The FDA’s Animal Efficacy Rule, 12 Years Later

Brian Bollwage, JD
Vice President, Regulatory Affairs
Introduction
In the aftermath of the Sept. 11, 2001, terrorist attacks the realization that a future terrorist attack using chemical, biological, radiological or nuclear agents might occur encouraged the U.S. Food and Drug Administration (FDA) to enact regulations intended to expedite the development and approval of new drug and biological products as anti-terrorism countermeasures.

The rule “New Drug and Biological Products: Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible” was promulgated in May 2002. This white paper will take a look at the products that have received FDA approval as a result and how these products leveraged this rule, commonly known as the Animal Efficacy Rule. I’ll also examine the FDA’s recently updated guidance (May 2014) for hints to the potential future use of the rule.

The Rule
The Animal Efficacy Rule created a new regulatory pathway for assessing efficacy by stating the FDA’s willingness to approve drugs and biologics for counter-terrorism uses based on animal data when it is unethical or unfeasible to conduct efficacy studies in humans. The Animal Efficacy Rules can be found in 21 CFR 314.60 and 601.91 for drugs and biologics respectively. Note that no similar provision was created for medical devices.

Under these rules, the FDA can rely upon evidence from animal studies to provide the substantial evidence of effectiveness needed to support approval when the following conditions are met:

• There is a reasonably well understood pathophysiological mechanism for the toxicity of the chemical, biological, radiological or nuclear substance and its amelioration or prevention by the product;

• The effect is demonstrated in more than one animal species that are expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a significantly well-characterized animal model for predicting the response in humans;

• The animal study end point is clearly related to the desired benefit in humans, which is generally the enhancement of survival or prevention of major morbidity; and

• The data or information on the pharmacokinetics and pharmacodynamics of the product or other relevant data or information in animals and humans is sufficiently well understood to allow selection of a dose in humans, and it is therefore reasonable to expect the effectiveness of the product in animals to be a reliable indicator of its effectiveness in humans.

Animal studies that will be used to support the effectiveness of a drug or biologic leveraging the Animal Efficacy Rule must be conducted in compliance with the requirements of the GLP regulations (21 CFR 58) and the Animal Welfare Act (7 USC 2131).

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The Animal Efficacy Rule created a new regulatory pathway for assessing efficacy by stating the FDA’s willingness to approve drugs and biologics for counter-terrorism uses based on animal data when it is unethical or unfeasible to conduct efficacy studies in humans.
It is also important to note that as the name “Animal Efficacy Rule” implies, this rule does not address the safety evaluation of such products. Indeed, the FDA has stated that products intending to invoke the Animal Efficacy Rule will be evaluated for safety under the preexisting requirements for establishing safety of new drugs and biologics. The notion of an approval based exclusively on animal data is therefore a misconception. In fact, the requirement for human data to establish safety and a reliable dose is emphasized in the FDA’s May 2014 guidance and even in the earlier 2008 version. Wishful thinking has apparently led some sponsors to have unreasonable expectations as to the burden of data necessary to support an approval.

FDA Approvals
Since its promulgation, the FDA has approved four products using the Animal Efficacy Rule:

1. Pyridostigmine bromide (NDA 20-414) was approved in 2003 for combat use by U.S. military personnel as a prophylaxis against the lethal effects of soman, a nerve agent poison. This was the first drug approved under the Animal Efficacy Rule. Evidence of effectiveness was obtained from studies in two species, monkeys and guinea pigs, showing that administration of the drug prior to soman exposure, together with atropine and pralidoxime given after exposure increases survival. The FDA’s safety assessment relied heavily upon long-term, high-dose experience of pyridostigmine bromide, approved in the U.S. in 1955 for treatment of patients with myasthenia gravis. The dose for prophylaxis against soman was lower than the approved dose used to treat myasthenia gravis patients.

2. Cyanokit (hydroxocobalamin) (NDA 22-401) was approved in 2006 for treatment of cyanide poisoning. In a controlled study in cyanide-poisoned adult dogs, the use of Cyanokit reduced whole blood cyanide content by more than 50 percent and significantly improved survival in treated dogs as compared to those dogs receiving a placebo. The safety and kinetics of Cyanokit were evaluated in 136 healthy adult human volunteers to ascertain safety and select an appropriate dose.

3. Levaquin (levofloxacin) (NDAs 20-634, 20-635 and 21-721) was approved in 2012 to treat pneumonic plague on the basis of a trial in green monkeys that were infected with the plague bacterium in a lab setting and then treated with a 10-day course of Levaquin or a placebo. Using the primary end point of survival, 94 percent of Levaquin-treated monkeys survived while none of the placebo-treated monkeys survived. Note that the size of the monkey study was small — 17 were treated with Levaquin and seven with a placebo. Levaquin’s safety had been demonstrated in both the prior approved NDA studies and also had extensive marketing experience for several existing medical uses.

4. Raxibacumab

The FDA has approved four products using the Animal Efficacy Rule:
1. Pyridostigmine bromide (NDA 20-414)
2. Cyanokit (hydroxocobalamin) (NDA 22-401)
3. Levaquin (levofloxacin) (NDAs 20-634, 20-635 and 21-721)
4. Raxibacumab
Raxibacumab was approved in 2012 to treat inhalational anthrax on the basis of one study in monkeys and three studies in rabbits. All animals were exposed to aerosolized B. anthracis spores and efficacy was determined by assessing survival at the end of the studies. Animals received either raxibacumab, antibiotics or a placebo. In all studies, raxibacumab-treated animals survived at significantly higher rates than placebo-treated animals. Treatment results between raxibacumab and antibiotic treatment were similar. The safety of raxibacumab was evaluated in 326 healthy human volunteers.

Lessons Learned
A number of significant themes present themselves from these four successful development programs that can be used to guide future programs. Perhaps it’s not surprising that these themes have now also been given greater emphasis in the recently released, May 2014 guidance on this topic. Most notably, the same end point — survival post-exposure to the causative agent versus placebo — was determined to be necessary. In addition, the use of multiple species were employed in at least two cases where a single definitive animal model was not considered adequate. Also, extensive experience in humans was pre-existing from earlier approved NDAs in at least two cases. Where prior human data did not exist, a significant number of healthy human volunteers were given the drug to establish safety and select an appropriate dose. The FDA’s recent guidance now speaks to a “threshold” number of human volunteers needed to establish safety: 300.

Important Considerations
Because approvals under the Animal Efficacy Rule are speculative, based on only animal efficacy data alone, the FDA’s regulations provide for some special controls to enhance patient safety. The FDA can require that a sponsor perform a post-approval study to verify and describe the drug’s clinical benefits in much the same way it requires for accelerated approval drugs. Likewise, if a drug’s benefit is not confirmed in a required post-approval study, the FDA may proceed to withdraw approval of the NDA.

The FDA may also rely upon restricted distribution to enhance the safe use of the product just as it does when it requires a risk evaluation and mitigation strategy (REMS). Because of the relative absence of human efficacy data, the FDA has also created a special requirement for patient informed consent; this requires that patients be informed that for ethical or feasibility reasons the drug product was approved based on efficacy studies conducted in animals only.

The FDA has also expressed a willingness to see the Animal Efficacy Rule used in non-counter-terrorism products, e.g., venomous snake bites, emerging viruses or similar life-threatening conditions where conducting human trials would be unethical or infeasible.
Because of the challenges and uncertainty inherent in relying upon animal studies to support approval of a new drug or biologic, the importance of establishing an early and ongoing dialogue with the FDA regarding the sponsor’s development plan is even more critical here. Sponsors may seek a favorable special protocol assessment (SPA) from the FDA, which would indicate the FDA’s agreement that a trial’s design, end point and statistical analysis are acceptable for support of regulatory approval. (The FDA has extended its use of the SPA program to include products that intend to rely on the Animal Efficacy Rule.)

Sponsors should also take note that the development of such products has not proven to be faster in practice as the requirements for dose selection and demonstrating safety remain the equivalent of a standard drug development. However, the flexibility to approve a drug or biologic on the basis of efficacy trials in animals is an important consideration for a select class of drug/disease combinations.

References

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