ANIMAL RULE II:
CDER PERSPECTIVE/CASE STUDIES

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ANIMAL RULE: GOALS OF PRESENTATION

- Review criteria for drug approval under the Animal Rule
- Examples of issues arising when applying the Animal Rule to the design and conduct of studies
- Examples of solutions to these issues

ANIMAL RULE

21 CFR 314 Subpart I
21 CFR 601 Subpart H
May 31, 2002

- Allows reliance on adequate and well-controlled animal studies as evidence of effectiveness
- Applies when studies in humans are unethical/infeasible

ANIMAL RULE

- Rationale: further development of treatments to reduce or prevent the toxicity of chemical, biological, radiological or nuclear substances
- Does not apply if efficacy evaluations are feasible under any other FDA regulation

ANIMAL RULE: FOUR SCIENTIFIC CRITERIA NEEDED FOR APPROVAL

- 1: Pathophysiology of disease AND mechanisms of action of the drug must be well understood
- 2: Therapeutic effect demonstrated in more than one animal species, or in one sufficiently well-characterized animal model, expected to react with a response predictive for humans

ANIMAL RULE: FOUR SCIENTIFIC CRITERIA (continued)

- 3: Animal study endpoint is clearly related to the desired benefit in humans
  - Enhancement of survival
  - Prevention of major morbidity
- 4: Pharmacokinetic and pharmacodynamic data of the product in the animal models allows selection of an effective dose in humans

ANIMAL RULE: ADDITIONAL REQUIREMENTS

- Research performed under GLP standards
- Safety data obtained from humans
- Need for post-approval (Phase 4) studies

EXAMPLE 1: PYRIDOSTIGMINE BROMIDE (PB)

- PB approved as pre-exposure antidote to nerve agent Soman (February, 2003)
  - To date, the only product to have an indication approved under the Animal Rule
  - Approval limited: “FOR MILITARY COMBAT USE ONLY”

PB APPROVAL (2)

- Key points regarding PB approval
  - Need to understand pathophysiology of the toxic agent, and the mechanism of the drug's activity against the agent
  - Need for more than one animal species expected to react with a response predictive for humans

PB APPROVAL (3)

- Pathophysiology of disease/mechanism of drug action
  - Soman and other nerve agents disrupt functioning of the neuromuscular junction
    - IRREVERSIBLE INHIBITION of acetylcholinesterase (A-ChE)
    - Excess acetylcholine (A-Ch) builds up
    - Overstimulation leads to respiratory arrest (failure of respiratory muscles, excessive respiratory secretions and bronchoconstriction, central respiratory depression)

PB APPROVAL (4)

- PB protective mechanism
  - Reversibly binds A-ChE, temporarily protecting against irreversible Soman effects
  - BUT, atropine and pralidoxime (2-PAM) needed to counter the effects of Soman and to prevent PB potentiation of the Soman effect

PB APPROVAL (5)

- Early difficulties in assessing PB activity in animal models
  - Studies in small animals (mice, rats) revealed PB effects to be small and inconsistent
  - PB effects in mice and rats masked by high blood levels of carboxylesterase in these species
    - Inactivates Soman in the blood, making the animals highly resistant to Soman effects

CARBOXYLESTERASE (CaE): INTERSPECIES DIFFERENCES

SPECIES	PLASMA CaE (uM)	SOMAN LD_{50} (uM)
Human	0	?
Rhesus	0	13
Rabbit	0.3	20
Guinea pig	0.9	28
Rat	4.2	104
Mouse	6.1	119

PB APPROVAL (6)

- Efficacy of PB + atropine + 2-PAM as prophylaxis against Soman first demonstrated consistently in guinea pigs
- Critical PB efficacy study performed in rhesus macaques
  - PB + atropine + 2-PAM increased Soman LD_{50} ≥40-fold over untreated monkeys
  - PB + atropine + 2-PAM increased Soman LD_{50} ≥25-fold over atropine and 2-PAM alone

PB APPROVAL: SUMMARY

- Precise understanding of the pathophysiological action of Soman and of PB's activity against the agent critical to ultimate approval and instructions for use
  - CAUTIONS
    - PB approved for use as PRETREATMENT for Soman
    - PB efficacy dependent upon rapid use of atropine and pralidoxime after Soman exposure
    - PB taken immediately prior to, or at the time of Soman exposure may exacerbate effects of a sub-lethal Soman dose
- Fundamental, unanticipated biological differences between species (presence or absence of carboxylesterase) resulted in differential efficacy of PB
  - Importance of understanding pathophysiological mechanisms
  - Importance of using multiple species

EXAMPLE 2: GENTAMICIN EFFICACY IN PNEUMONIC PLAGUE

- Key issues regarding the Animal Rule
  - Importance of understanding pathophysiology of disease and mechanism of drug action
  - Importance of pharmacokinetic (PK) studies, and PK bridging between animals and humans
  - Requirement for GLP standards

GENTAMICIN FOR PLAGUE: NATURAL HISTORY STUDY

- Indication sought: TREATMENT of pneumonic plague
  - Not pre- or postexposure prophylaxis
- Timing of gentamicin intervention was the key relevance of understanding plague pathophysiology
  - Key question: when to intervene?
- Approach taken: natural history study
  - Performed at USAMRIID, with NIAID support

GENTAMICIN FOR PLAGUE: NATURAL HISTORY STUDY (2)

- Goal: determine timing for gentamicin intervention
  - 6 African green monkeys exposed to aerosolized *Y. pestis*, strain CO92
    - Gentamicin MIC = 1 µg/mL
  - Planned dose: 100 ± 50 LD_{50}
    - Delivered via USAMRIID automated aerosol exposure platform

GENTAMICIN FOR PLAGUE: NATURAL HISTORY STUDY (3)

- Results
  - Four of six animals became bacteremic after aerosol exposure to > 20 LD_{50} of *Y. pestis*
    - Insufficient exposure to viable organisms likely responsible for failure to develop disease in two
  - All bacteremic animals were blood culture positive no later than 72 hours post-exposure
  - Fever was the most consistent early clinical sign of disease

GENTAMICIN FOR PLAGUE: NATURAL HISTORY STUDY (4)

- Natural history study of aerosolized *Y. pestis* exposure resulted in the following trial design regarding timing of gentamicin intervention for a *treatment* indication:
  - 76 hours after exposure to *Y. pestis*
  - Or development of consistent fever (≥ 1.5°C above baseline temperature x 2 hours) in the majority of the monkeys in the exposure cohort

GENTAMICIN FOR PLAGUE: PHARMACOKINETIC STUDY

- Goals
  - Determine gentamicin dose that would result in a peak serum gentamicin concentration of 10x the *Y. pestis* MIC (10µg/mL)
  - Determine the equivalent human gentamicin dose
- Performed at SRI, under NIAID contract

GENTAMICIN FOR PLAGUE: PHARMACOKINETIC STUDY (2)

- Methods
  - 12 AGMs (6 male, 6 female)
  - Single dose
    - IM (n = 6)
    - IV, 20 minute infusion (n = 6)
  - 3 mg/kg, 4.5 mg/kg, 6 mg/kg doses
    - Target peak serum concentration of gentamicin = 10µg/ml

GENTAMICIN FOR PLAGUE: PHARMACOKINETIC STUDY (3)

- Methods (continued)
  - 1 week washout between doses
  - Blood sampling: days 1, 8 and 15
    - IM: predose, 2, 20, 40 minutes and 1, 2, 3, 6, 8 hours after injection
    - IV: predose, end of infusion, 20, 40 minutes and 1, 2, 3, 6 and 8 hours after infusion

GENTAMICIN FOR PLAGUE: PHARMACOKINETIC STUDY (4)

- Results
  - Lowest gentamicin dose from the PK study achieving the target peak serum concentration (10 µg/ml) = 3 mg/kg
  - A once daily dose leaves the serum gentamicin concentration below *Y. pestis* MIC of 1 µg/ml for approximately 17 hours
  - Dosing every 12 hours results in greater time above the serum gentamicin MIC for *Y. pestis*

GENTAMICIN FOR PLAGUE: PHARMACOKINETIC STUDY (5)

- Results (continued)
  - 3 mg/kg every 12 hours gentamicin dose in AGMs mimics a daily human gentamicin dose of 10 mg/kg
  - **KEY PROBLEM**: 10 mg/kg daily gentamicin dose in humans is greater than the maximum recommended dose of 5 mg/kg/day in humans with life threatening infections
    - Would increase risk of ototoxicity and nephrotoxicity

GENTAMICIN FOR PLAGUE: PHARMACOKINETIC STUDY (5)

- **DECISION**: Use 3 mg/kg every 12 hour dose for INITIAL efficacy study
  - Achieve “proof of concept” (best chance of gentamicin efficacy)

GENTAMICIN FOR PLAGUE: PHARMACOKINETIC STUDY (5)

- **CONSEQUENCE**: Further studies will be necessary for applicability to humans under the Animal Rule
  - If gentamicin efficacy established against pneumonic plague in AGMs at 3 mg/kg every 12 hours, will need to test lower doses with acceptable relative toxicity profile in humans

GENTAMICIN FOR PLAGUE: GLP REQUIREMENTS UNDER THE ANIMAL RULE

- ISSUE: Efficacy studies must be conducted under GLP standards
  - 21 CFR 58
- PROBLEM: Animal aerosolization facilities not GLP-validated at USAMRIID

GENTAMICIN FOR PLAGUE: GLP REQUIREMENTS (2)

- SOLUTION: Members of CDER Division of Scientific Investigation (DSI) consulted early in the process
  - Education as to actual requirements under 21 CFR 58
  - Attempt to interpret regulations in a straightforward and minimally intrusive manner

CONCLUSIONS

- Animal Rule creates new opportunities, and new challenges, for researchers mobilized to combat bioterrorism
- Need for careful consideration and planning to address the four scientific criteria
  - Pathophysiological mechanisms
  - Demonstration of effect in animal species with response predictive for humans
  - Relationship of study endpoint to desired human benefit
  - Pharmacokinetic and pharmacodynamic data in animals that permit selection of effective human dose

CONCLUSIONS (2)

- Other requirements also must be considered
  - GLP requirements
  - Need for human safety data
  - Postmarketing studies

CONCLUSIONS (3)

- **EARLY COMMUNICATION WITH DIVISON OF COUNTER-TERRORISM, AND WITH REVIEW DIVISIONS, IMPORTANT IN ENSURING AN EFFICIENT PROCESS**
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