'Infectious Diseases - Laying out the Therapeutic and Regulatory Landscape'

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Bad Bugs - No Drugs

- Community acquired methicillin resistant *Staphylococcus Aureus*
- Multiple drug resistant gram negative hospital pathogens
- Multiple drug resistant tuberculosis

World Medical Association and the Declaration of Helsinki

- Building on the Nuremburg Code promulgated after WW II, the first Declaration in 1964
  - Admonished physicians to safeguard the interests of the individual patient
- The Declaration of 1975
  - Closed the door on studies that might benefit society or science but had the potential to put an individual patient's wellbeing at risk
- The Declaration of 1989
  - Only slightly modified from 1975
  - This is the last version that the FDA approves of !!!

World Medical Association and the Declaration of Helsinki

- The Declarations of 1996 and 2000
  - Eliminate the distinction of therapeutic and non-therapeutic research
  - All research had to benefit the research subject
  - Placebo controlled studies would be acceptable only when no acceptable therapy was available
- The Declaration of 2008
  - Softened only very slightly the restriction on placebo controlled studies

The FDA and the History of Antibiotic Drug Development

- Taste of Raspberries, 1937 Elixir of Sulfanilamide
  - Sulfanilamide, was useful in the treatment of streptococcal infection but no liquid form was available
  - S.E. Massengill Co, found that the drug was soluble in diethylene glycol, the liquid was pleasant to the taste and was immediately successful in the market
  - ***Over 100 patients died***
  - *The Massengill company didn't test the toxicity of diethylene glycol*
- The result was the 1938 FD&C act of 1938

Kefauver-Harris act of 1962 and Antibiotics

- Sulfa, Penicillins, Cephalosporins, Aminoglycosides, Chloramphicol, Tetracyclines, Macrolides, Lincosamides, Streptogramins, Glycopeptides, Rifamycines, Nitroimidazoles, and Quinolones - *were discovered and developed prior to the 1962 act requiring proof of efficacy!*
- Dihydrofolate reductase inhibitors (TMP) Oxazolidinones (Zyvox) and Lipoglycopeptides (Cubicin) – *registered 1998, 2000, 2002*

Antibiotic Drug Development - 1992

- The FDA and the Infectious Disease Society of America began working together to define acceptable study designs for a wide number of indications in the mid-1980's published their consensus document in 1992
  - Clarified the diagnosis and classification of disease
  - Increased to some extent the cost of introducing novel agents
- The European Society of Infectious Disease published their version in 1993
  - Complicated pharma's situation somewhat…..

Since the Consensus Documents of 1992 and 1993

- The predictive value of Pharmacokinetics and Pharmacodynamics (PK/PD) comes to the foreground in the mid-1990's
  - Just because a drug cures skin infection doesn't translate to efficacy in otitis media, sinusitis, or meningitis
  - Just because a drug eliminates one pathogen at a specific site doesn't mean that it eliminates all
- Proof of microbiological efficacy at the site of infection becomes critical to success at the agency and AIDAC *shortly after* the 1998 Guidance for the Industry documents are issued

2002 thru 2008 at the Agency and at AIDAC

- Microbiologic outcome - a more critical part of the discussion
- Abrupt halt in the idea of a “Clinical” Indication for Infectious Diseases
  - Acute Sinusitis
  - Acute Exacerbation of Chronic Bronchitis
  - Acute Otitis Media
  - Uncomplicated Skin Infections
- Proving efficacy

Acute *Bacterial* Sinusitis – Draft Guidance -2007

- Name of indication changes
- Clinical improvement, micro outcome, and safety are all critical
- Study designs using non-inferiority to comparator - not acceptable
- Patient reported outcomes (PRO)
- AE leading to withdrawal = Failure

Acute *Bacterial* Otitis Media –Draft Guidance 2008

- Name of indication changes
- Clinical improvement, micro outcome, and safety are all critical
- Study designs using non-inferiority to comparator - not acceptable
- Patient reported outcomes (PRO)
- AE leading to withdrawal = Failure

Acute *Bacterial* Exacerbations of Chronic Bronchitis in Patients *with COPD* – Draft Guidance 2008

- Name of indication changes
- Criteria for patient selection changes
- Clinical improvement, micro outcome, and safety are all critical
- Study designs using non-inferiority to comparator - not acceptable
- Patient reported outcomes (PRO)
- AE leading to withdrawal = Failure

Uncomplicated Skin and Soft Tissue Infections – Planning a study today

- Major changes are underway in the FDA's thinking on this subject
- Studies of uSSTI will likely share many of the characteristics of ABOM study
- A non-inferiority study comparing efficacy of the new drug to a currently licensed comparator… no longer an option?
- A superiority design

Studies of Complicated Skin and Soft Tissue

- Study designs
  - Double blind, randomized, controlled comparisons to a currently registered comparator acceptable but difficult
  - ↓ Non-inferiority margin
  - Alternate design should be considered
- PRO data will be expected

Community-Acquired Bacterial Pneumonia

- Application of preclinical PK/PD data
- Stratification by severity
- PRO data
- Study designs
  - Non-inferiority studies permissible but will not be easy
  - Alternate designs should be considered

General ICH Guidance documents and the Development of Anti-infectives

Each of the new draft Guidance documents issued by the agency reference:

- ICH E8 - General Considerations
- ICH E9 - Statistical Principles
- ICH E10 Choice of Control Groups

Current State of the Art
... Studies that Demonstrate Superiority

- Time to
  - Culture negativity
  - Resolution of lesion
  - Resolution of fever
  - Hospital discharge
  - ↓ relapses
- Patient Reported Outcomes ("PRO")

  Time to:
  - Symptomatic relief
  - Return of appetite
  - Ability to provide self care
  - Improved mobility
  - ↑ sense of well being
- ↓ side effects

The Animal Rule
(21 CFR 314, subpart I)

- Department of Defense
  - DoD “risk – benefit” analysis option
- FDA
  - Animal trials are not a substitute for clinical trials in man
  - Emergency use options

Issues Driving Regulatory Change in the Past Two Decades

- Evolution of clinical practice
- Application of Pharmacokinetics and Pharmacodynamics
- Societal changes
  - Risk Benefit Ratio's have changed
  - Consequences of not knowing enough

Questions?