



FDA Experience with Surrogate Endpoints and Drug Development in Other Therapeutic Areas

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- The opinion expressed in this presentation do not reflect official support or endorsement by the Food and Drug Administration.
- I have no conflicts.



Oncology Products

Courtesy of: Paul G Kluetz, MD
FDA Oncology

Clinical Trial Design

Two Approval Pathways

Regular Approval

- Regular approval requires
 - Substantial evidence of Safety and Efficacy
 - Well-controlled clinical trials (usually 2 or more)
 - based on **prolongation of life, a better life or an established surrogate for either of the above**

- Efficacy endpoints for Regular Approval normally Direct Measures or Established Surrogates:
 - Overall Survival (“Prolongation of life”)
 - Patient Reported Outcomes (“A better life”)
 - SRE in Prostate Ca or DFS in Breast Ca (“Established Surrogates”)

- “Safe and Effective” –no comparative efficacy
 - Allows for non-inferiority designs

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Accelerated Approval

- “Provide meaningful therapeutic benefit... over existing therapies”

- *Can be based on a “Surrogate endpoint... reasonably likely... to predict clinical benefit”*

- But are “Subject to the requirement that the applicant study the drug further”

- These Post-Marketing Clinical Trials are Required
 - Should usually be underway at the time of accelerated approval
 - Applicant should carry out studies with due diligence

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Risks/Benefits and Endpoints

Accelerated Approval

- **Benefits and Risks to the Accelerated Approval Pathway**

- **Benefits:**

- Use of an unestablished surrogate endpoint
 - Usually provides for earlier events and smaller, quicker trials

- **Risks:**

- Must demonstrate product is better than existing therapy (unlike regular approval, there is an implied comparative efficacy requirement here)
 - Must complete post-marketing trials and confirm meaningful clinical benefit

- **10% of Accelerated Approvals in oncology have been withdrawn for failure to confirm a benefit**

- NOT a failure of the accelerated approval program
 - We expect a small percentage of products to fail to verify this benefit
 - This is the anticipated tradeoff for earlier availability of promising anti-cancer agents.

Refresher! Efficacy Endpoint Categories

- Direct Measure of Clinical Benefit, "Feels, Functions, Survives"
 - Overall Survival, Measures of symptoms or function
- Established Surrogates of Clinical Benefit
 - Substantial existing data and regulatory precedence
 - Higher certainty that the surrogate is predicting true clinical benefit (DFS in Breast Ca)
- Unestablished Surrogate of Clinical Benefit
 - Limited existing data, lack of regulatory precedence
 - Lower certainty that the surrogate is predicting true clinical benefit (RR in Lung Cancer)

Risks/Benefits and Endpoints

Refresher! Efficacy Endpoint Categories



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Unestablished Surrogate of Clinical Benefit

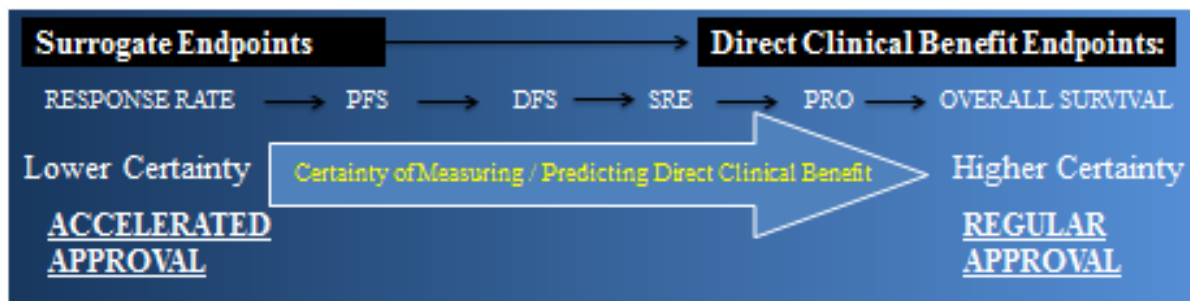
- Limited existing data, lack of regulatory precedence
- Lower certainty that the surrogate is predicting true clinical benefit (RR in Lung Cancer)

Accelerated Approval

- Benefits and Risks to the Accelerated Approval Pathway
 - Benefits:
 - Use of an unestablished surrogate endpoint
 - Clinically provides for earlier access and smaller, quicker trials
 - Risks:
 - Most depressive product is being than existing therapy (with regular approval, there is an implied collaborative regulatory requirement later)
 - Most complete post-marketing trials and confirm meaningful clinical benefit
- 10% of Accelerated Approvals in oncology have been withdrawn for failure to confirm a benefit
 - NOT a failure of the accelerated approval program
 - We expect a small percentage of products to fail to verify this benefit
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Oncology Summary

Efficacy Endpoints and Approval Pathways



- The ~~greater uncertainty~~ that exists that the endpoint measures direct clinical benefit, the more data that will be required to support approval:
 - Large magnitude of effect
 - Internal consistency via key secondary endpoints
 - Randomized Data
 - Supporting Clinical Trials
 - Confirmatory Post-Marketing Trials (Accelerated Approval)

Antimicrobial Products

Courtesy of: John H. Rex, MD
Keynote Speaker ICAAC 2014

Enabling drug discovery & development to
address the crisis of antimicrobial resistance:

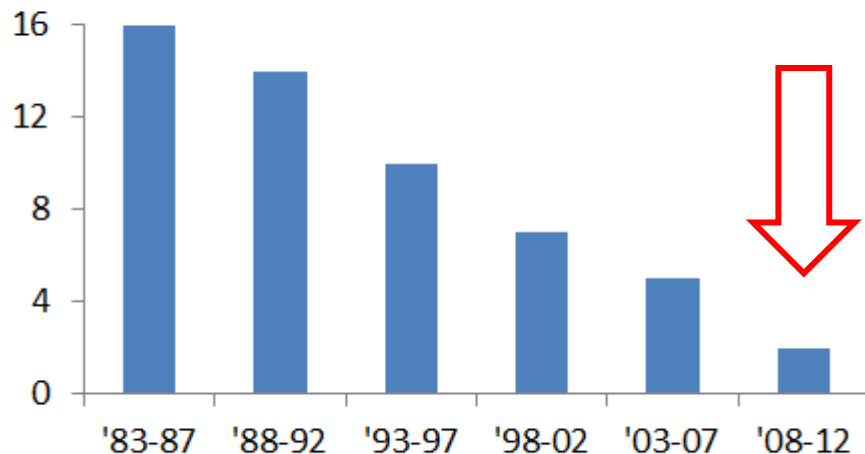
New tools, new pathways, & remaining
challenges

The Challenge: Declining Antimicrobial Development

IDSA: “Bad Bugs No Drugs”

In the face of this, few new drugs!

Rate of new antibacterials over 30 years¹



¹Boucher et al. Clin Infect Dis 56:1885-94, 2013. Note: This graph does not show several recent new approvals (see later in this talk). But, the overall message remains correct – very few new drugs!

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Why so few new drugs?

For today, let's break it down to four things

Three big problems

1. It's hard to discover new antibiotics
2. It's hard to develop new antibiotics
3. The economic value of a new antibiotic to a developer can be close to zero

And the idea that

4. Fixing this requires us to see it as an ecosystem
- This lecture will explore these themes in detail – But first, one more introductory comment...

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Challenge with Clinical Trials

Development is hard

A series of linked challenges

- The superiority-based approaches that work for other areas do not offer a long-term path to a diverse, vibrant antibiotic pipeline
- We have to make non-inferiority (NI) work. How?
 - The tiered framework
- The necessity for pathogen-focused labeling
- The role of (rapid) diagnostics
- Other issues

The problem with superiority

- For superiority in a prospective, randomized study to be a reliable path for antibiotics, **we have to be in a situation in which randomization to potentially ineffective or toxic therapy is acceptable^{1,2}**
 - Remember: Untreated infections are lethal
 - Unless we have no other choice, we must not enroll if the patient's pathogen is resistant and the comparator thus likely ineffective
 - For comparator-susceptible pathogens, modern comparators at full dose are very effective

Framework for— “diverse, vibrant pipeline”

That’s a problem we must solve

- To restore vitality to the pipeline and ensure we have the life-saving drugs we will need in the future,
- We have to move these models back into positive territory

And, we’re now doing just that...

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Global Leadership: A partial list

2003 et seq: IDSA: “Bad Bugs, No Drugs”



17 Sep 2009: (EU) Swedish presidency

- “Innovative Incentives for Effective Antibacterials”



7 April 2011: WHO World Health day on AMR

- “No action today, no cure tomorrow”



17 Nov 2011: (EU) ND4BB program

- PPP for Discovery & Development



2011 forward: (US & EU) FDA & EMA

- A steady stream of new guidances



2012: (US) GAIN Act (see subsequent slide)

3-4 Oct 2013: (EU) Chatham House Conference

- “Antimicrobial resistance: Incentivizing Change Towards a Global Solution”



2014: (US) PCAST Report

- Hopefully out soon



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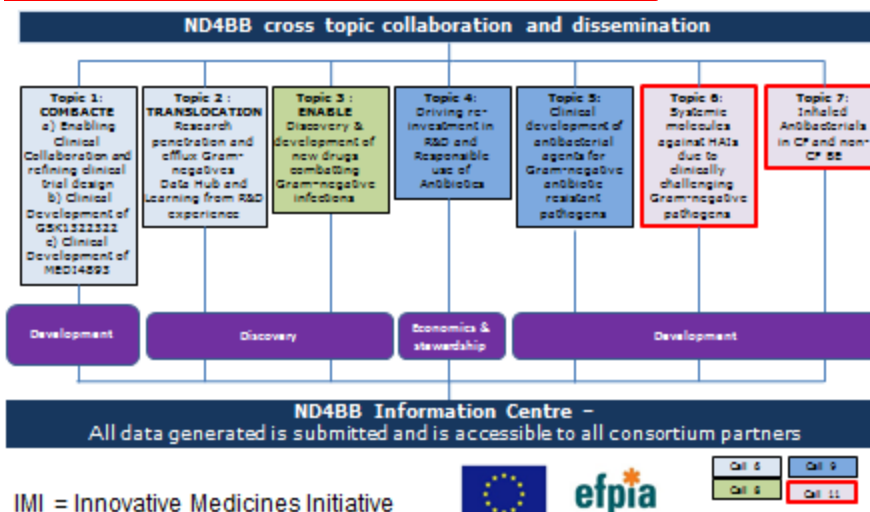
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Collaboration

Public-Private Partnerships *In the US: NIAID & BARDA*

- NIAID: Antibacterial Resistance Program
 - Extensive array of preclinical services
 - Phase 1 clinical units
 - ARLG (Antibacterial Resistance Leadership Group)
 - Modeled on ideas such as I-SPY, master protocols are being considered as a way to provide infrastructure that would support development efforts
- BARDA (Biomedical Advanced Research & Development Authority)
 - Several public-private partnerships established to date

In the EU: IMI's ND4BB program (New Drugs For Bad Bugs)



IDSA - 10 by '20 initiative

Net Present Value (NPV) Tackling the NPV model

Two intriguing economic ideas

Updated

• (Push) Refundable tax credits

- For some percentage (e.g., 50%) of qualified expenses, the company either gets a tax credit (if the company has income) or receives a payment of that amount
- Has immediate impact on NPV while also ensuring the company has "skin in the game" that ensures delivery

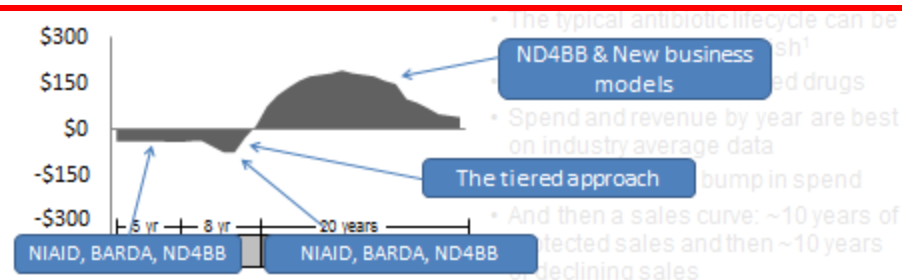
• (Pull) Insurance-based approaches

- National acquisition at a fixed, predictable rate (e.g., US buys \$100m/year of a new antibiotic for 5 years)
- Annual fee guarantees availability of a certain number of courses of therapy, whether used or not
- We should be pleased to buy but not use the drug, just as we are pleased when our life insurance does not pay off

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We're now tackling the entire model!



- With support from NIAID, BARDA, ND4BB, & others plus the tiered approach, we are truly taking a **systems approach** to this problem
- The Discovery and Development support + the tiered approach is already having an impact
- **Last step: Rethinking value and business models**

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GENERATING ANTIBIOTIC INCENTIVES NOW (**GAIN**)

FDASIA created Section 505E for Qualified Infectious Disease Products (**QIDPs**). A QIDP is defined as "an antibacterial or antifungal drug for human use intended to treat serious or life threatening infections" including those caused by antibiotic or antifungal resistant pathogens, novel or emerging infectious pathogens, or "qualifying pathogens.

Parallels in Transplantation

- Effective therapy is available for many patients
 - Analogous to “susceptible pathogens”
- New therapies are needed
 - To address unmet medical needs
- Superiority vs. Non-inferiority trials challenging
 - Ineffective comparator regimen (no treatment) unethical
 - Additional primary endpoint(s) (beyond AR)
 - Measure direct clinical benefit
 - Measure (unestablished) surrogate endpoint

Parallels in Transplantation

- Regular approval vs. Accelerated Approval
 - For the latter need to identify (unestablished) surrogate endpoints
 - Risks and benefits of surrogates (experience in oncology)
- Orphan indication(s) and patient enrollment challenge
- Role of rapid diagnostics
 - Incorporate in clinical studies
- Stalled/stopped innovation & drug development



THANK YOU