8 Nov 2013 Workshop: Best of use new medicines legislation to bring new antibiotics to patients and combat the resistance problem

Innovative Medicines Initiative

Session 1 (Approval of new antibacterials): Using totality of evidence for antibiotic approval, interpretive breakpoint setting, and pediatric development

Barry Eisenstein, MD, *on behalf of EFPIA and its Industry partners*

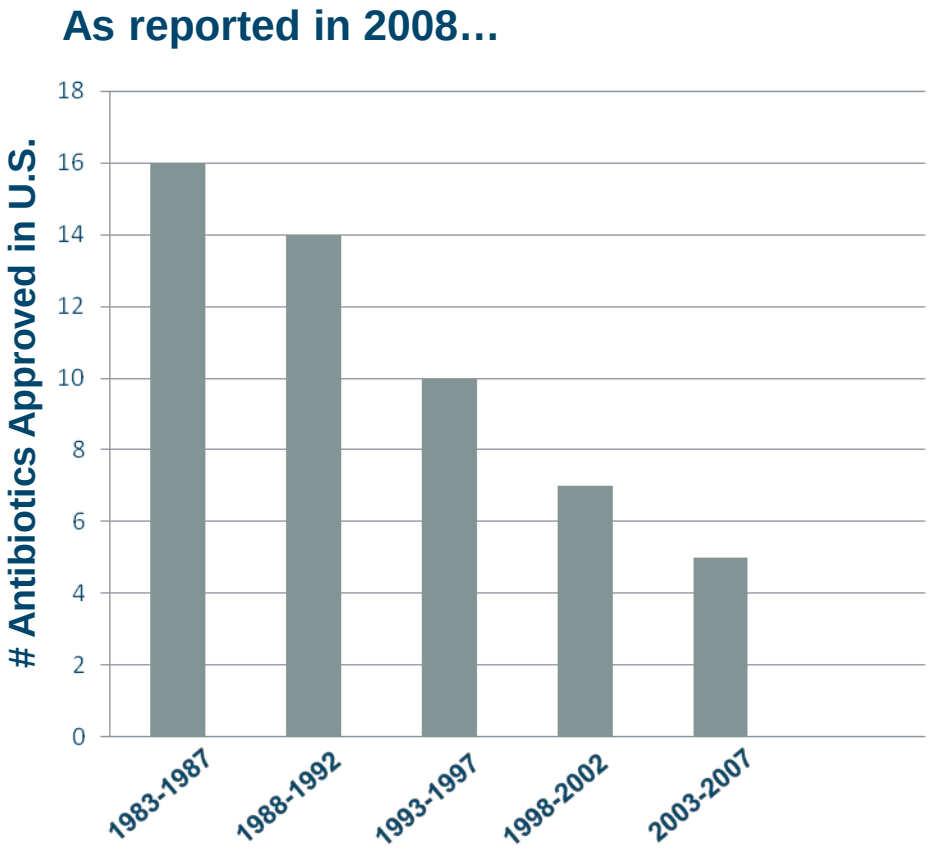
efpia

Three themes:

- **The importance of facilitating small programs**
  - Without this paradigm shift, we will be unable to prevent future epidemics particularly amongst our most vulnerable
  - The science of pharmacodynamics provides a path forward
- Interpretive breakpoints: A small thing with big impact
  - How do we decide if organism is (S)usceptible or (R)esistant?
  - It's not so simple and small programs make it even harder
  - Again, pharmacodynamics allows a successful paradigm shift
- Pediatric development
  - Clinical trials typically focus on adults, particularly the elderly
  - But, the little ones need our help, too
  - Pharmacodynamics again comes to the rescue

The Regulatory Gap

- The traditional regulatory paradigm depends on the availability of a lot of people with the target illness
- From a public health perspective, we should not wait until we have a lot of people with a life-threatening, infectious disease to start drug development
- Currently, there is no fully defined regulatory pathway for the approval of antibiotics for multi-drug resistant pathogens before a public health crisis develops



Modified from:

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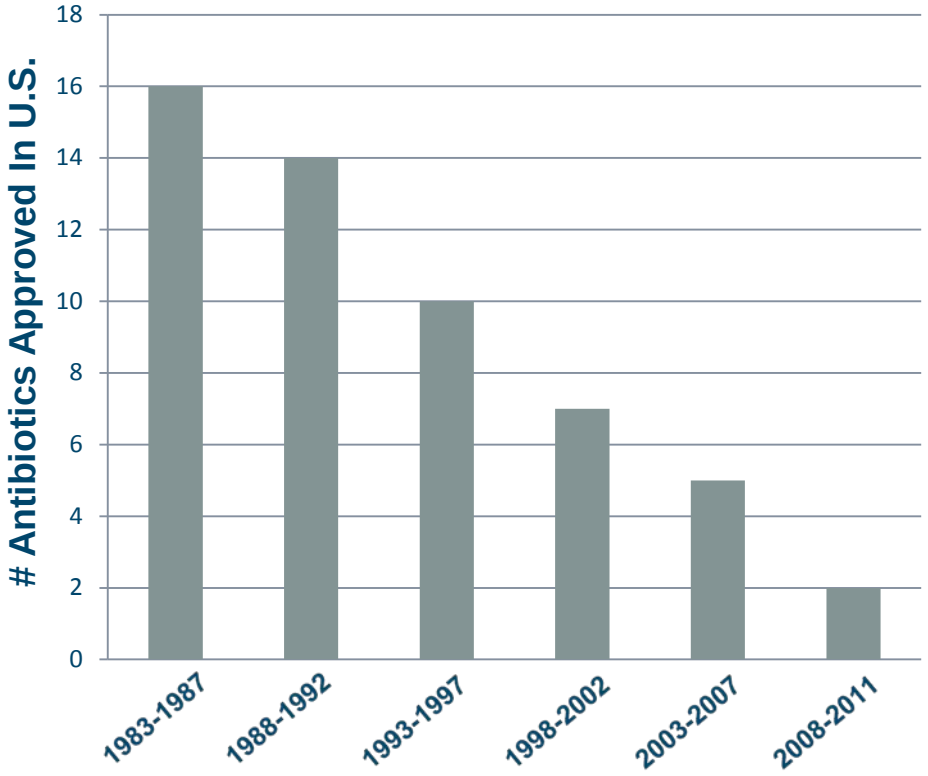
Update: The news only gets worse



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The Paradigm Issues

- 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 (e.g., *Pseudomonas*) or type of resistance (e.g., Carbapenem-Resistant Enterobacteriaceae [CRE])?
- 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
  - Ethics prevent use of placebo/ineffective drugs – **superiority is not possible**
- **The greatest risk is being unprepared! We need greater trial feasibility and regulatory predictability. We found a path for HIV/AIDS**

We've now spent several years talking about how to resolve this….

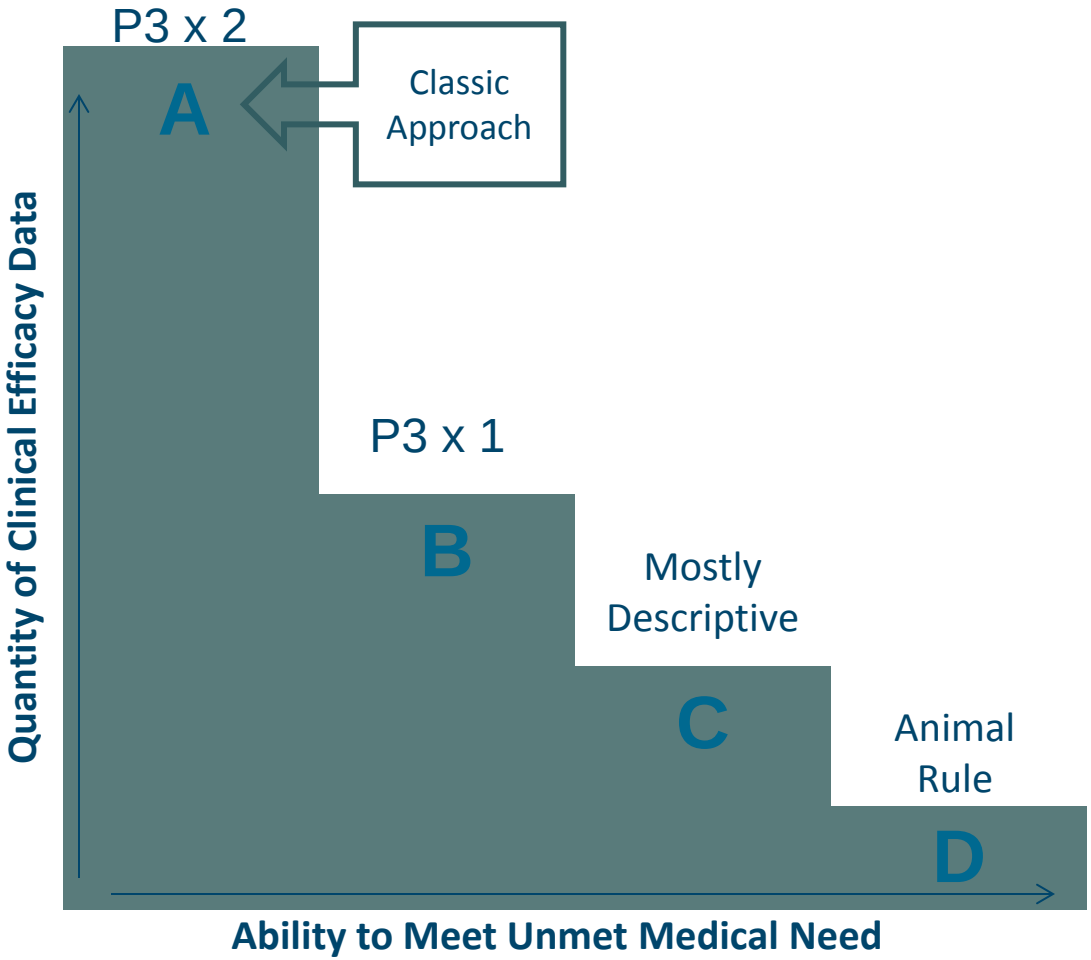
And it's exciting to see that we've found the basis for forward path that will facilitate a robust and sustainable R&D infrastructure

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

Tiered Approach: Aligning Feasibility and Quantity of Clinical Data with Unmet Medical Need



- The need for a tiered approach is real – there are real products at each tier that need a path forward
- Determination of the appropriate tier should be based on ***context***:
  - Feasibility
  - Unmet medical need
  - Strength of the preclinical data
  - By utilizing the totality of data, ***existing*** regulatory requirements can be met at each tier

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 Lancet Infectious Diseases*, 13:269-275, 2013

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

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The logic behind Tier B and Tier C

- Target of antibiotics is a pathogen, not a physiological process, and ID **clinical practice** is **pathogen-susceptibility-focused**

- Consequence: Early safety risk, low efficacy risk
  - If safety is good in Phase 1 & 2, you probably have a drug
  - Preclinical and early clinical data provide uniquely powerful predictions of efficacy → significant prior knowledge of efficacy going into Phase 3

- Infection is unusually rich in non-clinical confirmatory data. This permits an approach to approval based on TOTALITY OF DATA:
  - Use the uniquely powerful preclinical estimates* of antibiotic efficacy
  - Use the fact that the way antibiotics work (i.e., their 'pharmacological effect')† is identical across all settings (assuming adequate drug levels at site of infection, which is testable)
  - Use our ability to show exposure-response correlations from human studies that reproduce exposure-response effects proven in animals

*We can determine the critical exposure required for efficacy in a test tube and in a mouse. If this exposure is achieved in man, the likelihood of efficacy is very high.

†That effect is, of course, the drug's effect on bacteria. The "receptor" for all current antibiotics is some aspect of microbial physiology. Ultimately, the patient's improved symptoms are an "off target" consequence of bacterial clearance.

Risks justified by the therapeutic need

- The ideas of Tier B/C carry risks
  - Small datasets in sick patients → more risk from patient heterogeneity
  - There will be a lot of confounding / confusing signals
- With fewer safety & efficacy data…
  - Less depth for subset analyses to explain small variations
  - Less context for safety signals
  - *Note: Tier B/C is about efficacy. The sponsor may very well need to find ways to supplement the safety database. Model-based drug design ideas[1] may really help here.*
- Adding a single P3 study (Tier B) is really helpful
  - Will enroll only *susceptible* strains of the target pathogen
- Tier B & C must be **justified by the relative unmet need**
  - the label explicitly states the small clinical data package and limits therapeutic use to appropriate situations

1. E.g., Lalonde RL, Kowalski KG, Hutmacher MM, et al. Model-based drug development. Clin Pharmacol Ther 2007;82:21-32.

Central role of PK-PD in Tier B & C

- Totality of the data
  - Preclinical PK-PD and pharmacometric analyses to justify dosing
  - Demonstration of adequate PK in man
  - Demonstration of consistent clinical response and safety
- Tier B
  - Single P3 trial in non-MDR pathogens
  - MIC for new drug is same for MDR and non-MDR pathogens
  - Thus, PK-PD & efficacy in MDR is same as for non-MDR of the P3 trial
- Tier C
  - It's all about PK-PD. The clinical data provide a consistency check
  - Depending on showing clinical superiority is next to impossible given the ethical limitations of using placebos or non-effective therapy

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- **Interpretive breakpoints**: A small thing with big impact
  - How do we decide if organism is (S)usceptible or (R)esistant?
  - It's not so simple and small programs make it even harder
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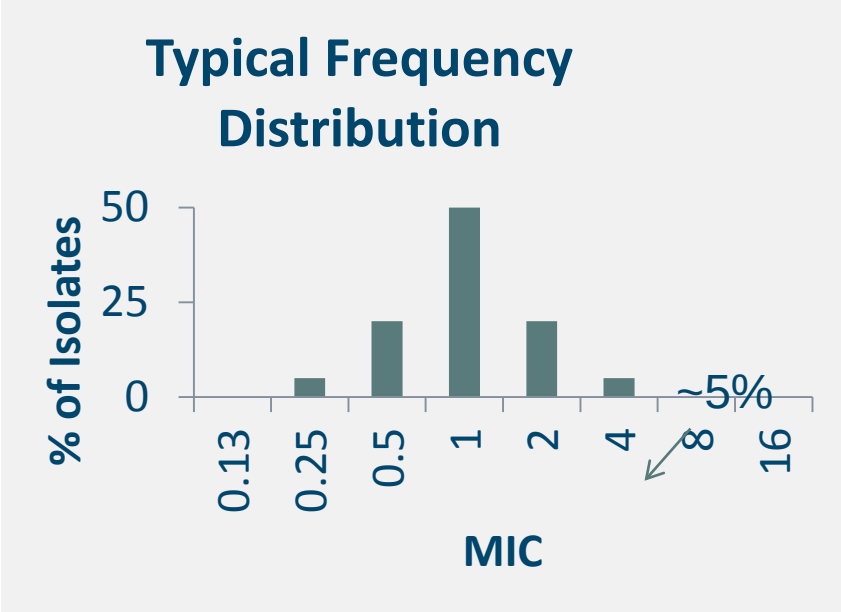
Clinical data are inadequate for breakpoint setting

- Breakpoints can only rarely be set based on clinical data
  - MIC distributions usually span 4-5 dilutions
  - Relatively few patients are infected with isolates at the highest MIC



- **We've in the past only being willing to set the breakpoint at the highest observed MIC in a clinical program**
  - **We've ignored the powerful pre-clinical pharmacodynamics evidence**
- Thus, breakpoints will be too low if we limit breakpoints to MICs for which we have clinical data **thereby negating a potential therapeutic option**
- As with Tier C programs, we have to learn to **trust the science**

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Pediatric development programs

- These have become large, expensive, and (worst of all) *slow*
- For an antibiotic, what do you really need to know?
  - The organism is the same as for adults
  - The pharmacodynamics are the same as for adults
- So, what we really need is to generate
  - Some PK data
  - Some safety data
  - For a reasonable range of ages
- Should be the approach for **all** special patient groups
- We should agree that this is reasonable and **globally harmonize** the requirements

Closing the Paradigm Gap

- An approach to the paradigm gap is suggested
  - Tier B & C: focused mostly on the pathogen, which is what physicians mostly think about anyway in their therapeutic approach
  - Implementation is not simple: Challenges to overcome
  - Implementation carries **manageable** risks for all stakeholders
- But, we must **act now** to **increase regulatory predictablity**: New options are desperately needed[1] for **new drug development**, for **interpretative breakpoint setting**, and for **pediatric approvals.**
  - By acting quickly to create approaches to describe and manage the (slight) uncertainty of smaller data packages (as we did for HIV/AIDS),
  - We will provide patients with timely access to urgently needed, life-saving antibiotics, and
  - Avoid the paradoxical situation of being forced in the future to accept even **greater** degrees of therapeutic uncertainty **(and RISK)** as antimicrobial resistance progresses in the face of no new drugs.

[1]Hersh et al., Clinical Infectious Diseases 54:1677, 2012. Among 562 respondents in a 2011 survey of the Emerging Infections Network (EIN), 64% reported using colistin during the previous year and 63% reported caring for a patient with an infection resistant to all available antibacterials