

Development of Broad Spectrum Antibiotics

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Safe and effective

Substantial evidence from adequate and well controlled studies so that a physician qualified on the basis of training and experience could reasonably conclude that the drug has the effect claimed in labeling...

No added value

There is no requirement that a drug be better than what is already available either by safety or efficacy. Ultimately it must be efficacious and “appropriately” safe.

Areas of “Unmet Need”

Gram + Infections

Gram – Infections

Fungal Disease

Viral Disease

Countermeasures

Facilitate Development

- Early Guidance
 - Formal and informal communication
 - Advisory committee input
- Regulatory Tools
 - Subparts “E” & “H”
 - Fast Track designation
 - Exclusivity

Definition of Broad Spectrum

- Has evolved over time
 - Recognition of new pathogens
 - Impact of antimicrobial resistance
- Today would encompass both gram + and gram – organisms
 - Atypical agents that cause pneumonia
 - Non-bacterial pathogens
- Broad spectrum could apply to antifungals and antivirals as well

Certain Basics for all Drug Development

- Chemistry and manufacturing information
- Pre-clinical safety information
- Clinical pharmacology information

Additional information for Anti-Infective Development

- Relevant microbiology information both “in vitro” and ideally “in vivo”
- PK/PD information as available
 - The role for this type of data in anti-infective drug development is still evolving

A Broad Range of Indications

- Serious disease with high treatment effect of antimicrobials
 - Meningitis
 - Community Acquired Pneumonia
- Less serious disease where benefit of therapy is less certain
 - AECB
 - Sinusitis

Overview of Trial Design for Anti-Infectives

- Trials generally have active –controlled designs
- Placebos acceptable in certain limited situations
- Superiority vs. Non-Inferiority
- Issues with Non-Inferiority Trials

Overview of Trial Design for Anti-Infectives –II

- Choice of comparator
- Initiation and duration of therapy
- Endpoints
 - Type
 - Timing

Clinical Trial Issues

- Reduce the size of the clinical trial program
- Address the tradeoff between our ability to assess effectiveness and the resources required to perform a trial.
- Substituting quality for quantity in at least some clinical studies
- Strengthening the link to clinical inference
 - How studies and data fit together as a package
- Consequences of the above

How Much Clinical Data is Required?

- How many clinical studies are needed to support an indication?
- How many clinical cases due to a given organism are needed to support inclusion of that organism in the indications section?

Clinical Data for a Broad Spectrum Anti-Infective

- Information on activity against relevant organisms in appropriate body sites (indications)
- Can information from different indications “support” one another?
- Can information on similar organisms isolated in different indications support one another?
- Can information on different organisms “support” one another?

Can We Leverage Clinical Data?

- PK
- Tissue penetration
- Severity of illness
- Performance of the drug

Can We Leverage Microbiology Data?

- Pre-Clinical considerations
- Clinical considerations
- Can activity against susceptible isolates support a resistance claim?

The Animal Rule: Overview

- Definitive human efficacy trials cannot be conducted and field trials have not been feasible
- The animal rule is not applicable when other regulatory tools such as accelerated approval can be employed
- Human safety data is still required

The Animal Rule: Overview

Continued

- Pathophysiology of disease and/or toxicity of the substance and mechanism of prevention or reduction of severity by CM are reasonably well understood
- Effect that is demonstrated in more than one species that is expected to be predictive of response in humans. An effect single species may be acceptable if that species is sufficiently “well characterized” to be predictive of response in humans.

The Animal Rule: Overview Continued

- Animal endpoint clearly related to desired human endpoint generally enhancement of survival or prevention of major morbidity
- PK and PD information and other relevant data in animals and humans allows adequate dose selection in humans

The Animal Rule: Possibilities and Potential issues

- Otherwise impossible to study organisms
- Considerations with models
 - Pathophysiology of disease as opposed to that in humans
 - Dosing regimen
 - Experimental design
- Need for adequate safety data
- How do we know the drug will really work?

New Indication for an Already Approved Drug

- How does the new indication relate to already approved indications?
- How do the likely organisms in the new indication relate to those in the already approved indications?
- Can already approved indications support a new indication under the animal rule?

Broad Spectrum Countermeasures

- Most of the principles previously discussed will remain applicable
- How much if at all data from studies in one disease could support an approval in another disease would depend upon the specifics of the situation
- Animal models for efficacy for each indication will almost surely be required

Availability of New Products

- IND
- EUA: Emergency Use Authorization
- Approval