

Animal models for assessing countermeasures to bioterrorism agents

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US Department of Defense- Transformational Medical Technologies Initiative

- TMTI: Protect the warfighter from disease and biological warfare agents
- **Broad-spectrum** medical countermeasures/technologies against advanced threats, including unknown biological diseases (and emerging infectious diseases): one drug against multiple pathogens
- **Accelerated development time**
- **Accelerated FDA licensure**



Challenges in TMTI-funded MCMs

- Diseases not endemic in the US:
 - lack of natural history information and disease progression in humans
 - no high-risk population at hand (studies not feasible)
 - no reliable treatment available

Challenges in TMTI-funded MCMs (cont.)

- Reliance on animal models
 - unethical to conduct human clinical trials: “do no harm” principle
 - do we have a good understanding of agent involved
 - natural history and progression of disease in animals
 - may need more than one animal model
 - can we cross-over animal-based information to humans and do animal models adequately portray the human condition?
- Need a product to demonstrate that a model works and vice versa
- Well-controlled studies to understand causes of failure (e.g., species vs. model)
 - Ability to standardize the model
 - Offer proof-of-concept (reproducibility of study)
- GLP conditions in biocontainment

NAS study-Statement of Task

- Evaluate how well the existing TMTI-employed or candidate animal models reflect the pathophysiology, clinical picture and treatment of human disease as related to the agents of interest
- Address the process and/or feasibility of developing new animal models for critical biodefense research, placing emphasis on the need for a robust and expeditious validation process in terms of FDA's Animal Rule
- Evaluate alternatives to the use of animal models based on the premise of The Three Rs vis-à-vis the Animal Rule and FDA licensure. The evaluation will also consider the development of more humane models for infectious diseases research that do not incorporate death as an endpoint (i.e., humane endpoints)
- Report by the end of 2010
- <http://www8.nationalacademies.org/cp/projectview.aspx?key=49112>

The Animal Rule (21 CFR Parts 314 and 601)

- For drugs whose efficacy cannot be tested in humans (**not** devices or diagnostics)
- Animal studies for efficacy data in GLP conditions
 - the pathophysiology is well understood and the product ameliorates or prevents damage
 - the effect of the product is demonstrated in more than one animal species or one well-characterized animal model
 - the endpoint is beneficial to humans (survival or prevention of major morbidity)
 - Based on PK/PD select effective dose

Criteria for Emergency Use Authorizations (EUAs), Investigational New Drug Applications (INDs), Emergency Investigational New Drug Applications (EINDS), and FDA-Approved Prescription Products

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	EUA, in General (and for Peramivir)	EIND	IND	FDA-Approved Prescription Product
Access	Broad or restricted according to the letter of authorization (peramivir: seriously ill, hospitalized patients)	Single patient with serious illness or immediately life-threatening condition	Limited to clinical trials or expanded access	By prescription
Use	According to the conditions of authorization (peramivir: intravenous administration in a hospital)	Limited to single patient	Limited to clinical trials or expanded access	According to labeling and practice of medicine
Efficacy requirements	Reasonable to believe based on totality of scientific evidence, including adequate and well-controlled trials as available (peramivir: benefit observed in patients with acute, uncomplicated influenza)	Rationale for intended use, risk from treatment should be no greater than risk from disease or condition	No efficacy requirements, but safety data from animal studies are needed	Substantial evidence based on adequate and well-controlled clinical trials
Prescriber safety reporting	According to the conditions of authorization (peramivir: mandatory)	Required per IND regulations	Required per IND regulations	Voluntary MedWatch reporting
Informed consent	No	Yes	Yes	No
Approval by institutional review board	No	Exempted but must be reported to institutional review board within 5 days	Yes	No

Birnkrant D and Cox E. N Engl J Med 2009;10.1056/NEJMp0910479

Global challenges

- Animal Rule is unique
 - scientific and legislative hurdles toward sharing MCMs
- Ethical issues with animal use in biodefense research
 - how do we uphold the 3Rs?
 - NHPs
 - humane endpoints (death as an endpoint; supportive treatment)
 - veterinary training
- **Need global integrated and coordinated framework of development, production, and licensing**