited even though 80% of ICU patients have been on antibiotics and those are the ones we want to study to recruit those with resistant infections.
- New antibiotics under study = 0.

Sample Size: NI Trials

Using Odds Ratio



Urinary Tract Infection

- The FDA just (2/23/12) released their new Draft guidance.
- A 10% NI margin on the microbiologically evaluable population requires a study of 2-3000 patients over two trials.

One possible out – the FDA offers to discuss the possibility of a single trial – but everything depends on the margin and the use of prior antibiotics.



- The proscription against all antibiotic use during the 48 hours prior to enrollment will be a significant roadblock.
- **The guidance as it stands, is infeasible.**